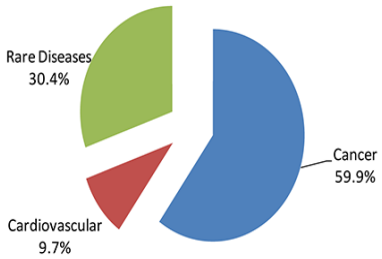
INDUSTRY OVERVIEW

Gene therapy involves the administration of a gene to treat a disease. Treatment is delivered only once (or a few times) rather than as a medicine administered over the long-term.

Gene therapies could potentially cure a disease using methods such as adding a gene, correcting it, or using genetic material to cause cell death. This emerging market has attracted interest from pharma companies big and small, a trend likely to continue.

Global Gene Therapy Market: Market, By Indication, 2015



Global Gene Therapy Market, By Indication, 2015

Indication	Revenue - Market Size ($ million)
Cancer	**5.5**
Cardiovascular	**0.9**
Rare Diseases	**2.8**
Total	**9.2**

Source: Visiongain 2016

This 45-page report focuses on BLUE (Pages 13-25). KITE (Pages 26-32) and JUNO (Pages 33-36) are also covered.

Global Gene Therapy Market

The gene therapy market is gaining popularity in the global medical community. The advent of advanced techniques for gene transfer has enabled the use of gene therapy for various new applications. Although it is still at an **INFANT** stage, its promise has led to a range of bullish estimates. Market research firm BCC Research forecasts the global market for DNA vaccines to grow at a 54.8% CAGR to $2.7 bln by 2019, while two other observers -- Roots Analysis and Research and Markets -- predict the **Gene therapy market as a whole to reach ~$11 bln by 2025**. Another report from market intelligence firm Transparency Market Research forecasts that the global stem cell market will grow at a CAGR of > 20% in the next few years and said there is a rich pipeline of more than 500 cell and gene therapy products, which will drive significant capacity as the pipeline matures and progresses to commercial supply.

Key factors driving market growth include demand for novel and efficient therapies to treat cancers and other indications with high unmet needs. Other market drivers include completion of the human genome project, rising incidence and prevalence of cancers and other critical diseases, and the prospective launch of gene therapies in major global markets.

Most gene therapy products are in the pre-clinical or clinical research stage. To-date, there are only five marketed drugs, namely Glybera, Neovasculogen, Gendicine, Rexin-G, and Oncorine. However, these products constitute very little revenue for the **gene therapy market.** Most revenue for the gene therapy market is generated from products used in clinical trials.

Need for Gene Therapy: It is estimated that, approximately 5% of the global population suffers from a rare disease and half of the global population affected by rare diseases are children, making rare disease treatment a concern for children across the globe. There are about 7,000 known rare diseases that comprise the most complex healthcare challenges for researchers and health professionals -- with most being difficult to diagnose due heterogeneity in disease epidemiology.

Rare diseases that affect 200,000 people in the US (as per the FDA definition) and a similar percentage in Europe are typically genetic in nature, and thus present a significant unmet need for potential regimes in the market.

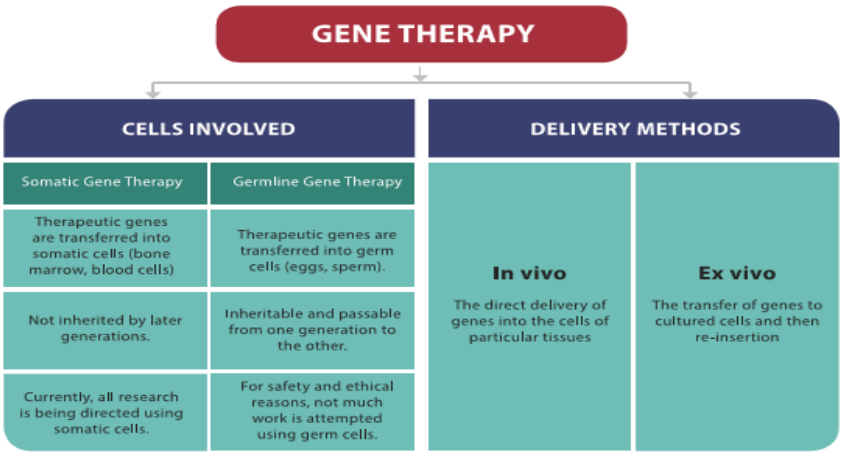
As per World Health Organization, 80% of rare diseases are caused due to genetic abnormality and are inherited for generations. Approximately 5% of the rare diseases have a treatment and most of the current therapeutic approaches include gene therapy and cell therapy. A significant gap between demand and supply of rare disease drugs is expected to create a massive opportunity for manufacturers and researchers in the area of rare disease treatment.

