EDISON

Transgene

H1 update

Combinations define strategy

Pharma & biotech

Transgene has further expanded on its new strategy announced in January 2016 and clarified timelines for combination trials of its product candidates with immune checkpoint inhibitors. Six clinical trials are due to start before 2017 year end; its lead product candidates, Pexa-Vec (oncolytic virus) and TG4010 (therapeutic vaccine) in combination with Yervoy and Opdivo respectively should start phase II trials by year end. Restructuring in 2015 has significantly reduced costs and it is now financed through major inflection points in 2017. HY16 net cash of €33.4m includes short-term financial assets. We value Transgene at €4.40/share (€169.5m).

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/14	11.1	(38.9)	(1.03)	0.0	N/A	N/A
12/15	9.6	(28.9)	(0.78)	0.0	N/A	N/A
12/16e	6.1	(27.2)	(0.71)	0.0	N/A	N/A
12/17e	7.8	(31.5)	(0.82)	0.0	N/A	N/A

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

Pipeline focus

Transgene strategic focus is now on its therapeutic vaccines and oncolytic viruses in combination with other treatments, predominately immune checkpoint inhibitors (ICI). Its lead therapeutic vaccine product candidate, TG4010 is to initiate two trials in first- and second-line non-small cell lung cancer (NSCLC) in combination with ICIs. The first of which will start before year end in second-line treatment of NSCLC alongside Opdivo (Bristol-Myers Squibb, BMY). Transgene plans to start six trials across all product candidates in the next 3-18 months, five of which are in combination with ICIs.

Pexa-Vec: New ICI combinations

Transgene's lead Oncolytic virus product candidate, Pexa-Vec is currently being tested in combination with sorafenib (Bayer) (TKI Inhibitor) in a phase III trial (run by its partner SillaJen) in hepatocellular carcinoma (HCC) (data readout 2019). The company plans to independently test Pexa-Vec in combination with ICIs with trials initiating in the next three to 12 months with the first data readout in combination with Yervoy (BMY) expected in 2017.

Valuation: €4.40/share (€169.5m)

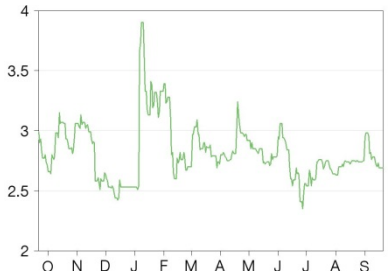
We value Transgene at €169.5m, €4.40/share, an increase from our previous valuation of €4.15/share (€160m) due to the rolling forward of our model. The company reported net loss from continuing operations of €11.6m in H116 (vs €21.7m H115) and had cash and short-term financial assets of €33.4m as at the end of June (vs €31.6m at December 2015). A further €10m from the second tranche of the European Investment Bank (EIB) loan and a €10m commitment from Institut Mérieux has yet to be drawn. Cash burn guidance has been confirmed at c €35m for the year.

21 September 2016

Price	**€2.69**
Market cap	**€104m**

Net cash and ST investments (€m) at 30 June 2016	33.4
Shares in issue	38.5m
Free float	43%
Code	TNG
Primary exchange	Euronext, Paris
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(2.2)	0.0	(14.3)
Rel (local)	(2.4)	(1.9)	(12.8)
52-week high/low		€3.9	€2.4

Business description

Transgene is a French drug discovery and development company focused on the treatment of cancer and infectious diseases with immunotherapies. The lead products are Pexa-Vec (in Phase III for HCC) and TG4010 (Phase IIb complete for NSCLC).

Next events

TG4010 +Opdivo NSCLC (second-line) trial start	H216
Pexa-Vec +Yervoy Solid Tumours trial start	H216

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Edison profile page

Immunotherapy combinations drive strategy

Transgene has a pipeline of immunotherapies for the treatment of cancer and viral indications. It has shifted its strategy away from monotherapies or combinations with chemotherapy towards combination therapies with immune checkpoint inhibitors. This is based on recognition within the immunotherapy sector that a combination approach can provide substantial efficacy improvements over monotherapies.

