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Leading The Dawn Chorus

An Interview With Bluebird Bio's UK General Manager Nicola Redfern

by Jo Shorthouse

Spearheading discussions with NICE, bluebird bio's UK general manager Nicola Redfern has been central to efforts to introduce fresh reimbursement models within the health technology assessment process and commercial framework. Success could change the way cell and gene therapies are assessed and affect the outlook for many patients living with rare diseases.

Nicola Redfern has been in position as *bluebird bio Inc.*'s UK general manager for less than two years, before that heading up UK market access from 2017. In that time, there has been an increased interest in the curative possibilities and market access challenges of cell and gene therapies, Britain's exit from the European Union, and bluebird bio's first drug approval.

Redfern's new role at bluebird came at a pivotal time for its European operations. With its gene therapy Zynteglo (autologous CD34+ cells encoding βA-T87Q-globin gene) for transfusion-dependent beta-thalassaemia (TDT) approved in the EU in June 2019, the European team is testing the landing ground for pricing talks with payers in the continent's patchwork of reimbursement bodies. TDT is a genetic, inherited blood disease characterized by reduced or absent production of hemoglobin, which leads to decreased red blood cell production. The most severe form of TDT requires regular blood transfusions to enable survival.

In June 2019, the European Commission (EC) granted Zynteglo conditional marketing authorization in Europe, with the German launch in January this

year the first time Zynteglo was commercially available. The collaborative discussions that led to this launch will pave the way for future entry into other markets.

With a price tag of €1.575m, the company is pushing its outcomes-based payment over time model, which asks for five payments of €315,000 ($356,000) over five years contingent on Zynteglo's ability to eliminate TDT patients' needs for blood transfusions. In Germany the University Hospital of Heidelberg has been set up as a treatment center, with other hospitals starting to get set up. Now all eyes will be on country heads in Italy, the UK and France to bring back equally successful negotiations to the bluebird nest.

While the German reimbursement picture looks to be a successful blueprint, Redfern has the unenviable job of leading the discussion about this innovative payment model with England's Department of Health and Social Care (DoH), the health technology assessment institute NICE and NHS England (NHSE).

NICE To Meet You

Redfern said in a February 2020 interview with *In Vivo* that the company is "deep in conversation" with NICE and NHSE, with NICE in the process of reviewing the dossier. Bluebird has a "very good rapport" with NICE, she said. It engaged very early with the HTA and NHSE, was a pilot for the Office for Market Access, and has engaged with NICE scientific advice for future research. Redfern said that the "big discussion point" is, inevitably, around outcomes-based payment over time and how to shape that within the UK environment.

"The outcomes piece brings certain hurdles and challenges because you have to have good registries and data sets to track those patients. I also think our proposal about payment over time is resulting in lots of discussions because it may need Treasury and accountancy rules to change in order to facilitate those separate invoices and payments. It's getting complicated," Redfern told *In Vivo*.

There has been engagement, she says, in some "very open conversations" with NICE and NHS England on bluebird's aspiration to introduce this type of model. Some of these conversations have been taken forward to the DoH and the Treasury, but Redfern admits that "where that will land, we don't yet know."

This topic has been discussed in the industry holistically, with the NHS and NICE pondering how to bring forward new payment models and introduce new innovations for many years. For cell and gene therapy companies, these conversations are imperative. "There are multiple products coming through over the next decade, many of which have highly prevalent populations and from an affordability point of view, although its perhaps not an issue now, it could be an issue in the future," said Redfern. Bluebird is determined to ask how it can recode the system. "How do we make sure it is fit for purpose for the future?" she asks. "Not only from a bluebird bio point of

view, but for the industry as a whole, so as those new innovations come through, we don't hit future hurdles or delays based on affordability."

Gene therapies are able to come to market quite quickly, based on data from relatively small patient numbers in the clinical trials. From a health economics perspective, the bluebird models lifelong benefit but with a limited duration of follow-up after treatment. "That inherently brings uncertainty to the table and the company feels that we have an obligation to underwrite some of that uncertainty and take joint responsibility," Redfern explained. "It's about how we take some of that risk on and how we can share that risk with the NHS. Resulting in the NHS only paying if the patient benefits, and again that is a different model."