How Gene Therapy Works?

Advances in biotechnology have brought gene therapy to the forefront of medical research. The prelude to successful gene therapy, the efficient transfer and expression of a variety of human gene into target cells, has already been accomplished in several systems.

Gene therapy may be defined as the introduction of genetic material into defective cells for a therapeutic purpose. While gene therapy holds great potential as an effective means for selective targeting and treatment of disease, the field has seen relatively slow progress in the development of effective clinical protocols. Although identifying genetic factors that cause a physiological defect is straightforward, successful targeted correction techniques are proving continually elusive. Hence, safe methods have been devised to do this (using several viral and no-viral vectors). Two main approaches have emerged – in-vivo modification and ex-vivo modification. Retrovirus, adenovirus, adeno-associated virus are suitable for gene therapeutic approaches; these are based on permanent expression of the therapeutic gene. Non-viral vectors are far less efficient than viral vectors, but they have advantages due to their low immunogenicity and large capacity for therapeutic DNA.

Creating an ideal delivery vector to target diseased and only diseased tissue has proved difficult for those researchers toiling away tirelessly in their search for the safe treatments of tomorrow.



Source: Aranca Report – GENE THERAPY: Advanced Treatments for a New Era

Viral Vectors: These are virus-based vectors. Examples include retrovirus vector, adeno virus vector system, adeno associated virus vector, and herpes simplex virus. Extensive research is being conducted on the various viral vectors used in gene delivery.

Non-viral Vectors: Examples of non-viral vector systems include pure DNA constructs, lipoplexes, DNA molecular conjugates, and human artificial chromosomes. Owing to the following advantages, non-viral vectors have gained significant importance in the past few years as they are less immune-toxic; there is risk-free repeat administration; and relative ease of large-scale production.

A major disadvantage is that the corrected gene needs to be unloaded into the target cell, and the vector has to be made to reach the required treatment site.

Number of Gene Therapies in Active Development

Source: Pharmaprojects, 2016

Growth is supported by FDA evidence showing the number of applications for investigational new drugs (IND) and investigational device exceptions (IDE) related to cellular and gene therapies; this has steadily increased since 2010.

FDA Approval Status for Key Gene Therapy Players

Company/Institution	Collaborator	Disease Targeted	Status
Amgen	–	Metastatic melanoma	Late-stage human trials
Advantagene	–	Prostate cancer	Expected to complete last stage clinical trials in September 2015
UniQure	–	Fat metabolism disorder	Approved for sales in Europe
Bluebird Bio	–	Neurodegenerative disease	Mid- and late-combination trials completed in 2013
Glybera Europe	–	LPDL	EU commercial plan launched for 2015
Glybera US	–	LPDL	IND filing initiated in 2014
AnGesMG	–	Artery failure in limbs	To commence late-stage global testing
Children's Hospital of Philadelphia	–	Hereditary blindness	Human trials ended in April 2015
Human Stem Cell Institute	Neovasculogen	Critical limb ischemia	Marketing in Russia since 7 December 2011

The first commercial gene therapy for cancer (Gendicine) was approved in China in 2004. Regulators in the United States and Europe have been more skeptical of the technology, with the US yet to approve a gene therapy treatment. The first gene therapy to be licensed in Europe, called Glybera (alipogene tiparvovec), was approved in November 2012. So far, only three gene therapies have now been approved by European regulatory authorities.

Commercialization Status of Gene Therapies in Key European Countries

Commercialization Status	Product EMA Approval	Glybera July 2012	Imlygic October 2015	Strimvelis May 2016
Country (as of Nov 2016)	France	–	–	–
	Germany	+ (1 case)	+	–
	UK	–	–	–
	Italy	–	–	+ *
	Spain	–	–	–

* So far, Strimvelis can only be administered in one center in Italy for technical reasons.

