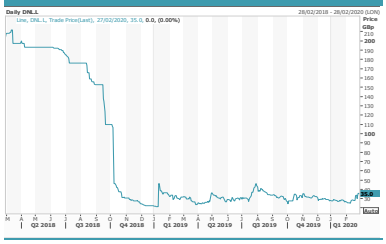
Pharmaceuticals & Biotechnology



Source: Refinitiv

Market data	
EPIC/TKR	**DNL**
Price (p)	**36.0**
12m High (p)	46.5
12m Low (p)	21.0
Shares (m)	86.7
Mkt Cap (£m)	31.2
EV (£m)	26.6
Free Float*	40%
Market	AIM

**As defined by AIM Rule 26*

Description

Diurnal is a European specialty pharma company targeting patient needs in chronic, potentially life-threatening, endocrine (hormonal) diseases. Alkindi is approved in Europe and has been filed in the US. Chronocort has completed the largest and only Phase III trial in CAH and is awaiting EMA approval.

Company information

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

Key shareholders

Directors	4.0%
IP Group	39.7%
Finance Wales	13.3%
Polar Capital	8.1%
Richard Griffiths	7.2%

Diary (calendar year)

1Q'20	DITEST details pres.
1H'20	US partner
1Q'21	Chronocort EMA approval

Analysts

Martin Hall	020 7194 7632
	mh@hardmanandco.com
Dorothea Hill	020 7194 7626
	dmh@hardmanandco.com
Grégoire Pavé	020 7194 7628
	gp@hardmanandco.com

DIURNAL GROUP

… and more to come (news flow)

Diurnal (DNL) is a commercial-stage specialty pharmaceutical company focused on diseases of the endocrine system. Its two lead products are targeting rare conditions where medical need is currently unmet, with the aim of building a long-term 'Adrenal Franchise'. Its first drug, Alkindi, is being rolled out through key European markets, and sales exceeded £1.1m in 1H'20. Despite unexpected Phase III trial results, positive feedback from the EMA has opened a pathway for regulatory submission of Chronocort for adult CAH and AI in Europe. Discussions with potential US partners for both products are also expected to crystallise in the first half of calendar 2020.

- **Strategy:** DNL's goal is to create a valuable 'Adrenal Franchise' that can treat patients with chronic cortisol deficiency diseases from birth and for the rest of their lives. The long-term vision, once Alkindi and Chronocort are established in Europe and the US, is to expand the product offering to other endocrine conditions.

- **Advancing pipeline:** Four market authorisations have been submitted by DNL and its commercial partners for Alkindi and Chronocort in key countries. In addition, a successful Phase I trial with DITEST in male hypogonadism has prepared DNL for discussions on the way forward with regulators in the US.

- **US partner(s):** DNL is progressing discussions in its search for a US partner for the sale and distribution of Alkindi, as well as clinical support for the Phase III Chronocort trials in CAH. The final outcome might be with more than one company, and an announcement is expected during 1H calendar 2020.

- **Risks:** Filing of Chronocort with the EMA has allayed some of the US concerns, but a partner is needed to run and fund a revised US Phase III trial in CAH. The time to conclude a deal with a US commercial partner remains uncertain, affecting the timing and quantum of the company's need for more capital in 2020.

- **Investment summary:** Alkindi, a cortisol replacement therapy designed for children under 18 years of age, is DNL's first product on the market. It is expected to be followed by Chronocort for adults – a larger market – which now has a clear pathway for regulatory approval in both Europe and the US. Despite this, the share price is still languishing well below valuations determined by peer group and DCF (344p) analyses, due possibly to the need for more capital during 2020.

Financial summary and valuation

Year-end Jun (£m)	2017	2018	2019	2020E	2021E	2022E
Sales	0.00	0.07	1.04	2.41	5.76	16.16
SG&A	-3.23	-6.21	-5.83	-5.75	-6.46	-7.81
R&D	-8.34	-10.02	-8.69	-4.80	-5.04	-5.29
EBITDA	-12.07	-16.97	-14.50	-9.42	-7.33	0.60
Underlying EBIT	-12.08	-16.98	-14.53	-9.45	-7.35	0.58
Reported EBIT	-12.08	-16.98	-14.53	-9.45	-7.35	0.58
Underlying PBT	-12.16	-17.11	-14.40	-9.40	-7.29	0.59
Statutory PBT	-12.16	-16.91	-14.40	-9.40	-7.29	0.59
Underlying EPS (p)	-18.04	-27.16	-14.54	-9.27	-5.05	1.32
Statutory EPS (p)	-18.04	-26.78	-19.70	-9.27	-5.05	1.32
Net (debt)/cash	16.37	17.28	9.15	10.65	1.77	1.21
Equity issues	0.05	13.40	5.53	9.40	0.00	0.00

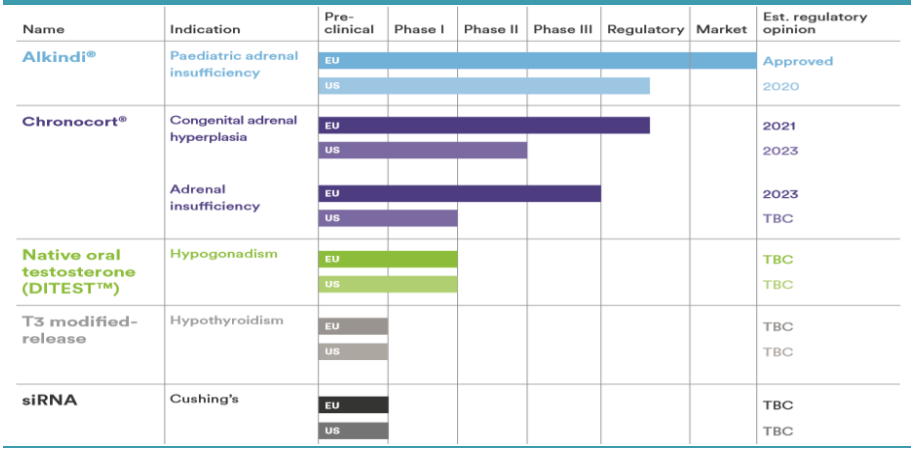
Source: Hardman & Co Life Sciences Research

Table of contents

Executive summary

DNL is a commercial-stage specialty pharmaceutical company focused on endocrine (hormonal) diseases. Founded as a spin-out from the University of Sheffield in 2004, it listed on AIM in 2015. DNL's vision is "to become a world-leading endocrinology speciality pharma company" by maximising its commercial infrastructure in the niche field of endocrinology, which is dominated currently by small biotech. As well as developing drugs internally, management has remained open about considering all available options – product acquisitions, in-licensing and partnership opportunities.

Diurnal – pipeline



Source: Diurnal 2019 Annual Report

Cortisol replacement products

Alkindi

Alkindi is a paediatric cortisol replacement for treating new-borns to 18-year-olds with paediatric Adrenal Insufficiency (AI), including Congenital Adrenal Hyperplasia (CAH). It has been approved by the European Medicines Agency (EMA) and is being rolled out across Europe, with the aim of ultimately accessing markets representing 80% of the European population. Sales in fiscal 1H'20 were £1.1m, exceeding those for the whole of the financial year 2018/19. Following the New Drug Application (NDA) submission in November 2019, the US Food and Drug Agency (FDA) has now accepted the review of DNL's application for Alkindi (Alkindi Sprinkle in the US). The Prescription Drug User Fee Act (PDUFA) date set by the FDA is 29 September 2020. Meanwhile, discussions are ongoing to find a US partner; DNL expects to crystallise an agreement by calendar 1H'20.

Alkindi – current status

Territory	Status	Comments
Europe	Approved	DNL selling/distributing Alkindi itself in main European countries, and uses partners in territories that recognise EMA market authorisation
US	NDA filed with FDA	NDA submission accepted by FDA; approval due by end 3Q'20-4Q'20 (PDUFA date 29 September 2020). DNL will use a partner to commercialise Alkindi in US

Source: Diurnal, Hardman & Co Life Sciences Research

Chronocort

Chronocort is a hydrocortisone preparation designed to mimic the natural circadian rhythm of cortisol, primarily targeting adult patients with AI and CAH. The Market Authorisation Application (MAA) dossier for CAH has been submitted to the EMA,

and approval is expected by 1Q'21. In AI, no further studies are required, assuming approval in CAH, and DNL will submit an application for market authorisation depending on the outcome of the CAH dossier. In the US, discussions for partnering Phase III in CAH and Phase II in adult AI are taking place, and these are expected to be concluded in calendar 1H'20.

Chronocort – current status

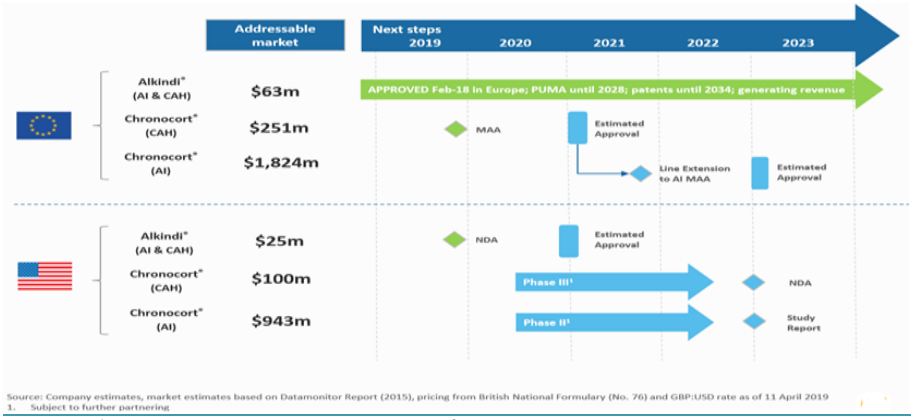
Territory	Condition	Status	Comments
Europe	CAH	MAA submitted (16 December 2019)	CHMP opinion and market authorisation expected in 1Q'21
Europe	AI	No further studies needed	Submission of MAA dependent on positive outcome from CAH filing
US	CAH	Phase III ready	DNL in discussions to find US partner to co-run and fund Phase III trial
US	AI	Phase II ready	DNL contemplating its options (grant-funding, partnering or further capital)

Source: Diurnal, Hardman & Co Life Sciences Research

Commercial opportunity

With no real evolution in disease management for many years, cortisol replacement therapy is still a high unmet medical need. In the paediatric space, it is dominated by unlicensed hydrocortisone-based products, whereas, in the adult population, it is dominated by glucocorticoids (steroids), with their associated poor compliance and high levels of side effects that could lead to death. The overall market population is estimated in excess of 520,000 for cortisol replacement therapy for Europe and the US.

Diurnal – development timetable in Europe and US



[1] *Subject to confirmation from the FDA,* [2] *Subject to NIH Grant, further funding or partnering*
Source: Diurnal 2019 results presentation, September 2019

Addressable market

DNL has indicated that the benchmark price for Chronocort and Alkindi is $6,138 for a year's treatment. While this would be higher than the price for immediate-release hydrocortisone, the argument that cortisol levels would be much more tightly controlled in these potentially life-threatening conditions should be accepted. Taken together, the overall markets being targeted by Chronocort and Alkindi would be ca.$3.3bn.

