CALVINE

Diurnal Group

18 January 2021

The evolving treatment options for cortisol deficiency

Share Price	**61p**
CP Fair Value	**99p**
Market Cap (£m)	84
Net Cash (£m)	20
Enterprise Value (£m)	64
Country	UK
Code	DNL
Index	FTSE AIM

Source: Calvine Partners Research

As Chronocort moves towards regulatory action in Europe and the UK in its lead indication of Congenital Adrenal Hyperplasia (CAH), it is worthwhile revisiting the rapidly evolving treatment environment. The treatment of CAH has typically involved the use of glucocorticoid replacement therapy to reduce the clinical consequences of low/no levels of cortisol. Treatment isn't straightforward since replacement therapy must provide a fine balance between preventing an adrenal crisis and reducing the consequences of high levels of androgens. Additionally, there is a great deal of inter and intra-patient variability, and treatment needs to be highly individualised. While normal physiological levels of glucocorticoid should alleviate the risk of adrenal crisis, supraphysiological levels are often required to reduce androgens towards normal levels. Inevitably, chronic administration of supraphysiological steroid levels has been associated with its own issues, including diabetes and metabolic syndrome.

Chronocort remains well positioned

The emergence of alternative approaches to reduce high androgen levels through CRF-1 inhibition has rightly caught investors imagination. Data looks highly encouraging, and one of the consequences may be a reduction in the need for supraphysiological glucocorticoids. However, replacement therapy will still be required to minimise the risk of a life-threatening adrenal crisis and to ensure good control. We believe the data supports the need for Chronocort's optimised delivery which mimics normal physiological circadian release. This is important given the accumulation of androgens during the night and the need to provide disease control in the early morning (4 am to 8 am) as cortisol levels increase in healthy adults.

Adrenal insufficiency is an overlooked opportunity

Low cortisol production is also a feature of the much larger adrenal insufficiency (AI) condition. Chronocort's optimised circadian delivery is highly relevant in AI and competition is absent here - patients often suffer from low androgen levels, with some females requiring androgen replacement therapy. Diurnal has already completed a successful Phase I study in AI patients and while US clinical evaluation is paused for now, Europe looks more straightforward. Indeed, regulatory feedback from EMA suggests that no additional clinical data will be required with a potential CAH approval effectively de-risking the AI opportunity. We have previously speculated that we expect the US to represent a market where Diurnal is most likely to attract a partner for Chronocort for both CAH and AI. This is a larger market than CAH, and we suspect that broader use of Chronocort in AI will also increase awareness in the eyes of endocrinologists generally, likely helping its position in CAH. (For Risks see Page 12).

Dr Brian White
Partner
bw@calvinepartners.com

Andrew Keith
Partner
ak@calvinepartners.com

Towards a new treatment paradigm in CAH

CAH represents a needy patient population

Congenital adrenal hyperplasia (CAH) refers to a range of autosomal recessive genetic diseases which are a direct result of a deficiency of cortisol secretion. When combining both classic (salt wasters with impaired cortisol and aldosterone levels) and non-classic (often asymptomatic) patients, CAH is a relatively common genetic disorder affecting 1 in 200 to 1 in 1000 individuals. For Diurnal and others seeking to provide therapeutic intervention to improve the clinical manifestation of CAH, it is the classic patient that is the target audience, and here the prevalence is closer to 1 in 10,000 and 1 in 20,000. Consequently, this is an Orphan disorder.

Despite glucocorticoid replacement, many patients suffer from poor control

Fortunately, the molecular basis of CAH is well understood, leading to a range of development programmes seeking to treat differing patient requirements. Mutations in CYP21A2 results in a lack of 21-hydroxylase, an enzyme which is responsible for the production of the hormones cortisol and aldosterone in the adrenal cortex. The clinical manifestation, however, is more far-reaching with multiple cascading effects leading to significant morbidity and a real risk of mortality. Less cortisol directly leads to overproduction of pituitary corticotropin, which stimulates the accumulation of cortisol precursors and their subsequent diversion through the steroid pathways that produce adrenal androgens. Additionally, with a lack of cortisol production, patients often suffer from adrenal hyperplasia.

Individualised treatment adds to the complexity for physicians

Further compounding the complexity of successful control is the need for tailored individualised treatment based on age and gender. Adolescents and adults for example with 21-hydroxylase deficiency can experience long-term complications such as short stature, precocious puberty, obesity, hypertension, hirsutism, polycystic ovary syndrome, adrenal or testicular tumours, infertility, and osteoporosis.

Inter and intra-patient variability

Unfortunately, this is also a heterogeneous disorder with the amount of cortisol produced dependent on the particular mutation. To us, it is quite surprising that even those patients suffering from deletions of the 21-hydroxylase gene can have functional enzyme.

Fine balance between hyperandrogenism and hypercortisolism

It's fair to say that most of the adverse outcomes experienced by CAH sufferers are caused by the impact of low cortisol and the efforts to replace this with sufficient glucocorticoid to provide adequate control while minimising the impact of excessive exposure.

