EDISON

Oxford BioMedica

CTL019 update

CTL019 approval likely in pALL, ad-com positive

Pharma & biotech

With a probable approval for Novartis's CTL019 (tisagenlecleucel) (OXB manufacture a key component) in both paediatric ALL and DLBCL on the horizon, Oxford BioMedica (OXB) is in position to crystallise a potentially significant revenue stream. Building on the original 2014 agreement with Novartis, the new commercial supply agreement for CTL019 includes $10m upfront and in excess of $90m in additional revenue over the next three years. Additionally, the company has refinanced its Oberland facility with Oaktree Capital Management to the tune of $55m (c $10m undrawn) on improved terms. Our valuation has increased to £251.6m (8.15p/share) vs £208.5m (6.75p/share), mainly as a result of updating CTL019 assumptions.

Year end	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
12/15	15.9	(16.6)	(0.49)	0.0	N/A	N/A
12/16	27.8	(20.0)	(0.59)	0.0	N/A	N/A
12/17e	40.2	(5.5)	(0.05)	0.0	N/A	N/A
12/18e	43.8	0.5	0.15	0.0	60.7	N/A

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

CTL019 ad-com unanimous but cautious on safety

Novartis has filed its lead CAR-T CTL019 (OXB manufacture a key component) with the FDA for approval in paediatric ALL patients. At the FDA advisory committee (ad-com) on 12 July, CTL019 was reviewed by independent experts and unanimously recommended for approval; while multiple concerns were raised with regard to its long-term safety, we believe approval later this year is likely (PDUFA date: 3 October). We anticipate launch in the US and Europe for paediatric ALL by the year end.

Novartis deal: Confirms commitment to supply chain

OXB's recent agreement with Novartis for the commercial and clinical supply of lentiviral vectors used to generate CTL019 builds on the original contract signed in October 2014. In addition to the $10m upfront, fee it could provide in excess of $90m in the next three years. OXB is the sole supplier of the lentiviral vector and the deal comes ahead of the anticipated clinical launch of CTL019. OXB will also receive undisclosed royalties on potential future sales of Novartis's CAR-T products.

Refinancing: Better terms reflect new strength

OXB recently announced the creation of a new $55m debt facility with Oaktree Capital Management to redeem the existing debt facility (FY16 results represented a net fair value of £34.4m). Improved deal terms (the potential cost of the loan is 11.5% compared to 15% previously) will aid OXB as it looks to become profitable.

Valuation: CTL019 core to near-term value

We value OXB at £251.6m (8.15p/share) vs £208.5m (6.75p/share) previously. We have rolled forward and updated our model, notably in relation to CTL019 assumptions. We note that the price of CTL019, the royalty rate received from Novartis and penetration rates all have a material impact on our valuation.

25 July 2017

Price	**9.10p**
Market cap	**£282m**
Net debt (£m) at end December 2016	19.1
Shares in issue	3,088.4m
Free float	83%
Code	OXB
Primary exchange	LSE
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	71.7	85.7	108.2
Rel (local)	73.6	78.7	85.6
52-week high/low	10.8p		3.0p

Business description

Oxford BioMedica (OXB) has a leading position in gene-based therapy. The lenti-vector technology is wide ranging and underpins much of the development pipeline, notably OXB-102, OXB-202 and OXB-302. OXB's manufacturing expertise is gaining valuable commercial traction.

Next events

CTL019 approval in B-ALL	Q417
CTL019 BLA in DLBCL	H217
Further partnership deals	2017/18
Licensing deals/spin-outs	2017/18

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FDA advisory panel: Efficacy clear, safety the focus

OXB provides a critical component (lentiviral vector) of Novartis's T- cell therapy CTL019 (tisagenlecleucel). CTL019 is known as a chimeric antigen receptor T-cell (CAR-T), a new generation of therapies that aim to engineer a patient's immune system to fight their cancer. This process is complex and requires both significant expertise and manufacturing capabilities. Novartis has submitted a biologics license application (BLA) to the FDA for the treatment of relapsed/refractory paediatric ALL (r/r pALL) patients (EU submission expected shortly). Additionally, Novartis expects to file a BLA in DLBCL in both the US and EU shortly. A potential FDA approval in pALL is expected in the autumn (PDUFA action date: 3 October), with an EU approval and approval in DLBCL (in both regions) potentially by year end. Key to this approval process was the recent FDA advisory committee meeting (ad-com), which invited independent experts to pass their guidance of CTL019 in pALL. The 10 person committee voted unanimously in recommending approval based primarily on data from the Phase II ELIANA trial (study B2020). Assuming a positive PFUDA meeting, CTL019 would be the first ever CAR-T approved.

