EDISON

Diurnal Group

Initiation of coverage

Improving treatments for endocrine disorders

Pharma & biotech

We are initiating coverage on Diurnal Group, which is developing and commercialising multiple products from the class of steroid hormones. The company's first product, Alkindi, is marketed in the United States and Europe and it is aiming to launch its second product, Chronocort, in 2021. These products are oral formulations of hydrocortisone developed to treat disorders of the adrenal glands. Additionally, Diurnal is developing an oral testosterone, DITEST, which will be re-entering the clinic in 2021. We are initiating with a valuation of £199.6m or 144p per basic share.

Year end	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
06/19	1.0	(13.6)	(18.6)	0.0	N/A	N/A
06/20	6.3	(5.1)	(4.1)	0.0	N/A	N/A
06/21e	5.0	(11.5)	(7.0)	0.0	N/A	N/A
06/22e	7.9	(17.8)	(9.9)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

Alkindi: Approved in the US and Europe

Alkindi is a formulation of hydrocortisone intended to treat adrenal insufficiency (AI) in paediatric patients. Before its approval in Europe (2018) and the United States (2020), there were no hydrocortisone products provided in paediatric doses. Additional formulation improvements in the product include it being provided in a sprinkle format (which eases administration in children) and a taste masking layer. Diurnal reported sales of £1.21m for the product in H121 (ending December 2020).

Chronocort: European approval decision imminent

Diurnal Group has also developed Chronocort for the treatment of congenital adrenal hyperplasia (CAH), a rare congenital form of AI; the product was submitted for marketing approval in Europe in late 2019 and a response is expected imminently. Chronocort is designed to address some of the pharmacokinetic limitations of hydrocortisone dosing by providing a controlled release of product that more closely mimics the daily bodily cycle of the hormone and improves negative outcomes associated with excess androgen formation often caused by CAH.

DITEST: Testosterone without dosing your family

In addition, Diurnal has an earlier-stage programme to develop a novel oral formulation of testosterone. Testosterone products are typically topically applied, because it has been difficult to develop an effective oral formulation. However, these topical products have the risk of transference to family members, which can induce puberty in children or cause hirsutism in women and girls.

Valuation: Initiated at £199.6m or 144p/share

Our initial valuation is £199.6m or 144p per basic share, driven primarily by Chronocort, which we value at £157m. Diurnal ended 2020 with £20.3m in cash, and we expect it to need £25m in additional capital to reach profitability in FY24.

12 March 2021

Price	**60.5p**
Market cap	**£84m**
	$1.40/£
Net cash (£m) at 30 December 2020	20.3
Shares in issue	138.3m
Free float	75.5%
Code	DNL
Primary exchange	LSE
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	0.0	19.8	78.1
Rel (local)	(3.0)	14.8	52.4
52-week high/low	74.92p	20.98p	

Business description

Diurnal Group is a speciality pharma company developing new formulations of hormone-based products for the treatment of endocrine disorders. Its product Alkindi is marketed for paediatric adrenal insufficiency in the United States and Europe, and it is seeking approval of Chronocort for the treatment of congenital adrenal hyperplasia. It has a novel oral testosterone DITEST entering patient dosing studies.

Next events

Chronocort MAA approval decision	Q121
DITEST IND submission	Q221

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Edison profile page

Diurnal Group is a research client of Edison Investment Research Limited

Investment summary

Company description: Improving hormone replacements

Diurnal Group is a specialty pharmaceutical company developing treatments for endocrine disorders. In particular the company has developed two novel, oral formulations of hydrocortisone: Alkindi for treating paediatric AI patients, approved in the US and Europe, and Chronocort for treating adult CAH patients, which has been submitted for approval in Europe. Chronocort is a controlled-release product designed to address some of the pharmacokinetic limitations of oral hydrocortisone, and we believe it has higher market potential than Alkindi given these characteristics. Diurnal intends to expand Chronocort to the US CAH market and to the broader adult AI population. Additionally, it has developed a novel oral formulation of testosterone (DITEST) that is ready to enter a multiple ascending-dose study in 2021.

Valuation: Initiated at £199.6m or 144p/share

Our initial valuation is £199.6m or 144p per basic share, based on a risk adjusted net present value (NPV) analysis. We model Alkindi and Chronocort for the US and European markets and DITEST for the US market. The valuation is driven primarily by Chronocort, which we value at £157m. The nearest value inflection point for Diurnal will be a response to the MAA files in Europe for the approval of Chronocort for adult CAH, which is expected in Q121, and we assign an 80% probability of success for approval. Other indications for Chronocort will require additional clinical study and have lower probabilities of success (30–50%).

Financials: £20.3m in cash

Revenue for fiscal H121 was £1.21m, primarily from Alkindi sales in Europe (£1.13m). Revenue has been roughly flat year-on-year, but we expect sales to ramp up again with a reduced threat from COVID-19. Operating expenses were £6.72m, which we expect to increase with the preparations to launch Chronocort in FY22. Diurnal ended 2020 with £20.3m in cash following a Q420 fund-raise of £9.1m (net). We expect the company to need £25m in further capital to complete the development and launches of its lead products, which we record as illustrative debt in FY22.

Sensitivities: Trading clinical risk for commercial hurdles

Like many other specialty pharmaceutical companies, Diurnal Group's strategy has comparatively lower clinical risk than the development of new chemical entities. However, development risks still exist. For instance, despite strong effect sizes, Diurnal's prior Phase III clinical study for Chronocort failed to meet its primary endpoint. This being said the company has been able to file for European approval with the data from this study. However, we expect the majority of the hurdles that Diurnal will face to be commercial in nature. Alkindi and Chronocort are formulations of hydrocortisone, which is widely available as a generic. To be able to market these products successfully Diurnal will need to establish a clear proposition for their utility in the clinic versus existing generics. This will be harder with Alkindi because although it is formulated to be easier to dose and for use in paediatrics, it is otherwise similar to lower priced generics, and sales have been slow since its launch in 2018. By comparison, Chronocort has a more specialised delivery formulation that differentiates it. Some of these risks will be mitigated because AI and CAH are orphan diseases and the total potential cost exposure to payers will be small. Moreover, there is little in the way of branded competition for these products. DITEST on the other hand will be entering a market (male hypogonadism) with many competing products. In addition to these development and commercial hurdles, Diurnal will need additional capital to reach profitability, which we model as £25m (in FY22).