Notable recent data are the combination of nivolumab (Opdivo) (BMY) and ipilimumab (Yervoy) (BMY) for the treatment of metastatic melanoma, approved by the FDA in October 2015. The objective response rate increased to 50% for the combination compared with 40% for nivolumab (Opdivo) and 14% for ipilimumab alone. Progression-free survival increased to 11.5 months for the combination vs 6.9 months (Opdivo) and 2.9 months (Yervoy). However, adverse reactions in the combination arms were more severe and more common. 73% of patients in the combination arm had a serious adverse reaction (defined as grade 3 or 4, consisting of fatigue, edema, musculoskeletal pain, rash, pruritus, erythema, vitiligo and upper respiratory tract infection) compared with 37% in Opdivo alone.

If Transgene's product candidates can demonstrate both the improved efficacy that has been demonstrated by some immunotherapy combinations, along with a more favourable safety profile then what is currently available, potential valuation uplifts are possible.

Exhibit 1: Transgene Clinical pipeline

Compound	Combination Compound	Indication	Phase	Collaborators	Trial start date	Data Readout
TG4010	Opdivo (Nivolumab) (BMY) anti-PD-1	Second-line NSCLC	II	UC Davis Medical Centre (US)	H216	2017
TG4010	Unspecified ICI	First-line NSCLC	II	N/A	H117	N/A
Pexa-Vec	Sorafenib	First-line HCC	III	Conducted by partner SillaJen	Ongoing	2019
Pexa- Vec	Yervoy (Ipilimumab) (BMY) anti CTLA-4	Solid Tumours	II	Centre Leon Berard	H216	2017
Pexa- Vec	Opdivo (Nivolumab) (BMY) anti-PD-1	First-line HCC	II	N/A	H117	N/A
TG4001	Unspecified ICI	HPV positive head and neck cancer	II	Prof Christopher Le Tourneau, Institut Curie, principal investigator	H117	N/A
TG1050	Standard of care antiviral	Chronic hepatitis B	I/Ib	N/A	Ongoing	H217
TG6002	N/A	Glioblastoma	I	Assistance Publique Hôpitaux de Paris (P.I: Pr Delattre), support from French national cancer institute	H117	N/A

Source: Edison Research Investment, Transgene

TG4010: Addressing PD-L1 negative patients

Transgene's lead product candidate is TG4010, a therapeutic vaccine that expresses MUC1 protein and the cytokine Interleukin-2 (IL2). It should enable a patient to develop an immune response against cells that express the MUC1 protein (a large glycosylated protein). This protein is only expressed at low levels in normal tissues, but is expressed at high levels (often with reduced or aberrant glycosylation) in many tumours (70% of lung, 90% of breast, 60% of prostate and 70% of colorectal cancers). It is in development for the treatment of advanced non-small cell lung cancer (NSCLC).

Transgene has decided against initiating a Phase III trial of TG4010 in combination with chemotherapy for the first line treatment of NSCLC patients. Instead, the focus will be on Phase II trials in combination with immune checkpoint inhibitors (Exhibit 1). The first of these trials will be a combination trial of TG4010 with Opdivo in collaboration with the UC Davis Medical Centre (US). The trial is expected to initiate by year end with initial data expected in 2017.

The second trial Transgene plans to initiate with TG4010 in combination with an ICI will aim to address NSCLC patients in second-line treatment of NSCLC who express low or undetectable levels of PD-L1. Information revealed so far does not indicate whether a PD-L1 ICI or others like CTLA-4 will be utilised. As PD-L1 monotherapy treatments currently dominate the ICI market, any improvements in non PD-L1 patient treatment with a combination approach would be able to address a significant patient population.

