EDISON

# Oxford Biomedica

Outlook

## In a cell and gene therapy sweet spot

Pharma & biotech

**Oxford Biomedica (OXB) is a pioneer and global leader in the development and manufacture of commercial-scale lentiviral vectors (LVV), a critical component of cell and gene therapies (CGT). OXB has numerous value streams, including manufacturing, royalties and milestones on partnered product sales. Its technology and R&D pipeline have been validated by numerous partnerships (Novartis's CAR-T Kymriah, Axovant deal for AXO-Lenti-PD). We believe the greatest opportunity lies in OXB's own gene therapy R&D capabilities; higher investment now is imperative to reap future economic returns in this highly innovative and potentially lucrative therapy area. We value OXB at £649m.**

| Year end | Revenue (£m) | PBT* (£m) | EPS* (p) | DPS (p) | P/E (x) | Yield (%) |
|---|---|---|---|---|---|---|
| 12/17 | 37.6 | (13.1) | (16.7) | 0.0 | N/A | N/A |
| 12/18 | 66.8 | 0.3 | 4.3 | 0.0 | 169.8 | N/A |
| 12/19e | 75.8 | 5.5 | 11.5 | 0.0 | 63.5 | N/A |
| 12/20e | 88.6 | 12.5 | 20.2 | 0.0 | 36.1 | N/A |

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

## The future looks bright, but challenges remain

Gene therapy has the potential to re-write treatment paradigms for genetic disorders; the industry is benefiting from wide-ranging investments and a plethora of CGT approvals and launches. Despite some initial challenges (pricing, reimbursement and manufacturing), this nascent treatment area continues to hold much promise and we expect CGT to remain in the spotlight for the conceivable future. While we downgrade Kymriah forecasts (deepening competitive landscape and Novartis's manufacturing issues), we note that OXB's other LVV manufacturing deals will enable it to remain at break-even in the near term. The Axovant deal for AXO-Lenti-PD highlights the potential of OXB's pipeline; although high risk, this therapy has blockbuster potential for Parkinson's disease (PD).

## Vector supply driving top-line growth

By mid-2020 OXB's LVV production capacity will have doubled as it invests heavily in expanding its state-of-the-art manufacturing capability. We expect further platform deals to be announced, as OXB benefits from its position as the only FDA-approved commercial-scale LVV manufacturer. In the long term, much value resides in OXB's ability to develop and monetise its own gene therapies; we expect OXB to ultimately use its capacity for its own assets; with ~20 years of experience OXB is well positioned to bring its proprietary CGT to the fore, changing its revenue mix to higher-value streams.

## Valuation: £649m or 858p/share

Our valuation of OXB is £649m, versus £632m previously. We have reduced our Kymriah forecasts in diffuse large B-cell lymphoma (DLBCL), offset by increasing the probability of success on AXO-Lenti-PD and some other minor adjustments. We also roll forward our model and update net cash; specifically, we remove OXB's debt position reflecting Novo Holding's recent 10% investment in OXB. Our core driver remains OXB's partnerships, which represent 517p/share of our total value.

**4 June 2019**

| | |
|---|---|
| **Price** | **730p** |
| **Market cap** | **£552m** |
| | US$:£0.79 |
| Net debt (£m) at 31 December 2018 | 8.9 |
| Shares in issue | 75.6m |
| Free float | 78% |
| Code | OXB |
| Primary exchange | LSE |
| Secondary exchange | N/A |

### Share price performance


| % | 1m | 3m | 12m |
|---|---|---|---|
| Abs | 7.6 | 15.4 | 6.3 |
| Rel (local) | 10.8 | 14.8 | 14.6 |
| 52-week high/low | | 1050p | 605.7p |

### Business description

Oxford Biomedica's (OXB's) LentiVector technology underpins the company's strategy. OXB generates significant revenue from partners that use its technology, notably Novartis, Bioverativ, Orchard Therapeutics and Boehringer Ingelheim. OXB is implementing significant capacity upgrades to enable more partnering/out-licensing agreements.

### Next events

| | |
|---|---|
| New out-license or partnership | 2019 |
| H119 results | September 2019 |
| OTL-101 BLA/MAA submission | 2020 |

### Analysts


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# Investment summary

## Company description: Leader in its field

OXB is a UK biopharmaceutical company specialising in the development of gene and cell therapies; specifically, it is the first and only FDA -approved lentiviral vector manufacturer worldwide. As of 31 December 2018, OXB has 432 employees; this is expected to increase to ~600 (end-2019) as the company expands to meet increasing global demand for its technology. OXB has multiple partnerships, notably with Novartis, Axovant, Sanofi/Bioverativ, Boehringer Ingelheim and Orchard Therapeutics. Additionally, OXB owns its proprietary CGT assets in development; the major licensing deal signed with Axovant for PD treatment AXO-Lenti-PD (previously known as OXB-102) demonstrates the increasing interest in this field. In 2018 OXB raised a net £19.3m, which is being used for creating new manufacturing facilities. We expect these new facilities, which will more than double capacity, to be commercially operational by mid-2020. In May 2019 life science investment company Novo Holding invested £53.5m for a 10% shareholding in OXB; this raise will be used to repay debt and invest in its platform and pipeline.

## Valuation: £649m or 858p/share

We value OXB at £649m or 858p/share, vs £632m (957p/share) previously. Our valuation is based on a risk-adjusted NPV comprised 20.9% from Novartis (Kymriah and an undisclosed CAR-T), 22.9% from Axovant (AXO-Lenti-PD), 12.4% from Sanofi/Bioverativ (Haemophilia A&B, SAR422459 and SAR421869), 4.0% Orchard Therapeutics (OTL-101, OTL-201 and ORTX equity stake), 10.8% from OXB's proprietary pipeline and 28.9% from a terminal value plus net cash. In all partnerships except Sanofi's ocular assets, we value royalty, milestone and bioprocessing (manufacturing) revenues; with SAR422459 and SAR421869 we only value potential future royalties and milestones.

## Sensitivities: Operational risks as growth continues

While OXB's partnership model minimises many of the usual biotech and drug development risks, it is still susceptible to clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks and financing and commercial risks. The key short-term sensitivities for OXB relate to crystallising value from the early-stage pipeline, the reliance on existing partners for revenue and manufacturing capacity constraints. Additionally, OXB's current rapid growth in terms of employees and facilities brings operational risks including increased costs and hiring shortfalls or failures. From a drug pricing and reimbursement perspective, CGT are moving into uncharted territory and payors may prove reluctant to pay for these costly therapies. The ability for OXB's partners to achieve appropriate reimbursement for its assets is critical to its long-term success.

## Financials: Reinvestment and top-line growth the focus

FY18 maiden operating profit of £13.9m (vs a loss of £5.7m in FY17) highlights the strength in the company's diversified business model. We continue to expect ongoing growth in the top line, driven in the near term by Kymriah (Novartis), the progression of Sanofi/Bioverativ's haemophilia products to the clinic and the rapid advancement of its partnered products with Orchard and Axovant. OXB is in a growth phase and ongoing investment in advancing manufacturing technology and developing its pipeline are necessities to ensure future growth. We expect OXB to remain at break-even or positive operating income in the near term and as such cash of £32.2m (at 31 December 2018) should be sufficient for ongoing operations.

## CGT breaking new grounds

CGT are treatments of diseases by the genetic modification of a patient's cells either in vivo (gene therapy) or ex vivo (cell therapy). CGT represents a completely new paradigm of treatment with the potential to positively affect clinical outcomes or provide lifelong cures to intractable diseases. However, as with the advent of any transformative therapeutic class, challenges exist, whether that is efficacy vs safety trade-offs, pricing and reimbursement implications, or constraints in manufacturing. In this note we examine these broader industry themes and highlight how OXB is positioned in this blossoming subsector.

The commercial launch of ex vivo CAR-Ts, Kymriah (Novartis) and Yescarta (Gilead/Kite pharma), and in vivo gene products, Strimvelis (Orchard Therapeutics) and Luxturna (Spark Therapeutics), has renewed interest in CGT, which in turn has driven significant investment and M&A activity in recent years. According to the Alliance for Regenerative Medicine, M&A in the area totalled $20bn in 2018 ($13.5bn in 2017 and $1bn in 2016), driven by Celgene acquiring Juno Therapeutics for $9bn and Novartis buying AveXis for $8.7bn. This activity has continued into 2019, with Merck acquiring Immune Design for $300m and proposed acquisitions of Nightstar (by Biogen) and Spark (by Roche) for $800m and $4.3bn, respectively. There have been over 60 biotech IPOs in the US since the start of 2018 raising in excess of $7bn, with IPOs and secondary financings in the CGT subsector totalling over $2bn (Exhibit 1) and highlighting the increased appetitive for CGT companies.