Company description: Endocrine specialty pharma

Diurnal Group is a specialty pharmaceutical company founded in 2004 in the UK. Diurnal was founded to address shortcomings in the treatment of patients with endocrine disorders. It is achieving this aim by developing improved formulations of drugs for diseases that are currently underserved. The first disorders targeted by the company are the closely related conditions AI and CAH. These are diseases characterised by a failure of the body to generate adrenal hormones like cortisol.

Diurnal has received approval for Alkindi, an oral formulation of hydrocortisone for the treatment of AI in paediatrics. The drug was approved in Europe in 2018 and in the US and other geographies in 2020. It is the only product labelled for paediatric AI that we are aware of. The drug is currently being rolled out in the US by the company's marketing partner Eton Pharmaceuticals.

Diurnal Group is also developing Chronocort, an extended release formulation of hydrocortisone for adult patients with AI or CAH designed to better mimic the natural daily cycle of cortisol in the body. Mimicking this rhythm has been shown to provide better disease control and limit adverse effects. The goal with Chronocort is to initially seek approval for CAH and later expand to the broader adult AI patient group. It has completed its European clinical studies for CAH and the company submitted an MAA in December 2019 (response expected in Q121). A North American Phase III CAH study is planned to start in H221.

Finally, Diurnal is developing a novel oral formulation of testosterone called DITEST. This formulation uses a proprietary excipient mixture to effectively deliver unmodified testosterone, making the product the only oral, unmodified testosterone if it were to be approved. The product has completed initial Phase I testing. The company intends to file an IND in Q221 and initiate a multiple ascending dose (MAD) study shortly thereafter.

Exhibit 1: Diurnal Group lead products

Product	Drug	Indication	Status EU	Status US
Alkindi/Alkindi Sprinkle	hydrocortisone	Paediatric AI	Approved	Approved
Chronocort	controlled release hydrocortisone	CAH	Submitted	Phase III ready
		AI	Phase III planned	Phase I complete
DITEST	testosterone	hypogonadism	Phase I complete	Phase I complete

Source: Diurnal reports

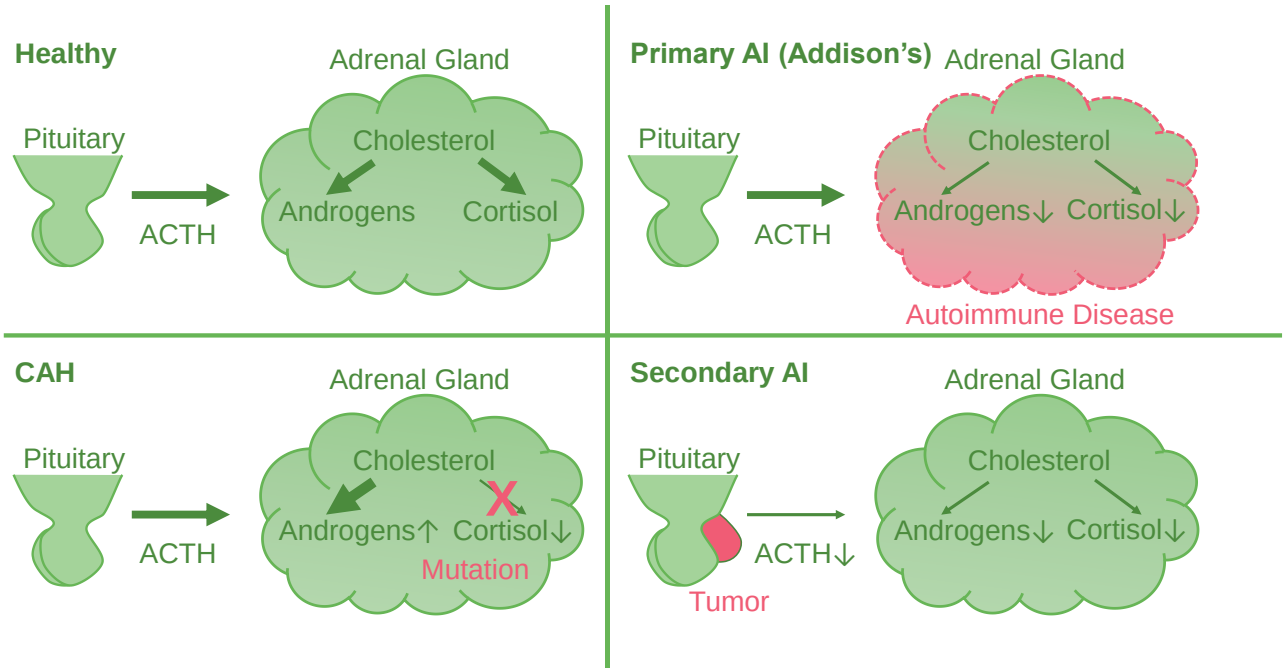
AI and CAH

The adrenal glands are a core component of the endocrine system, producing a range of hormones that control the body's physiological state. These include the titular adrenaline (which controls the fight-or-flight response) as well as sexual hormones like testosterone and progesterone, and cortisol, which controls the body's response to stress, among others. A shortage of adrenal hormones, in particular a shortage of cortisol, can result in a medical condition called AI, characterised by extreme fatigue, weight loss and GI issues. In addition to these chronic symptoms, patients are at risk for an acute adrenal crisis, a potentially life-threatening medical emergency caused by low cortisol that can result in dangerous low blood pressure, sudden weakness, shock and coma. Adrenal crisis is a major cause of negative outcomes in these AI patients and a motivating factor in the management of the disease.