Treatment in children well understood, less so in adults

Individuals with CAH have benefited from both neonatal screening (usually 17-OHP levels) and management of their low cortisol with treatment by administration of various glucocorticoid preparations. Depending on the severity of the symptoms, patients may receive several different steroid preparations to deal with the lack of cortisol. Common steroid preparations are hydrocortisone, prednisolone or dexamethasone. Hydrocortisone is generally

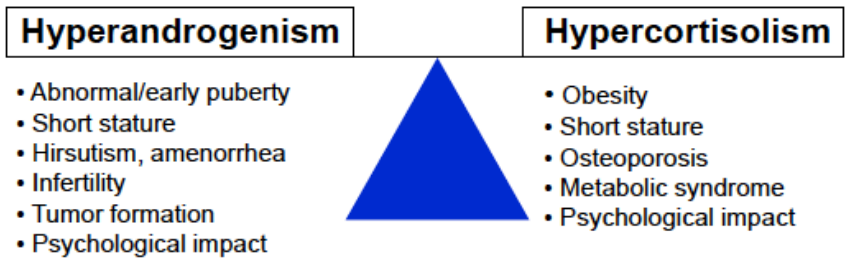
preferred in the paediatric (pre-puberty) population since it is short-acting, has fewer side effects than more potent preparation and lends itself to dose titration (once target androgen levels are achieved). Prednisolone is generally reserved for adult (post-puberty) patients while dexamethasone, as the most potent, is generally reserved for the most challenging patients. More recently, efforts have been made to provide modified release products (such as once-daily hydrocortisone preparations like Plenadren® in Europe) instead of multiple immediate release (60 min) preparations which provide no resemblance to the circadian release of cortisol.

Treatment is complex with unpredictable patient responses

While this may sound relatively straightforward, the management of patients can be very complex. CAH is a heterogenous disorder complicated by the wide dosage range of steroids combined with varied (and difficult to predict) patient responses. Additionally, the female sufferer faces significantly greater challenges from excess androgens than their male counterparts. Sadly, despite early diagnosis and treatment, existing therapies have been unable to prevent many of the clinical consequences of CAH, and although rare, death from adrenal crisis is still a risk.

Difficult to get it right and despite treatment, the risk of adrenal crisis remains

Unlike many examples of replacement therapy treatment, one of the challenges is that there are two aspects to treating patients with CAH. Firstly, the lack of physiological levels of cortisol can lead to an adrenal crisis and secondly, high levels of androgens can lead to other disorders which include., precocious puberty, obesity, hypertension, polycystic ovary syndrome, infertility, tumour, osteoporosis, and reduced quality of life. The main challenge of glucocorticoid replacement is to strike a balance between hyperandrogenism and hypercortisolism.



Use of supraphysiologic doses needs to be minimised

Further complicating matters is the observation that while the risk of adrenal crises can be lowered through administration of physiological glucocorticoid dosing, effective lowering of androgen levels often requires supraphysiologic doses. This is important because the primary objective in treating paediatric CAH, in addition to reversing adrenal insufficiency, is to enable children to attain normal growth and development. Consequently, the focus is on control of androgen excess, and while great strides have been made, early sexual development and growth retardation remain

common. Additionally, patients may suffer from adrenal tumours and men from testicular adrenal rest tumours (TARTs).

CAH requires lifelong treatment while adult patients often overlooked

With CAH patients reaching adulthood now a realistic expectation, the control of excess androgens can be relaxed in order to reduce the consequences of exposure to high levels of glucocorticoid. However, management of CAH during adolescence and into adulthood, provides new challenges with puberty bringing developmental change and the risk of inadequate androgen control. Indeed, high dose glucocorticoid therapy can lead to cushingoid features (round moon face), short stature, weight gain, hypertension, hirsutism, infertility, osteoporosis, and impaired glucose tolerance.

Need to optimise treatment given long term consequences

One of the clear benefits from the success associated with glucocorticoid replacement therapy is that patients now expect to reach adulthood. With this relatively newfound attainment, has been the realisation that current glucocorticoid based treatments are far from perfect, particularly given the need for lifelong chronic therapy. Risks associated with chronic high glucocorticoid therapy include diabetes, an increased risk of infection, high blood pressure and other cardiovascular disorders as well as bone loss.

Conventional treatment requires high doses of glucocorticoid

The side effects associated with long term supraphysiological administration of steroid-based treatment should not be underestimated. CAH treatment often requires the use of high doses of hydrocortisone which can be up to 25mg/m2/day in the CAH affected infant and although this can be lowered over time, it remains relatively high at between 10 and 15mg/m2/day.

Promise of better control for the CAH patient if new approaches successful

There are several aspects to this, with Diurnal seeking to improve and optimise the use of hydrocortisone to improve control of symptoms in CAH patients, while others (Spruce Biosciences and Neurocrine Biosciences) are seeking to address the heightened androgen levels caused by the lack of a negative feedback loop. Potentially, the approach followed by Spruce and Neurocrine could lead to a reduction in the amount of glucocorticoid required to control hyperandrogenism.