**Exhibit 1: Key 2018 and 2019 Nasdaq IPO and secondary financings for CGT-focused biotechs**

| Company (ticker) | Type | /Year | Amount raised ($m) | Market cap ($m) | Pipeline notes |
|---|---|---|---|---|---|
| Unum (UMRX) | IPO | 2018 | **62.2** | 94.0 | Developing antibody-coupled T-cell receptor (ACTR) and chimeric antigen receptor T-cell (CAR-T) cancer therapies. **3 x Phase I and 4 x pre-clinical assets** |
| AVROBIO (AVRO) | IPO | 2018 | **100** | 341.9 | Focused on lentiviral-based cell therapies for lysosomal storage diseases. **1 x Phase I/II (Fabry disease) and 3 x pre-clinical assets** |
| Orchard (ORTX) | IPO | 2018 | **225.5** | 1,623.8 | Focused on autologous cell therapy for rare inherited, immune, metabolic and blood disorders. **1 x EMA approved (Strimvelis), 3 x Phase II/III (including OTL-101), 2 x Phase I/II and preclinical assets** |
| Rubius Therapeutics (RUBY) | IPO | 2018 | **277.3** | 1,155.8 | Allogeneic cellular medicines to treat rare enzyme deficiencies, cancer and autoimmune conditions. **Multiple preclinical plus two assets poised for Phase I** |
| Allogene (ALLO) | IPO | 2018 | **372.6** | 3,188.0 | Developing allogenic chimeric antigen receptor T-cell (CAR-T) cancer therapies. **3 x Phase I/II and 4 x preclinical assets** |
| bluebird bio (BLUE) | Secondary | 2018 | **651.3** | 6,610.0 | Developing various CGT. **3 x Phase II/III (including bb2121 and LentiGlobin), 2 x Phase I/II and >15 pre-clinical assets** |
| | | 2018 | **632.5** | | |
| AveXis (AVXS*) | Secondary | 2018 | **439.1** | N/A* | Was developing various AAV-based gene therapies, acquired by Novartis primarily for Zolgensma, which is pending regulatory approval SMA type 1 in May 2019. **1 x NDA (plus additional clinical studies in SMA), 4 x pre-clinical assets** |
| Audentes (BOLD) | Secondary | 2018 | **231.4** | 1,555.5 | Developing AAV based gene therapies for rare neuromuscular disease. **2 x Phase I/II and 3 pre-clinical assets** |
| Sangamo (SGMO) | Secondary | 2018 | **230.0** | 1,009.4 | Developing various AAV an mRNA-based CGT. **7 x Phase I/II (4 partnered) and > 5 pre-clinical (3 proprietary) assets** |
| REGENXBIO (RGNX) | Secondary | 2018 | **201.8** | 1,576.3 | Developing various AAV based gene therapies in retinal, neurodegenerative and metabolic diseases. **4 x Phase I/II and 2 pre-clinical assets** |
| TCR2 Therapeutics (TCRR) | IPO | 2019 | **86.3** | 359.1 | Developing next generation T-cell therapies for cancer. **1 x Phase I/II and 4 pre-clinical assets** |
| Precision Biosciences (DTIL) | IPO | 2019 | **145.4** | 676.4 | Utilises its genome editing platform ARCUS for various cell and gene therapies. **Multiple preclinical assets plus one CD19 allogenic CAR-T which started Phase I/II in Q219** |

Source: Company websites, EvaluatePharma. Note: *AveXis was acquired by Novartis in May 2018 for $8.7bn. AAV: adeno-associated virus.

Many of the companies highlighted in Exhibit 1 have a single asset in clinical development plus pre-clinical candidates; with OXB's multiple pre-clinical and clinical assets, existing partnerships and vector manufacturing IP, we believe it would benefit from a US exchange listing. Cash raised from an offering could be used to progress its multiple preclinical assets; we believe the greatest

economic value resides in OXB's ability to develop, and potentially commercialise, its own gene therapies. The out-licensing deal signed with Axovant in 2018 for AXO-Lenti-PD (formerly OXB-102) has served as a major validation of OXB's capability to add significant value to its internal assets through investing in their clinical development. OXB's proprietary product pipeline consists of five preclinical/Phase I assets that OXB is looking to spin out or out-license.

As the global leader in the development and manufacture of LVV, OXB has benefited from the rapidly advancing CGT field, establishing multiple sources of revenue through its platform deals, where it provides its partners with LVV development and/or supply. These partners include Novartis (Kymriah and a second CAR-T asset), Orchard Therapeutics (ADA-SCID and Sanfilippo A), Sanofi/Bioverativ (haemophilia A and B) and Boehringer Ingelheim/UK Cystic Fibrosis Gene Therapy Consortium/Imperial Innovations (cystic fibrosis). The latter two deals have only been made possible by OXB's continued investment in its manufacturing capabilities (single-use bioreactors) and innovation in its platform technology (automated stable cell-line production and TRiP technology).

While many competitor (and partnered) companies have adequate R&D facilities, OXB is one of a few globally that can manufacture LVV on the scale needed for late-clinical and commercial scale. The £26m capacity expansion (completed in 2016) and the ongoing £21m expansion (construction to be completed by end-2019, production of commercial batches by mid-2020) will maintain OXB's market-leading position as the go-to LVV contract development and manufacturing organisation. This expansion enables it to deliver on its current commitments, while also providing the ability to attract and establish new partners and will enable top-line growth in the near term.

Near-term catalysts ahead include the biologic licence application (BLA) filing by Orchard Therapeutics for OTL-101 (ADA-SCID), the continued ramp up of Kymriah sales (and disclosure of the undisclosed second CAR-T) by Novartis, maturing data from AXO-Lenti-PD and entry of a Bioverativ haemophilia product into the clinic (forecast in 2020) will continue to give confidence to OXB's strategy. Additionally, further contracts with new and existing partners provide upside to our investment case.

A critical and widely debated factor for the CGT companies is the pricing of these innovative therapies and reimbursement outcomes. We note that pricing of gene therapies remains a key sensitivity and, as the market evolves and these dynamics change, our forecasts will likely change too. We assume pricing of $700,000 for rare diseases and $350,000 for more common indications; we believe these to be fairly conservative pricing assumptions.

## Sparking the pricing and reimbursement debate

It is widely recognised by payors and prescribers that gene therapies could provide huge clinical benefit and in some conditions be curative, but the high potential cost of such therapies remains of concern. In late 2017 the FDA approved Spark Therapeutics' Luxturna (inherited retinal disease as identified by RPE65 genetic test), the first US gene therapy to receive approval. Luxturna is a corrective gene therapy and is priced at $850,000 ($425,000 for a single dose to each eye); this initiated the debate on how much these innovative therapies are worth. Subsequent approval of Kymriah and recent Zolgensma pricing at $2.1m has focused patients, prescribers and payers on price, reimbursement and the value of the outcomes generated by these potential 'once-and-done' therapies.

While the proposed cost per patient is so high for some gene therapies, the duration of the outcomes is uncertain and healthcare budgets are typically annual, rather than being apportioned over the lifetime of a patient. On pricing of Zolgensma for spinal muscular atrophy, Novartis has highlighted the overall cost savings for payors versus current standard of care in that it represents

50% of the 10-year total cost of Spinraza. Both Bluebird Bio and Novartis have discussed outcomes-based price models.

Novartis recently secured a contract in Germany for an outcomes-based payment structure with GWQ ServicePlus, which represents approximately 13 million medical insurance policyholders. The contract is arranged so that Novartis will repay part of the drug cost to GWQ if certain undisclosed survival outcomes are not reached. We note this is only a temporary pilot programme until the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband), which represents 90% of the population of Germany, concludes its negotiations with Novartis.

In the UK, after extensive discussions, NICE approved Kymriah in paediatric acute lymphoblastic lymphoma (pALL) in September 2018 and more recently (February 2019) in DLBCL. Originally NICE did not deem Kymriah cost effective in DLBCL; however, further negotiations have led to a lower price.

In the US, the fragmented healthcare system has generated varied and distinct reimbursement challenges for Kymriah. Reimbursement discussions with the Centres for Medicare and Medicaid Services (CMS) are ongoing and the CMS has recently revealed new guidelines for the coverage of CAR-T therapies. CMS has to date only committed to partial coverage of the total cost (including hospitalisation costs) of treatment with CAR-T therapies, with significant cost being put on the hospitals and the patients. Additionally, in the case of Medicaid, all states have their own authority, with negotiations needed for each.

The paradigm for innovative gene and cellular therapies is different to that of the traditional drug pricing models, in that a small patient population is treated once with an innovative therapy and the price of a single treatment will have to recoup many years of investment by the drug sponsor and reflect the total subsequent healthcare cost to the payer, had that patient not been treated with an innovative therapy. The duration of the response to the therapy or the length of the cure to the patient would lead to incremental payments, perhaps annually, based on its continued success. In central-payer markets such as the UK, where patients can be closely followed, this is not likely to be difficult, but in much larger fragmented markets such as the US, where patients can move jobs (and therefore health insurers) across the country, monitoring the duration of their responses and therefore the reimbursement to the drug manufacturer could be problematic. Bluebird Bio has proposed an instalment payment plan for its Lentiglobin gene therapy; insurers can pay the cost of therapy over up to five years and Bluebird will charge an initial upfront payment but only be entitled to receive the rest of the cost if the patient continued to see benefit.

## Novartis: Kymriah sales slower than expected

Kymriah, a CD19 targeting CAR-T, is now approved in the US, EU, Australia, Canada and Japan for adult patients with DLBCL and pALL. Previously, revenue from the Novartis collaboration has come predominately from bioprocessing (development and manufacturing of LentiVector batches) and development milestones. With Kymriah now commercialised, we expect this mix to alter as the royalty stream builds. Although OXB does not report the proportion of income generated in royalties from Kymriah sales in 2018, total sales figures release by Novartis (FY18: $76m) combined with an assumed low-digit royalty rate (1–2%) suggest 2018 royalty income was likely below £1.5m. Sales of Kymriah to date have been slower than we originally forecast although they are experiencing sustained double-digit quarter-on-quarter growth (Q119: $45m vs Q418: $28m). We have adjusted our sales ramp up for Kymriah in 2019/2020 to reflect the slower than expected uptake of the drug as result of difficulties with reimbursement and manufacturing, among other factors. In the long term we have revised our assumptions down, reflecting the changing treatment landscape for DLBCL.