Diurnal Group's lead programmes Alkindi and Chronocort are both treatments seeking to address AI. They are hormone replacement therapies that provide oral hydrocortisone to replace the missing cortisol in the body (note: by convention when referred to as a drug, the molecule cortisol is called hydrocortisone).

There are two major classes of AI: primary and secondary. When the lack of cortisol is caused by dysfunction in the adrenal glands themselves, due to tissue damage, injury or congenital disorder, this is termed primary AI. The most common cause of primary AI is Addison's disease, an autoimmune disorder in which the body attacks the adrenal glands. At times historically, primary AI and Addison's disease have been conflated as the same disorder, and although there are other causes of primary AI of a genetic origin (as outlined below), they are a small fraction of the total number of cases and have been studied less. The estimated prevalence of primary AI due to Addison's is 82–144 patients per million.[1] However more commonly, the adrenal glands are otherwise healthy and AI is caused by a deficiency in the hormone corticotropin (ACTH), due to a tumour on the pituitary gland or other reason. This so-called secondary AI is about twice as common as primary AI at 150–280 patients per million.

Exhibit 2: Types of AI



Source: Various

CAH

Although Addison's disease is considered the biggest single cause of primary AI, it can also be caused by a range of genetic mutations that impact the body's ability to produce cortisol. This cluster of related genetic diseases is referred to as CAH. In healthy individuals, the androgen hormones (such as testosterone) are converted into cortisol by enzymes present in in the adrenal glands. In CAH individuals, these enzymes are deficient or absent, which causes a deficiency in cortisol as well as an accumulation of androgens. This accumulation of androgens can be significant and can result in the appearance of secondary sexual characteristics in females, including ambiguous genitals, and infertility in both sexes. This is different from Addison's, which is characterised by low androgen levels. The treatment of CAH is therefore different than for other forms of AI because both the effects of low cortisol and high androgen levels must be addressed. Androgen levels are reduced by treatment with hydrocortisone or other steroids because of a feedback mechanism that reduces ACTH, but current treatment modalities have trouble achieving around-the-clock control of androgen levels (see below for more detail). Incidence estimates for the

[1] Chabre O, et al. (2017) Group 1. Epidemiology of primary and secondary adrenal insufficiency: Prevalence and incidence, acute adrenal insufficiency, long-term morbidity and mortality. *Annl Endocrinol (Paris)* 78, 590-494.

disorder range from 1/10,000 to 1/18,000 live births.[1] Unlike other forms of AI, CAH typically presents in childhood and represents the lion's share of AI in this population. In many geographies, CAH is diagnosed at birth with a genetic test.

Treatment options

The standard treatment for all forms of AI is replacement therapy with corticosteroids. The steroid of choice is hydrocortisone in most cases, although longer lasting steroids such as prednisone and dexamethasone are used with CAH to achieve better androgen control. All of these drugs are commoditised generics. They are typically dosed at multiple times throughout the day to attempt to approximate the natural daily time course of cortisol release.

The drug Plenadren (Takeda) is a controlled release formulation of hydrocortisone that was approved in Europe for the treatment of AI. The drug is taken once a day and has a much longer release profile than generic hydrocortisone tablets, and its release profile more closely resembles the cycle of cortisol level during the day. This both simplifies administration of the drug and showed improvements in adverse effects associated with steroid overdosing such as weight gain, high blood pressure, glucose tolerance and other quality of life measures.[2] The product however does not provide overnight hydrocortisone release, which can lead to androgen formation in CAH patients (see below). Otherwise, there are no other products approved in the United States or Europe specifically for the treatment of AI.

There are no approved treatments for CAH, but there are some in development. These drugs are generally taking a slightly different approach (compared to the current standard of care), by attempting to address the issues of androgen accumulation in these patients, as opposed to AI. Crinecerfont (Neurocrine Biosciences) and tildacerfont (Spruce Biosciences) are inhibitors of corticotropin-releasing factor type 1 (CRF1) receptor, and they work upstream of cortisol in the signalling cascade to reduce the amount of androgen generated in these patients. CAH patients taking these drugs would still need to supplement with corticosteroids, albeit at potentially milder doses due to better androgen control. Crinecerfont is in Phase III testing and tildacerfont is in Phase IIb. CRN04894 from Crinetics is similarly designed to inhibit androgen generation by inhibiting ACTH activity and is currently in a Phase I healthy volunteer study.

Exhibit 3: Drugs approved and under development for AI

Drug	Company	Disease	Stage	Details
Oral Corticosteroids	Generic	AI, CAH	Approved	hydrocortisone, prednisone, dexamethasone
Plenadren	Takeda	AI	Approved (EMA)	controlled release hydrocortisone
Crinecerfont	Neurocrine Biosciences	CAH	Phase III	CRT1-R inhibitor
Tildacerfont	Spruce Biosciences	CAH	Phase IIb	CRT1-R inhibitor
Nevanimibe	Millendo Therapeutics	CAH	Phase II (discontinued)	ACAT1 inhibitor
CRN04894	Crinetics Pharmaceuticals	CAH	Phase I	ACTH antagonist
BBP-631	Bridge Bio	CAH	Preclinical	Gene therapy

Source: Evaluate Pharma

Alkindi

Alkindi is Diurnal's first commercial product. It was approved in Europe in 2018 and was recently approved in the United States (under the trade name Alkindi Sprinkle) in 2020. The product is a formulation of hydrocortisone for the treatment of paediatric AI. This being said, although the product is labelled for the treatment of paediatric AI, in the paediatric population the vast majority of patients with AI have CAH. It is the first and only product approved for paediatric AI, and it is designed with the dosing of paediatric patients in mind, with formulations between 0.5mg and 5mg.

[2] Johannsson G, et al. (2011) Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. *J Clin Endocrinol Metab* 97, 473-481.

