EDISON

Kiadis Pharma

Initiation of coverage

A smart approach to stem cell transplantation

Pharma & biotech

Kiadis Pharma is developing T cell-based therapies to address the issues associated with haematopoietic stem cell transplantation (HSCT). The company is leveraging its Theralux technology to develop ATIR101 and ATIR201 as adjunct therapies to HSCT in leukaemia and thalassemia, respectively. On the back of Phase II data, Kiadis is aiming for accelerated filing of ATIR101 with the European Medicines Agency (EMA) in Q117. A Phase III trial will start in H216. ATIR201 will start a Phase I/II trial in H216. Cash at end June 2016 was €23.7m, sufficient to fund operations until early 2018. We value the company at €327.3m or €27.1/share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/14	0.00	(7.21)	(0.07)	0.0	N/A	N/A
12/15	0.00	(17.35)	(0.14)	0.0	N/A	N/A
12/16e	0.00	(9.99)	(0.08)	0.0	N/A	N/A
12/17e	0.00	(13.47)	(0.11)	0.0	N/A	N/A

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

Looking to a fast path to market

Following ATIR101 Phase II data, Kiadis has decided to file for conditional approval with the EMA in Q117, setting a potential approval date in Q118. We believe it is possible that Kiadis may get approval given the precedent set by MolMed, which recently received Conditional Marketing Authorisation (CMA) from the European Commission on data from a small Phase II study that showed a one-year survival rate of 49% vs 37% for historical control. The regulatory pathway is also clear in the US; the Phase III primary endpoint and active comparator arm have been defined after an end of Phase II meeting with the FDA. This Phase III trial is needed for full approval in both the US and EU.

A smart approach in a rapidly growing market

Kiadis's Theralux platform is a photodynamic system that removes donor cells that are reactive to the host's immune cells and may cause complications after HSCT, thereby providing immunological support post-transplantation without increasing the risk of graft vs host disease (GVHD). This allows for a better response to tumour (graft vs leukaemia effect), reduces opportunistic infections, diminishes treatment-related mortality (TRM) and prolongs survival. The EMA has granted orphan drug designation expansion to ATIR101 for its use in HSCT regardless of the underlying cause of disease, expanding its market potential.

Valuation: Starting with an rNPV of €327.3m

We estimate a risk-adjusted value of €27.1/share, using a 12.5% discount rate. We assume ATIR101 will be approved in the EU in Q118 and sales will ramp up quickly to combined peak sales of $501m. We estimate a 70% probability to reach the market in the EU and 50% in the US, where a full Phase III study is needed for approval. Our valuation includes net cash of €7.7m at end of June 2016.

15 September 2016

Price	**€11**
Market cap	**€154m**
	US$1.11/€
Net cash* (€m) at June 2016 *Excludes Hospira debt	16.2
Shares in issue	12.06m
Free float	31.1%
Code	KDS
Primary exchange	Euronext Amsterdam
Secondary exchange	Euronext Brussels

Share price performance

%	1m	3m	12m
Abs	(5.2)	4.8	(0.1)
Rel (local)	(2.4)	(0.4)	(3.1)
52-week high/low		€12.4	€9.75

Business description

Kiadis Pharma is a Dutch biotech company focused on cell-based immunotherapies to overcome complications associated with stem cell transplants in blood diseases. Lead product ATIR101 for leukaemia is undergoing a Phase II trial and will file for EU approval in Q117. ATIR201 is in preclinical stage and has potential for thalassemia. A Phase I/II study will start in H216.

Next events

Phase II one-year data	H216
ATIR101 Phase III start	H216
ATIR201 Phase I/II start	H216
ATIR101 EU filing	Q117

Analysts

Juan Pedro Serrate +44 (0) 20 3681 2534

Lala Gregorek +44 (0) 20 3681 2527

healthcare@edisongroup.com

Edison profile page

Kiadis Pharma is a research client of Edison Investment Research Limited

Investment summary

Company description: Cellular immunotherapies for HSCT

Kiadis Pharma is a biopharmaceutical company headquartered in Amsterdam focused on cell-based immunotherapies. Kiadis was spun out of the University of Leiden in 1997 and its recent history begins in 2006 when it merged with Canadian company Celmed BioSciences and focused on T cell-based therapies for the immune system. Following a €10m financing round in 2012, a Phase II trial started. This trial, which is still running, but has already met its primary endpoint of transplant-related mortality at six months, will present one-year data in H216.

Kiadis's products ATIR101 and ATIR201 stem from its proprietary Theralux technology platform; they are adjunct therapies designed to support the immune system of leukaemia and thalassemia patients after haematopoietic stem cell transplantation. The company intends to submit an application for approval of its lead product ATIR101 to the EMA in Q117, with a potential decision in Q118. To gain full approval in the EU and US, Kiadis has to run a Phase III trial that will start in H216.

Kiadis floated on Euronext Brussels and Euronext Amsterdam in July 2015, raising gross proceeds of €34.7m (€31.2m net) at a price of €12.5 per share, and valuing the company's shares at €150.7m.

Valuation: rNPV of €327.3m or €27.1/share

Our valuation of Kiadis is €327.3m or €27.1/share, based on a risk-adjusted NPV analysis using a 12.5% discount rate. We assume peak sales of $227.75m in the EU and $273.3m in the US. This is based on $125,000 per treatment in the EU and $150,000 per treatment in the US and 20% market share in the small subpopulation of haplo-HSCT. We assume the company does not out-license the rights for the Theralux platform.

Financials: Enough cash to complete milestones

At the end of June 2016 Kiadis had cash and equivalents of €23.7m, which will be sufficient to fund operations into early 2018. Cash burn will increase over the next two years as a result of the Phase III clinical trial initiation. The company completed a public listing in July 2015, offering 2.6m shares at €12.5/share, raising net proceeds of €31.2m. The company has a debt facility of up to $25.7m with Hospira (Pfizer), which is contingent on sales and will pay royalties on worldwide net sales of 5% until the debt is repaid, falling to 3.5% on EU sales indefinitely.

Sensitivities: Development of cell-based products

The main sensitivities for Kiadis Pharma are clinical development, manufacturing, regulatory applications and reimbursement for its products. Lead product ATIR101 has generated proof-of-concept data, but it has to successfully complete a Phase III programme compared with an active arm to gain full approval. Conditional approval based on the Phase II data in the EU seems plausible, mainly in light of the conditional approval obtained by competitor MolMed. Still, Kiadis must complete the regulatory process and await the EMA's decision. Manufacturing will define consistency and cost of goods therefore affecting gross margin. Moreover, pricing and reimbursement will be dependent on the survival benefit without chronic GVHD that the product shows in the Phase III trial. Second product ATIR201 has to enter clinical trials, complete a full clinical development programme and satisfy regulatory requirements to enter the market.