Moving towards a new treatment paradigm

Focus on high androgen levels has caught investor imagination

Our view and the received wisdom are that a reduction of the overproduction of androgens by targeting corticotropin releasing factor (CRF), should allow a reduction in the need for supraphysiological levels of hydrocortisone. Ultimately, the goal is to provide a balance which prevents both hyperandrogenism and hypercortisolism. Ideally, this would address the adverse effects of high androgen levels as well as reducing the impact of chronic glucocorticoid administration.

CRF represents a relevant target for intervention

As a result of reduced cortisol production, the hypothalamus increases the secretion of CRF leading to the pituitary increasing ACTH production. Given that this pathway directly leads to the observed increase in androgens, it represents an obvious target for therapeutic intervention. This should be an attractive proposition

resulting in a requirement for a significantly lower (physiological) dose of glucocorticoid solely to treat the risk of adrenal crises.

Data limited but highly encouraging

Data supporting this approach may be limited but has been highly encouraging. There are two companies pursuing the development of a CRF-1 inhibitor. Spruce Biosciences licensed tildacerfont from Eli Lilly in May 2016, while Neurocrine Biosciences is developing crinacerfont.

Splitting the CAH population into poor and good disease control a novel approach

Tildacerfont is a highly selective, potent orally available inhibitor of CRF-1. Tildacerfont has completed two Phase 2a trials in CAH patients. The studies highlighted the variable nature of treatment with two discrete (apparently homogenous) groups identified in a post-hoc analysis, who experienced either poor or good disease control. Patients with good control (elevated 17-OHP, normal ACTH & A4) had used supraphysiological doses (36mg) of glucocorticoid, whereas those with poor control (highly elevated 17-OHP, ACTH & A4) used lower but still supraphysiological doses of glucocorticoid (25mg). We believe these data suggest that those with poor disease control were probably not taking a sufficiently high dose to control androgen levels

Impressive reductions in key hormones

In the Phase 2a study (SPR001-202), patients with poor disease control experienced mean maximum reductions in 17-OHP, ACTH & A4 of 80%. This is clearly an impressive result, and we look forward to greater detail to better understand the importance of tildacerfont in the CAH patient. Patients continued to receive their normal dose of glucocorticoid.

Potential to lower GC dose

As a result of these data, the subsequent development programme for tildacerfont has focussed on these two discrete patient groups. One of the key conclusions of the completed Phase 2a programme was that patients with good disease control could be receiving a higher than required glucocorticoid dose given the ability of tildacerfont to reduce the levels of 17-OHP, ACTH & A4 by 80%.

Potentially registrational study will evaluate potential for steroid sparing

The potentially registrational Phase 2b programme will evaluate tildacerfont in both patient groups. In the poor disease control group (study ‘203) the intention is to administer tildacerfont for up to 40 weeks with a protocol that not only assesses its impact of key hormones (17-OHP, ACTH & A4) but also the potential to reduce the dose of glucocorticoid received.

Potential for regulatory filings if successful

In the good disease control group (study ‘204), the main objective is to reduce supraphysiological glucocorticoid use. Glucocorticoid use will be standardised prior to treatment with tildacerfont and the primary endpoint of the trial will be the reduction in glucocorticoid use by week 24. Spruce Biosciences has indicated that if the trial data in the steroid-sparing study are positive the intention is to meet with requisite regulatory authorities to discuss the potential for a regulatory submission.

Data suggests that there could be multiple CRF-1 inhibitors approved.

Neurocrine Biosciences has taken a similar approach targeting CRF-1 with crinecerfont. Data from an open label dose finding Phase 2 study in adult CAH sufferers have been similarly encouraging with substantial reductions in key hormones 17-OHP,

ACTH and A4 observed. Although numbers were small (n=18) At the highest dose of crinecerfont (100 mg twice daily), which represents the selected crinecerfont dose, 75% of patients benefited from a response of at least 50% reduction from baseline for each of the three hormones at day 14.

Phase 3 trial underway

Unlike Spruce, Neurocrine has not endeavoured to split the CAH population into those with either good or poor disease control. Instead, the company has initiated a global Phase 3 registrational study in 165 adult classic CAH patients. With a start date of July 2020, the estimated primary completion date for the study is February 2023.

How Chronocort fits into this new treatment paradigm

It is important to note that despite the encouraging data presented for the CRF-1 inhibitors tildacerfont and crinecerfont, neither have been approved. Nevertheless, based on the positive nature of the data that we have seen so far, our expectation is that we will see the addition of this treatment approach.

Continued requirement for GC administration

Both sets of pivotal studies are on top of currently used glucocorticoid treatment with the tildacerfont approach, specifically looking to reduce the burden of supraphysiological doses of glucocorticoid. However, it is important to note that there will be a continued requirement for glucocorticoid use in these patients. Based on currently expected timelines, neither Chronocort nor either of the CRF-1 inhibitors will be approved as each progress through Phase 3 development in the US. Therefore, it appears unlikely that a Chronocort/CRF-1 inhibitor combination study will be conducted prior to approval.