Source: Genes Communication - Early Insights from Commercialization of Gene Therapies in Europe

Top Players in Gene Therapy

Most big pharma and biotech companies are actively involved in conducting research with respect to various aspects of gene therapy, along with universities. Players with high patenting activity are as follows.

Despite the high number of patents being filed, very few gene therapy products have been commercialized, and some are in clinical trial stage. A few examples are as follows:

Historical Perspectives and Current Status of Clinical Trials

The practice of gene therapy is nearly 30 years old -- since the first authorized gene transfer study took place at the National Institute of Health in 1989. However, gene therapy was not readily adopted worldwide, until recently.

The first successful gene therapy trial was performed on a 4-year-old girl named Ashanti Desilva, with a rare genetic immune system disorder called severe combined immune deficiency (SCID) on September 14, 1990, at the National Institute of Health, under the direction of professor William French Anderson. In 1992, Claudio Bordignon of Italy performed the first procedure of gene therapy using hematopoietic stem cells as vectors to correct a hereditary disease.

In 2003, a Los Angeles research team used liposome coated in a polymer to insert genes into the brain. This method has potential for treating Parkinson's disease. One of the first demonstrations of the efficacy of gene therapy in treating cancer comes from the success of the scientists at the National Institute of Health, who successfully treated metastatic melanoma in two patients using killer T-cells that were genetically retargeted to attack cancer cells.

In 2007, Moorefield's Eye Hospital and University College London's Institute of Ophthalmology announced the world's first gene therapy trial for a type of inherited retinal disease -- Leber's congenital amaurosis, caused by a mutation in the RPE65 gene. Sub-retinal delivery of recombinant AAV carrying the RPE65 gene yielded positive results with no apparent side-effects. A paper by Komaromy, et al., published in April 2010, deals with gene therapy for a form of achromatopsia (complete color blindness) in dogs. It is presented as an ideal model to develop gene therapy directed to cone photoreceptors. In July 2012, the European Medicines Agency approved a gene therapy treatment called Adipogene tiparvovec (Glybera), which compensates for lipoprotein lipase deficiency.

In April 2013, researchers in the UK and the US performed gene therapy experiments to combat heart diseases. Clinical trials were designed to increase the level of SERCA2a protein in the heart muscles to improve their function.

In July 2013, the Italian San Raffaele Telethon Institute for gene therapy reported that the treatment of two severe hereditary diseases, i.e., Metachromatic Leukodystrophy and Wiskott-Aldrich Syndrome, yielded positive results after 7-32 months of gene therapy.

In January 2014, researchers at the University of Oxford reported an improvement in the sight of six people suffering from choroideremia, an inherited genetic eye disease. These patients had been treated with a genetically engineered AAV with a copy of the REP1 gene.

In March 2014, researchers at the University of Penn reported that 12 patients with HIV had been treated since 2009 in a trial with a genetically engineered virus with a rare mutation known to protect against HIV (CCR5 deficiency).

Gene Therapy / path-changing treatment for the coming era

Gene therapy has transitioned from the conceptual, technology-driven, laboratory research, to clinical trial stages for a wide variety of diseases. In addition to curing genetic disorders such as Hemophilia, Chronic Granulomatous Disorder (CGD), and Severe Combined Immune Deficiency (ADA-SCID), it is also being tested to cure acquired diseases such as cancer, neurodegenerative diseases, influenza, and hepatitis.

Gene therapy is not limited to any particular disease. It is proving to be a promising treatment for rare diseases such as X-linked adrenoleukodystrophy. The therapy has proved effective in research conducted for the following diseases:

- **Fat Metabolism Disorder –** Gene therapy is used to correct rare genetic diseases caused due to lipoprotein lipase deficiency (LPLD). This deficiency leads to fat molecules clogging the blood stream. An adeno-associated virus vector is used to deliver the corrected copy of the LPL to the muscle cells. This corrected copy prevents excess accumulation of fat in the blood by breaking down the fat molecules. In 2012, the EU approved Glybera, the first viral gene therapy treatment for LPLD, manufactured by UniQure. Glybera is likely to be approved for the American market by 2018.