Data from the Phase IIb TIME trial compared chemotherapy plus TG4010 to chemotherapy plus placebo in patients with advanced NSCLC (n=222). The overall response rate (ORR) and duration of response (DR) data are supportive of the potential of TG4010: for the total population (squamous and non-squamous NSCLC), those patients receiving TG4010 benefited compared to the placebo arm (ORR: 39.6% vs 28.8%; DR: 30.1 vs 18.7 weeks). The benefit was greatest in those patients with non-squamous NSCLC and low TrPAL (ORR: 39.3% vs 30.3%; DR: 43.1 vs 18.1 weeks).

Importantly, in post-hoc analysis of all non-squamous NSCLC patients there was a similar level of PFS and OS benefit in the 97 patients with low levels of PD-L1 expression (<5%) to that observed with all non-squamous NSCLC patients. In various studies it has been shown that non-squamous NSCLC patients with low levels of PD-L1 will not benefit as much from ICIs targeting PD-L1 and PD-1 as those with high levels of PD-L1 expression. This suggests that TG4010 could potentially become a valuable treatment in those non-squamous patients less likely to benefit from treatment with PD1 or PD-L1 inhibitors, in addition to the potential synergistic approach discussed previously.

TG4010 was well tolerated; the most frequent TG4010-related adverse events were mild to moderate injection site reactions. This data supports the potential of TG4010 as any improvement of safety over ICI treatments would be openly welcomed if efficacy was comparable. To date, over 350 patients have been treated with TG4010.

Pexa-Vec: Additional combinations may drive value

Pexa-Vec, an oncolytic virus in a Phase III trial (conducted by partner SillaJen but for which Transgene still retain access to the data) in 1st line hepatocellular carcinoma (HCC) is ongoing with first data expected by 2019. It is a randomised (1:1), open-label study comparing Pexa-Vec followed by sorafenib (Bayer) (tyrosine kinase inhibitor) versus sorafenib alone in patients with advanced HCC who have not received prior systemic therapy (n=600). Pexa-Vec will be administered as three bi-weekly intratumoral injections at day one and weeks two and four, followed by sorafenib at week six; the comparator arm will receive sorafenib 400mg twice daily starting on day one. The primary endpoint is overall survival (OS); secondary endpoints include time to progression, progression-free survival and overall response rate. Initial OS data are expected in 2019. Additionally SillaJen have announced plans to file for an IPO in 2H16 to provide funds for further development and commercialisation of its primary asset Pexa-Vec (SillaJen retain the rights outside of Europe).

Transgene plans to initiate two further trials, one in combination with Yervoy, the other in Opdvio within the next 12 months (Exhibit 1) with initial data readouts potentially as soon as 2017 for the Yervoy combination. Data here could drive the value of Pexa-Vec before the expected readout of the phase III trial in 2019. In addition, Transgene has announced that the partnership deal with SillaJen does not cover the data generated from Pexa-Vec combination trials; Transgene retains these rights.

Pexa-Vec has historically been involved in more than 10 clinical trials with contrasting results. It has been shown to be more effective in 1st line treatment then 2nd line treatment potentially as a result of lower tumour burden. A phase II dose-finding study in HCC patients (sorafenib-naïve) (n=30; 80% first-line) found that those receiving high-dose Pexa-Vec (intratumoral delivery) had a median overall survival (OS) of 14.1 months compared to 6.7 months for those on a low dose (HR: 0.39; p=0.02; Exhibit 2). However, the subsequent Phase IIb TRAVERSE study in second-line HCC

(patients who have previously failed Sorafenib treatment through either disease progression or intolerance to treatment) was terminated early in 2013 as data from the first 80 events showed no evidence of OS benefit associated with Pexa-Vec. The decision to continue development of Pexa-Vec was based on the detailed analysis of TRAVERSE and the prior Phase I/II trials with data from over 300 patients.

Strength in breadth

While advancing its lead product candidates remains a priority, Transgene plans to initiate trials with two other product candidates (TG4001and TG6002) before H217 with data expected from the ongoing TG1050 phase I/Ib trial in H217.