Generic oral hydrocortisone is commercially available, but not in dosing levels for paediatrics (5mg is the smallest dose), so this population has historically been addressed using compounded pharmaceuticals. In addition to more convenient dosing, the product provides a couple of additional quality-of-life improvements over compounded hydrocortisone. The product is intended for sprinkling over food, which eases administration in children. Moreover, it is provided with a taste-masking coating to improve palatability. The ease in administration for paediatric labelled products is a major contributing factor to compliance, so these are non-trivial improvements.

Diurnal is using a combination of strategies to market the product. In most of Europe, the company is using a direct salesforce to market the product throughout major markets in Europe and is using distributers to address Nordic countries and smaller markets (although the details of these agreements are not disclosed). Diurnal had £2.39m in Alkindi sales (all from Europe) for the year ending in June 2020, up 130% from the previous year. As of the last update from the company, the product had been launched in the UK, Germany, Austria, Sweden, Denmark, Norway, Iceland and Italy. In the US the product is marketed by Eton Pharmaceuticals, which licensed the drug in March 2020. For the rights Eton paid $3.5m in cash, $1.5m in stock and agreed to pay $2.5m at the launch of the drug (with confirmed orphan drug status). Additionally, Diurnal is owed low double-digit to high-teen royalties and up to $45m in sales milestones. We expect the sale of first units of the product in the US in Q121.

Alkindi is a niche product for a relatively small population, but it is a population of patients that has historically been underserved, without even an approved drug until recently. Compounding has been able to meet the medical needs of these patients, but the lack of controls puts patients at risk. This has been documented for this patient population: one 2017 study found that 12/56 (21.6%) batches of compounded hydrocortisone (in Germany from 37 different pharmacies) did not provide consistent dosing, and two batches (3.6%) did not contain hydrocortisone at all.[3] Alkindi is currently priced in Europe ($6,000 per year) at about twice the cost of compounded generics (approximately $3,000 per year).

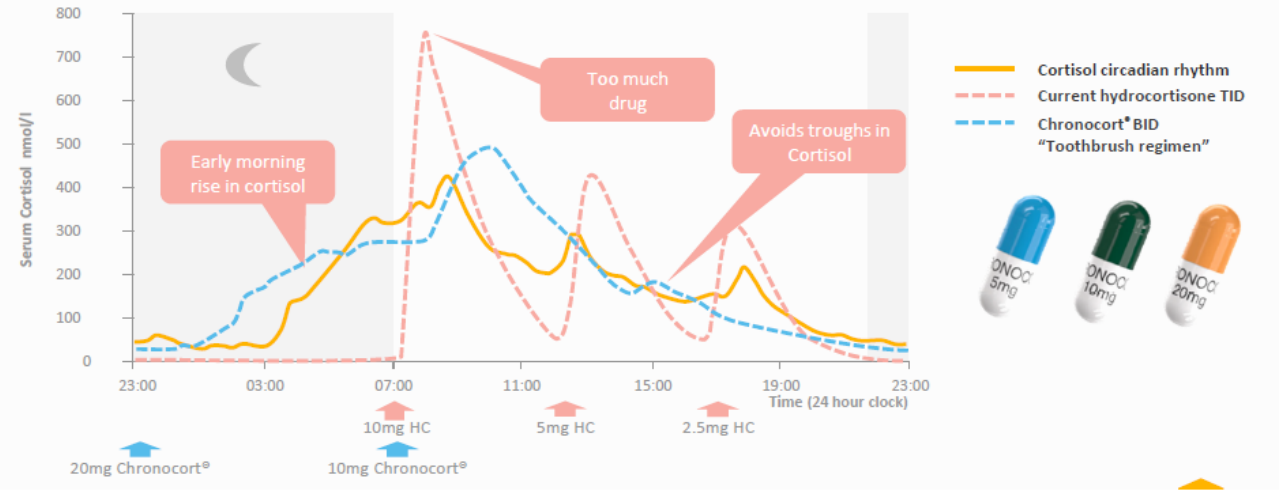
We also believe that there are strategic benefits in the launch of Alkindi as it serves as the beachhead for the later potential approval of Chronocort. Also if and once Chronocort is approved, Diurnal will be providing 'cradle-to-grave' treatment options for CAH sufferers which may also assist in marketing.

Chronocort

Diurnal is developing a novel oral formulation of hydrocortisone for adult sufferers of CAH and AI that is has designed to more closely mimic the natural circadian rhythm of cortisol release from the adrenal glands. The course of cortisol release is one of the factors controlling our state of arousal during the day: hormone levels start to rise early in the morning before waking, peak in the mid-morning, and then slowly decline through the day until bedtime (Exhibit 4, orange line). However, hydrocortisone has a very short half-life in the body (~1.5h), so treatment with immediate release drug typically leads to a sawtooth pattern of over and underdosing (Exhibit 5, dashed pink line). The goal is that by more closely mimicking this diurnal cycle, the product can avoid the effects of over- and underdosing. This is of particular importance to CAH patients because underdosing of corticosteroids leads to the accumulation of androgens and negative outcomes (eg infertility and hirsutism), and it can be difficult in these patients to avoid underdosing in the early morning hours. Longer lasting corticosteroids (eg prednisone) are used frequently to avoid this but at the cost of more overdosing side effects such as risk of infection, ulcers and osteoporosis (among others). The intention is that with a twice-a-day (BID) 'toothbrush' dosing regimen (at waking and bed time) Chronocort can limit these exacerbations and limit the production of androgens.

[3] Neumann U, et al. (2017) Quality of compounded hydrocortisone capsules used in the treatment of children. *Eu J Endocrinol* 177, 239-242.