Company description: Pure immunotherapy play

Kiadis Pharma is focused on the development of T cell-based immunotherapies to address complications associated with HSCT. For patients with blood disorders an HSCT is deemed curative. In an HSCT, immune stem cells from a healthy donor are administered after destroying the host's bone marrow. While the new immune cells populate the host's bone marrow and it becomes competent again, the patient is at risk of opportunistic infections and cancer relapse. To avoid this, Kiadis Pharma is leveraging its Theralux system to develop a generation of ATIR products (Allodepleted T-cell ImmunotheRapeutics) to support the patient's immune system while it becomes fully functional. The Theralux system allows the infusion of lymphocytes from a partially matching (haploidentical) family member to the donor as it eliminates cells that could react against the host's immune cells and cause GVHD. The lead product is ATIR101, an adjunct therapy to HSCT for leukaemia patients currently in Phase II, with a Phase III trial slated to commence in H216. The company anticipates an EU regulatory filing in Q117. Additionally, ATIR101 is undergoing a Phase II study in which a second dose of the product is administered to patients before the 100-day period post-transplantation to support faster immune-reconstitution. Full enrolment and safety readout will be completed in H217.

The second product, ATIR201 for thalassemia, is currently in the preclinical stage. A Phase I/II programme is slated to start H217. The development pipeline is summarised in Exhibit 1.

Exhibit 1: Kiadis Pharma product portfolio

Product	Indication	Status	Potential launch	Comments
ATIR101	Leukaemia	Phase II	2018	Presented positive primary endpoint data. One-year data expected H216. Regulatory filing in EU in Q117. Phase III start in Q316.
ATIR201	Thalassemia	Preclinical	2022	Preclinical stage. Start Phase I/II trial in H216.

Source: Edison Investment Research, Kiadis Pharma

Addressing the limits of stem cell transplantation

The degree of compatibility between donor and host is primarily determined by the human leukocyte antigen (HLA) system. These are the main proteins that are recognised by the immune system to determine whether they are own cells or foreign. Transplant from a matching donor improves the chances of success and reduces the risk of potential complications. A matching donor must have the same HLA type and is a sibling (SIB) in less than 25% of cases; or an unrelated donor found in a database (MUD) in around 45-55% of cases. Yet a matching donor is not always available. In these cases, cells from a mismatching donor (mmUD) or unrelated cord blood (UCB) can be used. However, there is an increased risk of side effects and limited availability. Therefore, for approximately 35% of patients who are in urgent need and cannot find a matching donor in time, a haploidentical (half matched) family donor is usually available.

The main complications involve graft vs host disease (GVHD), transplant rejection, disease relapse, and infections. Exhibit 2 shows the main complications associated with HSCT, which Kiadis aims to address.

Exhibit 2: Complications arising from HSCT

Complication	Description	Management
Graft rejection	The recipient's immune system reacts against the donor's cells.	Re-transplantation mainly from another donor. T cells of the recipient have to be removed by treatment with anti-lymphocyte antibodies before a second transplant can be performed.
Graft versus host disease (GVHD)	Donor cells attack host tissues in an immunocompromised recipient	First-line: immuno-suppression with corticosteroids. No consensus on second-line and third-line therapy for steroid-refractory GVHD.
Opportunistic infections	Infections take advantage of the host's immunodepression after chemotherapy.	CDC guidelines.
Relapse	Disease comes back after first treatment. Patients have a poor prognosis after relapse.	Re-treatment. Further chemo and another HSCT.

Source: Edison Investment Research

Graft vs host disease after stem cell transplantation

Graft versus host disease occurs when an immunocompetent donor's cells recognise and attack cells from an immunocompromised host after HSCT. GVHD is divided into acute GVHD (aGVHD), when symptoms develop before 100 days after transplant, and chronic GVHD (cGVHD), when symptoms develop 100 days post-transplantation. Acute GVHD is graded (grade I-IV) according to the number and extent of organ involvement. GVHD symptoms typically involve the skin (rash and dermatitis), liver (hepatitis and jaundice) and the digestive system (diarrhoea, abdominal pain). Grade III/IV GVHD is a life threatening condition; the 10-year survival rate for patients with chronic GVHD is lower than 5%.

Acute GVHD occurs in c 30% of recipients of full matched sibling donor grafts and in up to 52% of recipients of unrelated matched grafts. Similarly, for patients with cGVHD, these numbers are 30% and 60-70% respectively. Patients receiving grafts from unmatching donors have an almost 100% risk of GVHD. These percentages largely depend on various factors such as the degree of HLA disparity, age, conditioning and GVHD prophylaxis therapy.

Treatment and prevention of GVHD

Ideally, a transplant regimen should ensure high engraftment rates and minimal post-transplant toxicity. It should allow a graft-versus-tumour (GVT) effect, and lower rates of aGVHD and cGVHD.

To prevent GVHD, T cells can be depleted from the donor tissue. This strategy has been used for more than three decades and has decreased the incidence of GVHD, reduced the need for immunosuppression, and decreased organ toxicity and early transplant-related mortality. Administration of topical or systemic corticosteroids remains the mainstay first-line treatment for GVHD, depending on degree of organ involvement. Responses vary between 30% and 50% across different organs (skin, liver and gut). Patients not responding to first-line therapy have few options available and none of them has shown convincing long-term benefit. As a result, refractory patients have high morbidity and mortality rates.

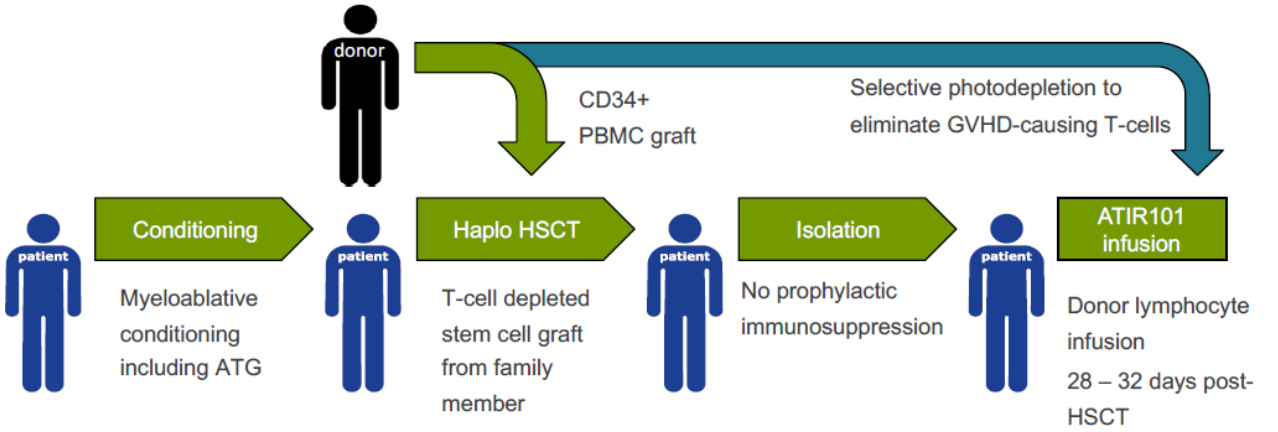
Supporting the immune system without increased risk of GVHD