A phase II trial of the therapeutic vaccine TG4001 in combination with an ICI for the second-line treatment of HPV positive head and neck cancer aims to initiate in H117 and will be led by Professor Christophe Le Tourneau of Institut Curie. Transgene will sponsor this trial although exact details have not been disclosed. Data from a Phase 2b trial of 206 female patients with CIN2/3 Intraepithelial Cervical Neoplasia demonstrated that it cleared 38% (20/52) of HPV16 mono-infected patients compared with 9% for placebo (2/23)(P value = 0.009). It demonstrated a favourable safety profile with non-serious injection site reactions as the most frequent adverse event.

TG1050, a therapeutic vaccine for the treatment of chronic hepatitis B is currently in an ongoing Phase I/Ib trial. It recently announced that the Safety Review Committee recommended its continuation. The first patient was dosed in November 2015 with TG1050 alongside standard-of-care antiviral treatment. It is an international, randomised, double-blind, placebo-controlled safety and dose-finding study evaluating single and multiple doses of TG1050 in patients who are currently being treated for chronic HBV infection with standard-of-care antiviral therapy (n=48). Secondary objectives include the antiviral activity of, and immune responses to, TG1050. Data is expected in H217.

There are currently limited treatments for HBV. The cure rate from nucleotide analogues such as tenofovir (Viread) and entecavir (Baraclude) or pegylated interferon-α is only 3-5%, so that patients normally need long-term anti-viral therapy to control their infection. Preclinical data with TG1050 suggest that the vaccine could produce a sustained immune response against the virus in chronic HBV patients, thereby preventing relapses without the need for antiviral therapies. Given the size of the potential market (the WHO estimates that 240 million people have chronic HBV infection), Transgene will look to partner TG1050 once it has proof-of-concept data from this study.

TG6002 is Transgene's next generation immunotherapy and both aims to induce cancer cell lysis and cause the cells to express the FCU1 gene. Transgene believes the expression of this gene will enable the infected cancer cells to transform the non-cytoxic pro-drug into a chemotherapeutic agent. A phase I trial in glioblastoma with Assistance Publique Hôpitaux de Paris (P.I: Pr Delattre) and support from French national cancer institute is expected to initiate in H117.

Valuation

Our valuation of Transgene has increased to €169.5m, €4.40/share, (from €160.0m, €4.15/share) due to the rolling forward of our model. Our valuation remains focused on TG4010, PexaVec and TG1050. The lack of information regarding the costs of trials (particularly costs of the immune checkpoint inhibitors) and/or the deal terms of current or future partnerships, mean costs are currently assumed at standard rates. While we recognise the potential of TG4001 and TG6002 we do not currently assign value to them as we await more clarity on both trial design and future development plans.

We note the following key assumptions on potential development timelines for TG4010, Pexa-Vec and TG1050:

- TG4010 – We predict a classical clinical development timeline for the project, starting with the Phase II studies planned for NSCLC in combination with ICIs. We currently assign a 40% probability of success and assume that it will be partnered post phase II trials with a 17.5% royalty rate. Additionally we have altered our assumptions on target patient populations for TG4010 based on Transgene's strategic shift to focus on patients who express low or no levels of PD-L1. We no longer believe patients expressing normal NK cell levels will be a core target. Academic literature points to contrasting PD-L1 expression and treatment correlation rates, however, most point to a higher proportion of patients being PD-L1 negative or low, as such we believe our 66% assumption of attainable patient population is reasonable.
- Pexa-Vec – We have assumed that the Phase III PHOCUS study, which plans to include EU trial sites, will be sufficient to file for approval in Europe, assuming a positive study result. Transgene will be responsible for funding, compiling and submitting the regulatory application in Europe.
- TG1050 – Our valuation includes the EU and US market and we have assumed that TG1050 will be out-licensed on completion of a successful Phase II proof-of-concept study.