Viral vectors: Places OXB on the global stage

OXB has developed and can manufacture engineered HIV (part of the lentivirus family, modified to be safe) to genetically modify a patient's T-cells to target cancer. OXB provides this lentiviral vector to Novartis, which utilises it in its manufacturing process to treat patients. While the technology is in its infancy, the approach has had clinical success in blood cancers like acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL).

One of the core focuses of the ad-com panel was to better understand the long-term safety of a genetically modified cell. Two points raised in the ad-com were insertional mutagenesis and the creation of replication competent lentiviral vector. The lentiviral vector technology that OXB utilise is based on a third-generation vector system where accessory genes are removed and the genome is split among plasmids. This makes the vector replicant incompetent, preventing the virus used to modify the T-cells from spreading to healthy cells in the body. In 13+ vector lots and 72+ patient-specific CTL019 lots that have been tested there has been no positive reading for replicant-positive lentivirus, validating OXB's technology as safe.

Insertional mutagenesis, where insertion of the gene may cause a change in activity of host genes through mutation, disruption or changes in activity is a long-term cause for concern as it could lead to new cancers. OXB has designed its vectors in a way to minimise this possibility; they lack enhancer sequences and as such are less likely to activate nearby genes. To date there has been no vector-associated leukaemia with CTL019 or any other vector-modified products. Based on data to date, we believe that OXB's viral vector technology in CTL019 is robust and, while a long-term study (Novartis plans a 15-year registry study) will monitor for these side effects, we believe they are not of significant concern, a point highlighted by the unanimous vote in favour of CTL019 by the advisory committee.

Efficacy never in doubt, adverse event management key

The efficacy of CTL019 (tisagenlecleucel) was not a core focus of the ad-com, as its efficacy is clearly evident. In the ELIANA trial, the overall response rate (set at three months) was 82.5% (n=52/63) (95% CI: 70.9, 91.0), with 40 of those patients experiencing a complete remission (CR) with complete blood count recovery and the remaining 12 experiencing complete remission without blood count recovery (CRi). All complete responses were minimal residual disease (MRD) negative in the bone marrow, indicating complete eradication of the cancer cells. Median duration of response (DOR) has not yet been reached (median follow-up of 4.8 months). The estimated relapse-free rate among responders at six months was 75.4% (95% CI: 57.2, 86.7). At the data cut-

off date (23 November 2016), 11 of the 52 subjects relapsed after treatment with CTL019 and a further two relapsed after treatment with both CTL019 and another cancer therapy. 22 remain in remission at data cut-off.

When looking at approved FDA therapies for r/r ALL we see how significant the efficacy of CTL019 is. Most recently Blincyto (blinatumomab), a bispecific CD19-directed, CD3 T-cell engager (BiTE) was approved in 2014. An open-label study (MT103-205) tested Blincyto in paediatric patients who had relapsed or were refractory to a range of treatments. It demonstrated a complete response (CR) of 17.1% (n=12/70, 95% CI: 9.2, 28.0). An additional 11 patients (15.7%) had complete remission with partial blood count recovery (CRi). In total 32.9% of patients had a CR or CRi (n=23/70, 95% CI: 22.1, 45.1). Median duration of response (time before relapse) was six months (range: 0.5-16.4) in the combined group. Blincyto prescribing information includes a black box warning for cytokine release syndrome and neurological toxicities.

While trial comparisons should be undertaken with caution, the substantial difference in complete responders (either with or without complete blood count recovery) between Blincyto and CTL019 is evident. Going forward, duration of response will be a key metric for CTL019, which will likely inform both pricing and treatment paradigms.

While efficacy has been remarkable, severe adverse events (SAEs), predominantly cytokine release syndrome and neurotoxicity, have been a serious cause for concern in many patients. In the ELIANA trial 69% of patients had a SAE in the first eight weeks after CTL019 infusion. While dose, disease burden and CAR-T construct (antibody fragment or co-stimulatory domain used) is theorised by some to predict the severity of side effects (and also the efficacy), Novartis clinically has no evidence that could point to any one component as being a key factor. Unlike some other CD19 CAR-Ts, notably the now cancelled JCAR015 from Juno Therapeutics, no cases of cerebral oedema have occurred with CTL019. It is thought that this may be due to the selection of the 4-1BB co-stimulatory domain by Novartis, while competitors Kite Pharmaceuticals and Juno utilise a CD28 domain. However, cases of cerebral oedema have occurred in patients treated with CAR-Ts containing the 4-1BB domain, indicating that a combination of factors is likely to be at play, including cancer type, starting T-cell populations and viral vector utilised.