## The challenges of cell therapy commercialisation

Manufacturing Kymriah is an incredibly complex process and Novartis has faced challenges in providing it at a commercial grade. Due to stricter specifications for commercial-grade Kymriah than clinical trial supply, some manufactured Kymriah products have not met the required criteria, predominately related to the percentage of viable cells created. Although these cells have not met commercial criteria, they are often still clinically viable and Novartis has allowed access to these therapies for free through an expanded access or compassionate- use programme. This has a minimal impact on royalties OXB receives for Kymriah and does not impact the much larger revenue stream from bioprocessing that OXB collects for the sale of vector batches to Novartis. The EU has accepted a widening of specifications; however, the FDA has not yet followed.

The process of reimbursement for cellular therapies, such as Kymriah, remains in its infancy with lengthy contract negotiations the norm, exaggerated by variances in individual markets and relatively immature data packages. We expect reimbursement challenges to continue in 2019 and 2020; however, as evidenced by recent approvals from authorities like NICE in the UK, we believe these challenges will be overcome in the long term.

In addition to reimbursement and manufacturing challenges, there are a limited number of centres globally that have the expertise or capability to manufacturer CAR-T therapies on the required scale. Novartis has made strong commitments to its CAR-T oncology franchise, implementing significant expansion of its cell processing facilities, aiming for a fourfold increase in overall capacity during 2019. This is highlighted by the acquisition of CellforCure (Les Ulis, France) in Q119, which has added to its global network of cell processing facilities, which include Morris Plains (New Jersey, US), Fraunhofer IZI (Leipzig, Germany) and the Foundation for Biomedical Research and Innovation (FBRI) (Kobe, Japan). Completion of this acquisition follows announcements in Q318 from Novartis that is investing CHF90m in a new production facility at its Stein site in Switzerland (completion 2020) and a strategic collaboration with Cellular Biomedicine Group to manufacture and supply Kymriah in China.

## Moving parts in the r/r DLBCL treatment landscape

The treatment landscape in relapsed-refractory (r/r) DLBCL continues to shift and the last year has seen the emergence of off-the-shelf treatment regimens that are demonstrating impressive clinical response rates in r/r DLBCL patients, on par to that of Kymriah and Yescarta. These antibody-based therapies could significantly affect Kymriah (and Yescarta) sales if long-term data demonstrate their effectiveness without the complexities associated with CAR-T treatments. In Exhibit 2 we have highlighted the most recent, comparative DLBCL efficacy data for CD19 targeting CAR-Ts (Kymriah and Yescarta) alongside Roche's CD79b antibody-drug conjugate (polatuzumab vedotin) and MorphoSys's CD19 antibody (tafasitamab), which are expected to be on the market in 2020. We note that comparisons of trial data should be made with caution as variability in patient demographics, disease states and previous lines of treatment could distort any observations.

**Exhibit 2: Recent trial data for r/r DLBCL treatment regimes (ASCT ineligible)**

| Company | Treatment combination (target) | Trial | ORR (no. pts) | CR (no. pts) | mDoR (95% CI) | mPFS (95% CI) | mOS (95% CI) | Notes |
|---|---|---|---|---|---|---|---|---|
| Novartis | Kymriah (CD19 CAR-T) | Phase II JULIET | 52% (48/93) | 40% (40/93) | NR (10.0, NR) | - | 11.7 mo (6.6, NR)* | Long-term safety and efficacy data published in New England Journal of Medicine January 2019 |
| Gilead | Yescarta (CD19 CAR-T) | Phase I/II ZUMA-1 | 83% (84/101) | 58% (59/101) | 11.1 mo (4.2, NR) | 5.9 mo (3.3, 15.0)* | NR (12.8, NR)* | Long-term (median follow-up 27.1 mo) efficacy and safety data published in The Lancet December 2018 |
| MorphoSys | MOR208: Tafasitamab (CD19) + lenalidomide | Phase II L-MIND | 60% (48/80) | 43% (34/80) | 21.7 mo | 12.1 mo | - | Results from the primary analysis announced May 2019, Data to be presented at ICML in June 2019, BLA planned to be filed with the US FDA before end-2019 |
| Roche | RG7596: Polatuzumab vedotin (CD79b ADC) + Rituxan + bendamustine | Phase I/II GO29365 | 45% (18/40) | 40% (16/40) | 10.3 mo (5.6, NR) | 7.6 mo (6.0, 17.0) | 12.4 mo (9.0, NR) | Data presented at ASH 2018, BLA filed with the US FDA in December 2018 with priority review, decision expected 19 August 2019 |

Source: Edison Investment Research. Clinicaltrials.gov Notes: ASCT: autologous stem cell transplant; ORR: objective response rate; CR: complete response; mDoR: median duration of response; mPFS: median progression-free survival; mOS: median overall survival, ADC: antibody-drug conjugate; NR: not reached;*based on patients who received transfusion with Kymriah or Yescarta.

## Novartis valuation assumptions

For the Novartis partnership we have modelled the opportunities for Kymriah in pALL and DLBCL in addition to now valuing the second undisclosed CAR-T. For the purpose of our valuation we have assumed the second undisclosed CAR-T is Novartis's most advanced second clinical candidate, MTV273, a BCMA targeting CAR-T for use in patients with multiple myeloma. We forecast that OXB will sell vector batches to Novartis for $1.5m per batch, with peak gross margins of 30%. We highlight that further collaboration on CAR-T assets between OXB and Novartis is possible as Novartis continues to invest heavily in its CGT capabilities.

Sales of Kymriah to date have been slower than we originally forecast, although they are experiencing sustained double-digit quarter-on-quarter growth (Q119: $45m vs Q418: $28m). We have adjusted our sales ramp for Kymriah in 2019 and 2020 to reflect the slower than expected uptake of the drug as result of difficulties with reimbursement and Novartis's cell manufacturing, among other factors. In the long term we have shifted our DLBCL assumptions downwards reflecting the changing treatment landscape, notably successful recent data from off-the-shelf product candidates like MOR208 (MorphoSys) and RG7596 (Roche). We now assume a 15% peak penetration of Kymriah in DLBCL vs 30% previously. Our other assumptions remain unchanged.

**Exhibit 3: Novartis valuation assumptions**

| CAR-T (indication) | Assumptions |
|---|---|
| Kymriah (pALL) | US and EU5 population, 25% of population below 20 years of age, 0.004% incidence of ALL, 15% fail first- and second-line therapies. At peak we expect a maximum patient population of approximately 1,000 patients in both the EU and US. Kymriah is first to market and for the foreseeable future the only CAR-T available in this indication. As such we anticipate a 50% peak market penetration. We assume a price of $475,000 in the US, based on information from Novartis. In the EU, we assume a 20% discount. We assume a peak royalty of 2%. Kymriah is approved in the US and EU. |
| Kymriah (DLBCL) | US and EU5 population, 0.02% incidence of non-Hodgkin's lymphoma, 48% have DLBCL, 35% fail first- and second-line therapies. At peak we expect a maximum patient population of approximately 20,000 patients. Kymriah is second to market and faces significant completion from Yescarta. As such we expect a 15% peak market penetration. This peak number will depend on the evolving dataset of the comparable long-term efficacy of both approved CAR-Ts. We also note Celgene's CD19 CAR-T JCAR017, which is expected to be approved and launched in mid-2020. We assume a price of $475,000 in the US, based on information from Novartis. In the EU, we assume a 20% discount. We assume a peak royalty of 2%. Kymriah is approved in the US and EU. |
| Second undisclosed CAR-T (assume this is MTV273 for MM) | US and EU5 population. 0.009% incidence of MM, 50% fail first- and second-line therapies. At peak we expect a maximum patient population of approximately 30,000 patients in both the EU and US. MTV273 faces significant completion in MM as multiple CAR-T and TCR products are in development, notably Bluebird's bb2121, which could be launched in 2019. We forecast a 25% peak market penetration. We assume a price of $475,000 in the US, based on information from Novartis. In the EU, we assume a 20% discount. We assume a peak royalty of 2%. We forecast that only a Phase II trial will be needed for approval and that there would be an accelerated approval process for MTV273. We forecast a launch in both EU and US in 2022. |

Source: Edison Investment Research. Notes: pALL: paediatric acute lymphoblastic leukaemia, DLBCL: diffuse large B-cell lymphoma, MM: multiple myeloma.

# Axovant: Aiming for a breakthrough in PD

In June 2018 OXB signed an out-licensing deal with Axovant for its PD gene therapy AXO-Lenti-PD (previously OXB-102) for impressive deal terms. The deal is worth up to $842.5m in development and sales milestones ($30m upfront payment, $55m in development milestones and over $757.5m in regulatory and sales milestones) plus 7–10% tiered royalties on sales. AXO-Lenti-PD is a re-engineered version of OXB's gene therapy ProSavin, which has previously completed a Phase I/II open-label study in 15 patients and demonstrated statistically significant improvements in motor behaviour. Given the unmet need for a truly disease-modifying treatment in PD and advanced stage of development, we believe Axovant could launch AXO-Lenti-PD in the US and EU in 2022. We forecast peak sales of $1.96bn across the US and EU.