Kiadis Pharma's process comprises the following steps:

- The patient first undergoes a myeloablative regimen, which consists of high dose chemotherapy with or without total body irradiation (TBI) treatment to destroy the diseased bone marrow.
- The patient receives a T cell depleted transplant from a family donor. The transplant only contains CD34+ stem cells that do not cause GVHD, which is the standard of care for stem cell transplantation. These multipotent stem cells have the capacity to generate any other blood cell. Grafted cells colonise the patient's bone marrow and replace damaged tissue, resulting in a blood forming and functional immune system.

- Kiadis introduces a smart step. 28-32 days post-transplant the patient is administered ATIR101 – GVHD-causing T cells have been removed and it contains only T cells that will help reconstitute the immune system, prevent infection and fight residual cancer cells.

Exhibit 3: Haplo-HSCT with ATIR101



Source: Kiadis Pharma

Ideally, a transplant regimen should ensure high engraftment rates and minimal post-transplant toxicity. It should allow a graft-versus-tumour (GVT) effect, and lower rates of GVHD. ATIR101 intends to balance the need of T cells that may increase the risk of GVHD with infection prevention, and therefore yield better outcomes.

Epidemiology

A 2014 survey conducted by the European Group for Bone Marrow Transplantation (EBMT) showed that 40,829 HSCTs were performed in Europe in 36,469 patients (15,765 allogeneic, or 43%; and 20,704 autologous, or 57%). One of the main indications was leukaemia: 11,853 (33% of total), of which the vast majority (96%) were allogeneic; while non-malignant blood disorders accounted for 2,203 procedures (6% of total; 88% allogeneic).

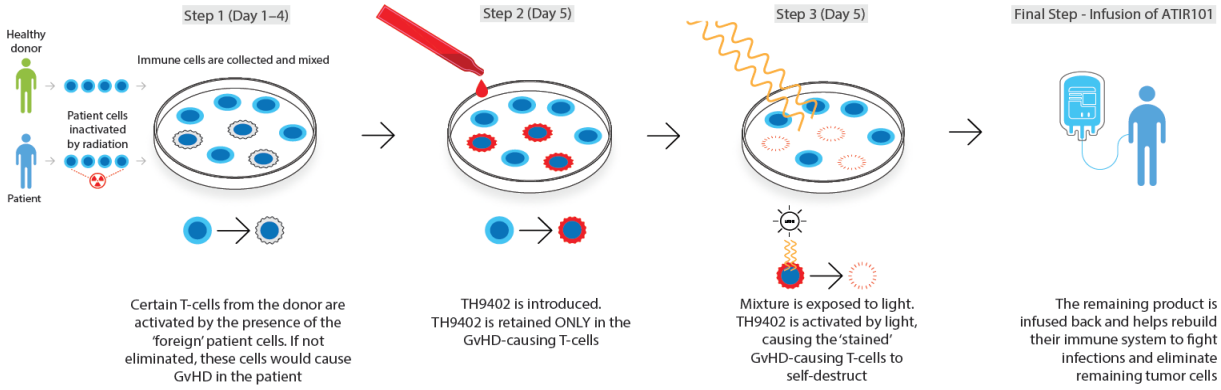
Kiadis is testing ATIR101 in patients transplanted with stem cells from partially matched related donors. The EBMT study shows that, since 2009, the number of transplants in this segment has been growing at approximately 25% a year. An estimated 2,000 transplants were performed in 2016 in the EU, with potentially similar numbers in the US. These transplants are performed in an academic setting, thus we believe that providing them as a commercial product may increase uptake. There is further market opportunity in the group of patients that find a matched unrelated donor of up to 19,000 patients, which remains upside to our estimates.

Theralux: A photodynamic allodepletion system

Theralux is a photodynamic cell therapy system that purges donor's cells responsible for potential post-transplant complications. Theralux achieves selective allodepletion of host-reactive donor T cells from HSCT by administering the proprietary compound TH9402.

TH9402 (4,5-dibromorhodamine methyl ester) is a photosensitiser similar to rhodamine. As with other dyes, it is transported in and out of cells by the P-glycoprotein (Pgp) system. Activated T cells have the Pgp system impaired and therefore TH9402 remains inside the cell, preferentially located in mitochondria. TH9402 becomes highly cytotoxic through oxidative damage when exposed to light delivered through the Theralux system. Therefore, the host-reactive cells containing TH9402 are eliminated, leaving only non-activated cells in the graft.

Exhibit 4: Theralux process



Source: Kiadis Pharma

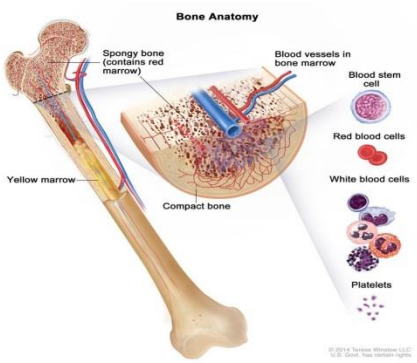
Kiadis Pharma has an exclusive licence for the intellectual property rights pertaining to the Theralux platform from the University of Montreal and Maisonneuve-Rosemont Hospital. Under the terms of the agreement, the company has to pursue development and commercialisation of products stemming from the Theralux technology and pay a royalty of 5% on net sales indefinitely.

The company has intellectual property pertaining to TH9402, the process and the Theralux device. Key IP will expire at end 2020, but we do not expect generic competition given the nature of the product. Moreover, the EMA's orphan drug designation provides 10-year market exclusivity. More recent IP on the manufacturing process is pending and has not been granted yet.