Cytokine release syndrome (CRS), the other common adverse event associated with CAR-Ts, is a systemic inflammatory response that can be severe and sometimes fatal. However, it is significantly more manageable than neurotoxicity. One approach which is gaining traction is the utilisation of tocilizumab (an antibody that targets inflammatory cytokine IL-6) to dampen down CRS. Importantly, Novartis noted that it could be utilised prophylactically to minimise CRS without any noticeable effect on efficacy.

Oxford BioMedica's manufacturing ready to deliver

For both Novartis and OXB, manufacturing will be a key limiting factor in delivering CTL019. Never before has a commercial medical product (if approved by the FDA and/or EMA) required the removal, modification and re-administration of a patient's immune cells. This is a labour-intensive technique that requires significant capabilities at all stages. Novartis is aiming for a 22-day manufacturing process (multiple patients have died while waiting for injection of CTL019, further highlighting both the need of the patient population and ideally a shorter manufacturing time) from extracting a patient's cells to re-administrating them. To enable this, Novartis needs OXB's lentiviral vectors, which take several months to manufacture. Once made, these are delivered to Novartis, which stores them to use later to modify multiple patient cell batches. Three vector batches were utilised to treat all 88 patients in the ELIANA Phase II trial. These vectors were produced via its Process A procedure and would not be able to produce the required vector volumes to meet any potential future commercial demand beyond paediatric ALL. As such, OXB has invested in and is gradually moving its manufacturing over to its Process B procedure. This involves the use of

bioreactors, which the company states will improve productivity at least tenfold. This will put OXB at the forefront of lentiviral manufacturing, as few if any companies globally possess the ability to manufacture on that scale.

Pipeline update

An internal review in April 2016 led to the prioritisation of three internally developed pipeline assets: OXB-102 (Parkinson's disease – Phase I/II), OXB-202 (corneal graft rejection – Phase I/II) and OXB-302 (cancer, multiple types – preclinical), which could deliver the best potential economic returns. The goal for each is to be advanced to at least proof-of-concept in humans via out-licensing or through the formation of externally funded SPVs. OXB will look to obtain value through upfront payments, equity stakes or developmental milestones and from royalties on sales.

Product candidates that fall outside the priority programme (OXB-201 for wet age-related macular degeneration and OXB-301 for multiple cancers) will only be progressed once suitable opportunities, like partnering, enable reduced investment from OXB.

The group will continue to invest in earlier-stage gene and cell therapy concepts (eg in ocular, central nervous system and respiratory indications) with the aim of identifying new candidates for further development via out-licensing or spin-outs.

We note that SAR422459 (licensed to Sanofi) for Stargardt disease has progressed into Phase II development.

Valuation

Our valuation has increased to 8.15p/share (£251.6m) vs 6.75p/share previously (£208.5m). This increase has been driven mainly by changes in our CTL019 assumptions and rolling forward our model. Our assumptions for OXB's pipeline remain unchanged. We note Novartis' ability to drive penetration of its treatment (mainly in the larger indication, DLBCL), its pricing of CTL019 and the royalty rate OXB receives all have a significant effect on our valuation. We believe significant upside for OXB could come from other partnerships as additional companies are likely to be attracted by OXB's expertise and its ability to commercially produce the lentiviral vector. However, at this time the ability to predict the scope and timing of any deals is difficult and not included in our valuation.