Cortisol is an important hormone in its own right

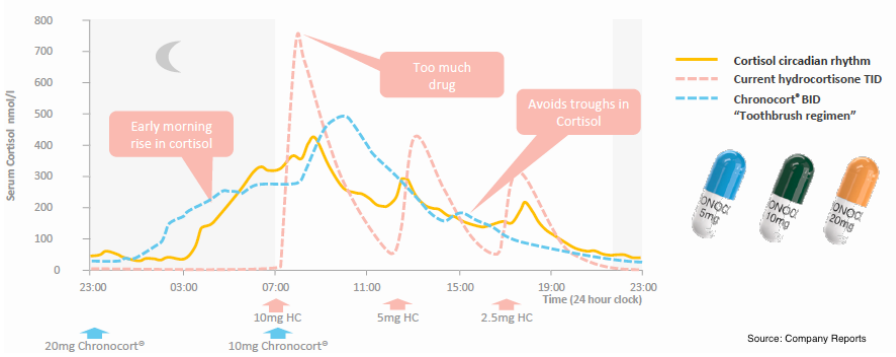
Adrenal crisis remains a life-threatening risk

While supraphysiologic levels of androgens remains an important target in treatment of CAH, cortisol plays multiple roles as part of the hypothalamic-pituitary-adrenal axis (HPA). Moreover, patients with low cortisol levels present with a broad range of symptoms. These include fatigue, a loss of appetite with nausea and vomiting, combined with diarrhoea, leading to a significantly impaired quality of life. While these symptoms are challenging enough, there is also a more sinister complication. With little warning, patients have the potential for an (acute) adrenal crisis (often during a period of significant stress). An acute adrenal crisis represents a life-threatening emergency and requires urgent treatment with a bolus of hydrocortisone.

Evidence surrounding the importance of circadian delivery well documented

Chronocort has been designed to mimic the physiological circadian release of cortisol which conventional glucocorticoid therapy is unable to achieve. This is important given the release of cortisol during the night in preparation for wakening. Cortisol levels begin to increase 2-3 hours after sleep onset and continue to rise into the early morning and early waking (4 am-8 am) period. The peak in cortisol is around 9 am with levels subsequently declining during the day. The importance of circadian release of cortisol has been well

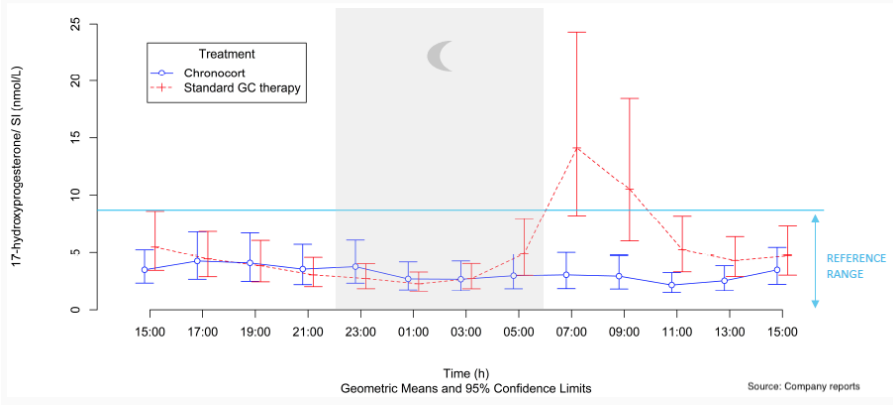
documented, with late afternoon administration linked to obesity, glucose intolerance, atherosclerosis and insomnia.



Furthermore, one of the issues for classic CAH patients is that conventional glucocorticoid treatment is unable to control the overnight build-up of androgens. Indeed, one of the key takeaways from the completed clinical evaluation of Chronocort (Phase 2 and Phase 3) was that 94% of patients receiving Chronocort achieved better disease control as measured by 17-OHP, compared to 31% receiving standard glucocorticoid therapy (Phase 2 study). In the Phase 3 trial, despite missing the primary endpoint, Chronocort was associated with clinically relevant benefits; in particular, it was associated with significantly better control of 17-OHP over the important morning to mid-afternoon (7 am–3 pm) period. We have also previously highlighted that Chronocort administration was associated with several important observations when compared to standard of care which included 1) lower variability, 2) control of androgens achieved on a lower dose (control of excess androgens is an important feature of treatment) 3) fewer sick days and 4) no (potentially life-threatening) adrenal crises. Importantly, hydrocortisone, the active ingredient in Chronocort, is a well characterised and understood molecule.