ATIR101: The Theralux approach to leukaemias

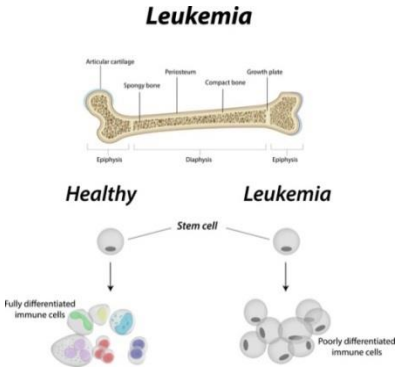
Leukaemias are cancers of the blood and bone marrow affecting white cells, also known as leukocytes. Leukaemias originate in the bone marrow where blood stem cells start dividing and impede the normal functioning of blood cells, therefore interfering with functions such as fighting infections, blood clotting or carrying oxygen.

Exhibit 5: Bone marrow description



Source: The website of the National Cancer Institute (www.cancer.gov)

Exhibit 6: Healthy stem cells vs leukemic cells



Source: US National Library of Medicine

Leukaemias are classified according to the speed at which they progress. Acute leukaemias progress rapidly, whereas chronic leukaemias develop slowly.

According to the Surveillance, Epidemiology, and End Results (SEER) programme, in 2013 there were 333,975 people with leukaemia in the US. Incidence was 13.5 per 100,000 people (44,550 patients), with a mortality rate of 6.9 per 100,000 people per year (22,700 patients). The overall five-year survival rate is 60%. According to EUCAN data, incidence in Europe is 9.2 per 100,000 people (46,736 patients), with a mortality rate of 5.2 per 100,000 people per year (26,416 patients). The overall five-year survival rate for acute leukaemias is around 30% and over 80% for chronic leukaemias. The four main types of leukaemias are:

- Acute lymphoblastic leukaemia (ALL), which is the most common type of leukaemia in children, but most deaths are in adults. It accounts for about 12% of all leukaemias in Western countries.
- Acute myelogenous leukaemia (AML), which accounts for about 12% of all leukaemias.
- Chronic lymphocytic leukaemia (CLL), which accounts for about 35% of all leukaemias in Western countries.
- Chronic myelogenous leukaemia (CML), which accounts for approximately 15% of all leukaemias in Western countries.

Before stem cell transplantation can take place, patients have to undergo chemotherapy with or without total body irradiation to remove cancerous cells and to create space in the bone marrow for new cells. The goal of therapy is to put the patient into a lasting remission, which means that there are no detectable (<5%) cancer cells in the blood or bone marrow. Most patients achieve remission after induction therapy; however, not all patients respond to treatment (classified as refractory) or disease comes back after a while (relapse).

Many recipients of HSCTs are multiple myeloma or leukaemia patients who would not benefit from prolonged treatment with, or are already resistant to, chemotherapy.

Allodepleted Immunotherapeutics 101 – Product description

ATIR101 (Allodepleted T-cell ImmunotheRapeutic) is Kiadis Pharma's lead product, intended as an adjunct therapy to HSCT to prevent undesirable effects derived from the transplant procedure and support the patient's immune system while it recovers. ATIR101 contains mature T-cells from a half matched family donor and has been treated with the Theralux system as previously described.

ATIR101 has orphan drug designation (ODD) from the EMA and the FDA for hematopoietic stem cell transplantation independent of the underlying cause of disease. ODD provides 10-year market exclusivity after approval and fee reductions. The product has been tested on partially matching, non-sibling, family donors, which is the population that Kiadis targets and we include in our model.

Exhibit 7: Kiadis Pharma clinical trials

Product	Trial ID	Phase	No of patients	Initiation	Primary completion	Observations	Primary endpoint
ATIR101	NCT00993486	I/II	19	Jan 05	Oct 08	Dose-ranging study. Completed	Dose limiting toxicity, defined as aGVHD grade III or IV within 30 days after ATIR101 infusion.
ATIR101	NCT01794299	II	23	Mar 13	Apr 16	Safety and efficacy trial. Ongoing	Primary endpoint TRM at 6 months 13%,.OS 83%.
N/A	NCT02188290	Observational	178	Sep 14	Jun 15	Retrospective trial to provide historical controls for NCT01794299 study. Completed	Transplant-related mortality up to 12 months after transplantation.
ATIR101	NCT02500550	II	15	Oct 15	H2 17	Safety and efficacy trial. Two doses. Recruiting	Incidence of aGVHD grade III/IV at 6 months.
ATIR101	N/A	III	~200	H216	2018	Randomised, controlled clinical trial. Haplo + ATIR101 vs Haplo + Cyclophosphamide (Baltimore regimen). Start H216	GVHD and relapse-free survival (GFRS), event-driven.

Source: Edison Investment Research, BioCentury, clinicaltrials.gov

Discussion of the data

Phase I data presented at the 2009 edition of the American Society of Hematology (ASH) meeting provided proof of principle. Of 19 patients with relapsed or refractory hematologic malignancies, none developed acute GVHD grade III or IV; 5 patients developed grade II GVHD; while 9 patients developed signs of chronic GVHD. Eight patients died; 4 due to relapse and 4 of infections. Treatment-related mortality at 2 years post-SCT was 27%. Overall survival at 2 years was 60%.

In a multicentre, open-label Phase II trial (CR-AIR-007, NCT01794299), 23 patients (17 AML and six ALL) underwent a T cell depleted haploidentical transplant followed by ATIR101 infusion on day 28 post HSCT. There was no transplant-related mortality (TRM) after 100 days of treatment. There were three deaths as a result of TRM within six months post-HSCT (primary endpoint), yielding a TRM rate of 13%. All three patients died from infection. In addition, one patient died from disease relapse in the first six months, resulting in an overall survival of 83%. There were no cases of grade III-IV acute GVHD and only two cases of grade II acute GVHD as reported in the last follow up on 24 March. One-year follow up data will be released in H216.

Data from the trial were matched against a historic control group. These historical data were obtained from the observational study CR-AIR-006 (NCT02188290). When compared to the historical control group (N=35), TRM was significantly lower in patients given ATIR101 after a T-cell depleted haplo HSCT with a six-month TRM of 13% versus 37% for HSCT only (p=0.005). In terms of OS, two patients developed disease relapse within 12 months after HSCT, which translates into a significantly improved OS (p=0.0026) of patients undergoing HSCT + ATIR101 compared to HSCT only. Kaplan-Meier curves estimate one-year survival in the HSCT + ATIR101 group of 64% vs 20% in the historical control group.

Historical data

The US Centre for International Blood and Marrow Transplant Research (CIBMTR) reported 10-year survival data for almost 31,000 patients with blood conditions, mainly leukaemias, at different stages of disease. The main findings are shown in Exhibit 8.