Exhibit 1: OXB sum-of-the-parts valuation

Product(s)	Indication	Partner	Status	Probability of success	Estimated launch year	Estimated maximum royalty or margin	Estimated peak sales ($m)	NPV (£m)	rNPV (£m)	rNPV/ share (p)
OXB-102	Parkinson's disease		Phase I/II	20%	2024	15%	$1,048.1	142.1	28.4	0.92
OXB-202	Corneal graft rejection		Phase I/II	20%	2026	15%	$381.3	39.9	8.0	0.26
OXB-201	Wet AMD		Phase I/II	20%	2026	15%	$337.5	53.0	10.6	0.34
OXB-301	Cancer (multiple)		Phase I/II	20%	2024	15%	$360.0	33.6	6.7	0.22
SAR422459 (StarGen)	Stargardt disease	Sanofi	Phase IIa	25%	2021	7%	$337.5	35.0	8.7	0.28
SAR421869 (UshStat)	Usher syndrome type 1B	Sanofi	Phase I/II	20%	2023	7%	$45.0	4.5	0.9	0.03
Manufacturing for all collaborations (predominately CTL-019)		Various		100%		40% operating margin	$21.6	63.3	63.3	2.05
Licence income & IP milestones (predominately CTL019)		Various		100%		100% operating margin		144.0	144.0	4.67
Less net debt as of 31 December 2016								(19.1)	(19.1)	(0.62)
Total								496.3	251.6	8.15

Source: Edison Investment Research

For CTL019 we have updated our EU population numbers conservatively to include the top five countries (by GDP) as we feel these are more likely to be initially targeted. We have increased the age range in ALL to include young adults. Based on the impressive efficacy data in both the ELIANA (r/r pALL) and JULIET trial (r/r DLBCL), we have increased our peak penetration rates (35% in DLBCL and 50% in ALL). We expect lower penetration rates in DLBCL compared to ALL, as we anticipate increased competition (Kite Pharmaceuticals likely first to market). In pALL, competitors are at least 18 months behind and we expect Novartis to gain significant market share. We have increased the expected price of CTL019 to £300k based on market sentiment and have altered our royalty rate, which now at peak is 2%. We anticipate launch of CTL019 for pALL in autumn this year (PDUFA action date: 3 October 2017) and in DLBCL at year end. We note that DLBCL represents the majority of revenue in both manufacturing and royalties due to the significantly larger patient population. Our core CTL019 assumptions can be seen in Exhibit 2. A key unknown factor which materially affects our valuation remains the royalty rate OXB receives from Novartis. We note that a 1% peak royalty rate lowers our overall valuation to £182.7m (5.92p/share), while a 3% peak royalty rate increases our valuation to £320.6m (10.38p/share). Please see our previous notes for a more in-depth look into our overall valuation metrics.

Exhibit 2: CTL019 assumptions

r/r pALL	DLBCL
EU (top 5) & US, 25% paediatric/young adult, 0.004% with ALL, 15% failed first and second line, 50% peak penetration, £300k, launch autumn 2017, CTL019 peak sales £158m, 2% peak royalty rate, £3.2m peak royalties.	EU (top 5) & US, 0.02% with NHL, 48% with DLBCL, 35% failed first and second line, 30% peak penetration, £300k price, launch end 2017, CTL019 peak sales £2.1bn, 2% peak royalty rate, £42.5m peak royalties.

Source: Edison Investment Research

Financials

We have updated our forecasts, which now reflect the creation of the new debt facility with Oaktree Capital Management, changes in our CTL019 assumptions and the $10m upfront payment in 2017 from the new supply deal with Novartis. We have adjusted our expectations for CTL019 (outlined in more detail in the valuation section), which has prompted us to revise our revenue expectations upwards in 2017, 2018 and 2019. Our 2018 and 2019 numbers are driven significantly by royalties and manufacturing of CTL019. In addition, we expect revenue from collaborations with Orchard Therapeutics and Green Cross LabCell to contribute meaningfully over this time period. The recently announced supply deal with Novartis consists of a $10m upfront in 2017 and an additional $90m committed over the next three years. Additional undisclosed CAR-T products are included in the deal and the supply agreement can be extended to five years with the agreement of both parties. We maintain our forecasts for R&D and bioprocessing costs, which we believe will see a significant reduction from 2017. This is a reflection of the near-term strategy to out-license or spin out the product portfolio (£21.5m in 2017, £18.5m in 2018 and £17.0m in 2019).

OXB recently announced the creation of a new $55m debt facility with Oaktree Capital Management. This facility has been used to redeem the existing debt facility with Oberland Capital Healthcare which, as last reported in the FY16 results, represented a net fair value of £34.4m. We estimate that c $10m is available to be drawn down when taking into account the original sum. Notably improved deal terms (potential cost of loan 11.5% compared to 15% for the previous Oberland facility) will aid OXB as it looks to become profitable in the near term. The loan is to be paid back by 29 June 2020 and has a 9% interest rate plus US$ Libor (minimum 1%). Subject to achieving certain conditions, the interest rate could drop 0.25% in both the second and third years. Additionally, the company has issued 134m warrants to Oaktree, which can be exercised over the next 10 years at a nominal share price of 1p.