She added, "I don't think we anticipated the discussions would be quick, there's a lot of stakeholders it impacts on," she said. The concern for Redfern and bluebird is that a pathway might not be found. Could that result in patients not being able to access new innovations in the UK? "Does it make the UK less attractive to cell and gene therapy companies? Are we going to continue to struggle to launch new innovations here, especially post-Brexit? And what does that mean for a family living with the disease?"

Methodology Review

The planned NICE Methodology Review marks a huge opportunity for cell and gene therapy companies to engage. Former NICE CEO Sir Andrew Dillon, on announcing the review, said that "NICE is undertaking this review at a time of unprecedented change in the health care system, where developments such as personalized medicine, digitalization of health, and use of cell and gene therapy, mean products are becoming ever more challenging to evaluate." There is a shortlist of topics considered in the review and for each, a case for change will be explored, and proposals presented for public consultation in late-2020. The review will cover NICE's single technology appraisals (STA), highly specialized technologies (HST), medical technologies and diagnostics assessment programs.

"There are opportunities within the methodology review to rebalance how NICE look at rare diseases, because I think it is widely recognized that there is a gap currently between the STA and HST programs and orphan diseases often fall between that gap," said Redfern. "The opportunity is there now to reshape it." For example, she said, bluebird bio would like to see the discount rate revisited as part of the methodology review. Generally NICE requires a 3.5% annual discount rate on costs and health outcomes, but Redfern notes clear guidance from the UK Treasury Green Book, stating that "Discounting of resources relating to health and life issues is carried out using the appropriate standard discount rate of 3.5% declining after 30 years. The value of VPFs, SLYs and QALY* effects should be discounted at the health rate of 1.5%, declining after 30 years."

Additionally, the NICE Report, *Exploring The Assessment And Appraisal Of Regenerative Medicines*

And Cell Therapy Products acknowledges that "the discounting rate applied to costs and benefits was found to have a very significant impact on analyses of these types of technologies." In Redfern's view, "this confirms that further consideration should be made to the use of the 1.5% discount rate for such therapies."

There are more questions up for discussion, she says:

- Are there other areas that specifically require or would lend themselves to having a higher threshold, such as the severity of a disease?
- Should something that has lifelong benefit be treated differently?
- Is rarity something that should be treated differently because it is more difficult to research?

There is certainly a need for joined up thinking. Although there is an awareness at NICE that innovative therapy assessments need to be revized, it needs the UK government and the NHS to express an aspiration for improvement for NICE to embrace those changes. To some extent all the key stakeholders are independent, and although NHSE and NICE work very closely together, if NICE puts something into place that makes higher prices viable, NHSE must pick up the bill.

"There has to be aspiration expressed at government level to treat cell and gene therapies differently. We want to deliver them to the UK population quickly and we recognize the long-term benefits these things might have that today aren't fully quantifiable, but by embracing that innovation now, you open up those choices to families and individuals and attract more investment into the UK," said Redfern.

Career Flight Path

Redfern has a long history of working with NICE. She was involved as a marketeer of one of the first drugs that NICE assessed, Eloxatin (oxaliplatin), a Sanofi colorectal cancer drug. Her varied career in pharma started in 1989 in sales and has since seen her work for 10 different companies during that time. In 1997 Redfern moved into the oncology field, and since has focused on cancer and rare disease.

With both her mother and grandmother working as nurses, she was already familiar with the possibility of health care as a career. A psychology degree led to a role in a children's hospice in 1987. Here, Redfern witnessed the the reality of not having any solutions to genetic disease. This, plus her 30-year pharma career, led her to bluebird bio, a firm she admired for its cultural makeup as well as its ground-breaking science.

"I like a really good balance between on-the-edge science, innovation and something that's very

patient-focused. Gene therapy is innovative, changing the way we approach medicine holistically. And potentially is giving life-long benefit," she said. "It is completely changing the way we think about treating a patient."