Exhibit 8: Survival at six months, one year and five years after HSCT by stage and donor type

Condition	Donor type	Stage								
		Early			Intermediate			Advanced		
		6 months	1 year	5 years	6 months	1 year	5 years	6 months	1 year	5 years
AML	MSD	85%	76%	49%	82%	70%	45%	60%	45%	20%
	URD	78%	67%	45%	75%	62%	42%	55%	38%	20%
ALL	MSD	86%	73%	50%	75%	60%	30%	66%	46%	22%
	URD	80%	70%	50%	70%	52%	33%	53%	35%	15%
CML	MSD*	85%	79%	65%	79%	65%	50%	55%	38%	20%
CLL	MSD	88%	77%	50%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	URD	80%	68%	37%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
MDS	MSD	76%	70%	48%	N.D.	N.D.	N.D.	76%	65%	38%
	URD	74%	62%	45%	N.D.	N.D.	N.D.	70%	56%	33%

Source: Edison Investment Research, Centre for International Blood and Marrow Transplant Research (CIBMTR). Note: MSD: matching sibling donor. URD: unrelated donor. N.D.= no data. *No URD data available.

Kiadis has so far presented six-month data from 23 patients, 17 with AML and six with ALL, aged between 21 and 64 years (median 41). Of the 17 AML patients, 12 were in first complete remission (CR1) and five were in second complete remission (CR2) at the time of HSCT. Of the six ALL patients, four were in CR1 and two were in CR2 at the time of HSCT.

Kiadis has tested ATIR101 on a population of partially matching family donors, and compared it with the closest population from the same centres. The CIBMTR numbers are either from matching siblings or matching unrelated donors. Thus, although it is not possible to draw exact parallels, we have compared it with the intermediate AML patient data from unrelated donors as the closest to Kiadis Phase II population.

Exhibit 9: Comparison between Kiadis Phase II study and historic CIBMTR data

Endpoint	Arm	6 months	1 year
TRM	Kiadis Ph II HSCT + ATIR101	13%	N/A
	Kiadis Ph II Historic controls	37%	N/A
	CIBMTR	N/A	N/A
Survival	Kiadis Ph II HSCT + ATIR101	83%	64%*
	Kiadis Ph II Historic controls	63%	20%*
	CIBMTR	75%**	62%**

Source: Edison Investment Research, Centre for International Blood and Marrow Transplant Research (CIBMTR), Kiadis Pharma. Note: *Kaplan-Mayer projection, actual data will be published in H216. **Assume intermediate stage data from AML URD patients as the closest to Kiadis population.

We conclude that six-month data shows an improvement in the ATIR101 study for the two endpoints compared with Kiadis's historic arm and also with the data gathered from the CIBMTR.

Next steps: Accelerated registration and full Phase III

Following interactions with the European Medicines Agency (EMA), Kiadis Pharma announced that it intends to file for conditional approval in Europe in Q117. This represents a potential approval in Q118 and commercialisation in H118 in the EU. Given the precedent of competitor MolMed, which has received Conditional Marketing Authorisation (CMA) from the European Commission, we believe that it is likely that Kiadis will receive conditional approval based on Phase II data. To gain full approval, Kiadis must run a Phase III trial designed to show survival without relapse, which will start in H216. Enrolment will take 1.5 years and final analysis is expected in H219. The trial will compare ATIR101 with the Baltimore approach. This protocol is considered the current standard of care for patients who lack a fully matched donor and consists of administering cyclophosphamide after transplantation to control alloreactivity.

The primary endpoint of the Phase III trial will be GVHD-free/relapse free survival (GFRS). This is a composite endpoint defined as grade III-IV aGVHD, cGVHD requiring systemic treatment, cancer relapse, or death one-year post-transplant. Essentially, it measures survival free of morbidity. One-year GFRS varies across donor type, patient age and other factors. A study comparing AML patients receiving the Baltimore regime with the company's projected one-year data from the ATIR101 Phase II study shows lower relapse (41% vs 10.5%), lower cGVHD (28% vs 4%), lower grade III-IV aGVHD (7% vs 0%) and lower grade I-II aGVHD (16% vs 4%). However, survival rates are similar (65% vs 64%) and non-relapse mortality is worse (12% vs 29%). Kiadis's assumption for the Phase III trial is that ATIR101 will improve GFRS at 1 year from c 40% to approximately 60%. The Baltimore regimen showed a 1-year GFRS of 31% for the entire population in a recent study by Soth et al. We are cautiously optimistic that the Phase III trial may meet the primary endpoint, taking into account that Kiadis Phase II patients had a higher disease-risk index and the fact that the populations are similar.

Both the primary endpoint and the comparator regime were confirmed after an end of Phase II meeting with the FDA. The company is not pursuing a Special Protocol Assessment (SPA) in order to retain flexibility.

Kiadis is testing a second dose of the product administered to patients before the 100-day period post-transplantation to potentially expedite immune reconstitution (NCT02500550). Full enrolment and safety readout in six patients will be completed in H216. This study will test the safety and help understand the potential impact of a second dose in improving outcomes.

If conditional approval is not achieved, the approval and marketing timelines in the EU would be pushed back two years, to 2019 and 2020, respectively. An end of Phase II meeting with the US FDA took place in June and the company has to decide on whether to file for Breakthrough Therapy Designation (BTD).

The GFRS endpoint ultimately will provide clarity on price and the real benefit of the product. Clinicians are focused on overall survival, while payers will want to see survival without chronic GVHD, which has a large impact on the total cost of treatment.

Kiadis is exploring a number of commercial alternatives, but since marketing will be concentrated on specialised transplant centres, the company for now plans to retain rights in all territories and market the product on its own.

Competitive landscape

Other companies developing therapies to prevent the risks and limitations of HSCT in haplo-HSCT transplants from family donors are the shown in Exhibit 10.

Exhibit 10: Marketed and experimental therapies for HSCT complications

Company	Exchange; market cap	Product, type	Phase	Comment
MolMed	Milan; €144m	Zalmoxis, suicide gene cells	Recommended for conditional approval	Received conditional approval from EC One-year survival rate 49% vs 37% from historical database in 45 patients.
Bellicum	Nasdaq; $374m	BPX-501, CID safety switch	Phase II	Data presented at ASH 2015 (n=39) in paediatric patients. BPX-501 was generally well tolerated. Seven cases of grade 1 and 2 GVHD that resolved without need of activating safety switch. No mortality associated to BPX-501. 2022 sales forecast $674m (EvaluatePharma).