Exhibit 2: Transgene valuation model and key assumptions

Product	Status	Market launch	NPV (€m)	Peak sales (€m)	Probability of success	Royalty estimate	rNPV (€m)	rNPV / share (€)	Key assumptions
TG4010 - NSCLC (EU)	Phase I/II	2025	93.8	1,062	40%	17.5%	34.2	0.89	c. 313k annual EU incidence of lung cancer; 85% NSCLC; 75% MUC1 +ve; 66% PD-L1 low or negative; 20% peak penetration; €30k treatment price; €30m upfront on Phase IIb completion.
TG4010 - NSCLC (US)	Phase I/II	2025	83.5	1,299	40%	17.5%	33.4	0.87	c. 221k annual US incidence of lung cancer; 85% NSCLC; 75% MUC1 +ve; 66% PD-L1 low or negative; 20% peak penetration; $50k treatment price
Pexa-Vec - HCC (EU)	Phase III	2020	105.4	424	50%	25.0%	49.9	1.30	c. 52k annual EU incidence of liver cancer; 80% HCC; 25% peak penetration; €30k treatment price
TG1050 - HepB (EU+US)	Phase I	2025	202.0	2,054	15%	20.0%	18.5	0.48	c. 5.4m chronic HepB prevalence in EU + US; 66% diagnosis rate; 33% require treatment; 5% peak penetration; €35k treatment price
Net cash and short-term financial assets (June 2016)							33.4	0.87	
Total							**169.5**	**4.40**	

Source: Edison Investment Research. Note: Peak sales represent the largest one-year sales that occur over the projected product lifespan. Spot rate $1.1/€.

For a more detailed description of our key assumptions please see our previous re-initiation of coverage (Worth a fresh look). We recognise the opportunity Transgene's product candidates have with ICIs; however, further valuation uplifts are dependent on data expected over the next 24 months from these trials.

Sensitivities

Transgene is subject to the usual risks associated with drug development, including clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks, and financing and commercial risks. The key sensitivities relate to the clinical performance of Pexa-Vec in the Phase III trial (initial data expected in 2019); the results of the ICI combination studies of Pexa-Vec and TG4010; and Transgene's ability to secure future partnerships.

The outcome of the TG4010 combination studies in particular will have an impact on its partnership and/or fresh financing prospects for the programme.

The revised agreement with SillaJen for the conduct of the Phase III trial of Pexa-Vec has reduced the financial burden on Transgene, which we see as more than compensating for the returned rights to Pexa-Vec for all Middle Eastern countries, Russia, Ukraine, Belarus and Turkey.

Financials

Transgene held €33.4m in cash and short-term financial assets as of 30 June 2016, and had access to a further €20m in funds. Of the €20m EIB loan announced in January, €10m has been drawn to date. A further €10m via the EIB loan alongside a €10m commitment from its largest shareholder have yet to be drawn. As a result, the company expects to have sufficient funds to conduct its pipeline development activities through 2016 and 2017 with a cash burn of €35m guided in 2016.

For modelling purposes we have assumed that the second tranche of the €20m EIB loan is drawn in H216. Limited details have been provided on the terms of this loan facility, except that it has a five-year tenure, with the principal and accumulated interest repaid from the fourth year. We then assume the additional €10m shareholder commitment is received in 2017, which we attribute to long-term debt for illustrative purposes, given the timing and nature of this 'commitment' is unknown at this stage.

We make no changes to our FY16 estimates following the release of H116 results. In H116, Transgene's operating revenues fell to €4.9m from €5.3m in H115. This included a €1.3m one-off payment from Sanofi Chimie and a research tax credit of €2.9m. We continue to expect revenues to fall to €6.1m in FY16 (vs €9.6m in FY15) on the back of the restructuring programme, which resulted in the withdrawal from outsourcing of process development and bio-manufacturing activities. R&D expenses for H116 fell to €12.5m compared with €16.9m in H115; this is attributable to a reduction in clinical trial activity following the reorganisation of the company in June 2015. The initiation of TG4010 and Pexa-Vec trials in H216 will see an increase in R&D expenses compared with H116. However, we expect a reduction in full year R&D spend of €27.5m compared with €32.1m in 2015. A lower R&D expenditure will also reduce the R&D related tax credits that Transgene also books as revenue. In all, we maintain our forecast of an operating loss of €25.6m in FY16 (operating cash outflow of €30.5m) and a net loss estimate of €27.2m.