2020-21 milestones

The next two years are expected to be characterised by several important milestones for the company. Currently, DNL is in negotiations with a number of European countries regarding the reimbursement rate for Alkindi, which needs to be resolved on a country-by-country basis. In addition, either directly or through local distribution partners, Alkindi is awaiting marketing approval in three countries,

including the all-important US, with the PDUFA date set by the FDA at 29 September 2020. Its second drug, Chronocort, has been submitted to the EMA for marketing approval. Meanwhile, management is continuing negotiations with several parties with respect to commercial and development deals for its products in the US, which is potentially game-changing for DNL.

Key value inflections point for 2019-20

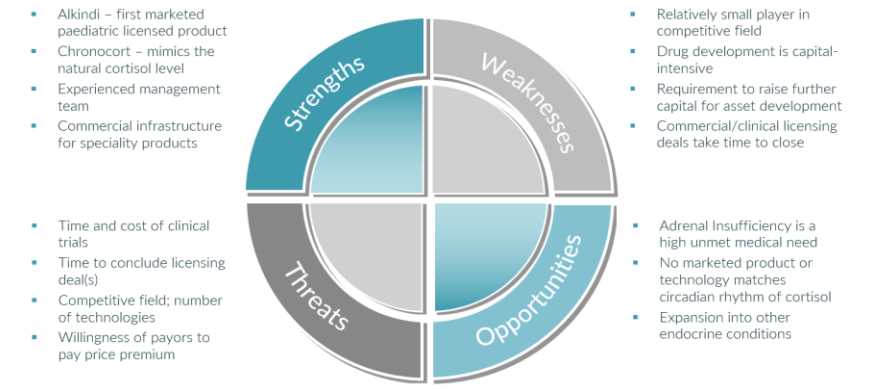
Milestones	Date	Status
Meeting with FDA to confirm NDA submission pathway for Alkindi	1Q'19	✓
Scientific Advice with EMA to confirm regulatory submission path for Chronocort	2Q'19	✓
DITEST Phase I/II readout	4Q'19	✓
Chronocort European regulatory submission (CAH)	4Q'19	✓
Alkindi US NDA submission (AI and CAH)	4Q'19	✓
Conclude US partnering discussion for Alkindi	1H'20	
Conclude US partnering discussion for Chronocort	1H'20	
Potential approval of Alkindi in US (PDUFA date set)	29 Sep 2020	
Potential approval of Chronocort in Europe	1Q'21	

Source: Diurnal, Hardman & Co Life Sciences Research

Financial position

At 31 December 2019, DNL had gross (and net) cash of £4.63m. The company will need an injection of an estimated £10m of new capital during the next six months to cover the working capital requirement for fiscal 2021. This could come from an upfront payment as part of any US licensing deal(s) and/or from one or more equity issues.

SWOT analysis



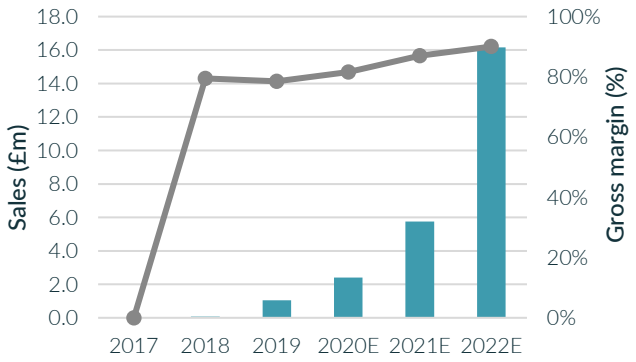
Source: Hardman & Co Life Sciences Research

Investment conclusion

In a DCF model of Alkindi and Chronocort, the net present value (NPV) of the cashflows that could be generated from these products equates to £455m 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 £298m, or 344p per share, but this still gives plenty of potential upside for shareholders.

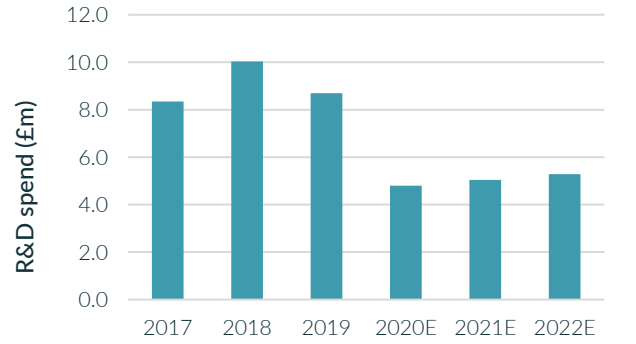
In addition, the EV of DNL compares well against an international peer group of specialty pharmaceutical companies with putative drugs in late-stage clinical trials for endocrine disorders. The shares are currently being held back by the market's awareness that the company will require further capital in the short term, and this is dependent, in part, on the outcome of licensing discussions with potential US partners and their willingness to fund the Phase III Chronocort trials.

Sales and gross margin



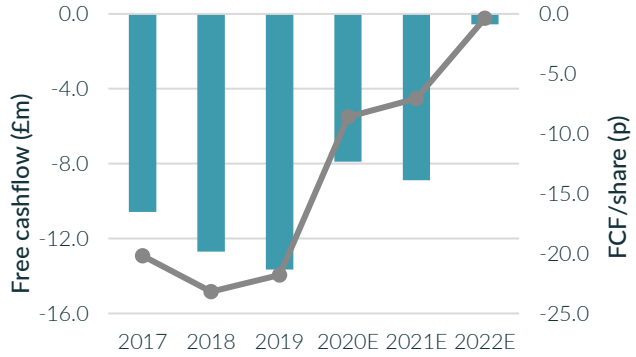
- Sales of Alkindi began in 2Q'18
- Alkindi sales exceeded £1.1m in 1H'20 (fiscal), and Alkindi is now available in eight countries in Europe
- Gross margin expected to stabilise at 90% in near term
- First sales of Chronocort anticipated to start around end-2021 in Europe

R&D investment



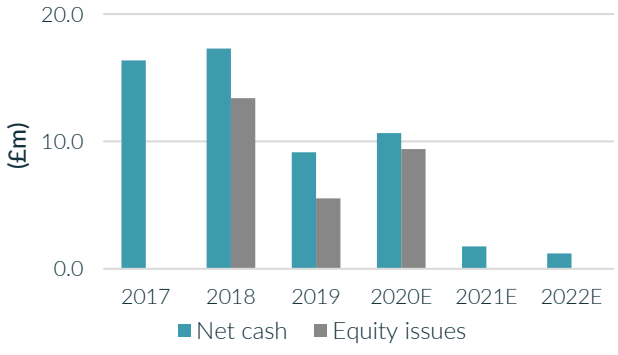
- Preparatory works for US Phase III trial (£2.3m) accounted for 2019 R&D fall
- R&D costs expected to reduce in coming years, as future trial costs will be shared with a US partner (to be announced in calendar 1H'20)
- US Phase II in AI with Chronocort now anticipated to start once a partner is on board

Free cashflow and FCF/share



- Cashflow driven by R&D investment and corporate overheads
- With the US partner to share the US trial costs for Chronocort, the cashflow is anticipated to improve and DNL to be cashflow-positive in 2023
- Monthly average cash burn at ca.£0.78m for 2020

Net cash and equity issues



- At 31 December 2019, net cash was £4.63m
- Placing and Open Offer raised £5.9m gross (£5.5m net) in June 2019
- Based on current forecasts, we estimate DNL will raise up to £10m gross before end of fiscal 2020 – this could be from equity or part equity and part upfront payments received from the US partner, depending on the timing

Source: Company data, Hardman & Co Life Sciences Research

Interim results to 31 December 2019

Key features

Operational highlights

- **Alkindi – Europe:** Initial launches in the UK, Germany and Austria have been followed by the Nordic countries (Sweden, Denmark, Norway and Iceland) through DNL's partner, Frost Pharma. Post period-end, Alkindi has also been launched in Italy.
- **Alkindi – US:** NDA has been submitted to the FDA, with the outcome expected by end-2020. Concomitantly, partnering discussions are ongoing for commercial rights to both Alkindi and Chronocort.
- **Alkindi – RoW:** Through specialist partners in other key territories, two additional market authorisations for Alkindi have been submitted.
- **Chronocort – Europe:** MAA for CAH has been submitted to the EMA, with first opinions expected by calendar 1Q'21.
- **Chronocort – US:** A revised protocol for the Phase III trial in CAH has been proposed, with the study now expected to commence following successful partnering discussions.
- **Oral testosterone:** Successful Phase I study delivering superiority of DITEST over conventional oral testosterone. DNL anticipates engaging with a partner to run and fund the subsequent trial.

Financial highlights

- **Sales:** Net sales of £1.15m were recorded for Alkindi in 1H'20, derived largely from Germany, the UK (34% and 40%, respectively) and the Nordic countries; the result was broadly in line with our forecast at £1.10m. Timing is difficult to predict, being dependent on pricing discussions on a country-by-country basis.
- **Gross margin:** The initial gross margin, at 74%, is expected to stabilise nearer to 90% in the near term, as volumes improve.
- **SG&A:** Underlying administration costs increased 40% to -£2.6m, from -£1.8m, reflecting increased regulatory activities.
- **R&D:** Spend for fiscal 1H'20, at -£2.39m, was much lower than the comparable period the previous year (-£7.62m), and below our forecast (£-4.50m). This was the direct result of the pause in clinical work for the US Phase III Chronocort trial, following the unexpected outcome from the European Phase III trial.
- **Net cash/(debt):** At 31 December 2019, the gross (and net) cash on the balance sheet was £4.63m (£6.86m), which was in line with our forecast of £4.53m.

Diurnal – 2020 interim results, actual vs. expectations

(£m)	1H'19 actual	1H'20 actual	Growth %	1H'20 forecast	Delta Δ
Sales	0.19	1.15	nm	1.10	+0.05
COGS	-0.03	-0.30	nm	-0.22	-0.08
Gross margin	82%	74%	-	80%	-
R&D spend	-7.62	-2.39	-68%	-4.50	+2.11
Administration costs	-1.85	-2.60	+40%	-3.02	+0.42
Underlying EBIT	**-9.74**	**-4.58**	**-53%**	**-7.05**	**+2.47**
Net cash/(debt)	6.86	4.63	-	4.53	+0.1

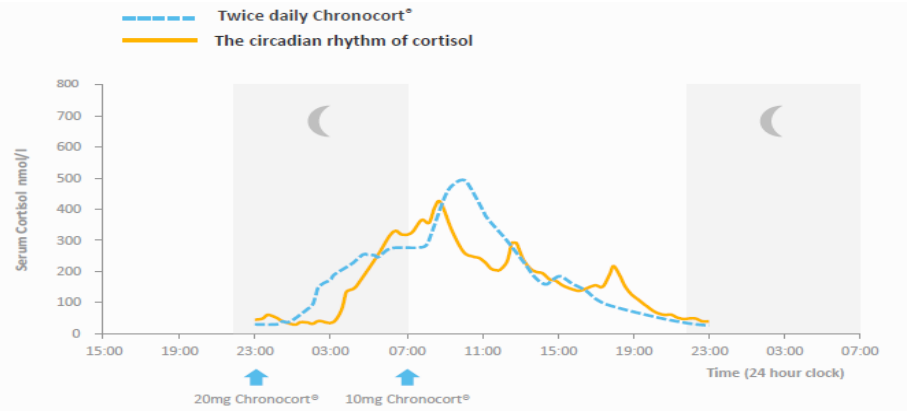
nm=not meaningful
Figures may not add up exactly due to rounding
Source: Diurnal, Hardman & Co Life Sciences Research

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, 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.