Exhibit 3: Financial summary

£'000s	2015	2016	2017e	2018e	2019e
Year end 31 December	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	15,909	27,776	40,154	43,792	48,317
Cost of Sales	(5,839)	(11,835)	(15,342)	(15,489)	(16,937)
Gross Profit	10,070	15,941	24,812	28,303	31,380
R&D	(20,274)	(24,299)	(21,500)	(18,500)	(17,000)
Other operating income	2,862	3,002	1,000	1,000	1,000
EBITDA	(12,456)	(7,638)	2,282	8,124	12,350
Depreciation	(1,264)	(3,340)	(3,719)	(3,365)	(3,056)
Operating profit (before GW and except)	(13,720)	(10,978)	(1,437)	4,760	9,294
Amortisation	(363)	(335)	(268)	(214)	(171)
Exceptionals	0	0	0	0	0
Operating profit	(14,083)	(11,313)	(1,704)	4,546	9,123
Net Interest	(2,899)	(8,994)	(4,081)	(4,227)	(4,379)
Other	0	0	0	0	0
Profit Before Tax (norm)	(16,619)	(19,972)	(5,518)	532	4,915
Profit Before Tax (reported)	(16,982)	(20,307)	(5,786)	318	4,744
Tax	3,963	3,666	4,000	4,000	4,000
Profit After Tax (norm)	(12,656)	(16,306)	(1,518)	4,532	8,915
Profit After Tax (reported)	(13,019)	(16,641)	(1,786)	4,318	8,744
Average Number of Shares Outstanding (m)	2,574	2,778	3,087	3,087	3,087
EPS - normalised (p)	(0.49)	(0.59)	(0.05)	0.15	0.29
EPS - reported (p)	(0.51)	(0.60)	(0.06)	0.14	0.28
Dividend per share (p)	0.00	0.00	0.00	0.00	0.00
Gross Margin (%)	63.3%	57.4%	61.8%	64.6%	64.9%
EBITDA Margin (%)	(78.3%)	(27.5%)	5.7%	18.6%	25.6%
Operating Margin (before GW and except) (%)	(86.2%)	(39.5%)	(3.6%)	10.9%	19.2%
BALANCE SHEET					
Fixed Assets	26,139	29,501	26,514	23,936	21,709
Intangible Assets	0	657	657	657	657
Intangible Assets	1,743	1,330	1,062	849	678
Tangible Assets	24,396	27,514	24,795	22,430	20,374
Current Assets	25,712	27,441	34,376	41,586	53,607
Stocks	2,706	2,202	2,855	2,882	3,151
Debtors	10,930	6,904	2,169	5,772	6,137
Cash	9,355	15,335	26,019	29,598	40,985
Other	2,721	3,000	3,334	3,334	3,334
Current Liabilities	(13,169)	(9,316)	(13,821)	(12,861)	(12,594)
Creditors	(9,286)	(6,003)	(10,508)	(9,548)	(9,281)
Provisions	(838)	0	0	0	0
Deferred income	(3,045)	(3,313)	(3,313)	(3,313)	(3,313)
Long Term Liabilities	(27,788)	(35,011)	(36,240)	(37,513)	(38,831)
Long term borrowings	(27,255)	(34,389)	(35,618)	(36,891)	(38,209)
Other long term liabilities	(533)	(622)	(622)	(622)	(622)
Net Assets	10,894	12,615	10,830	15,148	23,892
CASH FLOW					
Operating Cash Flow	(14,871)	(5,979)	10,870	3,534	11,448
Net Interest	(1,494)	(3,258)	(2,867)	(2,970)	(3,076)
Tax	3,247	4,131	3,666	4,000	4,000
Capex	(16,716)	(6,458)	(1,000)	(1,000)	(1,000)
Acquisitions/disposals	0	0	0	0	0
Financing	144	17,497	0	0	0
Dividends	0	0	0	0	0
Other	38	47	15	15	15
Net Cash Flow	(29,652)	5,980	10,684	3,580	11,387
Opening net debt/(cash)	(13,195)	17,900	19,054	9,599	7,292
HP finance leases initiated	0	0	0	0	0
Other	(1,443)	(7,134)	(1,229)	(1,273)	(1,318)
Closing net debt/(cash)	17,900	19,054	9,599	7,293	(2,777)

Source: Oxford BioMedica, Edison Investment Research

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