We believe Axovant will aim to launch the therapy based on the Phase II data from the ongoing SUNRISE-PD study plus historical ProSavin data, with an accelerated approval. However, we note that competitor Voyager Therapeutics, which is developing VY-AADC, an adeno-associated virus (AAV)-based gene therapy for PD, has been informed by the US FDA that its Phase II trial for VY-AADC is unlikely to be sufficient for a marketing application and it will require additional trials. In the Phase II study, dosing is being carried out between the medium and high doses studied in the Phase I trial ($2.5x10^{12}$ vector genomes). This is a result of the Phase I study establishing a relatively narrow therapeutic window with only the medium dose demonstrating a clinically meaningful improvement in Parkinson's symptoms.

While this implies the FDA could make this a pre-requisite for AXO-Lenti-PD, we note feedback from a pre-IND meeting with the US FDA in December 2018 indicated the totality of data from the ProSavin trials might be supportive of the planned BLA regulatory path. However, we highlight that insufficient data or failure to achieve an accelerated approval could cause our forecast 2022 launch timeframe to slip significantly.

## AXO-Lenti-PD: Leveraging know-how from ProSavin

PD is a progressive neurodegenerative disease characterised by a loss of dopaminergic neurons. Oral dopamine-based therapies, such as levodopa, are the current standard of care for patients who initially present with the disease. Although these are efficacious, in the long term their use is complicated by motor fluctuations caused by the intermittent stimulation of dopamine receptors with oral-dose regimes, which become progressively harder to control as the disease progresses. ProSavin is a gene-therapy delivered directly into the putamen of the brain, encoding for three proteins capable of producing a localised, continuous supply of dopamine; the aim is to improve basal dopamine levels, enabling a reduction in levodopa equivalent daily dosage, reducing the severity of the motor fluctuations patients experience through their normal intermittent oral dosing. AXO-Lenti-PD is an improved iteration of viral vector design and has been engineered to increase dopamine production 10-fold compared to ProSavin, potentially providing a more efficacious gene therapy.

Since signing the deal, Axovant has accelerated AXO-Lenti-PD into the clinic, with a Phase I/II dose-escalation study (SUNRISE-PD) in advanced PD patients initiating in October 2018. Early data from the first two patients in the lowest dose cohort of this study highlight the magnitude of the improvements in Unified Parkinson's Disease Rating Scale (UPDRS) scores for both motor function (Part III) and daily living (Part II) observed at the lowest dose of AXO-Lenti-PD study compared to that observed for the highest dose used in the ProSavin study.

**Exhibit 4: UPDRS-III score improvement after three months for motor function**

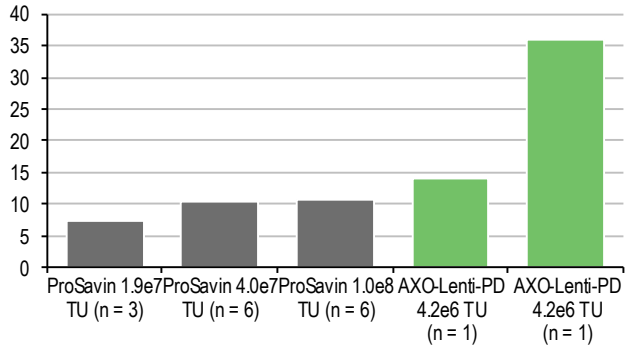
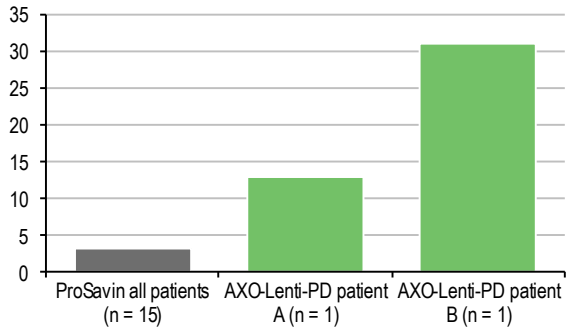



**Exhibit 5: UPDRS-II score improvement after three months for daily living**




Source: Adapted from Axovant R&D day presentation

## Axovant valuation assumptions

For the Axovant deal, we have modelled the opportunity for AXO-Lenti-PD in the US and EU, retaining our previous assumptions for PD in relation to incidence, peak penetration and price. We assume Axovant will aim to move AXO-Lenti-PD through the clinic rapidly and launch in 2022 and forecast that peak sales of $1.96bn can be achieved across the US and EU (c 6,000 patients on treatment). Axovant has announced that OXB will receive tiered royalties based on net annual sales, with 7% on net sales up to $1bn, 8% between $1bn and $2.5bn, 9% between $2.5bn and $4bn, and 10% over $4bn. As such, we assume that a peak royalty rate of 8% is achieved. We assume that OXB receives most development milestones ($50m of the total $55m announced) and a significant proportion of the commercial milestones over its lifetime ($500m of total $757.5m announced). We have increased our probability of success to 30% from 20%, reflecting Axovant advancing AXO-Lenti-PD into the ongoing Phase II SUNRISE study.

# Orchard Therapeutics: Focused on orphan indications

Orchard Therapeutics is a UK/US-based private biotechnology company focusing on the treatment of rare diseases with gene therapies. It has two products in development under its manufacturing agreement with OXB. OTL-101 for adenosine deaminase severe combined immunodeficiency (ADA-SCID) and OTL-201 for Sanfilippo A syndrome are in Phase II and preclinical trials, respectively. In March 2018, Orchard Therapeutics announced that it had reached an agreement with GlaxoSmithKline (GSK) to transfer the entirety of GSK's gene therapy programme to it, including Strimvelis (the first approved gene therapy for ADA-SCID, approved May 2016 and launched by GSK at a price of €594,000).

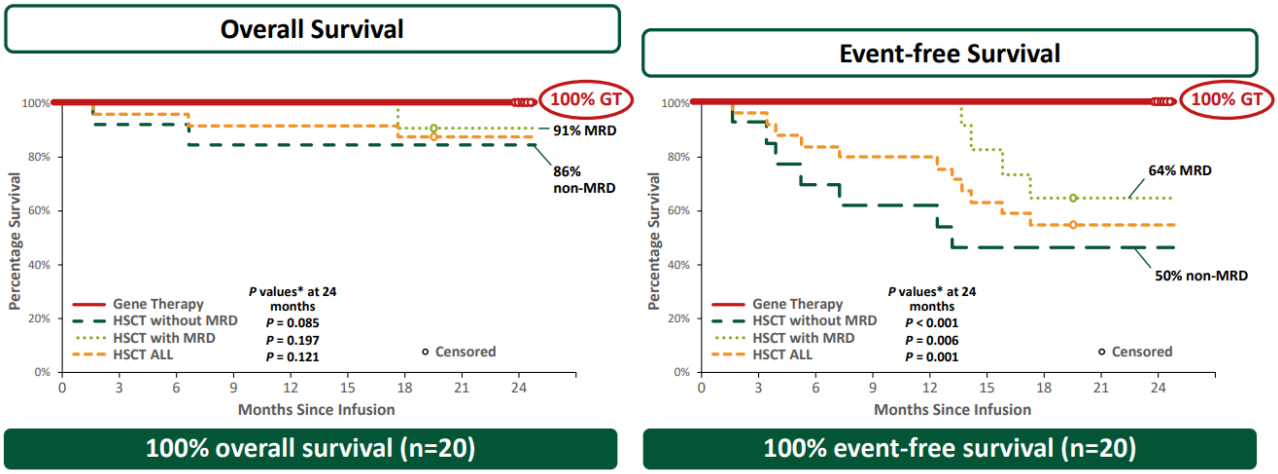
## OTL-101: Leapfrogging Strimvelis in 2020

SCID due to ADA deficiency is a form of SCID where ADA is deficient due to mutations in the ADA gene (autosomal recessive inheritance). The deficiency in ADA enzyme leads to a build-up of adenosine and its metabolites. These cause metabolic abnormalities that are directly toxic to lymphocytes causing T-, B- and NK-cell dysfunction and severe and recurrent opportunistic infections can result in early death in infancy. Most patients with ADA deficiency are diagnosed with SCID in infancy, and without treatment these infants do not usually survive past age two. ADA-SCID accounts for 10–15% of all cases of SCID. Its annual incidence is estimated to be between one in 200,000 and one in a million live births in the US.

Approved treatments for ADA-SCID include gene therapy Strimvelis and Leadiant Biosciences' Adagen (pegademase bovine), a modified enzyme used as enzyme replacement therapy by once a week injection (intramuscular). As an enzyme-replacement therapy Adagen is highly efficacious but not curative. We highlight that Strimvelis's approval is based on data collected from 18 patients. Strimvelis is an autologous product (cells taken from the patient and administered back into them after modification with a vector) and patients can only be treated at one site in Italy. It is priced at €594,000. Uptake to date has been slow, with only a handful of patients treated (fewer than five). We believe that once approved OTL-101 will likely replace Strimvelis given the latter's cost, administration and manufacturing limitations.