Chronocort® – mimicking the circadian rhythm



Source: Diurnal

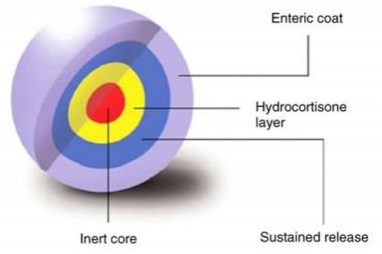
With Chronocort, DNL is targeting the large AI market, which includes CAH, estimated at $3.2bn.

Chronocort – current status

Territory	Condition	Status	Comments
Europe	CAH	EMA market authorisation submitted (16 December 2019)	CHMP opinion expected in 1Q'21 and market authorisation in 1Q'21
Europe	AI	No further study needed	DNL expects to submit for MAA for AI following positive outcome from submission for CAH
US	CAH	Phase III ready	DNL in discussions to find a US partner to co-run and fund the Phase III trial
US	AI	Phase II ready	DNL contemplating its options (grant-funding, partnering or further capital)

Source: Diurnal, Hardman & Co Life Sciences Research

Chronocort presentation



Source: Diurnal

Presentation

Chronocort is a patented, oral, modified-release formulation of hydrocortisone, which is intended to mimic, or closely match, the serum levels of endogenous cortisol. It is a multi-layered, multi-particulate formulation, containing micro-crystalline beads, using specialist multi-particulate manufacturing technology. Chronocort is produced by Glatt Pharmaceutical Services GmbH & Co. KG, an experienced specialist Good Manufacturing Practice (GMP) manufacturing company based in Germany. 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 (GI) tract, allowing release of the active ingredient, where it will be easily absorbed.

DNL intends to make Chronocort available initially in three doses (5mg, 10mg and 20mg), to give endocrinologists the flexibility to adjust the dose to a patient's needs.

Treatment with Chronocort

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

One of the key features of Chronocort is its delayed-release coat, which is sensitive to pH and is designed to dissolve in the alkaline environment of the GI tract, thereby allowing the slow release of hydrocortisone, where it can be absorbed optimally into the bloodstream. Owing to the short half-life of hydrocortisone, the release mechanism is important for a slow, but constant, absorption of the drug in order to achieve a therapeutic level that mimics the normal secretion of cortisol.

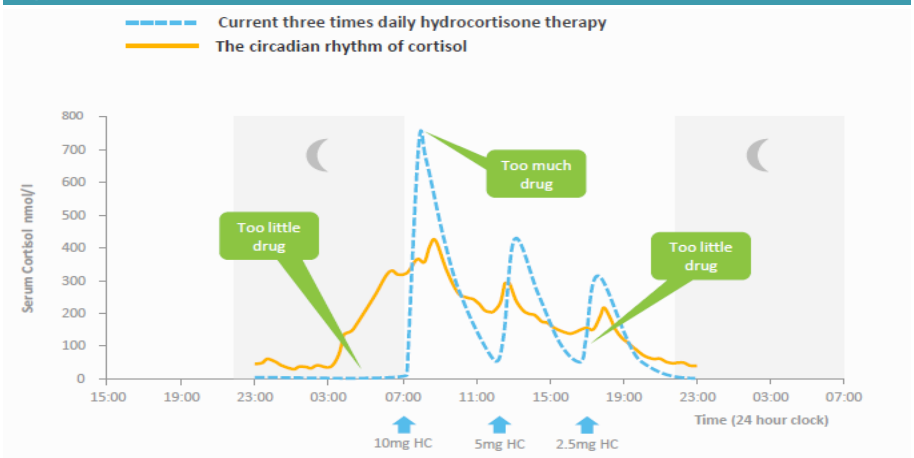
Hence, Chronocort has the unique potential to provide the best possible physiologic replacement of cortisol and promises to ameliorate many of the unresolved medical issues surrounding the management of subjects with CAH.

Standard-of-care

…whereas current standard-of-care causes big peaks and troughs

The current standard-of-care is administration of immediate-release (IR) hydrocortisone twice or three times daily, depending on body weight, which results in higher short-term blood levels that rapidly decline due to the short half-life.

Hydrocortisone blood levels



Source: Diurnal

Formulations of IR hydrocortisone and other glucocorticoids used in the treatment of CAH are recognised to be unsatisfactory, due to issues with:

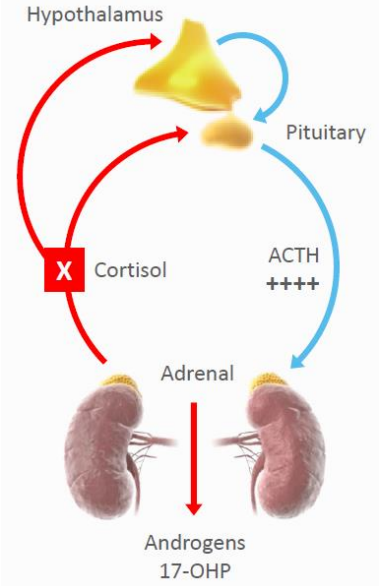
- suboptimal disease control (including risk of adrenal crisis);
- risk of glucocorticoid over-treatment;
- inconvenient dosing regimens;
- complex and inconsistent protocols for monitoring therapy; and
- poor compliance.

Rationale for Chronocort

Subjects with classical CAH receive replacement glucocorticoid and mineralocorticoid. It is often quite difficult to reduce excess of androgen levels without giving either too much or not enough glucocorticoid, respectively. This is because current therapies cannot replace the normal circadian rhythm of cortisol.

It is thought that Chronocort more closely matches natural cortisol levels compared with hydrocortisone because it is manufactured with specific modified release features, as a consequence of a better understanding of the circadian rhythm of cortisol.

What is CAH?



Source: Diurnal

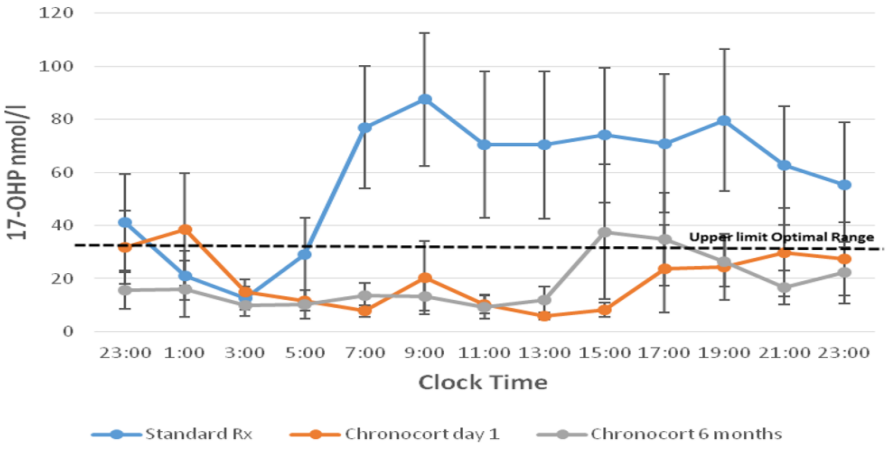
Physiological downstream effect of Chronocort

One of the androgens measured during clinical trials was the hormone 17-hydroxy-progesterone (17-OHP), a precursor of cortisol, given that ca.95% of CAH cases are due to an enzyme (21-hydroxylase) deficiency that converts 17-OHP into a precursor of cortisol. Therefore, lack of this enzyme results in a build-up of 17-OHP in the blood and a consequent deficiency of cortisol. The lack of cortisol triggers a feedback loop to the hypothalamus and pituitary gland, which initiates the synthesis and release of cortisol precursors, increasing the level of 17-OHP even further.

The graph below presents the results from a Phase II trial (DIUR-003, NCT01735617) comparing Chronocort with standard-of-care. It clearly shows two main outcomes of Chronocort:

- the therapeutic effect of Chronocort in controlling the 17-OHP levels could be seen from the first day of treatment; and
- the impact is maintained during the six months of treatment – this is within the limit of the optimal range and is opposed to the standard-of-care.

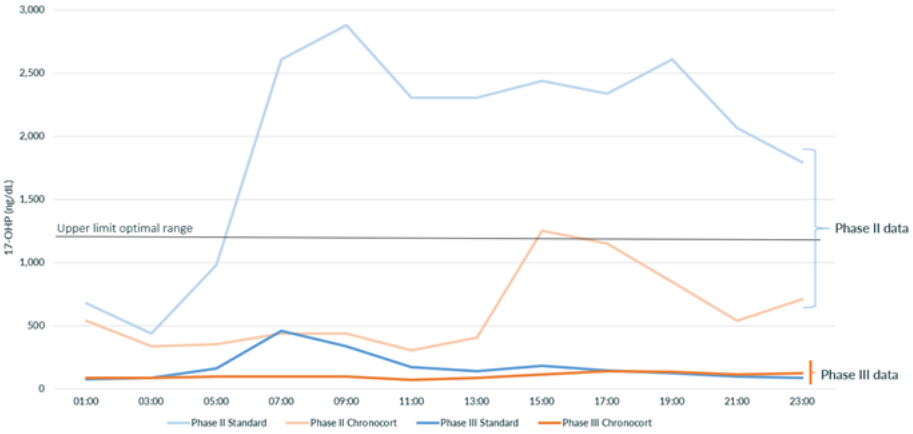
17-OHP levels at day 1 and following six months of treatment



Source: Diurnal DIUR-003 Phase I study

Given the results from this Phase II trial, the outcome from the European Phase III (DIUR-005, NCT02716818) trial was unexpected, where no statistical difference was observed initially between Chronocort and standard-of-care over a 24-hour period.

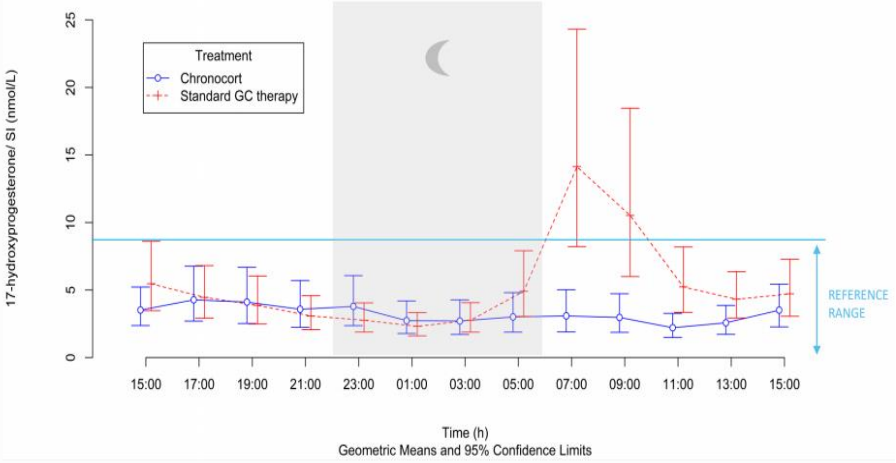
Phase II (DIUR-003) vs. Phase III (DIUR-005): 17-OHP level



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

However, full analysis of the data highlighted several crucial advantages that Chronocort exposed compared with standard-of-care, allowing submission of the MAA after consultation with the regulator.