Source: Edison Investment Research, BioCentury, clinicaltrials.gov

The main difference with MolMed and Bellicum is that both companies use cells that have a suicide gene that is activated to eliminate them in the event of toxicity. When patients develop the first GVHD symptoms, a compound is administered to trigger apoptosis of the cells. ATIR101, on the other hand, contains T cells that have been treated prior to being infused into the patient. Bellicum uses rimiducid and its data have been generated in children, while MolMed uses ganciclovir, a widely used antiviral drug. Moreover, MolMed's historical arm comes from an uncontrolled database

whereas Kiadis is using patients from the same centres with the same characteristics for the Phase II comparator arm. In spite of this, MolMed has secured conditional approval from the European Commission, which technically secures approval. We view this news as positive for the approval of Kiadis's ATIR101.

ATIR201: The Theralux approach to thalassemia

ATIR201 is the second product in Kiadis Pharma's pipeline. Clinical development will be focused on inherited blood disorders, ie genetic non-malignant disorders that are passed through families, such as haemophilia, sickle cell disease and thalassemia. The product uses the same Theralux technology as ATIR101 to eliminate host reactive cells from the donor.

Kiadis will initially target thalassemia, a genetic disorder characterised by defects of the gene that encodes haemoglobin, the protein that carries oxygen in red cells. When a gene or genes related to the production of alpha globin protein are missing or mutated, the disease is called alpha-thalassemia; while when beta genes are involved, the disease is referred to as beta-thalassemia. There are different types of beta-thalassemia; if only one gene is inherited, symptoms are mild; if two genes are inherited, symptoms are moderate to severe and it is called thalassemia major. Treatment for thalassemia involves regular blood transfusions and folate supplements. Thalassemia can also be treated with HSCT, but the same complications as leukaemias, such as GVHD, or infections, may occur.

A preparation is administered to the patient before performing stem cell transplantation. In general, this procedure yields better outcomes in this setting. For matched unrelated donors, a study from La Nasa et al. 2005b showed rates of survival, thalassemia-free survival, TRM and rejection of 70%, 70%, 30%, and 4%, respectively. The same research team (La Nasa et al. 2005a) shows that the incidences of acute grade II–IV or grade III–IV GVHD were 40% and 17%, respectively. 18% of patients developed chronic GVHD.

The two-year thalassemia-free survival was 71% for patients who received transplants from matched unrelated donors and 82% for patients who received transplants from matched related donors.

Kiadis's project is conducted in collaboration with non-governmental organisation Thalassaemia International Federation (TIF). This gives Kiadis access to a large pool of thalassemia experts and patients.

Kiadis will initiate a Phase I/II trial in H216, with initial data in 2017 and full readout in 2018.

Sensitivities

Kiadis is subject to the usual risks associated with development stage biotech companies, including potential clinical development delays or failures, regulatory risks, competition, partnering setbacks, financing, manufacturing and commercial risks (launch, uptake and competition dynamics). The sensitivities are:

- Clinical development: the most developed product is ATIR101. So far it has demonstrated its ability to reduce transplant-related mortality compared with a selected historical control arm. However, it still has to successfully complete a Phase III trial with an active comparator arm. ATIR201 has to enter clinical trials to fully demonstrate its potential in terms of efficacy and safety.
- Regulatory risk: the company has chosen to file for regulatory approval with the EMA, expected in Q117. It has provided little information on the dialogue with the EMA, which makes it difficult

to assign a probability of success for this event. Even if ATIR101 gets approved, the company will need to run a full Phase III trial with an approximate cost of €20-22m, which is included in our projections.

- Competition: MolMed has secured a Conditional Marketing Authorisation (CMA) from the European Commission. Although behind in development, other companies like Bellicum may also try to file for accelerated approval in the US and/or EU. An accelerated approval in the US would put them in an advantage with respect to Kiadis's ATIR101 programme, which will wait for full Phase III data to file with the FDA. Also, generic T cell depletion techniques have been used for years in the clinical setting with good results. In order to be commercially successful, ATIR101 must demonstrate a superior profile not only with regard to efficacy and safety, but also concerning manufacturing, administration and ease of use. Likewise, competitors may generate other products differentiated in terms of clinical data, manufacturing, commercial strategy, pricing and margins, hampering Kiadis Pharma's market penetration.
- Financial risk: as a development stage company with no revenues, we expect the company to remain loss-making until 2019, when we project positive cash flows from operations. Margins will be affected by the cost of goods sold, and ultimately by the manufacturing process. Furthermore, there is the risk of dilution and the amount and price at which the company can raise funds will be dependent on general market conditions.
- If data are positive and approvals are granted, pricing and reimbursement will be a key sensitivity. With the focus on value-based pricing models in Europe, limitations may be imposed that affect peak sales potential. ATIR101 has to demonstrate a survival benefit without chronic GVHD over a year to obtain premium pricing. Our valuation is based on our ATIR101 estimates for price and penetration, which we believe are reasonable. However, these could be affected by unknown future pricing dynamics.

Valuation

Using the discounted cash flow (DCF) method, we arrive at a risk-adjusted value of €27.1/share, using a 12.5% discount rate.

Assumptions

We have projected the future free cash flows using the following assumptions:

- We estimate a high probability of 70% that ATIR101 is marketed in Europe in by YE18, supported by MolMed's conditional approval. In the US, we use a 50% base-case probability that ATIR101 successfully completes the Phase III trial and enters the market in H220.
- We believe Kiadis can address 2,000 patients in Europe based only on the current number of haplo-HSCT transplants, with 25% growth the first years on the market that plateaus five years post-launch and 3% growth a year from 2022. We assume a similar opportunity in the US.
- We assume a price tag of $125,000 per treatment in the EU and $150,000 in the US, with a 20% penetration rate in both markets as we assume ATIR101 will be second to market.
- We assume Kiadis pursues a self-commercialisation strategy. Hence, we project no royalties/milestone payments from partners, except for a 5% royalty to the University of Montreal and 3.50% to Hospira post paydown of debt
- In Europe we assume sales from Q418, building rapidly to a peak of $227.75m. We forecast US approval in 2020, launch at the end of that year and peak sales of $273.3m. We apply a gross margin of 50% at the beginning, evolving to 80%.

We are not including ATIR201 in the valuation model because it is in the preclinical stage. Once clinical data are released, we will add them to our model.

Exhibit 11: Kiadis Pharma rNPV valuation

Product	Indication	Launch	Peak sales (US$m)	Probability	rNPV (€m)	rNPV/share (€)
ATIR101 EU	Leukaemia	2018	227.75	70%	309.7	25.7
ATIR101 US	Leukaemia	2020	273.3	50%	224.4	18.6
Expenses					-214.4	-17.8
Net cash June 2016*				100%	7.7	0.6
Valuation					**327.3**	**27.1**

Source: Edison Investment Research. Note: * includes Hospira debt.