Exhibit 4: Release profile of Chronocort and generic hydrocortisone



Source: Diurnal Group

The current lead indication for Chronocort is CAH and the clinical studies to date have focused on the ability of the drug to control levels of androgens in these patients. In Phase II (n=16), patients on Chronocort had lower overall exposure (as the 'area under the curve' (AUC)) to the androgens 17-hydroxyprogesterone (17OHP, p=0.024) and androstenedione (p=0.004) over 24 hours. This was achieved with lower hydrocortisone dose equivalents compared to the same patients on conventional immediate release hydrocortisone therapy.

This was followed up with a Phase III study, which completed in 2018.[4] Patients (n=122) were evenly split between Chronocort and immediate release corticosteroid arms and were observed for six months. Instead of androgen exposure (as measured by AUC) as in the Phase II study, the primary endpoint in this study was control 17OHP measured using improvements in the so called standard deviation score (SDS), which examines deviation from physiological reference levels. Frustratingly, the study showed superior control of androgens by every other metric and at every other timepoint except SDS measured at 24 weeks for 17OHP. This includes improvement in AUC for 17OHP (p=0.025 at 24 weeks, also statistically significant at four and 12 weeks) and androstenedione (p=0.013 at 24 weeks), similar to the results seen in Phase II. On average patients in the study on Chronocort had no morning spike in androgen levels, whereas this spike is readily apparent in the arm receiving conventional therapy. Conventional therapy and Chronocort were both effective at controlling androgens in the evening, as one might expect. The authors of the study determined two reasons why the SDS measurement was flawed and failed to capture this real effect:

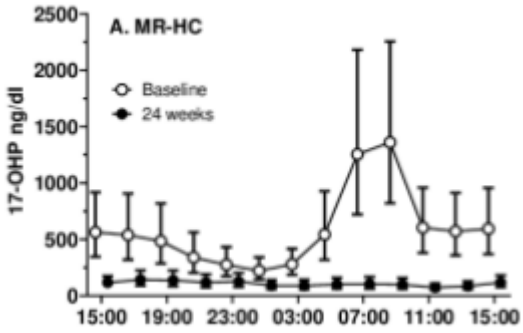
- SDS measured changes in 17OHP compared to the midpoint of the reference range (males 40–220ng/dl, females 40–285ng/dl). Some data was within this range but below the midpoint, and this was treated the same statistically as having too much 17OHP, dampening the quantitative impact from real exacerbations.
- The data was log normalised, which gave more statistical weight to baseline data and less to exacerbations.

We are confident based on the data that, despite missing the primary endpoint, Chronocort provided better outcomes. We do not believe that SDS was the optimal metric to evaluate androgen generation in this context because the low levels achieved in this study are indicative of good disease control but were treated statistically as poor control. Patients on Chronocort were able to

[4] Merke DP, et al. (2021) Modified-release Hydrocortisone in Congenital Adrenal Hyperplasia. *J Clin Endocrinol Metab* dgab051.

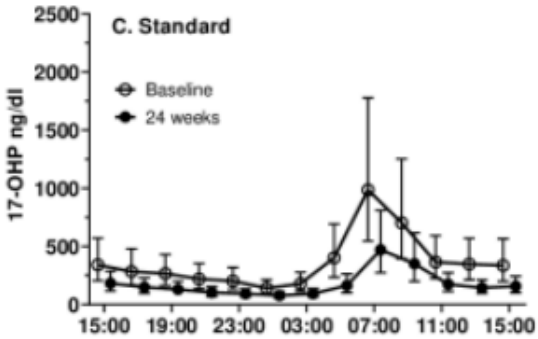
reduce their dosing levels and maintain adequate control when transitioning to a one-year extension study. Additional reports of improved outcomes include four female patients restored their menstrual cycle (compared to one on control) and two male patients achieved a partner pregnancy (compared to zero on control). In the open label extension study, this increased to eight total restored menses, four partner pregnancies, and three pregnancies.

Exhibit 5: 17OHP improvement from BID Chronocort in Phase III



Source: Merke, et al. 2021. X-axis = time of day, Y-axis, serum 17OHP concentrations, MR-HC = Chronocort.

Exhibit 6: 17OHP improvement from conventional therapy in Phase III



Source: Merke et al. 2021 X-axis = time of day, Y-axis, serum 17OHP concentrations.

Understandably, after this result, the future of Chronocort was unclear. Diurnal had a US clinical study ongoing for a short period before the results, but this programme was put on hold while it was determining the path forward. However, a later meeting with the EMA in Q119 was positive and Diurnal decided to submit an MAA based on the above clinical data. This was completed in December 2019 and Diurnal expects a response from the agency in Q121. In the US, the FDA has guided the company towards running additional clinical studies before NDA submission. Diurnal has submitted a request for a special protocol assessment (SPA) meeting to the FDA. If granted, the SPA would provide concrete guidance on what endpoints need to be met for approvability. The company has guided to the meeting taking place in Q121 and Diurnal is targeting starting a new US Phase III study in H221.

The longer-term plan for Chronocort is to seek approval for adult AI after the initial approval for CAH. The current plan is to run a head-to-head comparison study with Plenadren, which would support a label expansion in Europe. This study could begin as early as 2021. A separate study would also be needed to support labelling for AI in the United States, which could be run concurrently with the CAH studies, although this will likely be contingent on financing.

DITEST

In addition to its hydrocortisone products, Diurnal's is also developing a novel formulation of testosterone for the treatment of hypogonadism. Male hypogonadism is defined as testosterone levels below 300ng/dL and, like other endocrine disorders, can be of primary (a dysfunction in the testes) or secondary (a dysfunction in other hormone systems) origin. The crude prevalence of androgen deficiencies in the US male population is estimated to be 6%, making hypogonadism one of the most common endocrine disorders.[5] However, the number of men diagnosed with hypogonadism is markedly less at only 500,000 in the United States.

[5] Basaria S (2014) Male hypogonadism. *Lancet* 383, 1250-1263.

