Diurnal Group

23 February 2021

Final stretch

Share Price	**60p**
CP Fair Value	**99p**
Market Cap (£m)	83
Net Cash (£m)	20
Enterprise Value (£m)	63
Country	UK
Code	DNL
Index	FTSE AIM

Source: Calvine Partners Research

The H1 2020 results at Diurnal reflect a period of solid commercial and pipeline progress. The continued rollout of Alkindi in Europe has established a commercial base for future specialty launches, while the attraction of Eton Pharmaceuticals for the important US market has delivered an appropriate and relevant commercial partner for Alkindi Sprinkle. We await with keen anticipation the regulatory decision of the EMA and MHRA on the filing of Chronocort for the Orphan indication of congenital adrenal hyperplasia (CAH). Should the regulators deliver a positive recommendation, Diurnal is well placed to launch Chronocort in Europe through its now well-established (endocrinology focussed) commercial platform, with pre-launch activities ongoing. The pipeline has progressed too, with DITEST potentially a best-in-class addition to the large testosterone replacement (TRT) market opportunity, moving into the clinic.

Lots to look forward to

Diurnal has ambitions to become a leading (non-diabetes) endocrinology specialty pharma business. First up has been the development and approval of Alkindi in Europe and the US. Meanwhile, Chronocort is moving towards a regulatory conclusion in Q1 2021. There can be little doubt that the forthcoming regulatory action for Chronocort in Europe and the UK has overshadowed progress elsewhere at Diurnal. This is perhaps unsurprising given the excellent prospects for a CAH treatment which delivers physiological levels of the glucocorticoid hydrocortisone, effectively mimicking the circadian release of cortisol in these patients. The awareness of CAH generally has been heightened thanks to the efforts not only of Diurnal but also those developing potentially complementary treatments targeting CRF1. We remain enthusiastic about the commercial prospects for Chronocort not only in Europe but also in the US, which we believe offers a market opportunity which Diurnal could access effectively alone or with a suitable partner. Furthermore, a positive regulatory outcome for Chronocort could open up the larger and more lucrative adrenal insufficiency market opportunity with a comparator study (versus Plenadren) planned as part of the regulatory package.

Don't forget the pipeline

With the focus on Chronocort, it is also important to also look to pipeline progress. We have previously highlighted the native testosterone preparation DITEST where there is a large unmet need, with the requirement for safer, more convenient alternatives. We believe DITEST shows potential to provide a best-in-class addition, and with a streamlined branded generic regulatory pathway agreed with FDA, we look forward to further clinical DITEST progress for classical male hypogonadism. (Risks include regulatory, clinical and commercial. See Page 5)

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Alkindi and Chronocort dominate for now

Regulatory clarification of the US Phase 3 trial, with a Special Protocol Agreement for Chronocort, is expected to be agreed during H1 2021

Undoubtedly, near-term prospects at Diurnal are dominated by the adrenal franchise and in particular the potential for Chronocort to successfully navigate the European and UK regulatory processes, with decisions due soon. Alkindi is now approved in both Europe and the US for the treatment of paediatric adrenal insufficiency. Having been paused following the missed primary endpoint for the European Phase 3 study, regulatory clarification of the US Phase 3 trial, with a Special Protocol Agreement for Chronocort, is expected to be agreed during H1 2021. With the CAH opportunity in Japan also significant, we note that Diurnal is exploring regulatory options here too.

Alkindi established the adrenal franchise

We remain highly encouraged by Alkindi's apparent pricing power

Alkindi is a child friendly formulation of hydrocortisone for patients with cortisol deficiency and has proven to be an effective fast-to-market approach for Diurnal's ambition in treating adrenal disorders. Although European rollout has been predictably protracted, not helped by the current dislocation, we remain highly encouraged by its apparent pricing power. Additionally, it is reassuring to see that there is a clear need for a predictable dosing presentation of cortisol to replace the compounded and highly variable product used previously. In Europe, Diurnal has retained marketing rights to Alkindi, using Ashfield to help establish a commercial platform. Assuming a positive regulatory opinion for Chronocort in CAH, Diurnal should be well placed to expeditiously launch Chronocort through the existing endocrinology sales platform.

Delayed timing of bulk deliveries to Alkindi's Nordic partner resulted in overall muted growth

With Alkindi roll out taking place during the COVID-19 pandemic, it has been reassuring to see strong growth of over 20% in existing markets of the UK and Germany. Newer launch geographies have not fared so well, with modest growth due to the current environment. Delayed timing of bulk deliveries to Alkindi's Nordic partner resulted in an overall muted year over year growth of 4% to £1.19m. In trying to look for leading indicators and a future post-pandemic, we believe that 20%+ growth in the UK and Germany is reassuring. We suspect that growth should be significantly higher in a normal environment where endocrinologists are accessible to the promotional activities supporting Alkindi. Our view is that Alkindi is a straightforward proposition replacing inherently variable crushed/compounded hydrocortisone with a clinically proven preparation - we anticipate that revenues have been deferred and not lost.