Shortcomings of conventional glucocorticoid therapy well known in the endocrinology community

Chronocort® achieved significantly better control of 17-OHP in the key period 07:00-15:00



Androgens important but adrenal crisis life-threatening

As we have intimated previously, the dual purpose of treating the CAH patient is to replace the lost cortisol and minimise excess androgen production. One of the key benefits associated with Chronocort is that, unlike targeting CRF-1, it can potentially deal with both of these issues. However, while the development of the CRF-1 inhibitors has focussed attention on the downside impact of hypercortisolism, it is important to note that in clinical development, investigators have also been able to lower the overall glucocorticoid dose.

Optimal GC delivery remains a key tenet of improved disease control

Ultimately, replicating the physiological circadian nature of cortisol release has been a long-term goal of the pharmaceutical industry (Diurnal is not the first), and Chronocort appears to us to be the optimal method to achieve this objective. As the CRF-1 inhibitors progress, we suspect that the importance of optimising the glucocorticoid component should further increase. Also, this heterogenous disease with various important factors such as age and gender, requiring individualised treatment. Each CAH patient is different and there is also significant intra-patient variability. Hopefully, the availability of new treatments such as Chronocort, optimising glucocorticoid delivery, and the CRF-1 inhibitors (such as tildacerfont and crinecerfont) should transform the outlook for both children and adults with this life-threatening and debilitating disorder.

Replicating circadian release has been a long term goal with Chronocort well placed

,

Looking forward to upcoming regulatory decisions

Regulatory action dates approaching for Chronocort

Based on the totality of the data and following a positive meeting with EMA which confirmed the clinical and regulatory pathway for Chronocort, Diurnal submitted a regulatory application in December 2019. Notably, the filing also included data which confirmed the significant benefit associated with Chronocort to support its Orphan Drug Status, as well as relevance to other cortisol deficiency indications (AI for example). More recently and following the withdrawal of the UK from the EU, Diurnal has also filed for approval with MHRA. Regulatory decisions from both agencies are anticipated in Q1 2021.

We have used a 75% probability of approval based on available data

Our forecasts for market introductions of Chronocort in the CAH indication broadly match company guidance. Given the lingering uncertainty associated with the EMA decision in Q1 2021, we have employed a 75% probability of approval. This figure reflects our view that this is not a binary situation and that Diurnal has amassed sufficient information to persuade the EMA of the safety and activity of Chronocort, that it provides a benefit over existing therapies and is therefore deserving of Orphan Drug Status.

Chronocort franchise sales (£m)	2020A	2021E	2022E	2023E	2024E	2025E
US						
Patient number	16816	17153	17496	17846	18202	18567
growth	2%	2%	2%	2%	2%	2%
Penetration	0%	0%	0%	0%	5%	12%
Price GBP	4968	5068	5169	5272	5378	5485
growth	2%	2%	2%	2%	2%	2%
Probability of success	75%	75%	75%	75%	75%	75%
Revenue	-	-	-	-	**3.67**	**9.17**
growth					0.0%	149.7%
Unrisked sales	**0.00**	**0.00**	**0.00**	**0.00**	**4.89**	**12.22**
EU						
Patient number	51620	52653	53706	54780	55875	56993
growth	2%	2%	2%	2%	2%	2%
Penetration	0%	1%	5%	15%	25%	30%
Price GBP	4500	4500	4500	4500	4500	4500
growth	0%	0%	0%	0%	0%	0%
Probability of success	75%	75%	75%	75%	75%	75%
Revenue	-	**1.42**	**9.06**	**27.73**	**47.14**	**57.71**
growth			537.5%	206.0%	70.0%	22.4%
Unrisked sales	**0.00**	**1.90**	**12.08**	**36.98**	**62.86**	**76.94**

Source: Calvine Partners Research

.

Adrenal insufficiency – a significant and lower risk market opportunity with limited competition

Encouraging to see potential transformation of CAH treatment

Given the debilitating nature of CAH, where children and women are particularly badly affected, along with the observation that there are several novel therapies in development, it is perhaps unsurprising that interest in CAH has soared. Indeed, we suspect that the competitive noise from the developers of CRF-1 inhibitors has perhaps detracted from the importance of Chronocort's role in providing circadian delivery of the glucocorticoid component in this orphan disorder.

Larger AI indication has been overlooked in the excitement

However, Diurnal's approach of optimising (circadian) delivery of hydrocortisone is also highly relevant to the treatment of adrenal insufficiency (Addison's disease) where sufferers have a compromised adrenal gland and consequently low levels of cortisol. Unlike CAH, this is principally a disorder of adults (post-puberty) and hyperandrogenism is not generally an issue – in fact quite the opposite, with some females potentially requiring androgen replacement therapy. As a result, it is also important to note that another important differentiator for Diurnal is that CRF-1 inhibition is not relevant here, leaving glucocorticoid replacement therapy as the preferred approach.