Chronocort Phase III trial results



Source: Diurnal 2019 results presentation, Hardman & Co Life Sciences Research

- Chronocort achieved androgen control of both 17-OHP and another androgen marker, androstenedione (A4), at a lower dose (30mg) compared with standard treatments.
- Crucially, Chronocort achieved the desired level of 17-OHP in the critical early-morning period – a level that is usually too high in patients with standard-of-care (increased cortisol levels address morning fatigue).
- There was no adrenal crisis with Chronocort (an event requiring hospitalisation for several days) vs. three events in patients on standard-of-care.
- There were significantly lower overall 17-OHP levels over the 24-hour period, as measured by the area under the curve (see graph above).
- There were less variable biomarker levels on Chronocort.
- Chronocort was well tolerated and provided the natural overnight cortisol release, unlike standard therapy.
- There were fewer "sick days" in patients receiving Chronocort (during sickness, the cortisol level naturally increases): 26 days vs. 36 days with standard-of care.
- Additional unexpected benefits were seen with Chronocort, such as less fatigue and the return of menstrual cycles in female patients.

Regulatory status

EMA submission in CAH

Despite not meeting the complex primary endpoint of superior control over 24 hours, compared with conventional glucocorticoid therapy in the Phase III trial with Chronocort in adult CAH patients, representatives of the EMA confirmed the clinical and regulatory pathway.

The EMA representatives understood the statistical issue with the Phase III data, as well as the evidence of better control of biomarkers and improved quality of life using Chronocort. Importantly, the feedback confirmed that no new data were needed for the purpose of a regulatory submission.

DNL submitted its MAA for Chronocort in CAH in Europe on 16 December 2019, which will now be processed under a series of strict rules and timelines, as indicated in the following table.

Steps involved in obtaining European Market Authorisation

Steps	Timeline	Description	
Submission of eligible request	7-18 months before submission of MMA	To find out whether a product can be evaluated under the centralised procedure.	✓
Notification of intention to submit an application	7 months before submission of MMA	Notification to the EMA of the intended submission date.	✓
Appointment of rapporteurs	7 months before submission of MMA	The Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC) appoint rapporteurs to conduct the scientific assessment.	✓
Pre-submission meetings	6-7 months before submission of MMA	Pre-submission meetings with the EMA to obtain procedural and regulatory advices from the Agency.	✓
Submission and validation of the application	First day of assessment	Electronic submission of the application.	✓
Scientific evaluation	Up to 210 active days of assessment	The CHMP evaluates the application. The PRAC provides input on aspects related to risk management. Both committees have the possibility to come back to the company with further questions.	
CHMP scientific opinion	End of assessment	After the evaluation, the CHMP must issue a scientific opinion on whether the medicine may be authorised or not. The EMA sends this opinion to the European Commission, which issues the marketing authorisation.	
European Commission decision	Within 67 days of receipt of CHMP opinion	Commission decisions are published in the Community Register of medicinal products for human use, and the EMA publishes a European Public Assessment Report (EPAR).	

Source: European Medicines Agency, Hardman & Co Life Sciences Research

From the date of submission of the application of the dossier, the CHMP has up to 210 active days of assessment, taking the publication of the scientific opinion to the end of October 2020. Following this outcome, the European Commission will give the final decision to grant Market Authorisation before the end of January 2021. In parallel, DNL has applied for Orphan Drug Status in Europe.

Current clinical trial status

Extension study

Data from Phase III safety extension study with Chronocort helped discussions with EMA

Following completion of the Phase III study, DNL has been conducting an open-label safety extension study (DIUR-006, NCT03062280) for patients wishing to continue on Chronocort or electing to switch from their current glucocorticoid therapy (standard-of-care) to Chronocort. To date, a total of 91 patients have been enrolled. The main aspect of the trial is to assess the long-term safety and tolerability of Chronocort, with the study expected to run until commercial availability. DNL has indicated that there has been a low drop-out rate from the extension study (less than 10%).

In the last interim analysis (April 2019), DNL stated that a number of patients had been on Chronocort for more than 30 months and were all still continuing with the treatment. This analysis indicated additional benefits of Chronocort, such as:

- 17-OHP and a second key androgen androstenedione (A4) control maintained over the 24-month period;
- further steroid dose reduction over the period;
- weight and body-mass index (BMI) maintained during the period; and
- metabolic parameters unchanged.

DNL is continuing to assess these patients, and a further analysis is expected in the next six months. This will provide additional information to determine whether the positive effect of Chronocort can be maintained over the long term. This extension study will also help in the company's pricing discussions with the regulators.

Potential European submission in AI

Following the positive Scientific Advice meeting on Chronocort, held in March 2019, the EMA has indicated that no further trials are needed for Chronocort in order to be submitted for Market Authorisation in Europe. The meeting has set up the regulatory pathway for Chronocort in AI and has indicated that, depending on the outcome for Chronocort in CAH, expected in 1Q'21, DNL may submit for market authorisation in Europe.

US Phase III trial in CAH

Change to "non-inferiority" clinical endpoint for Phase III trial in US

The outcome of the EMA Scientific Advice meeting was important in guiding amendments to the US Phase III trial protocol and, importantly, also means that DNL can now resume all the regulatory and preparatory work. A different statistical measure of efficacy and a non-inferiority outcome of Chronocort versus standard-of-care will be adopted as the primary endpoint.

The study is anticipated to recruit up to 150 patients, and most of the groundwork has already been undertaken, including identification of the clinical sites. The US Phase III study will be run with a partner, and DNL has indicated that it is in advanced discussions with suitable specialist pharma companies.

US Phase II trial in AI

DNL also intends to start a US Phase II trial in order to address the large AI market. This trial is expected to be conducted at some of the same sites as the Phase III CAH trial, and DNL will investigate different options to finance it, such as grant-funding and further capital – but ideally with a partner.

Alkindi®

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

Alkindi is an immediate-release hydrocortisone preparation for the control of AI, including CAH in children. In February 2018, DNL received market authorisation from the European Commission through the Paediatric Use Marketing Authorisation (PUMA) route for Alkindi, targeting new-borns to 18-year-olds with AI. DNL has now received acceptance from the FDA for a review for Alkindi Sprinkle, with a PDUFA date of 29 September 2020. Alkindi represents the first-in-class licensed product with a goal to deliver improved compliance, improved disease control and a reduced side effect profile for this type of population.

Alkindi – current status

Territory	Condition	Status	Comments
Europe	Paediatric CAH & AI	Approved	DNL is selling/distributing Alkindi itself in the main EU countries and uses partners in territories that recognise EMA market authorisation.
US	CAH & AI	NDA submitted to FDA	NDA submission accepted by FDA; approval due by end 3Q'20-4Q'20 (PDUFA date 29 September 2020). DNL will use partners to commercialise Alkindi in the US.

Source: Diurnal, Hardman & Co Life Sciences Research

Alkindi – first product in the market

Alkindi being rolled out across Europe

In order to retain full value for this drug, DNL is selling it directly in major European countries through its own commercial infrastructure and, in the Nordic countries, through a distributor (Frost Pharma). When fully established, this will represent ca.80% of the European population. In other worldwide territories that recognise the EMA approvals, DNL is using distribution partners.

In its first full year on the market, Alkindi sales were over £1.0m, and, for fiscal 1H'20, sales were above expectations, at £1.15m (£0.20m). Despite being a centralised authorisation process, the rollout of Alkindi must be a staged process, influenced by the timetable for agreeing pricing with the relevant authorities in each country. This is normal practice for drugs approved in Europe.

To date, Alkindi has been launched by DNL in Germany (May 2018), the UK (September 2018), Austria (April 2019) and Italy (February 2020), with the Nordic countries (July 2019) being covered by its distribution partner, Frost Pharma. In addition, DNL received a positive Scottish Medicines Consortium (SMC) pricing and reimbursement decision recently. During 2020, further launches are expected in the Netherlands (1H'20) and Spain (2H'20).

Overall, the rollout of Alkindi launches has been slower than expected due to external factors beyond the company's control, such as the unpredictability of timing of pricing/reimbursement discussions and Brexit, as well as the implementation of new regulations (Falsified Medicines Directive), which require a unique bar code for each package.

Three market authorisations expected in 2020

Three market authorisations expected in 2020

In other territories, commercialisation will be through local distributors, with knowledge of either endocrine or niche markets, who will be responsible for dealing with the local regulatory authorities. Such deals also cover DNL's other products.

FDA submission for Alkindi in November-2019

United States

DNL filed its first-ever NDA with the FDA in November 2019, for Alkindi (Alkindi Sprinkle) in paediatric AI and CAH (from birth to 17 years of age). DNL received the acceptance for review from the FDA, with a PDUFA date of 29 September 2020, in line with the period of 10 months set for the FDA to review new drug applications. Approval is now expected in 3Q'20-4Q'20. The US addressable market is estimated at $28m. In parallel with the NDA submission, DNL will seek confirmation of Orphan Drug Status for Alkindi in paediatric AI. The company will need to provide evidence of significant clinical benefit over existing therapies.

To maximise the commercial opportunity, DNL does not intend to sell Alkindi directly in the US, but through a licensing partner, and discussions with potential partners have been initiated already, with an outcome expected in calendar 1H'20.

Israel

DNL signed a marketing and distribution agreement with Medison Pharma in 2018, to make Alkindi and Chronocort (once approved) available in Israel and the Palestinian Authority. Market authorisation has been filed, with an outcome expected in mid-2020. With ca.1,000 patients, the market opportunity for Alkindi and Chronocort is estimated at $6.1m.

Australia

DNL has licensed (February 2018) exclusive commercial rights to both Alkindi and Chronocort in Australia and New Zealand to Emerge Health, a specialist hospital pharma company. Emerge Health submitted an application for market authorisation in July 2019 to the Australian Therapeutic Goods Administration, with first sales expected towards the end of 2020. Around 1,750 patients are affected by paediatric AI and adult CAH, giving a market estimated to be worth $10.7m. DNL received the grant of Orphan Drug Application from the Australian regulators in mid-2019.

Japan

Patents for Alkindi and Chronocort have been granted by the Japanese Patent Office. DNL is seeking a local partner in Japan, where there are ca.6,700 patients with CAH and 58,000 with AI, giving an estimated market worth of nearly $400m.

Market potential for Alkindi (excluding Europe)

Country	Partner	Marketing and distribution agreement	First sales	Patents granted	Addressable market**
Israel*	Medison Pharma	Yes	2H'20	Yes	$6.1m
Australia & New Zealand	Emerge Health	Yes	2H'20	Yes	$10.7m
Nordic regions	Frost Pharma	Yes	2019	Yes	$3.1m
US	TBA***	TBA	Early 2021	Yes	$28m
Japan	TBA	TBA	TBC	Yes	$397m (Alkindi+Chronocort)

*Including the Palestinian Authority, **DNL estimates based on price of $6,138 per patient p.a., ***To be announced in calendar 1H'20*
Source: Diurnal, Hardman & Co Life Sciences Research

Brexit plan

DNL has developed its product supply chain to minimise any potential impact of Brexit through:

- manufacturing in Germany;
- packaging in France; and
- distribution from the Netherlands.

In addition, DNL has established a wholly owned subsidiary, Diurnal Europe B.V., in the Netherlands, which holds the Alkindi EU marketing authorisation and Wholesaler Dealer Licence.