The United States is by far the biggest market for testosterone replacement in the world, estimated at $1.1bn in 2018 ($1.6bn worldwide).[6] There are a number of both branded and generic testosterone products approved in the United States. These products are differentiated primarily based on how they are administered. The historic market leader for branded products has been Androgel, a testosterone supplement provided as a topical gel that is applied under the arms. It had peak sales of over $1bn in 2012, but lost significant market share after reports that it (and testosterone therapy more generally) could increase the risk of heart attack. Additionally, generics of Androgel were launched in 2019.

Exhibit 7: Branded testosterone products

Product	Drug	Company	2019 sales est. ($m)	Administration
Androgel	Testosterone	Abbvie	172	Gel applied to underarms
Xyosted	Testosterone enanthate	Anteres	21	Subcutaneous injection
Aveed	Testosterone undecanoate	Endo	43	Intramuscular injection
Testopel	Testosterone	Endo	55	Subcutaneous pellet
Jatenzo	Testosterone undecanoate	Clarus	*	Oral
Natesto	Testosterone	Acerus	1	Nasal gel
Androderm	Testosterone	Abbvie	55	Patch
Andriol	Testosterone undecanoate	Bayer	80	Oral

Source: Company websites. Note: Sales figures from EvaluatePharma are extrapolated where not explicitly reported. *Jatenzo approved in 2020.

One of the well-documented risks associated with Androgel has been the exposure of unintended people to the drug, such as the family members of the man taking the supplement. The topical nature of the drug makes physical transference easy, and there have been reports of the wives and prepubescent children of patients developing male secondary sexual characteristics (such as growing a beard) from cross-exposure. These gel-based products carry a black box warning for such issues of transference.

Oral testosterone supplements can avoid these issues of transference, although they make up a smaller portion of the market. Currently available oral products use a undecanoate ester of testosterone, which dramatically improves bioavailability over uncodified testosterone by avoiding first-pass metabolism. However, testosterone undecanoate has a substantial food effect: for instance, Jatenzo must be taken with a high-fat meal (30g of fat or more) to ensure complete absorption and this must be done twice a day. For reference, a tablespoon of butter has 12g of fat. Moreover, Jatenzo has a black box warning for cardiovascular side effects.

Diurnal's DITEST product is a formulation of unmodified testosterone that seeks to avoid the issues of poor bioavailability by using a proprietary, oil-based excipient mixture. It has not reported on how this excipient mixture avoids the issue of first-pass metabolism, but Diurnal has reported results from a Phase I study (n=25, 24 completed treatment) that showed similar pharmacological parameters to testosterone undecanoate, but without the food effect.

Historically, it has been difficult for new testosterone products to achieve approval due to a combination of factors. This is driven in part by concerns over safety, because it was discovered years after the first testosterone products were approved that testosterone replacement could be associated with cardiovascular risks. The agency is requiring companies to rigorously prove that their products are safe, and the increased statistical bar has made it difficult for some products. For instance, the oral testosterone Tlando from Lipocine has been rejected by the FDA three times (and is currently on its fourth submission) due to concerns over the safety of super-physiological concentrations of testosterone. In addition, there has been substantial disagreement between the agency and physician groups regarding clinical definitions of hypogonadism.

[6] Transparency Market Research

Diurnal met the FDA in July 2020 and confirmed with the agency that the product could be evaluated under the 505(b)2 pathway. This pathway is for products where the active pharmaceutical ingredient (in this case testosterone) has already been approved and allows the sponsor to use data from these previous applications in their clinical data package. The FDA guided Diurnal that it could seek approval for its DITEST after two additional clinical studies: a multiple ascending dose study and a single Phase III study. Diurnal anticipates filing an IND for the product in Q221 and we expect the dosing study to initiate shortly thereafter.

Sensitivities

Diurnal Group faces a series of challenges that are similar to other specialty pharmaceutical companies. Its development strategy has focused on improving established medicines, which substantially reduces clinical development and regulatory risk. This being said, there are regulatory risks. Although the EMA agreed that the company could file an MAA on the basis of the Chronocort Phase III study, this trial failed to meet its primary endpoints, which may raise issues during its review. Although the company's strategy reduces clinical risk, Diurnal will face increased commercial risk as a result, because it will have to compete with a standard of care that uses low-priced generic medications. Converting these patients has been a slow process since the launch of Alkindi in 2018. If its products are approved, Diurnal will likely face pricing pressure from payers because of the available of these low-cost alternatives. We expect pricing pressure to be mitigated somewhat in the case of Alkindi and Chronocort because the markets are small and the cost per covered life to payers will be small. Based on the available preclinical and clinical data, we believe novel formulations present in Chronocort and DITEST can potentially provide meaningful benefits to patients over the current standard of care. However, Diurnal will need to successfully market these drugs based on these differentiators, which can carry significant risk, especially if Diurnal markets the product without a partner. Alkindi is partnered in the US with Eton Pharmaceuticals but is one of only two products marketed by the company. Alkindi provides a differentiated dosing format, which can be more convenient, but the growth in sales for the product has been slow (£2.39m in sales two years after launch), which highlights these commercial hurdles. We expect Diurnal's hydrocortisone products to be protected primarily by orphan exclusivity in the United States and Europe. However, this will not prevent competition from off-label use and from compounded products, given hydrocortisone is already widely available. Finally, the company has insufficient capital to execute all of its commercial and development objectives. We include £25m in future financing to cover the shortfall, which the company may address by partnering its products (which carries its own risks) or on the capital markets (which may result in dilution).

Valuation

We arrive at an initial valuation of £199.6m or 144p per basic share based on a risk-adjusted NPV analysis of future cashflows from Diurnal's programmes. We model Alkindi and Chronocort for the United States and European markets and DITEST for the US market. The European testosterone market is substantially smaller than the United States, so we do not consider it a high priority. Our assumptions for these programmes are presented in Exhibit 9. In addition to these assumptions, for all programmes we assume a 30% gross/net discount to payers, 10% COGS and 2% price growth per year. We include clinical development costs in our models of $50,000 per patient. We have modelled the clinical development of Chronocort (in terms of number of patients and timelines) on the ongoing crinecerfont development programme from Neurocrine Biosciences. Our model for the DITEST development programme is based on company feedback following FDA meetings. We expect Alkindi and Chronocort to have product growth during their periods of orphan exclusivity (seven years in the United States, ten in Europe) followed by reduced market share thereafter. For

DITEST, although the company has patents protecting the formulation until 2030, we do not expect this to prevent other formulations from entering the market. We forecast five years of product growth before declines in market share as similar products enter the market.