To date, 62 ADA-SCID patients have received OTL-101 with 100% overall survival data in a follow-up period of up to 6.5 years (Exhibit 6). Orchard plans to submit a BLA for OTL-101 in 2020; we expect launch late in 2020 with approval granted through breakthrough designation.

**Exhibit 6: OTL-101 ADA-SCID trial data**




Source: Orchard Therapeutics corporate presentation

## OTL-201: Sanfilippo A syndrome

Orchard Therapeutics is developing a lentivirus-based vector (OTL-201) for Sanfilippo A syndrome that is in preclinical development. Sanfilippo A syndrome (also known as mucopolysaccharidosis III or MPS IIIA, a rare autosomal recessive lysosomal storage disease) is a metabolic disorder that arises from deficiency in the gene encoding for the enzyme N-sulphoglucosamine sulphohydrolase. The disease is incurable and treatment focuses on palliative care of symptoms. Average life expectancy is 15–20 years. It is estimated to occur in approximately one in 70,000 births. Gene therapies in development include Abeona Therapeutics' ABO-102, which is in Phase I/II trials, and Lysogene's LYS-SAF302, which has completed a Phase I/II study in four children and demonstrated moderate efficacy in addition to good tolerance. Lysogene is preparing a Phase II/III pivotal study for LYS-SAF302. Both these therapies are based on AAVs.

## Orchard Therapeutics valuation assumptions

For the Orchard partnership, we have modelled the opportunities for both OTL-101 and OTL-202. We forecast that OXB sells vector batches to Orchard for $1.5m a batch, with peak gross margins of 30%. With OTL-101, we assume an incidence of SCID of 0.0001%, of which 15% have ADA. We forecast a total market at peak of approximately 100 patients across the EU5 and US and assume a 50% peak penetration in both markets. We assume similar pricing to Strimvelis and have priced it at $700,000 in the US with a 20% discount in the EU5. We assume a peak royalty rate of 2%. We have pushed back US launch by one year to 2020; we expect fast-track approval through the FDA orphan drug designation for rare diseases.

With OTL-201, we assume an incidence of Sanfilippo syndrome of 0.0014%, of which 50% are type A. We forecast a total market at peak of approximately 5,000 patients across the EU5 and US and a 50% peak penetration in both markets. We assume similar pricing to Strimvelis and have priced it at $700,000 in the US with a 20% discount in the EU5. We assume a peak royalty rate of 2%.

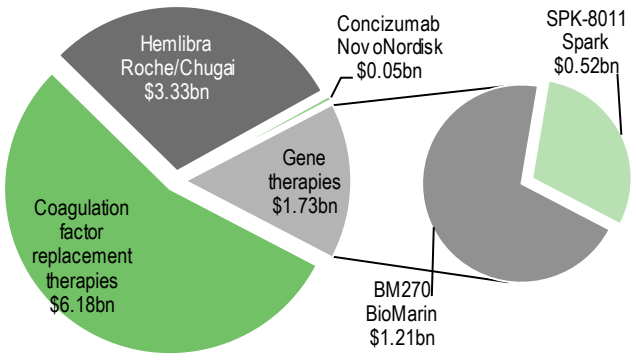
## Sanofi/Bioverativ: Focusing on haemophilia

In March 2018, OXB signed a partnership deal with Bioverativ (acquired by Sanofi for $11.6bn in early 2018) to develop in vivo gene therapies for haemophilia A (Factor VIII deficiency) and haemophilia B (Factor IX deficiency). OXB received $5m on the closure of the deal and is entitled to up to $100m in revenue from product development, regulatory and sales milestones, in addition to undisclosed royalties. The collaboration gives Sanofi/Bioverativ a licence to OXB's LentiVector technology and manufacturing capabilities. However, like the original CAR-T deal made with Novartis in 2014, the current haemophilia deal does not cover a clinical supply agreement, and we assume that the majority of £100m in potential future revenue is weighted towards product development. We forecast that most of this revenue could be realised over the next five years. We believe both gene therapies could launch in 2025, with accelerated approval after completing Phase II trials. A clinical manufacturing supply deal would provide upside to our forecasts.

### Haemophilia market outlook

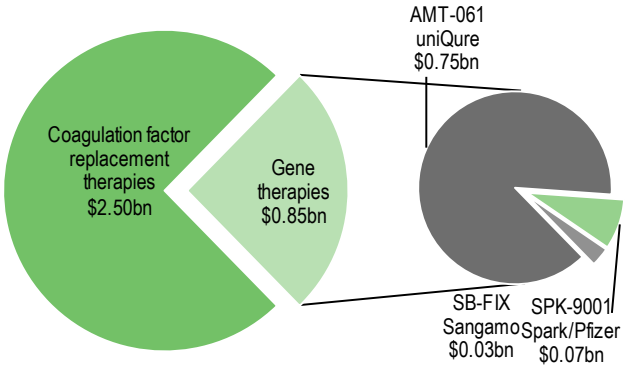
Haemophilia is an X-linked recessive disorder, predominately affecting males, and is characterised by an inability to produce coagulation factors resulting in uncontrolled bleeding episodes. Haemophilia A is approximately four times as common as B and is estimated to occur in approximately one in every 5,000 male births. Worldwide incidence is estimated to be approximately 400,000 cases. The gene therapies that OXB and Sanofi/Bioverativ are developing would encode for either Factor VIII (if addressing haemophilia A) or Factor IX (if addressing haemophilia B). The global market for haemophilia A and B treatments present multi-billion-dollar opportunities, with sales from key drugs totalling $11.3bn in 2018 and consensus forecasting this to reach $14.6bn in 2024 (source: EvaluatePharma).

**Exhibit 7: Global haemophilia A market forecast (2024)**




Source: EvaluatePharma

**Exhibit 8: Global haemophilia B market forecast (2024)**




Source: EvaluatePharma

- **Coagulation factor replacement therapy:** the current mainstay treatment for both haemophilia A and B is factor replacement therapy, with either plasma derived or recombinant Factor VIII or Factor IX, used lifelong either on-demand or prophylactically. The most serious complication for patients is resistance due to the formation of alloantibodies that inhibit the haemostatic effect of replacement coagulation factors; patients who become resistant require bypassing coagulation agents such as activated Factor VII (FVIIa) or an activated prothrombin

complex concentrate. Combined sales of factor replacement therapies represented c 98% ($11.1bn) of the haemophilia market in 2018.

- **Non-factor based therapy:** Roche's Hemlibra (emicizumab) is the first new agent approved in nearly 20 years for patients with haemophilia A, and the only approved non-factor based therapy. Sales growth has been strong since it launched in November 2017, achieving $230m in sales in its first full year on the market (2018). Hemlibra is used prophylactically and is a bispecific antibody that mimics the action of Factor VIII by simultaneously binding of FIXa to FX to enable formation of a blood clot. Hemlibra is administered with an initial subcutaneous loading dose followed by weekly/fortnightly/monthly maintenance dosing.
- **Gene therapy:** with the average annual cost of prophylactic treatment estimated to be $200–300k per patient in the US and a compliance rate of approximately 60% among young adults and adults, the prospects for a 'once-and-done' haemophilia gene therapy are strong. At present, no gene therapies have been approved for haemophilia; however, there are several assets (Exhibit 9) in clinical development (all AAV based), with BioMarin, Uniqure and Spark Therapeutics the most advanced with assets in pivotal Phase III trials. The early signs of efficacy that have been demonstrated highlight the potential for gene therapy to revolutionise the standard of care for haemophilia patients.

**Exhibit 9: Gene therapies under clinical investigation for haemophilia A and B**

| Indication | Company | Vector | Name | Phase/trial | Notes |
|---|---|---|---|---|---|
| Haemophilia A (Factor VIII deficiency) | BioMarin | AAV | BM270 | Phase III GENEr8-1 | Three-year follow-up data from the Phase Ib/II were recently announced (May 2019) and highlighted patients (n = 6) in the highest dose cohort (6e13 vg/kg) had a 96% reduction in mean annualised bleed rates (ABR) and a 96% reduction in mean FVIII usage over the three years. Mean FVIII expression (measured by activity levels) which is driving this efficacy, has tailed off over three years (-43% at year two and -10% at year three) and longer-term data will likely be require to confirm its proposed treatment persistence, which BioMarin believe will extend to eight years (based on a forecasted regression analysis). Complete enrolment of the ongoing 6e13 vg/kg dose cohort in the Phase III study can be expected in Q120, but will meet the FDA and EMA to discuss the timing of a marketing application. |
| | Spark Therapeutics | AAV | SPK-8011 | Phase III NCT03876301 | Data from the first 12 pts of the ongoing Phase I/II trial was presented at ASH2018 (November 2018) and highlighted a 97% reduction in ABR, irrespective of the dose-cohort. Spark has now started recruiting patients into a six-month lead-in for a Phase III study to collect baseline data (January 2019). |
| | Sangamo/ Pfizer | AAV | SB-525/ PF-07055480 | Phase I/II NCT03061201 | Interim data was announced in April 2019 from the dose escalation part of the study, which has established the highest dose (3e13 vg/kg) was well tolerated and has been recommended for the expansion cohort. |
| | Takeda (Shire) | AAV | TAK-754 (SHP654) | Phase I/II NCT03370172 | Trial started recruiting in March 2018. Shire had originally acquired this this asset (formerly BAX888) through its merger with Baxalta in 2016. |
| Haemophilia B (Factor IX deficiency) | Uniqure | AAV | AMT-061 | Phase III HOPE-B | Data from the Phase IIb study showed the therapy was generally well tolerated with a clinically meaningful improvement. First patient dosed in the pivotal study February 2019; enrolment of c 50 patients with severe haemophilia B expected to complete before end-2019; primary completion can expected March 2020. |
| | Spark Therapeutics/ Pfizer | AAV | SPK-9001/ PF-06838435 | Phase III BENEGENE-2 | Pfizer and Spark Therapeutics entered into a licence agreement in December 2014. Pfizer started recruiting patients into a 6-month lead-in study to collect baseline data (July 2018) prior to moving c 55 patients into the interventional the study, which will follow patients for 6 years following treatment; primary completion is expected January 2022. |
| | Sangamo | AAV/ ZFN | SB-FIX | Phase I/II NCT02695160 | Utilizes Sangamo's zinc finger nuclease (ZFN) genome editing to fully integrate a copy of the Factor IX gene into to liver cells, potentially providing a life-long cure for paediatric patients. First adult patient dosed in December 2018, safety and efficacy data can be expected in 2019. |

Source: ClinicalTrials.gov; Edison Investment Research. Note: AAV: adeno-associated virus.