Aside from the culture of the company, Redfern appreciated that it was engaging early with multiple stakeholders. "Even before I joined, which is nearly three years ago, the company had already started to engage with NICE and NHSE in some of the discussions. The aspiration to collaborate and partner with multiple stakeholders in the payer world is very much at the forefront of the way the organization works," she explained.

Bluebird Revises Business Priorities And Secures Upfront Cash From Bristol

By Jessica Merrill

11 May 2020
The company is deferring investment in a US commercial team and prioritizing R&D activities, but it outlined an accelerated path to approval for LentiGlobin in sickle cell disease.

Read the full article here

Redfern became UK general manager in 2018, and access and reimbursement remain a top priority. "If we can't come to some arrangements and get reimbursement it means patients can't access that treatment and they don't have that choice. On a day-to-day basis reimbursement is still very much at the forefront of everything we're doing," she stressed.

The Brexit Effect

Britain has repeatedly heard since the 2016 UK referendum result, in which the public voted to leave the European Union, uncertainty is the only certainty when planning for a post-Brexit world. Redfern questions how the UK Medicines and Healthcare products Regulatory Agency (MHRA) will treat orphan diseases. Whether it is still going to recognize conditional approval, at what speed it expects submissions in, and can it do things more quickly? ("Which would be potentially great for UK plc," she said.)

"My caution is, we can aspire to get things through the MHRA earlier, but if we don't have the right methodology for NICE, we're still going to hit reimbursement challenges later. Doing bits of the puzzle quickly is not necessarily going to solve patient access," Redfern said. One thing she is certain of is that Brexit is already having a tangible impact on her working life. She recalls a meeting in which bluebird was engaged with the EMA and European HTA

Bluebird Expects Three Filings In 2020, But US Zynteglo Submission Pushed Back

By Mandy Jackson

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bodies for joint scientific advice on a registry. NICE was actively supportive, she says, but post January 31st was told it could not continue to take part. Bluebird is engaging with NICE separately. "It does create re-work," she said. "Rather than have the one meeting with all stakeholders around the table, we're now looking at separate discussions. Although it is too early to necessarily know how things are going to work moving forwards, we're already starting to see things impact."

A BLA filing for Zynteglo in beta-thalassemia is expected in the second half of 2020 instead of the first half, but the first commercial patient in the EU will be treated in the first half of this year.

Read the full article here

Feathering The Nest

Redfern made the decision a long time ago to remain UK-based, she told *In Vivo*. The creation of her UK team, and finding opportunities for those individuals to develop was important, she said. Equally, the R&D that bluebird is currently doing will benefit patients with ultra-orphan diseases "more like the children I'd have worked with at the hospice," she said, remarking on how "it'll be really exciting to see those come through."

With other therapeutics in clinical trials for severe genetic diseases such as cerebral adrenoleukodystrophy and sickle cell disease, activity and excitement levels around the biotech is ramping up. The Cambridge, MA-based firm also has oncology assets, such as idecabtagene vicleucel (ide-cel; bb2121), a chimeric antigen receptor T-cell therapy targeting B-cell maturation antigen (BCMA) in the treatment of relapsed or refractory multiple myeloma, developed in partnership with *Bristol-Myers Squibb Co.*.

At the end of March 2020, the companies submitted their Biologics License Application to the US Food and Drug Administration for patients who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody.

Redfern commented that with these other assets in the pipeline, "it'd be great to stick around and see them come through." If the Zynteglo NICE negotiations are successful, with more products needing the same country knowledge, bluebird could not afford to let this UK bird fall from the corporate nest.

Editor's Note: Following up on our earlier interview with Redfern, it is clear that Covid-19 brings a new level of uncertainty to every aspect of society, including bluebird bio's operations. The team is continuing to support the clinical and patient community where appropriate, but some of the conversations that were underway have now been delayed. Discussions with NHSE and NICE will resume later in 2020 but patient access to this innovation will undoubtably push later into 2021.

** valuation of a statistically prevented fatality (VPF), statistical life-years (SLY) and Quality Adjusted Life Years (QALYs)*