Financials

We project the first sales to take place in Q418 after the EU approval of ATIR101. We expect total R&D and SG&A expenses to be in the range of €12-14m per year for 2017-18. At the end of June 2016 Kiadis had net cash of €7.7m. We estimate cash burn will increase over the next two years to €28m as a result of the initiation of the Phase III clinical trial. Therefore, we expect the company will raise €12m (that we class as long-term debt for illustrative purposes only).

.We assume a base case in which production is outsourced and there is no additional capital expenditure. In 2015 stock options are shown as SG&A; we do not project additional share-based payments. In our model Kiadis has €7.26m debt from the Dutch government that matures in 2020 and is paid in quarterly instalments of approximately €400,000. The debt with Hospira is contingent on future sales. According to the deal terms, Kiadis would have to pay 5% royalty on net sales in Europe until a certain threshold has been repaid and a 3.5% royalty on EU sales thereafter. The licencing agreement with the University of Montreal includes a 5% royalty on future net sales.

The company completed a public listing in July 2015, offering 2.6m shares at €12.5/share raising gross proceeds of €34.7m. Kiadis's shares are listed on the Euronext Amsterdam and Euronext Brussels exchanges.

Exhibit 12: Financial summary

€'000s	2013	2014	2015	2016e	2017e	2018e
Year end 31 December	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS						
Revenue	0	0	0	0	0	3,906
Cost of Sales	0	0	0	0	0	(1,953)
Gross Profit	0	0	0	0	0	1,953
R&D expenses	(3,548)	(4,692)	(7,715)	(7,230)	(10,000)	(10,000)
SG&A expenses	(1,444)	(1,476)	(8,292)	(1,476)	(2,000)	(4,000)
EBITDA	(4,890)	(6,042)	(15,867)	(8,606)	(11,900)	(12,142)
Operating Profit (before GW and except.)	(4,992)	(6,168)	(16,007)	(8,706)	(12,000)	(12,242)
Intangible Amortisation	0	0	0	0	0	0
Exceptionals/Other	0	0	0	0	0	0
Operating Profit	(4,992)	(6,168)	(16,007)	(8,706)	(12,000)	(12,242)
Net Interest	(831)	(1,045)	(1,344)	(1,284)	(1,476)	(1,473)
Exceptionals	0	0	0	0	0	0
Other	(1,062)	(598)	894	0	0	0
Profit Before Tax (norm)	(5,823)	(7,213)	(17,351)	(9,990)	(13,476)	(13,715)
Profit Before Tax (IFRS)	(6,885)	(7,811)	(16,457)	(9,990)	(13,476)	(13,715)
Tax	0	(2)	(1)	0	0	0
Discontinued operations	0	0	0	0	0	0
Profit After Tax (norm)	(6,885)	(7,813)	(16,458)	(9,990)	(13,476)	(13,715)
Profit After Tax (IFRS)	(6,885)	(7,813)	(16,458)	(9,990)	(13,476)	(13,715)
Average Number of Shares Outstanding (m)	10.90	10.47	12.06	12.06	12.06	12.06
EPS - normalised (€)	(0.06)	(0.07)	(0.14)	(0.08)	(0.11)	(0.11)
EPS - IFRS (€)	(0.06)	(0.07)	(0.14)	(0.08)	(0.11)	(0.11)
Dividend per share (€)	0.00	0.00	0.00	0.00	0.00	0.00
Gross Margin (%)	N/A	N/A	N/A	N/A	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET						
Fixed Assets	13,428	14,100	13,047	13,047	13,047	13,047
Intangible Assets	13,148	13,687	12,714	12,614	12,514	12,414
Tangible Assets	280	413	333	433	533	633
Other	0	0	0	0	0	0
Current Assets	6,760	6,112	29,229	19,239	17,763	3,852
Stocks	0	0	0	0	0	98
Debtors	51	196	145	145	145	391
Cash	6,482	5,674	28,666	18,676	17,200	2,946
Other	227	242	418	418	418	418
Current Liabilities	(1,619)	(8,727)	(2,913)	(1,747)	(1,746)	(1,745)
Creditors	(1,235)	(1,598)	(1,747)	(1,747)	(1,747)	(1,747)
Short term borrowings	(384)	(7,129)	(1,166)	0	0	0
Deferred revenues	0	0	0	0	0	0
Other short term liabilities	0	0	0	0	1	2
Long Term Liabilities	(13,210)	(8,820)	(13,713)	(14,879)	(26,879)	(26,684)
Long term borrowings	(10,021)	(5,090)	(13,713)	(14,879)	(26,879)	(26,684)
Deferred revenues	0	0	0	0	0	0
Other long term liabilities	(3,189)	(3,730)	0	0	0	0
Net Assets	5,359	2,665	25,650	15,660	2,185	(11,529)
CASH FLOW						
Operating Cash Flow	(4,369)	(6,062)	(7,955)	(8,606)	(11,900)	(12,485)
Net Interest	(28)	(13)	(141)	(1,284)	(1,476)	(1,473)
Tax	0	0	0	0	0	0
Capex	(102)	(259)	(59)	(100)	(100)	(100)
Acquisitions/disposals	0	0	1	2	3	4
Financing	0	5,051	31,229	0	0	0
Dividends	0	0	0	0	0	0
Other	89	28	4	0	0	0
Net Cash Flow	(4,410)	(1,255)	23,079	(9,988)	(13,473)	(14,055)
Opening net debt/(cash)	(505)	3,923	6,545	(13,787)	(3,797)	9,679
HP finance leases initiated	0	0	0	0	0	1
Exchange rate movements	25	(8)	22	0	0	0
Other	(43)	(1,359)	(2,769)	(2)	(3)	(5)
Closing net debt/(cash)	3,923	6,545	(13,787)	(3,797)	9,679	23,738

Source: Edison Investment Research, Kiadis Pharma accounts

Contact details	Revenue by geography
Entrada 231-234 1114 AA Amsterdam-Duivendrecht The Netherlands Telephone +31 (0)20 314 02 50 Fax +31 (0)20 314 02 512 www.kiadis.com	N/A