## LentiVector could provide a lifelong response

While impressive, the data for these AAV-based gene therapies are early and questions over the long-term efficacy still need to be answered. AAV-derived vectors do not readily integrate their genomic material into the transduced cell, which could be of particular importance for pricing and reimbursement negotiations, as well as treating paediatric patients whose livers are not fully grown. Product candidates being developed by Sanofi (Bioverativ) and OXB using LVV could gain

significant market share if they are able to improve on the AAV products in development. LVV can integrate the desired transgene into the host genome, potentially providing a superior duration of protein expression compared to AAV vectors.

Recently published Phase Ib/II data by BioMarin for its haemophilia A gene therapy BMN 270 (highlighted in Exhibit 9) show mean annualised bleed rates have reduced significantly and had a durable effect over three years. However, the factor VIII expression levels that are driving this efficacy have tailed off. Longer-term data will likely be required to confirm BioMarin's proposed persistence of eight years, particularly for reimbursement negotiations. This highlights the concerns of the long-term durability of an AAV-based gene-therapy, particularly in targeting the liver. Although the liver has a relatively slow cellular turnover, the ability for AAV-based gene therapies to persist is affected by this cellular turnover; with lentiviral-based gene therapy fully integrating into host cells, we believe it could provide the much-sought once-and-done treatment.

To treat haemophilia A and B, LVV that carry the appropriate genes would be injected into a patient either systemically or directly into the liver. This has been a rate-limiting step in targeting organs such as the liver and lungs. Addressing the liver will require huge quantities of vectors and we anticipate that to meet both the large patient numbers and large individual doses for commercial use, OXB will need to use both bioreactors and its in-house developed TRiP technology (which enable 10-fold vector yield vs bioreactors).

### Sanofi/Bioverativ valuation assumptions

For the Sanofi (Bioverativ) partnership we have modelled the opportunities in haemophilia A and B. We assume OXB receives $80m of the proposed $100m in milestone payments over the next five years as products in both indications are developed. We forecast that OXB sells vector batches to Bioverativ for $1.5m a batch, with peak gross margins of 30%. We assume an incidence of haemophilia A of 0.02% and 0.005% in haemophilia B, and approximate patient populations of 135,000 and 35,000, respectively, in both the US and EU5. We estimate that both are priced at $350,000 in the US with a 20% discount in Europe; both prices are a discount to current gene-therapy products but at the higher level of the cost per year for prophylactic treatments available on the market. We assume that gene therapy prices for non-orphan diseases will need to be priced below the current standard to drive appropriate uptake. We also forecast that decreasing COGS and increasing yields will enable this. We believe both could launch in 2025 with accelerated approval after completing Phase II trials. Due to significant competition in the space, in the form of gene therapies in development and existing treatments, we assume a 20% peak penetration rate and a single-digit royalty rate. We believe OXB will likely have to incorporate an array of next-generation technology such as TRiP to be able to reach the required manufacturing yields for these large indications, in turn driving increased royalties.

We note that Sanofi has decided to halt the ongoing clinical development for out-licensed ophthalmology asset SAR421869 (Usher syndrome type 1B); although it will continue the ongoing study of SAR42259 (Stargardt disease), following a strategic portfolio review, new partners will be sought for these assets. It is likely that OXB would be maintained as the primary manufacturing partner, similar to the transfer of development assets from GSK to Orchard Therapeutics. We retain the contribution of these assets in our model and will readdress this when new guidance becomes available.

## OXB's internal pipeline update

OXB has disclosed details of seven internally generated assets that are either in preclinical or early clinical development (Exhibit 10); management plans to spin-out/out-license at least one of its in-house product candidates in 2019. We understand that OXB is in active discussions with a number

of third parties regarding these assets. We note that gene therapies that target neurological or ophthalmological indications remain highly attractive, often due to the significant unmet need. The out-licensing deal with Axovant for AXO-Lenti-PD (formerly OXB-102) has served as a major validation of OXB's capability to add significant value to these assets through investing in the clinical development of its internal pipeline.

In the longer term, we believe economic returns would be enhanced by a listing on the Nasdaq to gain greater exposure to the US CGT space and utilise the capital raised to invest in developing its early preclinical stage gene therapies, either by itself or in collaboration with academic partners. Through doing this, we believe embedding its proprietary, licensable technology into these multiple assets at an early stage would ensure long-term, bottom-line growth through an increasing contribution of royalties (vs manufacturing fees).

**Exhibit 10: OXB's proprietary pipeline**

| Product | Indication (area) | Stage of development |
|---|---|---|
| OXB-201 | Wet AMD (ophthalmology) | Phase I complete |
| OXB-203 | Wet AMD (ophthalmology) | Pre-clinical |
| OXB-202 | Corneal graft rejection (ophthalmology) | Phase I/II in preparation |
| OXB-204 | LCA10 (ophthalmology) | Pre-clinical |
| OXB-208 | RP1 (ophthalmology) | Pre-clinical |
| OXB-302 | Solid tumours (oncology) | Pre-clinical complete |
| OXB-103 | ALS (neurology) | Pre-clinical |

Source: Oxford Biomedica, Edison Investment Research. Note: AMD: age related macular degeneration; LCA: Leber's congenital amaurosis; RP: retinitis pigmentosa; ALS: amyotrophic lateral sclerosis.

We only ascribe value to assets that have completed pre-clinical development and are positioned for out-licensing and/or further clinical development. As such, we will discuss OXB-201, OXB-202 and OXB-302 in turn; for an overview of OXB-204, OXB-208 and OXB-301, please refer to our November 2018 note Diversified strategy showing its strength.

## OXB-201: A one-and-done treatment for wAMD

OXB-201 (previously known as RetinoStat) is a gene-therapy for neovascular wet age-related macular degeneration (wAMD) that uses OXB's LentiVector technology to deliver two genes that encode for anti-angiogenic proteins (endostatin and angiostatin) into the eye. Anti-angiogenics are used in treating wAMD to attenuate the abnormal blood vessel growth (neovascularisation) responsible for loss of vision. The current mainstay treatments for wAMD are anti-angiogenics such as Regeneron's Eylea (aflibercept) and Roche's Lucentis (ranibizumab), which require repeat injection into the eye every one to three months. OXB-201 has the potential to be given as a single 'one-and-done' treatment, significantly reducing the injection burden for wetAMD patients. OXB announced at the American Society of Cell and Gene Therapy conference 2019 that it is also developing OXB-203, a gene-therapy that encodes for aflibercept, the anti-angiogenic component in Eylea.

Results from a 21-patient Phase I study showed that OXB-201 met the primary endpoints of safety and tolerability; patients demonstrated signs of clinical benefit, with visual acuity stabilisation and reduction in vascular leakage observed. Importantly, an ongoing long-term follow-up study has highlighted stable expression of both endostatin and angiostatin out to six years, which underlines the duration of response OXB's LentiVector technology can provide. OXB is looking for options to progress OXB-201, which include partnering or out-licensing. It is likely to attract strong partnering interest for its wAMD assets given the strong commercial potential of ocular anti-angiogenics; global sales of Eylea and Lucentis totalled $6.7bn and $4.2bn in 2018 from combined sales in wAMD, diabetic macular oedema and macular oedema retinal vein occlusion (source: EvaluatePharma).

## OXB-202: Corneal graft rejection

OXB-202 (previously known as EncorStat) is in development for preventing corneal graft rejection. Corneal graft or corneal transplantation is a surgical procedure where a damaged cornea is replaced by donated corneal 'graft' tissue. An estimated 70,000–100,000 corneal grafts (source: Apex) are performed worldwide each year and around one in five patients who undergo a corneal graft will have an episode of rejection. Some patients are more at risk than others, such as those with corneal revascularisation (blood vessels that have grown into the cornea from previous infections and inflammations) and those who have had prior corneal grafts or have pre-existing eye diseases such as glaucoma.

OXB-202 is a human donor cornea genetically modified with the same lentiviral vector as OXB-201 (RetinoStat) to secrete two proteins critical in the anti-angiogenesis process: endostatin and angiostatin. OXB-202 is used to treat the donor corneas ex vivo prior to transplantation, with the aim to inhibit the neovascularisation responsible for graft rejection. OXB-202 has demonstrated encouraging results in pre-clinical models and is anticipated to start recruiting patients (up to 40) in Phase I/II clinical trials at Moorfields Eye Hospital, a leading eye hospital in the UK, once funding has been secured.