Exhibit 8: Diurnal valuation assumptions

Programme	R&D	SG&A	Europe pricing ($/year)	US pricing ($/year)	Peak penetration	Exclusivity	Addressable number of patients
Alkindi	N/A	$4m/indication/geography, 20% variable costs	$6,000	$12,000	40% EU, 20% US	Orphan (7 years US, 10 Europe)	4800 US, 7500 Europe
Chronocort (adult CAH)	166 pts	$4m/indication/geography, 20% variable costs	$6,000	$12,000	50%	Orphan (7 years US, 10 Europe)	15,000 US, 24,000 Europe
Chronocort (adult AI)	333 pts	$4m/indication/geography, 20% variable costs	$6,000	$12,000	50%	Orphan (7 years US, 10 Europe)	80,000 US, 125,000 Europe
DITEST	200 pts	$4m/indication/geography, 20% variable costs	N/A	$2,200	10%	N/A, 5 years before copy cats	500,000 US

Source: Diurnal reports, Edison Investment Research

We model US Alkindi sales through the company's partner Eton with royalty rates from 12–18% and assume the delivery of the $2.5m approval milestone in calendar year H121 and $1m in an additional sales-based milestone. We assume a lower peak penetration for the product in the United States compared to Europe because the product will have comparatively less time on the market with exclusivity (seven years orphan exclusivity versus ten in Europe). We do not include cashflows from Alkindi sales outside of the United States and Europe in our valuation, although we may add them later if they become significant. For Alkindi we use a 10% discount rate (our standard for approved medical products) and we use 12.5% for the unapproved products Chronocort and DITEST. We assume the first sales for Chronocort in Europe will occur in FY22 if the product is approved.

Exhibit 9: Valuation of Diurnal

Product	Indication	Geography	Clinical stage	Prob. of success	Launch year	Peak sales ($m)	rNPV (£m)
Alkindi	Paediatric AI	Europe	Approved	100%	2018	16	7.28
		US	Approved	100%	2020	10	4.70
Chronocort	Adult CAH	Europe	Filed	80%	2021	63	62.83
		US	Phase III	50%	2024	84	29.25
	Adult AI	Europe	Phase III	50%	2023	131	44.35
		US	Phase II	30%	2026	150	20.15
Ditest	Hypogonadism	US	MAD study	25%	2025	70	10.73
Total							179.28
Net cash and deposits (Dec 2020) (£m)							20.34
Total firm value (£m)							199.63
Total basic shares (m)							138.34
Value per basic share (p)							144
Dilutive options (m)							4.83
Total diluted shares (m)							143.17
Value per diluted share (p)							140

Source: Diurnal reports, Edison Investment Research

Financials

Diurnal reported a revenue of £1.21m for FY H121 ending December 2020. This was almost entirely European sales of Alkindi (£1.13m) and these sales were roughly flat from the same period in 2019 (£1.15m). The company stated that COVID-19 has negatively affected the sales trajectory for the product, which makes sense to us considering the disease likely affected patients' willingness to go to a hospital for a new prescription. We expect a positive sales trajectory to resume in calendar year 2021 as the COVID19 vaccines are rolled out. We also expect the company's full-year revenue to be bolstered by a $2.5m one-time milestone payment from Eton for

the first commercial sale of Alkindi in the United States with orphan drug status, as well as the new revenue from this stream.

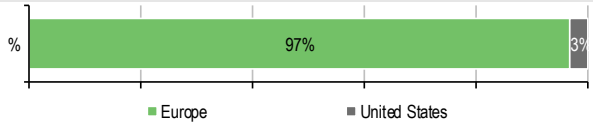
Operating expenses (excluding £0.3m COGS) for H121 were £6.72m and we expect these to increase in the latter half of the fiscal year as the company prepares for the commercial launch of Chronocort in Europe. We forecast operating expenses (excluding COGS) of £15.2m for the fiscal year and expect these to continue to expand, driven by marketing costs. We expect the company to achieve profitability in FY24 following the potential expansion of the indication for Chronocort in Europe to include adult AI.

The company ended 2020 with £20.3m in cash, following a fundraise in October 2020 (£9.1m net proceeds). We include a future financing expectation of £25m (in FY22 as illustrative debt) to cover the remaining financing shortfall before profitability.