Autoimmune destruction of renal glands responsible for majority of cases

Autoimmune destruction of the adrenal glands represents the most frequent cause of primary adrenal insufficiency in the developed world (prevalence of 70%-90% of cases). There are several causative factors which include tuberculosis and other infectious diseases (HIV for example) as well as some drugs (e.g. ketoconazole). Secondary adrenal insufficiency (hypopituitarism) results from a defect in the production of corticotropin releasing hormone (CRH) or adrenocorticotropic hormone (ACTH). This is due to a malfunction of the pituitary or hypothalamus, which results in the underproduction of cortisol. While primary AI is associated with both glucocorticoid and mineralocorticoid deficiencies, the secondary and the tertiary forms only exhibit cortisol deficiency

Low levels of cortisol (and aldosterone)

The symptoms of classic adrenal insufficiency are attributed to the low levels of cortisol and aldosterone. Characteristic symptoms include fatigue, gastrointestinal abnormalities and altered skin pigmentation. Increased excretion of water combined with low blood pressure can lead to dehydration.

Addison's is an adult disease and optimised circadian delivery equally relevant

The combined AI market opportunity (Addison's and hypopituitarism) in the US and Europe is circa $2.8bn. The AI indication represents a considerable opportunity for Diurnal with perhaps as many as 4.1m sufferers globally and should be as tractable as CAH to circadian delivery of cortisol. Indeed, there remains significant consternation within the endocrinologist community regarding the risks associated with current non-circadian delivery of high doses of hydrocortisone in AI. As with CAH, this is particularly the case in the afternoon with an increased risk of infection and cardiovascular disease. As we have already

detailed for CAH, supraphysiological levels of hydrocortisone in the evening have been associated with a plethora of metabolic disorders including glucose intolerance, obesity, atherosclerosis, and insomnia.

European opportunity should be straightforward

The development of Chronocort for AI in Europe looks straightforward, with regulatory feedback suggesting that no additional clinical data are required should Chronocort receive approval for the CAH indication by EMA in Q1. Nevertheless, we suspect that the availability of clinical data evaluating important parameters for Chronocort in AI patients would be helpful in persuading the endocrinology community of its merits. As a result, we expect Diurnal to provide appropriate and relevant clinical data prior to commercial launch in Europe.

Development for the US likely best with a partner

Our sense is that it is likely to be the US where Diurnal is most likely to attract a partner for Chronocort for both CAH and AI. Looking to the US market potential for the AI opportunity, we are forecasting a 2024 introduction recognising that the planned Phase II study has been paused. Nevertheless, we believe that the large size of the US AI market should further add to the general attraction of the Chronocort opportunity. We have assumed that two-thirds of patients are not controlled and available for Chronocort therapy. We have attributed a 50% probability of success to the AI programmes, resulting in 2030E revenues of £115m in the US. On an unrisked basis, our peak sales forecast would be £231m.

Diurnal's portfolio offers a lifelong treatment approach

Given the importance of glucocorticoid replacement therapy for patients who suffer from low cortisol (CAH and AI), it is important to remember that the child-friendly formulation Alkindi is already approved in Europe and the US. As a result, the portfolio of Alkindi and Chronocort (if approved) should be well placed to serve the needs of physicians and patients as they endeavour to improve disease control.

Adrenal franchise sales (£m)

	2019A	2020A	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
Alkindi sales US	-	-	0.31	0.65	1.26	1.75	2.74	3.42	3.56	3.70
Alkindi sales EU	1.02	2.39	2.44	6.92	9.60	9.99	10.39	10.81	11.25	11.70
Chronocort sales US	-	-	-	-	-	3.67	9.17	33.99	68.34	80.28
Chronocort sales EU	-	-	1.42	9.06	27.73	73.30	111.06	187.33	191.07	194.90
Adrenal franchise sales	1.02	2.39	4.17	16.63	38.60	88.71	133.36	235.55	274.22	290.58
Adrenal franchise sales unrisked	**1.02**	**2.39**	**4.65**	**19.65**	**47.84**	**131.81**	**209.01**	**391.31**	**458.23**	**488.38**

Source: Calvine Partners Research

Risks

The principal risks associated with Diurnal are largely clinical and commercial in nature. The failure of the European Phase 3 study for Chronocort was an unexpected disappointment although a review of the data has suggested significant support for Diurnal's approach. While we hope that the EMA will be pragmatic in its approach to reviewing the data, there are lingering risks in this approach.

Diurnal has retained European rights to its adrenal disorder franchise, which brings commercialisation risks. We note that Diurnal has engaged the services of Ashfield, which has a successful track record in helping life science companies launch new products. Nevertheless, the pace of uptake is difficult to predict which could affect our forecasts although we recognise that market expectations for Alkindi are modest.

If successful, and Chronocort ultimately achieves a market introduction, Diurnal is seeking to launch its products into what is largely a generic market environment. We have assumed a price for Chronocort that is consistent with the European price of Plenadren® – a once daily formulation of hydrocortisone which looks to be a reasonable proxy. We note that in this regard there is no equivalent product in the US. With Diurnal looking to partner its products in the US, including DITEST, there is an associated partnering risk.