Alkindi – Presentation

Multi-layered, and multi-particulate formulation…

Alkindi is an immediate-release hydrocortisone preparation that has been specifically designed to meet the dosing needs with AI, for which no licensed, child-friendly products exist, either in Europe or the US. Currently, pharmacists often grind hydrocortisone tablets into a fine powder and reconstitute it in individual capsules or sachets to achieve the lower doses required for children. This compounding is highly variable and often results in inaccurate dosing.

…in four dose levels

Alkindi is also using multi-particulate manufacturing technology with a multi-layered, multi-particulate formulation. In this case, there are four essential components:

- **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.

Alkindi – four dose levels

Source: Diurnal:

Glatt has established a full scale-up process under GMP conditions, which enables the manufacture of Alkindi in 190kg batches. Alkindi is available in capsules containing four different doses – 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.

Alkindi presentation

Source: Diurnal

Advantages of Alkindi

Accuracy in dosing

Alkindi allows a high accuracy of dosing…

The current practice of grinding hydrocortisone tablets into a fine powder in order to titrate the dose according to a baby's/infant's weight is prone to enormous error. An aliquot of this powder is put into a capsule or sachet for administration/mixing with food. The potential for mistakes and weight inaccuracy is inherent with such techniques, potentially 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 Alkindi are continuing, building on the shelf-life that already exceeds three years at ambient temperature, which represents superiority over existing (unlicensed) hydrocortisone alternatives. DNL continues to investigate the potential of extending the shelf-life further.

Child-friendly preparation

…to aid compliance in children

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 acceptable for children for regular administration.

Updated pipeline

Building the endocrine pipeline

DNL's vision is "to become a world-leading endocrinology speciality pharma company". It aims to maximise its commercial infrastructure in the niche field of endocrinology, which is dominated by small biotech. As well as developing internal products, management has remained open about considering all available options – product acquisition, in-licensing and partnership opportunities.

Diurnal – R&D pipeline

Name	Indication	Pre-clinical	Phase I	Phase II	Phase III	Regulatory	Market	Est. regulatory opinion
Alkindi®	Paediatric adrenal insufficiency	EU						Approved
		US						2020
Chronocort®	Congenital adrenal hyperplasia	EU						2021
		US						2023
	Adrenal insufficiency	EU						2023
		US						TBC
Native oral testosterone (DITEST™)	Hypogonadism	EU						TBC
		US						TBC
T3 modified-release	Hypothyroidism	EU						TBC
		US						TBC
siRNA	Cushing's	EU						TBC
		US						TBC

Source: Diurnal 2019 Annual Report

In addition, DNL has been investigating opportunities for alternative capital to support the early-stage programmes, such as grant-funding. DNL has applied for various grants, and it has already received positive feedback, due to the unmet needs that the company is aiming to address.

Successful Phase I trial with DITEST

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

Headlines

DNL announced that the proof-of-concept Phase I study had met both the primary and secondary endpoints with its oral native testosterone product, DITEST, in men with primary and secondary hypogonadism. The study (NCT02966652) enrolled 24 adult men, aged between 18 and 80, and provides the first evidence of superiority compared with oral testosterone undecanoate, a modified-testosterone treatment for patients with hypogonadism.

Key findings

The study compared a single dose of DITEST (120mg) with oral testosterone undecanoate (80mg) in the fed state in male subjects diagnosed with primary and secondary hypogonadism.

- DITEST showed a more physiological control of levels of testosterone.
- DITEST achieved testosterone levels within the range of healthy men.
- Importantly, DITEST shows similar testosterone absorption in both fed and fasted states, according to the FDA guidelines, which is a key differentiator compared with current oral treatment, providing a better testosterone level control.
- Safety and tolerability were established with two doses of DITEST (120mg and 200 mg), with no serious adverse events.
- Higher levels of the potent metabolite dihydrotestosterone (DHT) were seen in the testosterone undecanoate arm.

Positive Phase I in male hypogonadism

With positive Phase I DITEST results, including safety, tolerability and favourable pharmacokinetics in both the fed and fasted states, DNL is progressing a value-added testosterone product in a still unmet medical condition of primary and secondary hypogonadal men. The product also showed early signs of superiority over the current oral testosterone undecanoate. DNL has also revealed that it will soon engage with the US and European regulators for the next phase of clinical trials, which will probably be run with a partner.

This is the third product that DNL has progressed into the clinic, and the company is in the process of building on its vision of becoming one of the leading endocrinology speciality pharma companies.

Market opportunity

The market is highly fragmented, with a number of products utilising alternative routes of administration to oral therapy. However, the market opportunity for an oral Testosterone Replacement Therapy (TRT) product remains high, especially for a product that couples the more convenient oral administration with a formulation that avoids hepatic toxicity. With DITEST, DNL expects to gain a share of the $4.8bn global market.

Hypothyroidism

Early development of a modified-release T3 (triiodothyronine) product continues to progress. It is believed that up to 20% of the hypothyroidism population does not respond to thyroxine (T4) monotherapy, which is the current standard-of-care. DNL sees a considerable opportunity for this innovative product.

Potential treatment for Cushing's disease

DNL is reviewing its options with an oligonucleotide silencing RNA (siRNA) acting on the pituitary gland for a potential treatment for Cushing's disease, a condition characterised by an excess of cortisol secretion. *In vitro* studies, assessing the stability of the molecule in different formulations, have shown that the molecule is robust and efficacious. DNL owns the Orphan Drug Designation for this molecule in Europe.

Targeting the adrenal gland

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

The adrenal glands

The adrenal glands are a pair of organs situated just 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.

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 ACTH. This, in turn, triggers the adrenal glands to produce corticosteroid hormones, which also produce 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 turn, influences blood pressure.

Adrenal medulla

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

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:

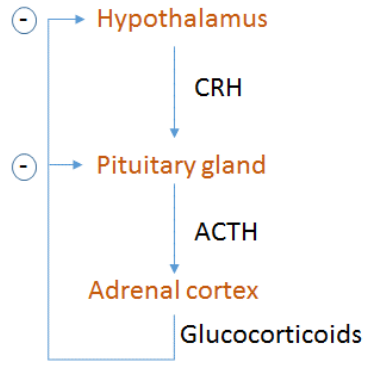
- **Metabolic response** – regulation of how the body converts fats, proteins and carbohydrate to energy by stimulation of glycogenesis (formation of glucose).
- **Immune response** – weakens the activity of the immune system by preventing the release of substances that cause inflammation.
- **Electrolyte 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.

Cortisol has a short half-life, being cleared from the plasma in about 120 minutes. When it is used as a medication, it is known as hydrocortisone.

Architecture of the adrenal glands

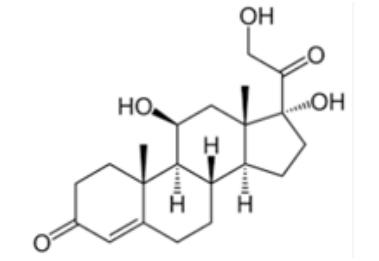
Source: www.netdoctor.co.uk

Glucocorticoid regulation



Source: Hardman & Co Life Sciences Research

Cortisol



Source: Hardman & Co Life Sciences Research

The level of cortisol in the plasma has many effects

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 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, which ultimately stimulates the adrenal gland to produce cortisol.

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

Cortisol deficiency is a life-threatening condition. Patients will die if this defect is not diagnosed and treated effectively. It is a life-long condition and affected patients will need constant cortisol replacement medication throughout their lives.

Adrenal Insufficiency (AI)

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

- **Primary AI** – direct impairment of the adrenal glands (Addison's disease).
- **Secondary AI** – an impairment of the pituitary gland or the hypothalamus having an indirect effect on the adrenal gland (hypopituitarism).

Primary AI

This condition 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.

Secondary AI

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

Hypopituitarism is where the pituitary gland is unable to effectively provide sufficient communication to the adrenal gland to produce enough 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** – due mainly to pituitary adenomas.
- **Infections** – meningitis, encephalitis, tuberculosis, syphilis.
- **Vascular** – mainly in pregnant women.
- **Physical causes** – including brain injury.

Temporary AI

This occurs when the body's natural production and release of cortisol have 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 used commonly to treat inflammatory conditions, by reducing the release of cortisol. On stopping medication, the body takes time to readjust, causing a temporary shortage of cortisol. This situation is quite common in transplant patients.

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 condition…

…that is poorly managed

Adrenal crisis is a life-threatening condition if not treated promptly; it 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[1] 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.

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

Glucocorticoids 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 try 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 Higher incidence of long-term consequences	£12
Dexamethasone 5mg	Small/generic companies		✓	Once daily	£157
Plenadren 20mg	Takeda	✓		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

[1] 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.

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

CAH 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 and urologists. 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 that 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

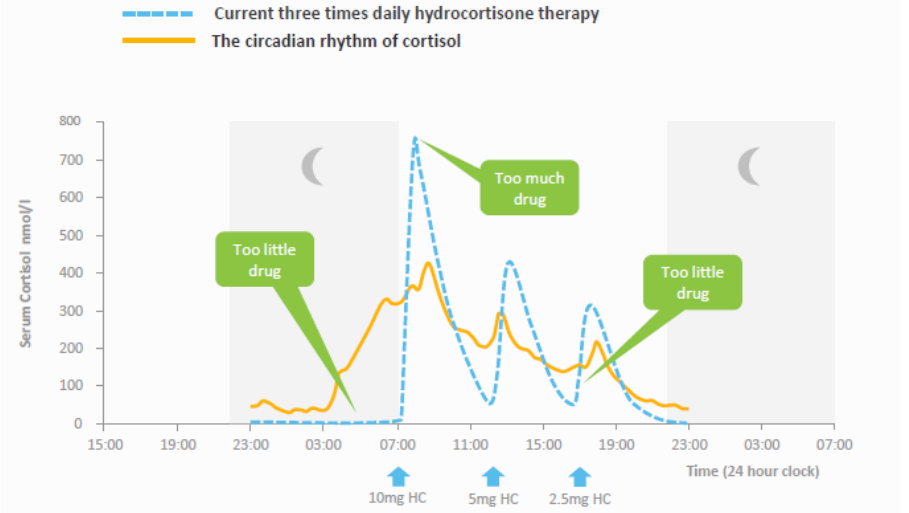
The current treatment is the use of hydrocortisone…

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.

…with a poor matching of the natural cortisol level…

- Hydrocortisone taken early in the morning is rapidly absorbed to produce an acute peak, corresponding to twice the normal level of cortisol. Owing to its short half-life, the concentration decreases sharply below normal levels of cortisol by mid-morning.
- A lower dose is given before lunch to mimic the lunchtime spike, which again rapidly decreases by mid-afternoon.
- The lowest dose is often given in the early evening.
- Critically, during the night, no cortisol is present in the blood system, when harmful androgens build up.

Serum hydrocortisone levels



Source: Diurnal

Earlier in this note (page 20), we discussed 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.

...and with a yoyo movement of hydrocortisone in the serum

The graphic above highlights the "yo-yo" movement of hydrocortisone in the serum with current treatment, which 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 affects adults and children

There are number of databases available with statistics for the prevalence of rare diseases in Europe and the US, which are the target markets for DNL. 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 have 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 for Europe) and *Childstats.gov* (0-18 for the US). These data have been used to calculate the target markets.