Management team

CEO Manfred Rüdiger, PhD	CFO: Robbert van Heekeren
Dr Rüdiger joined Kiadis Pharma in 2011. He holds a PhD in biochemistry from the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany. Dr Rüdiger is a member of the supervisory board of 4SC. Prior to joining Kiadis, he was a venture partner at Life Sciences Partners (LSP). Dr Rüdiger has held leadership positions at various pharmaceutical companies such as Affectis Pharmaceuticals, t2cure, Aphton Corporation, Igeneon and Cardion Pharmaceuticals.	Mr van Heekeren joined Kiadis in 2008. He has a master's degree in economics from Tilburg University and in industrial engineering from Eindhoven University of Technology. He has undertaken executive education courses at Stanford University and Harvard. Mr van Heekeren has held various positions at Organon related to finance, from senior financial analyst to executive director, head of global finance and control.
CMO: Jeroen Rovers, MD, PhD	**General Counsel & Corporate Secretary: Margot Hoppe**
Dr Rovers joined Kiadis Pharma in 2008. He obtained his medical doctor degree from Leiden University, specialising in the use of light-activated drugs for the treatment of cancer. Dr Rovers practised medicine as a resident in surgery at Leiden University Medical Centre and Ziekenhuis Bronovo. Dr Rovers has ample experience in clinical trials and clinical development. He has held medical and research positions at Organon and Wyeth Pharmaceuticals (Pfizer). He was chief medical officer at Ceronco Biosciences.	Ms Hoppe has been general counsel and corporate secretary at Kiadis Pharma since 2008. She has worked as a lawyer specialised in the pharmaceutical industry for more than 20 years. She has worked for DSM and Gist-Brocades Ms Hoppe has a master's degree in law and political science from the Erasmus University of Rotterdam.

Principal shareholders	(%)
Draper Esprit	22.85
Lenildis Holding BV	15.26
Achmea Pensioen	11.03
Life Sciences Partners	7.91
Alta Partners	6.38
Quest for Growth	3.64
NOM Investment and Development Agency for the Northern Netherlands	2.92

Companies named in this report

MolMed (4HW GR), Bellicum (BLCM US)

Edison, the investment intelligence firm, is the future of investor interaction with corporates. Our team of over 100 analysts and investment professionals work with leading companies, fund managers and investment banks worldwide to support their capital markets activity. We provide services to more than 400 retained corporate and investor clients from our offices in London, New York, Frankfurt, Sydney and Wellington. Edison is authorised and regulated by the Financial Conduct Authority. Edison Investment Research (NZ) Limited (Edison NZ) is the New Zealand subsidiary of Edison. Edison NZ is registered on the New Zealand Financial Service Providers Register (FSP number 247505) and is registered to provide wholesale and/or generic financial adviser services only. Edison Investment Research Inc (Edison US) is the US subsidiary of Edison and is regulated by the Securities and Exchange Commission. Edison Investment Research Limited (Edison Aus) [46085869] is the Australian subsidiary of Edison and is not regulated by the Australian Securities and Investment Commission. Edison Germany is a branch entity of Edison Investment Research Limited [4794244]. www.edisongroup.com

DISCLAIMER

Copyright 2016 Edison Investment Research Limited. All rights reserved. This report has been commissioned by Kiadis Pharma and prepared and issued by Edison for publication globally. All information used in the publication of this report has been compiled from publicly available sources that are believed to be reliable, however we do not guarantee the accuracy or completeness of this report. Opinions contained in this report represent those of the research department of Edison at the time of publication. The securities described in the Investment Research may not be eligible for sale in all jurisdictions or to certain categories of investors. This research is issued in Australia by Edison Aus and any access to it, is intended only for "wholesale clients" within the meaning of the Australian Corporations Act. The Investment Research is distributed in the United States by Edison US to major US institutional investors only. Edison US is registered as an investment adviser with the Securities and Exchange Commission. Edison US relies upon the "publishers' exclusion" from the definition of investment adviser under Section 202(a)(11) of the Investment Advisers Act of 1940 and corresponding state securities laws. As such, Edison does not offer or provide personalised advice. We publish information about companies in which we believe our readers may be interested and this information reflects our sincere opinions. The information that we provide or that is derived from our website is not intended to be, and should not be construed in any manner whatsoever as, personalised advice. Also, our website and the information provided by us should not be construed by any subscriber or prospective subscriber as Edison's solicitation to effect, or attempt to effect, any transaction in a security. The research in this document is intended for New Zealand resident professional financial advisers or brokers (for use in their roles as financial advisers or brokers) and habitual investors who are "wholesale clients" for the purpose of the Financial Advisers Act 2008 (FAA) (as described in sections 5(c) (1)(a), (b) and (c) of the FAA). This is not a solicitation or inducement to buy, sell, subscribe, or underwrite any securities mentioned or in the topic of this document. This document is provided for information purposes only and should not be construed as an offer or solicitation for investment in any securities mentioned or in the topic of this document. A marketing communication under FCA Rules, this document has not been prepared in accordance with the legal requirements designed to promote the independence of investment research and is not subject to any prohibition on dealing ahead of the dissemination of investment research. Edison has a restrictive policy relating to personal dealing. Edison Group does not conduct any investment business and, accordingly, does not itself hold any positions in the securities mentioned in this report. However, the respective directors, officers, employees and contractors of Edison may have a position in any or related securities mentioned in this report. Edison or its affiliates may perform services or solicit business from any of the companies mentioned in this report. The value of securities mentioned in this report can fall as well as rise and are subject to large and sudden swings. In addition it may be difficult or not possible to buy, sell or obtain accurate information about the value of securities mentioned in this report. Past performance is not necessarily a guide to future performance. Forward-looking information or statements in this report contain information that is based on assumptions, forecasts of future results, estimates of amounts not yet determinable, and therefore involve known and unknown risks, uncertainties and other factors which may cause the actual results, performance or achievements of their subject matter to be materially different from current expectations. For the purpose of the FAA, the content of this report is of a general nature, is intended as a source of general information only and is not intended to constitute a recommendation or opinion in relation to acquiring or disposing (including refraining from acquiring or disposing) of securities. The distribution of this document is not a "personalised service" and, to the extent that it contains any financial advice, is intended only as a "class service" provided by Edison within the meaning of the FAA (ie without taking into account the particular financial situation or goals of any person). As such, it should not be relied upon in making an investment decision. To the maximum extent permitted by law, Edison, its affiliates and contractors, and their respective directors, officers and employees will not be liable for any loss or damage arising as a result of reliance being placed on any of the information contained in this report and do not guarantee the returns on investments in the products discussed in this publication. FTSE International Limited ("FTSE") © FTSE 2016. "FTSE®" is a trade mark of the London Stock Exchange Group companies and is used by FTSE International Limited under license. All rights in the FTSE indices and/or FTSE ratings vest in FTSE and/or its licensors. Neither FTSE nor its licensors accept any liability for any errors or omissions in the FTSE indices and/or FTSE ratings or underlying data. No further distribution of FTSE Data is permitted without FTSE's express written consent.