- **Adenosine Deaminase (ADA) Deficiency –** Gene therapy has successfully been used to treat another inherited immune disorder -- ADA deficiency. More importantly, none of the patients undergoing this treatment developed any other disorder. The retroviral vector is used in multiple small trials to deliver the functional copy of the ADA gene. Primarily, all the patients involved in these trials did not require any injection of ADA enzyme as their immune functions had immensely improved.

- **Severe Combined Immune Deficiency (SCID) –** A lot of documented work is already available regarding treating this immunodeficiency with gene therapy; however, clinical trials have not shown promising results. The viral vectors used during the trials triggered leukemia in patients. Since then, focus of the research and trials has been on preparing new vectors that are safe and do not cause cancer.

- **Hemophilia –** Patients with hemophilia suffer excessive blood loss as the blood clotting protein (Factor IX) is absent. Researchers have successfully inserted the missing gene in the liver cells using an adeno-associated viral vector. After undergoing this treatment, patients experienced less bleeding as their body was able to create some of the Factor IX protein.

- **Cystic Fibrosis (CF) –** CF is a chronic lung disease caused due to a faulty CFTR gene. Genes are injected into cells using a virus. Recent studies also include testing the cationic liposome (a fatty container) to deliver DNA to the faulty CFTR gene, thus making the use of the non-viral gene carrier more successful. Phase II trials using this therapy were published in early 2015, which promised a novel therapeutic approach to CF.

- **β-thalassemia –** Clinical trials on gene therapy for β-thalassemia (the faulty beta-globin gene, which codes for an oxygen-carrying protein in RBC) can be tracked back to 2007. Blood stem cells were taken from the patient's bone marrow and a retrovirus was used to transfer a working copy of the faulty gene. The modified stem cells were re-injected into the body to supply functional red blood cells. This treatment, once conducted, lasted over seven years, with the patient not undergoing blood transfusion during this time.

☛ **Hereditary Blindness –** Currently, gene therapy is being tested to treat degenerative form of inherited blindness, where patients lose light-sensing cells in their eyes over time. Experimental data suggests that the animal models of a mouse, rat, and dog show slow or even reverse vision loss using gene therapy. The most important advantage associated with gene therapy for eye disorders is that AAV (adeno-associated virus) cannot shift from the eye to other body parts, and hence does not cause an immune reaction.

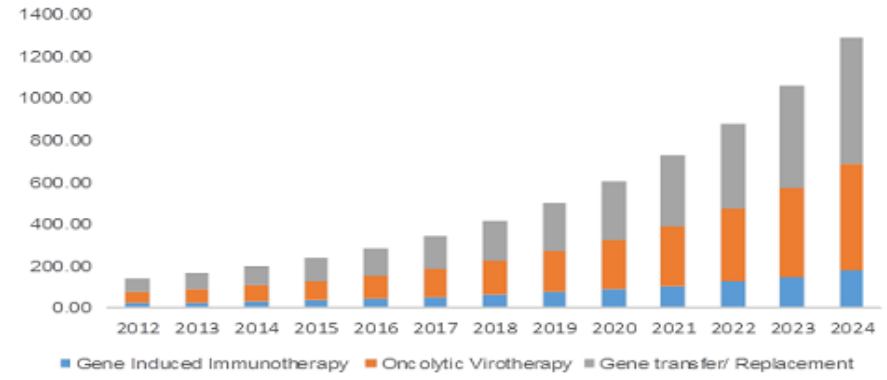
☛ **Parkinson's Disease –** Patients with Parkinson's disease lose the ability to control their movement as their brain cells stop producing the dopamine molecule used for signaling. A small group of patients showed improved muscle control when a small area of their brain was treated with a retroviral vector that contained dopamine-producing genes.

Over 2,000 gene therapy clinical studies are being conducted across diverse therapeutic areas, with 80% being conducted for various cancers.

This is because cancer genetics is a novel treatment method, marked by high R&D costs. The therapy targets diseases with high unmet needs; this has been the driving force behind academic research laboratories, small biotech firms, and large pharmaceutical companies. The therapy is of short-duration treatment or mostly one-time treatment customized to individuals, and often in small patient populations.