As a development stage company, Diurnal is currently loss-making. Diurnal has successfully raised funds to continue with its development plans and to aid the launch of Alkindi in Europe. Even with this near-term funding, our forecasts suggest that in order to progress its pipeline assets expeditiously, Diurnal may require additional funding.

Diurnal Group Cash Flow Statement

Year to June	2019A	2020A	2021E	2022E	2023E	2024E	2025E
Net income	(12.29)	(4.07)	(14.65)	(9.04)	2.91	23.32	35.22
Licensing income received as non-cash		(1.04)					
Fair value adjustment to investments		(0.63)					
Dep/Amort/Impair	0.02	0.03	0.01	0.01	0.01	0.02	0.04
Share- based payment	0.83	0.84	0.84	0.84	0.84	0.84	0.84
Net Fx gain	(0.01)	(0.36)					
Financial income	(0.13)	(0.11)	(0.15)	(0.11)	(0.02)	(0.05)	(0.28)
Financial expense	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Tax	(2.11)	(1.21)	0.00	0.00	0.97	7.77	11.74
(Increase) in receivables	1.36	0.12	0.02	(0.12)	(0.22)	(0.50)	(0.45)
Increase in payables	(3.14)	0.07	0.09	0.12	0.14	0.40	0.36
(Increase) in inventories	(0.55)	(0.57)	(0.05)	(0.58)	(0.71)	(0.23)	0.44
Interest paid	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
Tax paid/ received	2.28	2.12	0.00	0.00	(0.97)	(7.77)	(11.74)
CFO	(13.74)	(4.81)	(13.89)	(8.89)	2.95	23.81	36.17
PP&E	(0.03)	(0.01)	(0.01)	(0.01)	(0.08)	(0.10)	(0.17)
R&D capitalised	(0.04)	(0.04)					
Investments	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
Interest received	0.13	0.11	0.15	0.11	0.02	0.05	0.28
CFI	0.07	0.07	0.15	0.10	(0.06)	(0.05)	0.11
Net proceeds from issuance of share capital	5.53	10.67	9.30	0.00	0.00	0.00	0.00
Repayment of borrowings	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Net proceeds from new borrowings	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
CFF	5.53	10.67	9.30	0.00	0.00	0.00	0.00
Increase in cash	(8.15)	5.93	(4.45)	(8.79)	2.89	23.76	36.28
Cash brought forward	**17.28**	**9.14**	**15.07**	**10.62**	**1.83**	**4.72**	**28.48**
Fx		0.36					
Cash EOP	**9.14**	**15.07**	**10.62**	**1.83**	**4.72**	**28.48**	**64.76**

Source: Calvine Partners Research

Diurnal Group Income Statement

Year to June	2019A	2020A	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
Sales	**1.04**	**6.31**	**4.17**	**16.63**	**38.60**	**88.71**	**133.36**	**235.55**	**274.22**	**290.58**	**346.06**	**372.54**
COGS	(0.22)	(0.67)	(1.25)	(4.16)	(7.72)	(17.74)	(26.67)	(47.11)	(54.84)	(58.12)	(69.21)	(74.51)
Gross profit	**0.82**	**5.65**	**2.92**	**12.47**	**30.88**	**70.97**	**106.69**	**188.44**	**219.38**	**232.46**	**276.85**	**298.03**
gross margin	78.5%	89.4%	70.0%	75.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%
SG&A	(6.66)	(7.04)	(7.51)	(9.98)	(11.58)	(17.74)	(33.34)	(58.89)	(68.56)	(72.64)	(86.52)	(93.13)
R&D	(8.69)	(4.63)	(10.21)	(11.64)	(15.44)	(22.18)	(26.67)	(35.33)	(41.13)	(43.59)	(51.91)	(55.88)
Other operating income	0.00	0.63	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Operating profit	**(14.53)**	**(5.39)**	**(14.80)**	**(9.15)**	**3.86**	**31.05**	**46.68**	**94.22**	**109.69**	**116.23**	**138.43**	**149.02**
Finance income	0.13	0.11	0.15	0.11	0.02	0.05	0.28	0.65	1.36	2.20	3.09	4.14
Finance expense	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
PBT	**(14.40)**	**(5.28)**	**(14.65)**	**(9.04)**	**3.88**	**31.10**	**46.96**	**94.87**	**111.05**	**118.43**	**141.51**	**153.16**
Tax	2.11	1.21	0.00	0.00	(0.97)	(7.77)	(11.74)	(23.72)	(27.76)	(29.61)	(35.38)	(38.29)
Net income	**(12.29)**	**(4.07)**	**(14.65)**	**(9.04)**	**2.91**	**23.32**	**35.22**	**71.15**	**83.28**	**88.82**	**106.14**	**114.87**
EPS Basic (p)	-19.70	-4.30	-11.27	-6.54	2.10	16.86	25.46	51.44	60.21	64.21	76.73	83.04
EPS Diluted (p)	**-19.70**	**-4.30**	**-11.27**	**-6.54**	**2.10**	**16.86**	**25.46**	**51.44**	**60.21**	**64.21**	**76.73**	**83.04**