Exhibit 3: Financial summary

€'000s	2014	2015	2016e	2017e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	11,099	9,565	6,086	7,835
Cost of Sales	0	0	0	0
Gross Profit	11,099	9,565	6,086	7,835
R&D expenses	(41,731)	(32,138)	(27,465)	(32,958)
G&A expenses	(7,578)	(5,798)	(4,339)	(4,469)
EBITDA	(35,453)	(25,671)	(23,943)	(27,858)
Operating Profit (before GW and except)	(38,127)	(27,957)	(25,584)	(29,488)
Intangible Amortisation	(365)	(350)	(135)	(105)
Exceptionals (restructuring costs / discontinued operations)	(8,440)	(15,965)	0	0
Operating Profit	(46,932)	(44,272)	(25,719)	(29,592)
Other	0	0	0	0
Net Interest	(801)	(930)	(1,579)	(2,034)
Profit Before Tax (norm)	(38,928)	(28,887)	(27,163)	(31,522)
Profit Before Tax (IFRS)	(47,733)	(45,202)	(27,298)	(31,627)
Tax	0	0	0	0
Minority interest	(823)	(1,172)	0	0
Profit After Tax (norm)	(39,751)	(30,059)	(27,163)	(31,522)
Profit After Tax (IFRS)	(48,556)	(46,374)	(27,298)	(31,627)
Average Number of Shares Outstanding (m)	38.5	38.5	38.5	38.5
EPS - normalised (c)	(103.25)	(78.08)	(70.55)	(81.87)
EPS - IFRS (c)	(126.12)	(120.45)	(70.90)	(82.15)
Dividend per share (c)	0.0	0.0	0.0	0.0
BALANCE SHEET				
Fixed Assets	61,715	49,841	49,440	49,135
Intangible Assets	1,056	485	350	245
Tangible Assets	23,641	16,559	16,293	16,093
Other	37,018	32,797	32,797	32,797
Current Assets	79,238	51,028	42,772	28,237
Stocks	1,149	1,164	1,164	1,164
Debtors	1,540	1,784	1,784	429
Cash	65,935	31,650	26,894	13,713
Other	10,614	16,430	12,930	12,930
Current Liabilities	(21,563)	(26,725)	(19,697)	(20,796)
Creditors	(8,296)	(6,521)	(5,493)	(6,592)
Short term borrowings	0	0	0	0
Short term leases	(8,992)	(9,396)	(9,396)	(9,396)
Other	(4,275)	(10,808)	(4,808)	(4,808)
Long Term Liabilities	(47,551)	(47,597)	(66,953)	(76,316)
Long term borrowings	0	0	(20,000)	(30,000)
Long term leases	(43,199)	(44,401)	(43,757)	(43,120)
Other long term liabilities	(4,352)	(3,196)	(3,196)	(3,196)
Net Assets	71,839	26,547	5,561	(19,740)
CASH FLOW				
Operating Cash Flow	(55,037)	(46,082)	(30,495)	(24,915)
Net Interest	801	930	(1,579)	(2,034)
Tax	0	0	0	0
Capex	(2,602)	(1,527)	(1,374)	(1,429)
Acquisitions/disposals	0	0	3,500	0
Financing	62,735	477	0	0
Dividends	0	0	0	0
Other	12,527	12,975	5,836	5,836
Net Cash Flow	18,424	(33,227)	(24,113)	(22,542)
Opening net debt/(cash)	1,756	(13,744)	22,147	46,260
HP finance leases initiated	(3,191)	(2,646)	0	0
Other	267	(18)	(0)	0
Closing net debt/(cash)	(13,744)	22,147	46,260	68,802

Source: Transgene, Edison Investment Research

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