The cancer gene therapy market was valued at ~$800 million in 2015. It is estimated to grow at a CAGR of 20% over 2016-2024 to $4 billion, according to a new research report by Global Market Insights.

US Cancer Gene Therapy Market, By Type, 2012-2024 ($ million)



Rapid technological advancements, increased adoption of emerging genomic technologies, such as NGS, and high density micro array are some of the factors that will drive the global cancer gene therapy market over the forecast period.

The rising prevalence of cancer is expected to increase the demand for gene therapy. According to the World Health Organization, the number of new cases is projected to rise by 70% in the next two decades. The tremendous growth in the number of patients should fuel industry growth. Also, favorable government regulations will boost the growth of the cancer genetics industry. For instance, the Mainstreaming Cancer Genetics (MCG) program aims to develop clinical infrastructure, assays, informatics, education, and assessment, which will allow gene testing of patients. However, **the high drug development cost will act as an impediment to industry growth. It is expensive to conduct clinical trials, including Phase I, II, and III for approval**. The high cost of clinical trials will also serve as a major bottleneck over the forecast period.

Cancer Gene Therapy Market, By Therapy: Transfer cancer gene therapy market share was over 46% of global revenue in 2015, and is expected to witness growth of ~21% throughout the forecast period. Adenoviral vector is the most commonly used oncology application due to its competent nuclear mechanism and low pathogenicity. Adenoviral vectors are used in gene replacement approaches, suicide gene, gene-based immunotherapy, and syndicate gene with chemotherapy; over 20% growth is forecast for this segment.

Retroviral vector-mediated gene transfer dominates the development of the gene therapy industry. It provides significant benefits of converting single stranded RNA genome into a double stranded DNA molecule, which steadily integrates into the target cell genome. Retroviral vectors are used to permanently modify the host cell nuclear genome. Its oncolytic actions are mostly through stimulation of the immune system. It will grow at a ~20% CAGR over the forecast period.

Gene-induced immunotherapy is used for the treatment of cancer disease. It substitutes mutated gene with a healthy copy of the gene. A newly developed technique of supplementing novel genes into the tumor to help fight against cancer cells is extensively used. The cancer gene-induced immunotherapy market accounted for 14% of revenue in 2015, and is anticipated to exceed $590 million by 2024.

Cancer Gene Therapy Market, By Region: China's cancer gene therapy market was estimated to account for 35.4% of the APAC revenue in 2015, being the first country to commercialize gene therapy cancer drugs. Gendicine obtained license from SFDA for its recombinant Ad-p53 gene therapy for head and neck squamous cell carcinoma. Increasing healthcare expenditures and robust R&D facilities will enable the growth of the industry.

The US cancer gene therapy market accounted for most of the regional revenue share in 2015; this is attributed to the rise in the incidence and adoption of advanced treatments. The UK accounted for a major share of the European cancer gene therapy market in 2015 due to the rise in prevalence, coupled with increased adoption of gene technology. Japan was valued at over $78.2 mln in 2015, and it is expected to expand at a ~21% CAGR over 2016-2024.

Competitive Market Share: Major players include SiBiono, Shanghai Sunway Biotech, Altor Bioscience Corporation, Amgen, BioCancell, Aduro Biotech, OncoGeneX, GlobeImmune, New Link Genetics, MolMed, ZioPharm Oncology, Gradalis, GENELUX, and MultiVir. Small biotech firms also dominate the global cancer gene therapy market. Companies are constantly engaged in R&D to develop novel methods to treat various life-threatening diseases.

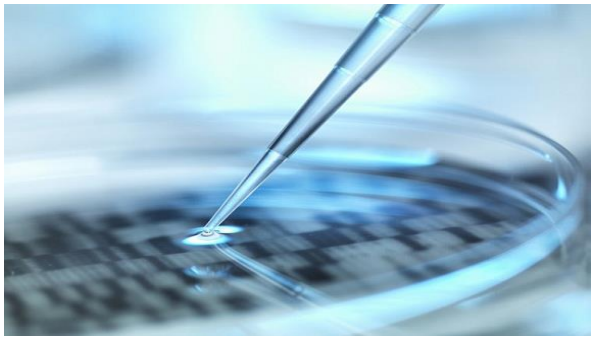
Key Opportunities and Challenges Associated with Gene Therapy

- **The development of gene therapies represents a new frontier in science; it has the potential to help many patients with serious or fatal conditions**.