Eton Pharmaceuticals brings a highly appropriate partner for Alkindi in the important US market

The attraction of specialty pharma company Eton Pharmaceuticals brings a highly appropriate partner for Alkindi Sprinkle in the important US (and Canadian) market with its focus on hospital-based products (including paediatrics and endocrinology). Commentary from Eton since in-licensing has been highly encouraging with a modest sales force of 5 expected to be able to

effectively target circa 900 paediatric endocrinologists. Fortunately, with all newborns receiving screening for AI, and patient numbers ranging from 5,000-11,000, the detailing opportunity looks straightforward. Eton has previously provided information suggesting a market opportunity in excess of $100m reflecting the unmet medical need.

Eton estimates an Alkindi market opportunity in excess of $100m

Pipeline in waiting

With the US Phase 3 Chronocort trial yet to get underway and DITEST clinical evaluation yet to begin, R&D expenditure remained modest for Diurnal at £2.6m. The company previously stated that it has sufficient funding to reach profitability, although clearly much depends on the outcome of the upcoming regulatory action on Chronocort, and Diurnal's view on the best way to progress Chronocort in the US.

In Europe and the UK, a positive regulatory outcome would be transformational for Diurnal and patients with CAH. We note that the timelines remain unchanged for a recommendation expected in Q1 and formal approval in Q2 2021. In anticipation of a positive outcome, Diurnal has undertaken market access activities for Chronocort as well as the manufacture of launch stocks with launch anticipated in Q3 2021. We also note that Diurnal recently received and has responded to Day 180 questions from the EMA. In addition to the approvability of Chronocort, Diurnal is also seeking to confirm the Orphan Drug status.

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Reassuringly, from a commercial perspective, Diurnal has already created one of the few specialised endocrinology salesforces in Europe with the launch of Alkindi, and as a result, we believe the company is well prepared to launch Chronocort into the European CAH opportunity. Chronocort should be well placed to offer an important treatment option since treatment of the CAH patient isn't as straightforward as it sounds. Replacement therapy must provide a fine balance between preventing an (life threatening) adrenal crisis as well as reducing the consequences of high levels of androgens (virilisation in females etc). We have previously detailed that despite the long-term use of glucocorticoids, the main challenge of glucocorticoid replacement therapy is to strike a balance between hyperandrogenism and hypercortisolism.

Indeed, one of the key stated objectives of Chronocort development has been to target the inability of conventional glucocorticoid therapy to adequately control androgen secretion, without the complications of supraphysiologic glucocorticoid treatment. In the Phase 2 and Phase 3 trials, several patients were able to have their glucocorticoid dose reduced.

Should Chronocort successfully navigate the European and UK regulatory decisions, we expect all eyes to turn to the US. We have previously stated that we expect a commercial partner to take the burden of the Phase 3 programme forward, but also recognise that this was a programme that Diurnal had committed to prior to the failed European Phase 3 study. In its favour, not only is this an

Should Chronocort achieve regulatory approval in Europe and UK, we expect the focus to turn to the US

Orphan indication, but 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 steroid preparations. As a result, we believe this is a market which could be effectively accessed with a small, specialised salesforce. Clearly, if Diurnal were to retain ownership in the US, this could be a very lucrative revenue stream in the longer term.

There is the far larger AI opportunity for Chronocort to look forward to

Additionally, there is the larger AI opportunity, and with additional funding in place, we look forward to the comparison trial between Chronocort and the existing modified release preparation Plenadren, which Diurnal will conduct as part of its ambition to optimally position Chronocort. Circadian delivery is also highly relevant, and the competitive noise is absent.

Finally, H1 2021 brought welcome news on the agreement on a lower risk (505(b)(2)) regulatory pathway for DITEST. We believe there is a clear requirement for safer, more convenient alternatives and DITEST shows potential to provide a best-in-class addition. With a streamlined branded generic regulatory pathway, we look forward to DITEST completing its non-clinical preparations prior to submitting an IND later this year. A multiple ascending dose study in classical hypogonadal males with low testosterone is planned, and if successful, regulatory discussions with FDA have confirmed that a single Phase 3 trial will be sufficient for US approval.

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 (and the effects of COVID-19 have clearly been unhelpful) which could affect out 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 potentially looking to partner its products in the US, including DITEST, there is an associated partnering risk.

As a development stage company, Diurnal is currently a loss-making enterprise. Diurnal has successfully raised funds to continue with its development plans and to aid the launch of Alkindi in Europe. Ultimately, given the opportunities available to the company as it seeks to maximise the value of its product portfolio and pipeline, Diurnal may require additional funding.

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