Source: Calvine Partners Research

CALVINE

Diurnal Group Balance Sheet

Year to June	2019A	2020A	2021E	2022E	2023E	2024E	2025E
Intangible assets	0.05	0.08	0.01	0.01	0.01	0.01	0.01
PP&E	0.03	0.02	0.02	0.02	0.10	0.17	0.31
Inv held at fair value through P&L		1.67	1.67	1.67			
Non-current assets	0.08	1.77	1.69	1.69	0.10	0.18	0.32
Trade and other receivables	3.56	2.53	0.04	0.17	0.39	0.89	1.33
Inventory	0.67	1.24	0.25	0.83	1.54	1.77	1.33
Financial assets	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Cash & Cash equivalents	9.15	15.43	10.62	1.83	4.72	28.48	64.76
Current assets	13.38	19.21	10.91	2.83	6.65	31.14	67.42
Total Assets	**13.46**	**20.98**	**12.61**	**4.53**	**6.75**	**31.32**	**67.74**
Loans and borrowings	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Trade and other payables	(2.50)	(2.56)	0.05	0.17	0.31	0.71	1.07
Current liabilities	(2.50)	(2.56)	0.05	0.17	0.31	0.71	1.07
Loans and borrowings	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Trade and other payables	(0.02)	(0.04)	(0.05)				
Non-current liabilities	(0.02)	(0.04)	(0.05)	0.00	0.00	0.00	0.00
Total Liabilities	**(2.52)**	**(2.59)**	**0.00**	**0.17**	**0.31**	**0.71**	**1.07**
Share capital	4.23	6.08	6.08	6.08	6.08	6.08	6.08
Share premium	42.15	50.97	59.47	59.47	59.47	59.47	59.47
Consolidation reserve	(2.94)	(2.94)	(2.94)	(2.94)	(2.94)	(2.94)	(2.94)
Other reserve	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Retained earnings	(32.49)	(35.72)	(49.87)	(58.41)	(55.00)	(31.18)	4.54
Total equity	**10.94**	**18.39**	**12.74**	**4.19**	**7.60**	**31.43**	**67.15**

Source: Calvine Partners Research

Disclaimers and disclosures

Calvine Partners LLP is an appointed representative of Midmar Capital LLP, which is authorised and regulated by the Financial Conduct Authority.

This publication has been commissioned and paid for by Diurnal Group and as defined by the FCA is non-independent research. This report is considered to be a marketing communication under FCA Rules, and it has not been prepared under the laws and requirements established to promote the independence of investment research and it is not subject to any prohibition on dealing ahead of the dissemination of investment research. This information is widely available to the public.

This report in the United Kingdom is directed at investment professionals, certified high net worth individuals, high net worth entities, self-certified sophisticated investors, eligible counterparties as defined by Financial Services and Markets Act 2000 (Financial Promotion) Order 2000. The report may also be distributed and made available to persons to whom Calvine Partners is lawfully permitted. This publication is not intended for use by any individual or entity in any jurisdiction or country where that use would breach law or regulations, or which would subject Calvine Partners or its affiliates to any registration requirement within such jurisdiction or country.

Calvine Partners may provide, or seek to provide, services to other companies mentioned in this report. Partners, employees, or related parties thereof may hold positions in the companies mentioned in the report subject to Calvine Partners' personal account dealing rules.

Calvine Partners has only used publicly available information believed to be reliable at the time of this publication and made best efforts to ensure that the facts and opinions stated are fair, accurate, timely and complete as at publication date. However, Calvine Partners provides no guarantee concerning the accuracy or completeness of the report or the information or opinions within. This publication is not intended to be an investment recommendation, personal or otherwise, and it is not intended to be advice and should not be treated in any way as such. Any valuation estimate, such as a those derived from a discounted cash flow, price multiple, or peer group comparison, do not represent an estimate or forecast of a future company share price. In no circumstances should the report be relied on or acted upon by non-qualified individuals. Personal or otherwise, it is not intended to be advice and should not be relied on in any way as such.

Forward-looking statements, information, estimates and assumptions contained in this report are not yet known, and uncertainties may cause the actual results, performance or achievements to be significantly different from expectations.

This report does not constitute an offer, invitation or inducement to engage in a purchase or sale of any securities in the companies mentioned. The information provided is for educational purposes only. This publication should not be relied upon when making any investment decision or entering any commercial contract. Readers should seek appropriate, independent advice before acting on any of the information contained herein. This report should not be considered as investment advice, and Calvine Partners will not be liable for any losses, costs or damages arising from the use of this report. The information provided in this report should not be considered in any circumstances as personalised advice.

Calvine Partners LLP, its affiliates, officers or employees, do not accept any liability or responsibility with regard to the information in this publication. None of the information or opinions in this publication has been independently verified. Information and opinions are subject to change after the publication of this report, possibly rendering them inaccurate and/or incomplete.