Exhibit 10: Financial summary

£'000s	2019	2020	2021e	2022e
Year end 30 June	IFRS	IFRS	IFRS	IFRS
INCOME STATEMENT				
Sales	1,044	2,390	3,134	7,802
Royalties & Milestones	0	3923	1876	137
Revenue	1,044	6,313	5,010	7,939
Cost of Sales	(224)	(668)	(2,324)	(720)
Gross Profit	820	5,645	2,686	7,219
EBITDA	(13,679)	(5,151)	(11,621)	(17,847)
Normalised operating profit	(13,701)	(5,176)	(11,646)	(17,872)
Amortisation of acquired intangibles	0	0	0	0
Exceptionals	0	627	0	0
Share-based payments	(825)	(843)	(843)	(843)
Reported operating profit	(14,526)	(5,392)	(12,489)	(18,715)
Net Interest	130	114	122	122
Joint ventures & associates (post tax)	0	0	0	0
Exceptionals	0	0	0	0
Profit Before Tax (norm)	(13,571)	(5,062)	(11,524)	(17,750)
Profit Before Tax (reported)	(14,396)	(5,278)	(12,367)	(18,593)
Reported tax	2,108	1,206	2,318	3,485
Profit After Tax (norm)	(11,584)	(3,905)	(9,363)	(14,422)
Profit After Tax (reported)	(12,288)	(4,072)	(10,048)	(15,107)
Minority interests	0	0	0	0
Discontinued operations	0	0	0	0
Net income (normalised)	(11,584)	(3,905)	(9,363)	(14,421)
Net income (reported)	(12,288)	(4,072)	(10,048)	(15,107)
Basic average number of shares outstanding (m)	62	95	134	145
EPS - basic normalised (p)	(18.6)	(4.1)	(7.0)	(9.9)
EPS - diluted normalised (p)	(18.6)	(4.1)	(7.0)	(9.9)
EPS - basic reported (p)	(19.7)	(4.3)	(7.5)	(10.4)
Dividend (p)	0.0	0.0	0.0	0.0
BALANCE SHEET				
Fixed Assets	82	1,770	1,826	1,826
Intangible Assets	49	79	79	79
Tangible Assets	33	23	79	79
Investments & other	0	1,668	1,668	1,668
Current Assets	13,381	19,206	19,233	31,474
Stocks	672	1,241	5,809	1,801
Debtors	1,457	1,337	1,235	1,958
Cash & cash equivalents	9,147	15,434	10,995	26,522
Other	2,105	1,194	1,194	1,194
Current Liabilities	(2,503)	(2,555)	(2,734)	(4,239)
Creditors	(2,503)	(2,555)	(2,734)	(4,239)
Tax and social security	0	0	0	0
Short term borrowings	0	0	0	0
Other	0	0	0	0
Long Term Liabilities	(16)	(36)	(36)	(25,036)
Long term borrowings	0	0	0	(25,000)
Other long term liabilities	(16)	(36)	(36)	(36)
Net Assets	10,944	18,385	18,290	4,025
Minority interests	0	0	0	0
Shareholders' equity	10,944	18,385	18,290	4,025
CASH FLOW				
Op Cash Flow before WC and tax	(13,679)	(5,151)	(11,621)	(17,847)
Working capital	(2,331)	(380)	(4,288)	4,791
Exceptional & other	(10)	(1,398)	0	0
Tax	2,279	2,120	2,318	3,485
Net operating cash flow	(13,741)	(4,809)	(13,590)	(9,570)
Capex	(62)	(45)	(81)	(25)
Acquisitions/disposals	0	0	0	0
Net interest	130	114	122	122
Equity financing	5,526	10,670	9,136	0
Dividends	0	0	0	0
Other	0	0	0	0
Net Cash Flow	(8,147)	5,930	(4,413)	(9,473)
Opening net debt/(cash)	(17,284)	(9,147)	(15,434)	(10,995)
FX	10	357	(26)	0
Other non-cash movements	0	0	0	0
Closing net debt/(cash)	(9,147)	(15,434)	(10,995)	(1,522)

Source: Diurnal reports, Edison Investment Research

Contact details	Revenue by geography
Diurnal Group Cardiff Medicentre Health Park Cardiff, CF14 4UJ United Kingdom +44 (0) 29 2068 2069 diurnal.co.uk	

Management team

CEO: Martin Whitaker

Martin has over 20 years' experience in the pharmaceutical industry and has led the Diurnal team since 2008. Previously, Martin worked with Fusion IP (now IP Group) with responsibility for commercialising research from the University of Sheffield. Prior to this, Martin was operations director of Critical Pharmaceuticals, a venture capital-backed drug delivery company developing long-acting growth hormone products. Martin is also a director of D3 Pharma, which successfully commercialised Plenachol, a high dose Vitamin D product. Martin has a PhD in pharmaceutical science from the University of Nottingham and a BSc (Hons) in biochemistry from Bristol University. He is honorary professor of medical innovation at the University of Sheffield.

CFO: Richard Bungay

Richard has over 25 years' experience in senior finance and strategic roles within the pharmaceutical and biotechnology sector. His prior experience includes CFO and COO of Mereo BioPharma, CFO of Glide Technologies, CFO of Verona Pharma, CEO (formerly CFO) of Chroma Therapeutics, Director of corporate communications and strategic planning at Celltech and finance director of the respiratory and inflammation therapy area at AstraZeneca. Richard is also a non-executive director of Cambridge Cognition Holdings and Chroma Therapeutics. He qualified as a chartered accountant with Deloitte and has a first class degree in chemistry from Nottingham University.

CSO: Richard Ross

Richard is a founding director of Diurnal. He is a professor of clinical endocrinology and head of the academic unit of diabetes, endocrinology and metabolism at the University of Sheffield and was previously a senior lecturer at St. Bartholomew's Hospital, London. Richard's primary research interest is pituitary and adrenal disease with a particular focus on hormone replacement. His research has yielded over 200 papers, more than 30 granted patents and publications in Nature Medicine, Nature Reviews Endocrinology, Nature Genetics, The Lancet, The BMJ and PNAS. He has been a member of the editorial boards of Clinical Endocrinology and the Journal of Clinical Endocrinology and Metabolism and served as an elected member of the executive committees for the European Society of Endocrinology (treasurer), the Society for Endocrinology, the Growth Hormone Research Society and the Pituitary Society. Richard is also a director of Asterion.

Interim Chairman: Sam Williams

Sam has over 20 years' experience in the biotechnology industry, both as a top-ranked equity analyst in the City and, subsequently, as an entrepreneur and chief executive. Sam is head of life sciences at IP Group and serves as executive chairman of Istesso; non-executive chairman of Microbiotica and Iksuda; and non-executive director of Genomics, Pulmocide and Psioxus Therapeutics. Sam has a PhD in molecular biology from Cambridge University and an MA in pure and applied biology from Oxford University.

Principal shareholders	(%)
IP Group	31.87
Polar Capital Partners	9.12
Development Bank of Wales	8.34
Amati Group	6.87

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