Equivalent patient numbers – from mean prevalence statistics			
	Europe	US	Total
Paediatric CAH	10,300	[f]4,100	14,400
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	**295,800**	**247,600**	**543,400**

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

Addressable market

Plenadren is used as a benchmark product

DNL has indicated that the benchmark price for Chronocort and Alkindi is $6,138 for a year's treatment. While this would be considerably higher than the price for which immediate-release hydrocortisone is available, 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 addressable adrenal market being targeted by Chronocort and Alkindi would be around $3.3bn.

The addressable market is worth $3.3bn

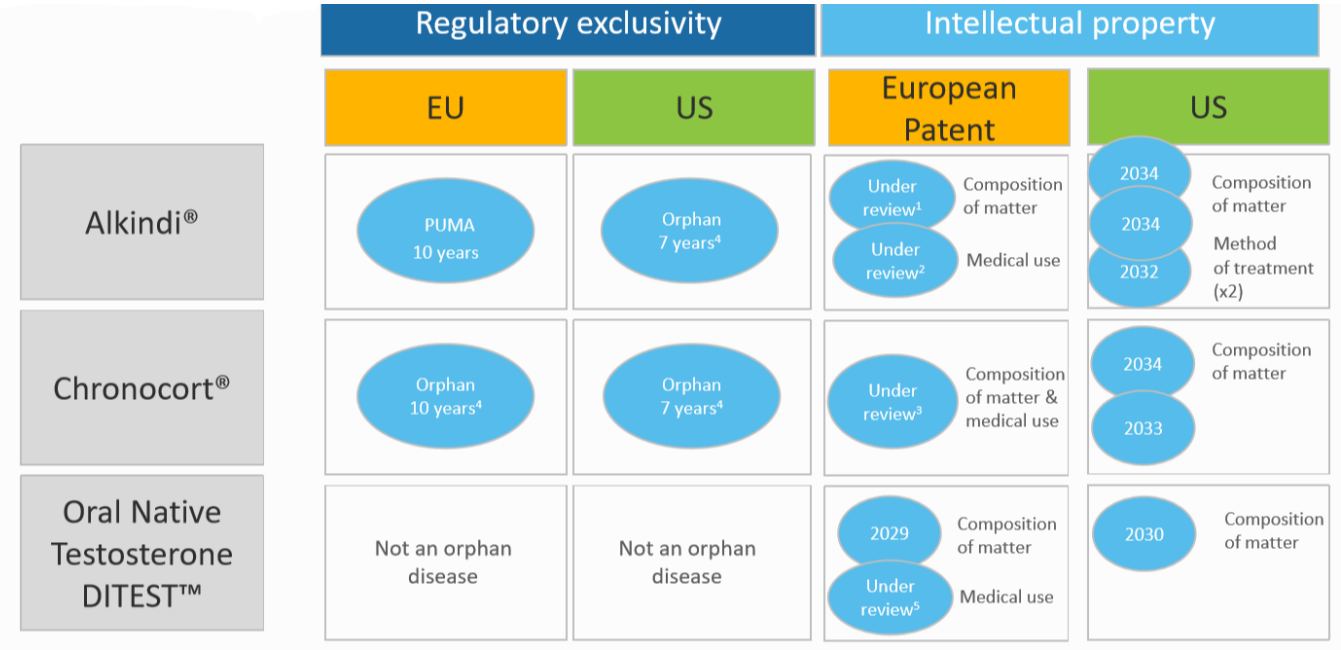
Addressable markets			
$m (EU/USD = 1.12)	Europe	US	Total
Annual price of drug (25mg)	$6,138	$6,138	
Paediatric CAH	63.2	25.2	88.4
Adult CAH	257.8	168.8	426.6
Addison's disease	322.2	98.2	420.5
Hypopituitarism	1,172.4	1,227.6	2,400.0
Target population	**1,815.6**	**1,519.8**	**3,335.4**

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, Europe and the US offer a range of incentives to encourage the development of these medicines, under specific conditions.

IP & regulatory exclusivity



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 Diurnal is the first sponsor to obtain market authorisation for the relevant product) and on demonstrating significant benefit;
5. GB patent application 2001514.5

Source: Diurnal 2020 interim results presentation

Chronocort and Alkindi have been granted Orphan Drug status...

Orphan Drug Designation

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 Europe or fewer than 200,000 in the US when the application is made.
- That it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in Europe and the US, and that, without incentives, it is unlikely that the marketing of the drug would generate a sufficient return to justify the necessary investment.
- That there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in Europe and the US, and, if such a method exists, that the drug will be of significant benefit to those affected by that condition.
- DNL will apply for Orphan Drug Designation in appropriate territories, when needed, such as in Australia, where it has already been granted for Alkindi, prior to market approval.

...with Chronocort already designated in the US and Europe for CAH and AI...

Chronocort

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 DNL with 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	Fewer than 5 in 10,000 (1 in 2,000)	Fewer 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 Reduced fees for marketing-authorisation applications	50% tax credit in clinical trials conducted in the US 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 Alkindi in the US for AI

Alkindi

Alkindi 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 the regulatory process, we believe Alkindi will be DNL'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 upfront with the paediatric committee of the European Medicines Agency. It must also:

- be already authorised;
- no longer be covered by a supplementary protection certificate or a patent; and
- be exclusively developed for use in children.

DNL has a PIP in place in respect of Alkindi. 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 Alkindi will provide DNL with clear marketing advantages:

... giving eight years of data exclusivity and 10 years of market exclusivity

- eight years of data exclusivity; and
- two years of market exclusivity, giving 10 years of exclusivity in total.

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 Alkindi in Europe by applying for a PUMA immediately following receipt of regulatory approval.

Competitive landscape

Low competition for Chronocort and Alkindi

DNL will be entering a market with Alkindi and Chronocort in CAH and AI, where competition is low, as it is a niche market. Essentially, the main competitor is immediate-release hydrocortisone (and synthetic steroids), due to its established position and low cost. These products provide a poor disease control, with no circadian release.

Competitive landscape

Product	Mimics circadian rhythm	Indication			Countries	Price
		AI/CAH paediatric	CAH	AI		
Hydrocortisone (generic)	✗	✓ Unlicensed[1]	✓	✓	EU, US	ca. $3k p.a.
Plenadren® (modified release)	✗	✗	✗	✓[2]	EU	ca. $6k p.a.
Diurnal "Adrenal Franchise"	✓ Chronocort®	✓ Alkindi®	✓ Chronocort®	✓ Chronocort®	EU, US	Targeting Chronocort® $6k+ p.a.

Source: Diurnal 2020 interim results presentation

On the other hand, companies such as Neurocrine, Millendo and Spruce are progressing non-natural, small molecule inhibitors acting upstream and having a different mode of action compared with DNL's products.

Neurocrine Biosciences

The US-based Neurocrine Biosciences is currently progressing Crinecerfont (NBI-74788) in two Phase II studies, one in adult and one in paediatric (14 to 17 years of age, started in 4Q'19) CAH. Interim results from the ongoing Phase II study in adults demonstrated a reduction of at least 50% from the baseline in 17-OHP and ACTH levels in more than 50% of CAH patients treated with Crinecerfont for 14 days. Meaningful reductions in other biomarkers were also observed, including androstenedione. Crinecerfont was shown to be well tolerated, with no serious adverse events reported to date. A global registration study is expected to start in mid-2020 in adult patients with CAH. Importantly, the long-term effect of Crinecerfont has yet to be established.

With this small molecule product, Neurocrine is engaging in a "non-natural" mode of action compared with DNL. Crinecerfont is a potent, selective, orally-active, non-peptide corticotropin-releasing factor type 1 (CRF1) receptor antagonist, under evaluation for the treatment of classic CAH. Blockade of CRF receptors in the pituitary has been shown to decrease the release of ACTH, which, in turn, decreases the production of adrenal steroids, including androgens, and potentially the symptoms associated with CAH. Research suggests that lowering ACTH levels could reduce the amount of corticosteroid treatment necessary for classic CAH patients.

Millendo Therapeutics

Millendo Therapeutics is currently progressing Nevanimibe (ATR-101), a first-in-class acyl coenzyme A: cholesterol acyltransferase 1 (ACAT1) inhibitor, in an open-label Phase IIb trial, representing also a novel specific approach. The Phase IIa trial showed a favourable safety profile, with seven of the first 10 patients demonstrating a reduction in 17-OHP levels. Top-line results from the ongoing Phase IIb, enrolling 20-24 patients, and started in September 2018 in CAH patients, are anticipated in 2H'20.

Nevanimibe is a potent and selective small molecule inhibitor of ACAT1, an enzyme that catalyses the transformation of free cholesterol to cholesterol ester. In the adrenals, cholesterol esters serve as a substrate reservoir for steroid biosynthesis.

Spruce Biosciences

Spruce Biosciences is progressing Tildacerfont (SPR001), an oral, small molecule, selective and non-steroidal CRF1 inhibitor. Tildacerfont works by blocking receptors on the pituitary gland to decrease ACTH release, and thus reduce excessive adrenal androgen production. Tildacerfont will not eliminate the need for steroids, as patients will still need them to replace the cortisol they do not produce, but it could lower the amount of steroid needed.

Following a positive Phase IIa trial, showing that Tildacerfont lowered patients' ACTH levels, with ACTH in 50% of patients down to normal levels, Spruce is currently recruiting for a three-month Phase IIb study in adult CAH to evaluate the safety and efficacy of Tildacerfont. Spruce recently raised $88m to take the drug to a Phase III study in adult CAH, as well as proof-of-concept trials in children.

Financials and investment case

In a move to further increase transparency, from fiscal 1H'20, the company has split its SG&A line into selling & distribution (S&D) expenses and administration expenses, and provided comparative figures for the last financial year.

Profit & Loss

- **Sales:** Growth in sales is dependent on two factors, both of which are difficult to predict: the timing of reimbursement discussions in remaining European countries, and the cycle of patients returning for clinic appointments.
- **Gross margin:** The gross margin is expected to improve over the longer term, through a combination of expanded volumes and process improvements, allowing an increase in the manufacturing batch size.
- **S&D:** The new split shows that DNL is continuing to invest in marketing in readiness for upcoming launches. This will continue into the foreseeable future in order to promote product advantages and drive market share.
- **Administration costs:** Greater transparency has shown that general administrative expenses, excluding share-based costs, are relatively low and tightly controlled. They are likely to increase only at the rate of inflation.
- **R&D:** The only trial currently being performed is that of DITEST. Consequently, R&D spend has reduced significantly. In addition, DNL is looking to have its US commercialisation partner fund the future Chronocort studies.