## OXB-302: 5T4 targeting CAR-T for solid cancers

OXB-302 uses LentiVector technology to generate a 5T4 targeting CAR-T therapy, which has scope to treat various solid cancers. 5T4 is a heavily glycosylated cell surface protein expressed on a range of cancerous tissues, ranging from 100% on metastatic prostate, lung, breast, renal and colorectal cancers to between 75–100% of the primary tumours, but has low levels of expression on non-cancerous tissues, making it an attractive therapeutic target. 5T4 targeting therapies as a class have demonstrated some exceptional efficacy, counterbalanced by a high incidence of severe side effects. OXB-302 has completed preclinical proof-of-concept studies, demonstrating efficacy both in vitro and in vivo (mice) in various ovarian cancer models; further development will likely commence once a partner has been sought.

## Internal pipeline valuation assumptions

For the internal pipeline, we value OXB-201 (wAMD, Phase I/II), OXB-202 (corneal graft rejection, Phase I/II) and OXB-302 (cancer, preclinical). We assume all will be out-licensed following Phase I/II data. We forecast that all are priced at $350,000 in the US, with a 20% discount in EU5. We forecast royalties of 15% for all assets and assume that partners will use OXB's manufacturing capabilities to provide vectors at $1.5m a batch, with peak gross margins of 30%. For OXB-102 in PD, we assume an incidence of 0.028% and peak penetration of 5%. For OXB-202, we forecast that 0.01% of the population will need a corneal graft, of which 15% will fail, and a peak penetration of 30%. For OXB-302, no specific cancer has been chosen for development so we have assumed it is used in DLBCL with an incidence of non-Hodgkin's lymphoma of 0.02%, of which 48% have DLBCL, 35% fail first- and second-line treatments and a peak penetration of 10%. For OXB-201 we assume 2% of the population have AMD, of which 10% have wAMD, of which a further 10% can be treated, and a peak penetration of 2.5%.

# Sensitivities: Operational risks as growth continues

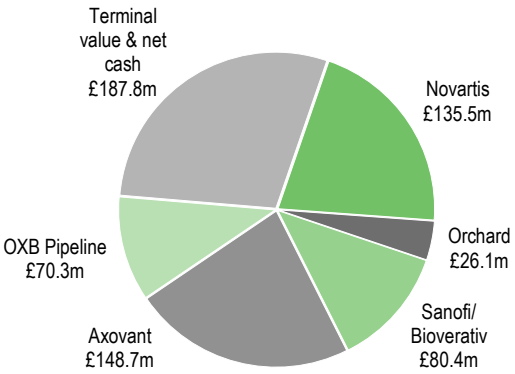
While OXB's partnership model minimises many of the usual biotech and drug development risks, it is still susceptible to clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks and financing and commercial risks. The key short-term sensitivities for OXB relate to crystallising value from the early-stage pipeline, the reliance on Novartis for revenue and manufacturing capacity constraints. Additionally, OXB's rapid growth in terms of employees and

facilities brings operational risks including, but not limited to, increased costs, hiring shortfalls or failures, loss of company culture, company structure failures, cash flow limitations and implementation failures of the new manufacturing facilities. From a drug pricing and reimbursement perspective, CGT are moving into uncharted territory.

## Valuation

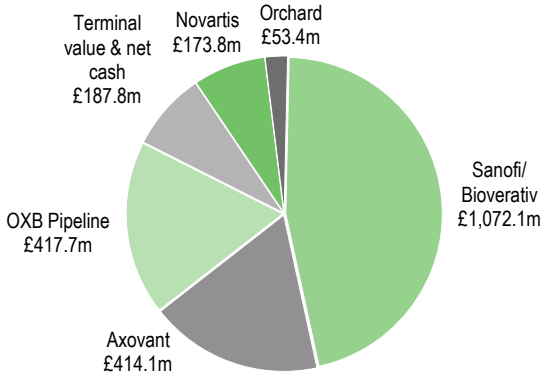
We value OXB at £649m vs £632m previously. The major changes are a slower ramp up of Kymriah sales forecasts in DLBCL offset by an increase in our probability of success for AXO-Lenti-PD to 30% from 20%. We have also pushed back Orchard Therapeutics' launch of OTL-101 for ADA-SCID by one year to 2020. We roll our model forward and update for exchange rates and net cash, and we include OXB's equity stake in Orchard (valued at £13m at market close on 29 May).

**Exhibit 11: Risk-adjusted NPV summary**




Source: Edison Investment Research

**Exhibit 12: NPV summary**




Source: Edison Investment Research

In Exhibits 11 and 12 we provide the relative partner contribution from our risk-adjusted (and unadjusted) net present values. In all partnerships except Sanofi, we value the royalty, milestone and bioprocessing (manufacturing) revenues; with Sanofi we only value potential future royalties and milestones. We forecast that all internal assets are out-licensed post Phase II data. We value all partnerships to 2040 and, due to an expanding and evolving long-term revenue stream, we include a terminal value (10% discount rate, 1% growth) for OXB, which contributes 2.1p/share to our valuation. We forecast that OXB will receive bioprocessing manufacturing revenue from partners throughout the collaborations and not just on commercial launch. We assume our standard 12.5% discount rate for assets, with a 10.0% discount rate for manufacturing revenues.

We note that pricing of gene therapies remains a key sensitivity and, as the market evolves and these dynamics change, we assume pricing of $700,000 for rare diseases and $350,000 for more common indications.

**Exhibit 13: OXB valuation**

| | OXB products | Partnered products | Net cash | Terminal value | Total |
|---|---|---|---|---|---|
| Total value (£m) | 70.30 | 390.57 | 32.2 | 155.5 | **648.6** |
| Value per share (p) | 93 | 517 | 43 | 206 | **858** |

Source: Edison Research Investment

A summary of our assumptions for each product can be seen in Exhibit 14. For detailed valuation assumptions please refer to the respective product sections throughout.

**Exhibit 14: Valuation summary**

| Product/partner/indication/status | Estimated launch year | Peak royalties (£m) | Peak manufacturing revenue (£m) | Probability of success | NPV (£m) | rNPV (£m) | rNPV per share (p/share) |
|---|---|---|---|---|---|---|---|
| Kymriah /Novartis/ r/r pALL/ approved in US & EU | Launched | 3 | 2 | 100% | 35 | 35 | 46.20 |
| Kymriah /Novartis/ DLBCL / approved in US & EU | Launched | 23 | 13 | 100% | 83 | 83 | 109.36 |
| 2nd CAR-T /Novartis/ Cancers/ Phase I/II | 2022 | 26 | 32 | 20% | 91 | 18 | 23.78 |
| OTL-101/ Orchard / ADA-SCID/ Phase II/III | 2020 | 0 | 1 | 70% | 7 | 6 | 7.61 |
| OTL-201/ Orchard/ Sanf A synd/ Pre-clinical | 2025 | 12 | 10 | 5% | 33 | 7 | 9.65 |
| OXB Orchard stake | N/A | N/A | N/A | N/A | 13 | 13 | 16.98 |
| Factor VIII/ Bioverativ/ Haemophilia A/ Pre-clinical | 2025 | 481 | 115 | 5% | 776 | 43 | 57.24 |
| Factor IX/ Bioverativ/ Haemophilia B/ Pre-clinical | 2025 | 120 | 29 | 5% | 206 | 15 | 19.56 |
| SAR422459/ Sanofi/ Stargardt/ Phase II | 2025 | 34 | N/A | 25% | 53 | 14 | 18.93 |
| SAR421869 Sanofi/ Usher/ Phase I/II | 2026 | 28 | N/A | 20% | 38 | 8 | 10.74 |
| AXO-LENTI-PD/ NA/ Parkinson's/ Phase I/II | 2022 | 80 | 17 | 30% | 414 | 149 | 196.87 |
| OXB-202/ NA/ Corneal graft/ Phase I | 2025 | 116 | 13 | 20% | 156 | 31 | 41.24 |
| OXB-302 / NA/ Cancer / Pre-clinical | 2025 | 61 | 61 | 5% | 86 | 4 | 5.14 |
| OXB-201/ NA/ Wet AMD/ Phase I/II | 2025 | 129 | 14 | 20% | 176 | 35 | 46.66 |
| **Total pipeline and partnership value** | | | | | | **461** | **609.97** |
| **Terminal value** | | | | | | **156** | **205.83** |
| **Net cash** | | | | | | **32** | **42.68** |
| **Total** | | | | | | **649** | **858.47** |

Source: Edison Investment Research

# Financials

In FY18 OXB reported gross income of £67.9m (+72%, 2017: £39.4m), which consisted of income from licence fees and milestones of £26.3m (FY17: £5.7m) and £40.5m (FY17: £31.8m) from bioprocessing/commercial development. The licence fees related to the deals signed with Bioverativ and Axovant in February and June, respectively (£18.6m). We note that £10.2m of the Axovant upfront ($30m total) was recognised; most of the income has been deferred and will be recognised as the related development work is performed. OXB received £5m in capital expenditure grants from Innovate UK for its investment in viral vector production and capacity. Exhibit 15 highlights historic and forecast revenue breakdown (platform vs product) and type (bioprocessing vs license and milestone).