Profit & Loss account						
Year-end Jun (£m)	2017	2018	2019	2020E	2021E	2022E
Sales	0.00	0.07	1.04	2.41	5.76	16.16
COGS	0.00	-0.02	-0.22	-0.45	-0.75	-1.61
Gross profit	0.00	0.06	0.82	1.97	5.01	14.55
Gross margin	0%	79%	79%	82%	87%	90%
S&D	-2.03	-4.71	-4.51	-4.50	-5.18	-6.47
Administration expenses	-1.20	-1.50	-1.33	-1.25	-1.28	-1.35
Share-based costs	-0.52	-0.81	-0.83	-0.87	-0.87	-0.87
R&D	-8.34	-10.02	-8.69	-4.80	-5.04	-5.29
EBITDA	-12.07	-16.97	-14.50	-9.42	-7.33	0.60
Depreciation	-0.01	-0.01	-0.02	-0.02	-0.02	-0.02
Licensing/royalties	0.01	0.00	0.00	0.00	0.00	0.00
Underlying EBIT	**-12.08**	**-16.98**	**-14.53**	**-9.45**	**-7.35**	**0.58**
Statutory EBIT	-12.08	-16.98	-14.53	-9.45	-7.35	0.58
Net interest	-0.09	-0.13	0.13	0.05	0.05	0.01
Underlying PBT	**-12.16**	**-17.11**	**-14.40**	**-9.40**	**-7.29**	**0.59**
Statutory PBT	-12.16	-16.91	-14.40	-9.40	-7.29	0.59
Tax liability/credit	2.73	2.28	2.11	0.96	1.01	1.06
Tax rate	-22%	-13%	-15%	-10%	-14%	179%
Underlying net income	**-9.43**	**-14.83**	**-12.29**	**-8.44**	**-6.29**	**1.65**
Statutory net income	-9.43	-14.62	-12.29	-8.44	-6.29	1.65
Ordinary 5p shares:						
Period-end (m)	52.32	61.34	84.53	124.53	124.53	124.53
Weighted average (m)	52.24	54.60	62.39	91.10	124.53	124.53
Fully-diluted (m)	56.66	59.42	66.85	95.57	128.99	128.99
Underlying basic EPS (p)	-18.0	-27.2	-14.5	-9.3	-5.0	1.3
Statutory basic EPS (p)	-18.0	-26.8	-19.7	-9.3	-5.0	1.3
Underlying fully-dil. EPS (p)	-16.6	-24.9	-18.4	-8.8	-4.9	1.3
Statutory fully-dil. EPS (p)	-16.6	-24.6	-18.4	-8.8	-4.9	1.3
DPS (p)	0.0	0.0	0.0	0.0	0.0	0.0

Source: Hardman & Co Life Sciences Research

Balance sheet

- **Inventory:** Stock levels of Alkindi have been increased in preparation for upcoming launches.
- **Working capital:** As is usual during the growth phase of a company, there is an increase in the working capital requirement. This will unwind over time.
- **Net cash/(debt):** At 31 December 2019, DNL had gross cash of £4.63m, and no debt. Current forecasts suggest that the company needs ca.£10m of working capital over the next 12-18 months, which has been shown as an equity raise. In reality, part of this could come in the form of an upfront payment in any US licensing deal.

Balance sheet						
@31 Jun (£m)	2017	2018	2019	2020E	2021E	2022E
Shareholders' funds	17.08	16.88	10.94	11.90	5.62	7.26
Cumulated goodwill	0.00	0.00	0.00	0.00	0.00	0.00
Total equity	17.08	16.88	10.94	11.90	5.62	7.26
Share capital	2.62	3.07	4.23	4.23	4.23	4.23
Reserves	14.46	13.81	6.72	7.68	1.39	3.04
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
Lease liabilities	0.00	0.00	0.00	0.00	0.00	0.00
Long-term debt	3.51	0.00	0.00	0.00	0.00	0.00
Short-term loans	0.00	0.00	0.00	0.00	0.00	0.00
less: Cash	8.88	17.28	9.15	10.65	1.77	1.21
less: Deposits	11.00	0.00	0.00	0.00	0.00	0.00
Invested capital	**0.71**	**-0.40**	**1.80**	**1.25**	**3.85**	**6.05**
Fixed assets	0.02	0.03	0.03	0.04	0.06	0.08
Intangible assets	0.00	0.02	0.05	0.05	0.05	0.05
Inventories	0.00	0.12	0.67	1.55	3.71	5.20
Trade debtors	*0.00*	*0.08*	*0.51*	*0.55*	*1.44*	*2.69*
Other debtors	*4.03*	*5.02*	*0.95*	*0.90*	*0.85*	*0.81*
Tax credit/liability	*0.00*	*0.00*	*2.11*	*1.53*	*0.98*	*1.03*
Trade creditors	*-1.72*	*-3.32*	*-1.15*	*-1.05*	*-1.35*	*-1.55*
Other creditors	*-1.62*	*-2.35*	*-1.37*	*-2.33*	*-1.90*	*-2.26*
Debtors less creditors	0.68	-0.57	1.04	-0.39	0.04	0.73
Invested capital	**0.71**	**-0.40**	**1.80**	**1.25**	**3.85**	**6.05**
Net cash/(debt)	**16.37**	**17.28**	**9.15**	**10.65**	**1.77**	**1.21**
Stock days	-	615	235	168	167	101
Debtor days	-	385	178	80	63	47
Creditor days	-	nm	nm	nm	585	328

Source: Hardman & Co Life Sciences Research

Cashflow

- **Underlying EBIT:** The P&L is the main driver of cashflow, and we forecast that EBITDA will turn positive in 2022.
- **Working capital:** The build-up of inventories, debtors and creditors is consistent with the product launch and growth phase of a company.
- **Capital increase:** In order to support the commercialisation of products and the clinical trial programme, the company will need to raise capital before the end of fiscal 2020. Our model anticipates a gross capital increase of ca.£10m. However, this may not all be in the form of new equity, with some coming from an upfront payment associated with a US co-development/commercial deal. Hence the timing would be important in the amount of new capital to be raised.

Cashflow						
Year-end Jun (£m)	2017	2018	2019	2020E	2021E	2022E
Underlying EBIT	-12.08	-16.98	-14.53	-9.45	-7.35	0.58
Depreciation	0.01	0.01	0.02	0.02	0.02	0.02
Share-based costs	0.52	0.81	0.83	0.87	0.87	0.87
Inventories	*0.00*	*-0.12*	*-0.55*	*-0.88*	*-2.15*	*-1.49*
Receivables	*-0.77*	*-1.54*	*1.36*	*-0.04*	*-0.89*	*-1.25*
Payables	*1.86*	*2.32*	*-3.14*	*0.10*	*-0.30*	*-0.20*
Change in working capital	1.09	0.66	-2.33	-0.82	-3.35	-2.95
Other	-0.27	0.00	0.00	0.00	0.00	0.00
Company op. cashflow	**-10.74**	**-15.50**	**-16.01**	**-9.37**	**-9.81**	**-1.48**
Net interest	0.19	0.11	0.13	0.05	0.05	0.01
Lease payments	0.00	0.00	0.00	-0.03	-0.03	-0.03
Tax paid/received	0.00	2.74	2.28	1.53	0.98	1.03
Operational cashflow	**-10.55**	**-12.66**	**-13.60**	**-7.82**	**-8.80**	**-0.47**
Capital expenditure	-0.02	-0.02	-0.03	-0.03	-0.04	-0.04
Free cashflow	**-10.57**	**-12.69**	**-13.66**	**-7.89**	**-8.88**	**-0.56**
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 investments	**-10.57**	**-12.69**	**-13.66**	**-7.89**	**-8.88**	**-0.56**
Share repurchases	0.00	0.00	0.00	0.00	0.00	0.00
Equity issues	0.05	13.40	5.53	9.40	0.00	0.00
Change in net cash/(debt)	**-10.51**	**0.91**	**-8.14**	**1.51**	**-8.88**	**-0.56**
OCFPS (p)	-20.2	-23.2	-21.8	-8.6	-7.1	-0.4
Opening net cash	26.88	16.37	17.28	9.15	10.65	1.77
Closing net cash/(debt)	**16.37**	**17.28**	**9.15**	**10.65**	**1.77**	**1.21**

Source: Hardman & Co Life Sciences Research

Changes to forecasts

Our forecasts have been adjusted to reflect the change in strategy, whereby commercial partners will co-fund future clinical trials, particularly in the US; this resulted in an improved operating performance in fiscal 1H'20. The effect of this is to improve the balance sheet through a lower cash burn rate.

- **Product sales:** Good fiscal 1H'20 sales of Alkindi have resulted in a modest upward adjustment to our sales forecasts.
- **Operating costs:** These are now shown on the new basis but are significantly reduced overall.
- **R&D costs:** Our forecasts for R&D costs have been reduced significantly to reflect the change in strategy to have the US trials co-funded with DNL's US commercial partner. The company will make new R&D investments only if it has the appropriate cash resources available.
- **EBIT:** Significantly reduced operational costs have positively affected both the EBIT and cashflows of the group. We now expect DNL to be profitable in 2022.

Changes to forecasts									
Year-end Jun	2020E			2021E			2022E		
(£m)	Old	New	Δ	Old	New	Δ	Old	New	Δ
Product sales	2.14	2.41	+13%	5.48	5.76	+5%	15.60	16.16	4%
S&D	-	-4.50	-	-	-5.18	-	-	-6.47	-
Administration expenses	-	-1.25	-	-	-1.28	-	-	-1.35	-
Total SG&A	-7.52	-5.75	-23%	-9.22	-6.46	-30%	-10.92	-7.81	-28%
R&D	-9.43	-4.80	-49%	-8.96	-5.04	-44%	-11.20	-5.29	-53%
Underlying EBIT	**-16.03**	**-9.45**	**-41%**	**-14.34**	**-7.35**	**-49%**	**-9.10**	**0.58**	**-**
Net cash/(debt)	0.26	10.65	-	-13.88	1.77	-	-22.78	1.21	-

Source: Hardman & Co Life Sciences Research

Valuation

DCF

DCF valuation of 344p per share

The increased use of commercial partners has caused us to reassess our DCF analysis, moving it more towards a distribution and royalty-based model. Our original DCF valuation, based on clearly stated assumptions, was published on 25 April 2019. The NPV of the cashflows that could be generated from DNL's first two products has changed from £389m to £455m. Risk-adjustment to take account of the different stages of development in different territories reduces this to £298m, or 344p per share.

Diurnal – DCF valuation summary

WACC	NPV (£m)	Risk-adjusted NPV (£m)	Risk-adjusted NPV per share (p)
8%	556	365	421
9%	503	330	380
10%	**455**	**298**	**344**
11%	412	270	312
12%	374	245	283

Source: Hardman & Co Life Sciences Research

Peer group comparisons

Valuation uplift potential for DNL, as it makes further progress in the US

For our comparative valuation analysis, a group of quoted specialty pharma companies working in the field of endocrinology – but not working in diabetes/insulin – have been selected, to provide a guide for the relative valuation of DNL. This gives an indication of the valuation uplift potential for DNL, as it makes further progress in the US. The peer group comparative valuations are shown in the following table. Since our last publication on DNL in November 2019, *Approaching a number of near-term milestones*, Ascendis has seen an appreciation of its EV by 33%, reflecting positive news flow, while the EVs of Corcept, Millendo, Neurocrine and Viking have stayed relatively stable. Over the same period, DNL's EV has appreciated by 5%, despite a number of positive news flow items, reflecting poor sentiment towards the biotechnology sector in the UK market.

Comparative valuation

Company	Ascendis	Corcept.	Diurnal	Millendo	Neurocrine Bio	Viking
Ticker	ASND	CORT	DNL	MLND	NBIX	VKTX
Local currency	$	$	£/p	$	$	$
Share price	129.9	13.5	36.9	9.0	94.3	6.4
Shares in issue (m)	47.6	114.3	86.7	13.5	92.3	72.3
Market cap. (lc, m)	6,183.5	1,539.4	32.0	120.6	8,696.6	465.4
Market cap. (£m)	4,793.4	1,193.3	32.0	93.5	6,743.1	360.8
Cash (lc, m)	658.7	231.6	4.6	47.2	670.5	288.1
Debt (lc, m)	0.0	0.0	0.0	-0.5	-408.8	0.0
EV (lc, m)	5,524.8	1,307.7	27.4	73.9	8,436.8	177.3
EV (£m)	4,771.0	1,013.7	27.4	57.3	6,540.2	137.4
Relative EV (x)	**174.3**	**37.0**	**-**	**2.1**	**238.9**	**5.0**
2020E sales (£m)	0.0	286.0	2.4	0.0	710.0	0.0
EV/sales (x)	-	4.7	7.7	-	13.6	-

lc = local currency
Share prices and currencies taken at close of business on 26February 2020
Source: Hardman & Co Life Sciences Research

As seen many times before with UK small-cap biotech companies, US peers trade at much higher valuations and tend to be very well capitalised, allowing these companies to realise their full potential. However, such analysis should provide an indication of upside potential in the event that DNL's products become further de-risked.

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 29 2068 2069
www.diurnal.co.uk

Board of Directors

Board of Directors				
Position	**Name**	**Nominations**	**Remuneration**	**Audit**
Chairman	Peter Allen	C	M	M
Chief Executive Officer	Martin Whitaker			
Chief Financial Officer	Richard Bungay			
Chief Scientific Officer	Richard Ross			
Non-executive director	John Goddard	M	M	C
Non-executive director	Alan Raymond	M	C	M
Non-executive director	Sam Williams	M	M	

M = member; C = chair
Source: Company reports

Peter Allen – Non-executive Chairman

Peter joined DNL in July 2015. He has a wealth of experience at board level in a wide portfolio of healthcare companies. Currently, he is non-executive Chairman of Abcam plc, Advanced Medical Solutions plc, Clinigen plc and Oxford Nanopore Technologies Ltd. He was formerly Chairman of ProStrakan Group plc, Proximagen Group plc and Future plc. Prior to this, he was CFO of Celltech Group plc (1992-2004) until its acquisition by UCB. Peter is a qualified chartered accountant and has a joint degree in Accountancy and Law.

Martin Whitaker – Chief Executive Officer

Martin joined the group in January 2008, supporting Fusion IP's investment, and became CEO in 2012. Martin has 20 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, Martin is also a director of D3 Pharma Limited. He trained as a biochemist at the University of Bristol and has a PhD in Pharmaceutical Science from the University of Nottingham.

Richard Bungay – Chief Financial Officer

Richard has over 25 years' experience in senior finance and strategic roles within the pharmaceutical and biotechnology sector. His experience was gained at Mereo BioPharma (CFO and COO), Glide Technologies (CFO), Verona Pharma (CFO), Chroma Therapeutics (CEO and CFO), and in senior management positions at Celltech and AstraZeneca. He qualified as a Chartered Accountant with Deloitte and has a first-class degree in Chemistry from the University of Nottingham.

Richard Ross – Chief Scientific Officer

Founding director and Chief Scientific Officer, Richard is contracted to perform work for DNL by the University of Sheffield pursuant to the terms of secondment and research agreements. He is Professor of Clinical Endocrinology and Head of the Academic Unit of Diabetes, Endocrinology and Metabolism. Richard's research interest is pituitary and adrenal disease, with a particular focus on hormone replacement. He has published over 200 papers on these areas and has more than 30 granted patents. He is also a director of Asterion Ltd.

John Goddard – Non-Executive Director

John joined DNL in November 2015, after a career in the global pharmaceutical industry, mostly at AstraZeneca. Currently, he is also a non-executive director of Intas Pharmaceuticals Limited. Previously, he was Chairman of two AstraZeneca subsidiaries, Aptium Oncology and Astratech. John is a Fellow of the Institute of Chartered Accountants and a Member of the Association of Corporate Treasurers.

Alan Raymond – Non-Executive Director

Alan has over 30 years' experience in international marketing and general management. He was appointed to the board of DNL by Development Bank of Wales (formerly Finance Wales) in April 2015. During his career, Alan has held senior positions in Aesica Pharmaceuticals Ltd, Banner Pharmacaps, RP Scherer, Reckitt & Colman, Eli Lilly and MSD. Alan holds a PhD in Invertebrate Neurobiology from the University of St. Andrews and was a postdoctoral researcher at the Cardiothoracic Research Institute. He is currently Chairman of AniPOC Ltd and ADV Biotechnology Ltd.

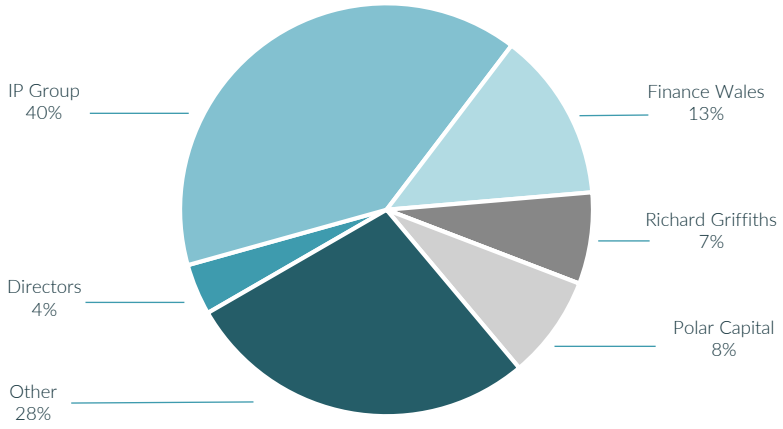
Sam Williams – Non-Executive Director

Sam has 28 years' experience in biotech, as both an investment banking analyst and an entrepreneur. After leaving Lehman Brothers in 2007, he established Istesso Ltd, focused on autoimmune and inflammatory diseases. Sam is currently the Head of Life Sciences at IP Group. He has an MA in Pure and Applied Biology from the University of Oxford and a PhD from the University of Cambridge. He is also the non-executive Chairman of Microbiotica Ltd and Iksuda Ltd.

Share capital

The company has 86,725,987 shares in issue and 5,132,824 Options.

Major shareholders



Source: Company reports

Glossary

17-OHP	17-Hydroxyprogesterone
ACTH	Adrenocorticotropic hormone
AI	Adrenal Insufficiency
CAH	Congenital Adrenal Hyperplasia
CHMP	Committee for Medicinal Product for Human Use
CRH	Corticotrophin-releasing hormone
EMA	European Medicines Agency
FDA	US Food and Drug Agency
GMP	Good Manufacturing Practice
MAA	Market Authorisation Application
NDA	New Drug Application
PDUFA	The Prescription Drug User Fee Act
PIP	Paediatric Investigation Plan
PUMA	Paediatric Use Marketing Authorisation
TRT	Testosterone Replacement Therapy

Notes

Disclaimer

Hardman & Co provides professional independent research services and all information used in the publication of this report has been compiled from publicly available sources that are believed to be reliable. However, no guarantee, warranty or representation, express or implied, can be given by Hardman & Co as to the accuracy, adequacy or completeness of the information contained in this research and they are not responsible for any errors or omissions or results obtained from use of such information. Neither Hardman & Co, nor any affiliates, officers, directors or employees accept any liability or responsibility in respect of the information which is subject to change without notice and may only be correct at the stated date of their issue, except in the case of gross negligence, fraud or wilful misconduct. In no event will Hardman & Co, its affiliates or any such parties be liable to you for any direct, special, indirect, consequential, incidental damages or any other damages of any kind even if Hardman & Co has been advised of the possibility thereof.

This research has been prepared purely for information purposes, and nothing in this report should be construed as an offer, or the solicitation of an offer, to buy or sell any security, product, service or investment. The research reflects the objective views of the analyst(s) named on the front page and does not constitute investment advice. However, the companies or legal entities covered in this research may pay us a fixed fee in order for this research to be made available. A full list of companies or legal entities that have paid us for coverage within the past 12 months can be viewed at http://www.hardmanandco.com/legals/research-disclosures. Hardman may provide other investment banking services to the companies or legal entities mentioned in this report.

Hardman & Co has a personal dealing policy which restricts staff and consultants' dealing in shares, bonds or other related instruments of companies or legal entities which pay Hardman & Co for any services, including research. No Hardman & Co staff, consultants or officers are employed or engaged by the companies or legal entities covered by this document in any capacity other than through Hardman & Co.

Hardman & Co does not buy or sell shares, either for their own account or for other parties and neither do they undertake investment business. We may provide investment banking services to corporate clients. Hardman & Co does not make recommendations. Accordingly, they do not publish records of their past recommendations. Where a Fair Value price is given in a research note, such as a DCF or peer comparison, this is the theoretical result of a study of a range of possible outcomes, and not a forecast of a likely share price. Hardman & Co may publish further notes on these securities, companies and legal entities but has no scheduled commitment and may cease to follow these securities, companies and legal entities without notice.

The information provided in this document is not intended for distribution to, or use by, any person or entity in any jurisdiction or country where such distribution or use would be contrary to law or regulation or which would subject Hardman & Co or its affiliates to any registration requirement within such jurisdiction or country.

Some or all alternative investments may not be suitable for certain investors. Investments in small and mid-cap corporations and foreign entities are speculative and involve a high degree of risk. An investor could lose all or a substantial amount of his or her investment. Investments may be leveraged and performance may be volatile; they may have high fees and expenses that reduce returns. Securities or legal entities mentioned in this document may not be suitable or appropriate for all investors. Where this document refers to a particular tax treatment, the tax treatment will depend on each investor's particular circumstances and may be subject to future change. Each investor's particular needs, investment objectives and financial situation were not taken into account in the preparation of this document and the material contained herein. Each investor must make his or her own independent decisions and obtain their own independent advice regarding any information, projects, securities, tax treatment or financial instruments mentioned herein. The fact that Hardman & Co has made available through this document various information constitutes neither a recommendation to enter into a particular transaction nor a representation that any financial instrument is suitable or appropriate for you. Each investor should consider whether an investment strategy of the purchase or sale of any product or security is appropriate for them in the light of their investment needs, objectives and financial circumstances.

This document constitutes a 'financial promotion' for the purposes of section 21 Financial Services and Markets Act 2000 (United Kingdom) ('FSMA') and accordingly has been approved by Capital Markets Strategy Ltd which is authorised and regulated by the Financial Conduct Authority (FCA).

No part of this document may be reproduced, stored in a retrieval system or transmitted in any form or by any means, mechanical, photocopying, recording or otherwise, without prior permission from Hardman & Co. By accepting this document, the recipient agrees to be bound by the limitations set out in this notice. This notice shall be governed and construed in accordance with English law. Hardman Research Ltd, trading as Hardman & Co, is an appointed representative of Capital Markets Strategy Ltd and is authorised and regulated by the FCA under registration number 600843. Hardman Research Ltd is registered at Companies House with number 8256259.

(Disclaimer Version 8 – Effective from August 2018)

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 & Co research and, specifically, whether it can be accepted without a commercial arrangement. Hardman & Co's research is paid for by the companies, legal entities and issuers 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 a 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 Hardman & Co is 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 & Co is not inducing the reader of our research to trade through us, since we do not deal in any security or legal entity.

research@hardmanandco.com

35 New Broad Street
London
EC2M 1NH

+44(0)20 7194 7622

www.hardmanandco.com