**Exhibit 15: Historic and forecast revenue by type**

| £000s | 2017 | 2018 | 2019e | 2020e |
|---|---|---|---|---|
| **Platform** | | | | |
| Bioprocessing | 31,849 | 39,034 | 49,114 | 53,483 |
| Licence and milestone | 5,741 | 15,970 | 5,796 | 11,774 |
| **Product** | | | | |
| Bioprocessing | - | 1,470 | 1,195 | 3,622 |
| Licence and milestone | - | 10,304 | 19,725 | 19,725 |
| **Total** | **37,590** | **66.778** | **75,830** | **88,603** |

Source: Edison Investment Research

Research, development and bioprocessing increased to £29.7m in FY18 (FY17: £21.6m) and COGS increased to £22.8m (FY17: £18.4m). OXB reported a maiden operating profit of £13.9m in 2018 (FY17 loss of £5.7m). The company expects to remain at break-even or slightly profitable in the foreseeable future as it continues to invest in its pipeline and manufacturing capabilities. We forecast £9.8m operating profit in 2019 but note that multiple sensitivities remain including cost sensitivities in R&D, facilities and personnel, in addition to revenue sensitivities with regard to Kymriah sales growth, the extent of bioprocessing revenue and the execution of any new deals.

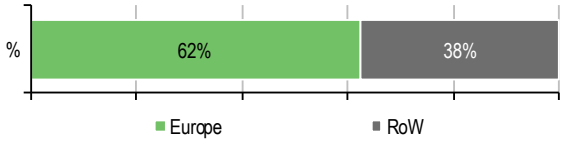
During 2018 OXB raised gross proceeds of £20.5m, which is being used to fund the expansion and fit out of additional bioprocessing facilities at the new site in Oxford. Gross cash was £32.2m at 31 December 2018 and net debt of £8.9m. In May 2019 OXB announced that Novo Holding had

agreed to invest up to £53.5m in the company, representing up to 10.1% of the outstanding shares after the capital increase. These funds in part will be used to repay the existing debt facility with Oaktree Capital Management leaving OXB debt free and cash positive.

**Exhibit 16: Financial summary**

| Accounts: IFRS, Yr end: December, GBP: Thousands | 2016 | 2017 | 2018 | 2019e | 2020e |
|---|---|---|---|---|---|
| Income statement | | | | | |
| Total revenues | 27,776 | 37,590 | 66,778 | 75,830 | 88,603 |
| Cost of sales | (11,835) | (18,442) | (22,763) | (24,028) | (26,428) |
| Gross profit | 15,941 | 19,148 | 44,015 | 51,801 | 62,175 |
| Administrative expenses | (5,957) | (7,276) | (7,433) | (10,035) | (13,547) |
| R&D costs | (24,299) | (21,611) | (29,714) | (31,941) | (36,379) |
| Other income/(expense) | 3,002 | 1,774 | 1,064 | 0 | 0 |
| Exceptionals and adjustments | 0 | 2,297 | 5,983 | 0 | 0 |
| Operating profit/(loss) | (11,313) | (5,668) | 13,915 | 9,826 | 12,250 |
| Finance income/(expense) | (8,994) | (6,093) | (8,901) | (4,300) | 242 |
| Reported PBT | (20,307) | (11,761) | 5,014 | 5,526 | 12,491 |
| Income tax expense (includes exceptionals) | 3,666 | 2,744 | 2,527 | 2,653 | 2,786 |
| Reported net income | (16,641) | (9,017) | 7,541 | 8,179 | 15,277 |
| Basic average number of shares, m | 56 | 62 | 65 | 71 | 76 |
| Basic EPS (p) | (29.9) | (14.6) | 11.6 | 11.5 | 20.2 |
| | | | | | |
| Adjusted EBITDA | (6,773) | (2,645) | 13,535 | 15,337 | 17,608 |
| Adjusted EBIT | (10,448) | (7,020) | 9,178 | 9,826 | 12,250 |
| Adjusted PBT | (19,442) | (13,113) | 277 | 5,526 | 12,491 |
| Adjusted EPS | (28.4) | (16.7) | 4.3 | 11.5 | 20.2 |
| | | | | | |
| Balance sheet | | | | | |
| Property, plant and equipment | 27,514 | 25,370 | 31,791 | 40,444 | 39,346 |
| Intangible assets | 1,330 | 97 | 117 | 96 | 79 |
| Other non-current assets | 657 | 2,954 | 10,966 | 10,966 | 10,966 |
| Total non-current assets | 29,501 | 28,421 | 42,874 | 51,507 | 50,391 |
| Cash and equivalents | 15,335 | 14,329 | 32,244 | 37,158 | 48,324 |
| Inventories | 2,202 | 3,332 | 4,251 | 4,487 | 4,935 |
| Trade and other receivables | 6,904 | 17,088 | 30,585 | 34,731 | 40,581 |
| Other current assets | 3,000 | 2,232 | 2,446 | 2,653 | 2,786 |
| Total current assets | 27,441 | 36,981 | 69,526 | 79,030 | 96,627 |
| Non-current loans and borrowings | 34,389 | 36,864 | 41,153 | 0 | 0 |
| Contract liabilities and deferred income | 0 | 0 | 6,434 | 6,434 | 6,434 |
| Other non-current liabilities | 622 | 630 | 1,566 | 1,566 | 1,566 |
| Total non-current liabilities | 35,011 | 37,494 | 49,153 | 8,000 | 8,000 |
| Trade and other payables | 6,003 | 8,690 | 11,422 | 12,057 | 13,261 |
| Contract liabilities and deferred income | 3,313 | 13,072 | 17,084 | 17,084 | 17,084 |
| Total current liabilities | 9,316 | 21,762 | 28,506 | 29,141 | 30,345 |
| Equity attributable to company | 12,615 | 6,146 | 34,741 | 93,395 | 108,672 |
| | | | | | |
| Cashflow statement | | | | | |
| Opertaing profit/(loss) | (11,313) | (5,668) | 13,915 | 9,826 | 12,250 |
| Depreciation and amortisation | 3,675 | 4,375 | 4,357 | 5,512 | 5,359 |
| Share based payments | 865 | 945 | 1,246 | 0 | 0 |
| Other adjustments | (579) | (1,326) | (8,012) | 0 | 0 |
| Movements in working capital | 1,423 | 141 | (2,292) | (3,747) | (5,094) |
| Income taxes paid | 4,081 | 4,512 | 3,654 | 2,446 | 2,653 |
| Cash from operations (CFO) | (1,848) | 2,979 | 12,868 | 14,036 | 15,168 |
| Capex | (6,458) | (1,969) | (10,148) | (14,144) | (4,243) |
| Other investing activities | 47 | 38 | 52 | 186 | 242 |
| Cash used in investing activities (CFIA) | (6,411) | (1,931) | (10,096) | (13,958) | (4,002) |
| Net proceeds from issue of shares | 17,497 | 385 | 19,808 | 50,475 | 0 |
| Movements in debt | 0 | 8,361 | 0 | (41,153) | 0 |
| Interest paid | (3,258) | (10,800) | (4,665) | (4,486) | (0) |
| Other financing activities | 0 | 0 | 0 | 0 | 0 |
| Cash from financing activities (CFF) | 14,239 | (2,054) | 15,143 | 4,836 | (0) |
| Increase/(decrease) in cash and equivalents | 5,980 | (1,006) | 17,915 | 4,914 | 11,166 |
| Currency translation differences and other | 0 | 0 | 0 | 0 | 0 |
| Cash and equivalents at beginning of period | 9,355 | 15,335 | 14,329 | 32,244 | 37,158 |
| Cash and equivalents at end of period | 15,335 | 14,329 | 32,244 | 37,158 | 48,324 |
| Net (debt) cash | (19,054) | (22,535) | (8,909) | 37,158 | 48,324 |

Source: Company accounts, Edison Investment Research

| Contact details | Revenue by geography |
|---|---|
| Windrush Court<br>Transport Way<br>Oxford OX4 6LT<br>United Kingdom<br>+44 (0) 1865 783 000<br>www.oxfordbiomedica.co.uk/ |  |



**Management team**

| CEO: John Dawson | CFO: Stuart Paynter |
|---|---|
| John joined as non-executive director in August 2008 and was appointed CEO in October 2008 (acting CEO from August to October 2008). He previously worked at Cephalon (2008–14), including as CFO and head of BD Europe. | Stuart joined as CFO in August 2017. He previously held multiple roles at Shire Pharmaceuticals including senior director of finance business partnering and global head of internal audit. Prior to joining OXB, he was head of finance business partnering at De La Rue. |

| Principal shareholders | (%) |
|---|---|
| Vulpes Investment Management | 15.3 |
| Prudential | 15.3 |
| Novo Holdings | 10.1 |
| Cannaccord Genuity Wealth Management | 4.9 |
| Hargreaves Lansdown Asset Management | 4.4 |
| Aviva Investors | 4.0 |
| Mr S Shah | 3.8 |
| Oaktree Capital Group Holdings | 3.6 |
| Nomura Holdings | 3.1 |

**Companies named in this report**

Bioverativ, Gilead (GILD), Novartis (NVS), Sanofi (SNY). Orchard Therapeutics (ORTX) , Axovant (AXGT) , Bluebird Bio (BLUE), Novo Holding

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