Gene therapy offers the potential to address significant unmet clinical needs. Many genetic diseases produce serious or life-threatening clinical consequences. There are often no effective treatments beyond supportive care, and those treatments that do exist may not improve outcomes significantly, may have serious risks and side effects, and are quite expensive. However, as an emerging area of therapeutics, the development of gene therapies is scientifically challenging and has been marked by several cases, wherein there were setbacks, including unforeseen serious treatment side-effects.

The scientific and business risks of developing gene therapies are therefore high, especially for small biotechnology companies. If these therapies are to reach patients, manufacturers are likely to require that these risks be balanced by sufficient financial returns, such that investment in the science underlying these technologies can be sustained.

- **Uncertainty regarding clinical outcomes further complicates the challenges of assessing the value of potential cures.** The clinical gains offered by potential "cures" will be difficult to evaluate when, in the absence of long term data, there is no guarantee of long-term safety or of the durability of the clinical benefits. Similarly, the potential long-term cost offsets may also be difficult to estimate, based on the limited data that will be available at launch. These uncertainties only complicate perennial questions about how "society" values a cure relative to typical incremental gains observed with other therapies. What magnitude of premium pricing is fair for a cure that may or may not last? Should it matter whether current treatment for a condition is very expensive (hemophilia) or not?



- **Gene therapies will intensify concerns about the affordability of emerging treatments under existing paradigms of pricing and payment.**

More than any other challenge, that of affordability looms the largest over this area. The health budgets of public insurers (Medicaid and Medicare), and payers in the private insurance system (employers, health plans) are already constrained, and pressure to control costs are expected to increase in the future. Estimates suggest that 10% of the US populace have a rare condition related to a genetic defect. Based on the initial pricing experience with gene therapy in Europe, should a growing number of gene therapies come into use at costs of $1-$2 million, the cumulative budget impact would be substantial, and perhaps unsustainable. Even if gene therapies are developed to treat only 1 in 10 patients with a genetic condition -- approximately 1% of the total (US) population -- the cumulative budget impact at that price could rise to **$3 TRILLION** -- as much as is currently spent in a year on all healthcare in the US. Of course, a genetic therapy will not be found for every rare condition (and some may not be for rare conditions) and the emergence of gene therapies will not snowball quickly enough over the next few years to approach this budget impact. Additionally, it is more likely that pricing for these therapies will be in the $250,000-$500,000 range (and that is the more conservative range I am using in my valuation model). In fact, I am not only looking at a lower pricing range – I am also looking at the low end of that range. In the case of **BLUE**, where margins are high, I expect the company will clear $150,000-$200,000 per patient.

Some of the other risks associated with gene therapy and problems they pose are as follows:

- **Short life of gene therapy**: Before gene therapy can become a permanent cure for any condition, the therapeutic DNA introduced into the target cells must remain functional and cells containing the therapeutic DNA must be long-lived and stable. Problems with integrating therapeutic DNA into the genome and the rapidly dividing nature of many cells prevent gene therapy from achieving any long-term benefits. Patients are required to undergo multiple rounds of gene therapy. It is possible that the new gene fails to express itself or the virus does not produce the desired response.

- **Immune response**: Anytime a foreign object is introduced into human tissues, the immune system evolves to attack the invader. The risk of stimulating the immune system in a way that reduces gene therapy effectiveness is always a possibility. Furthermore, the immune system's enhanced response to invaders makes it difficult for gene therapy to be repeated in patients.

- **Multi-genic disorders:** Conditions or disorders that arise from mutation in a single gene are best candidates for gene therapy. Unfortunately, some of the most commonly occurring disorders, such as heart disease, high blood pressure, Alzheimer's disease, arthritis, and diabetes, are caused by the combined effects of variations in many genes. Multi-genic or multi-factorial disorders will be especially difficult to treat effectively using gene therapy.

- **Insertional mutagenesis**: The main problem facing geneticists is that the virus may target the wrong cells. If the DNA is integrated in the wrong place in the genome; for example, in a tumor suppressor gene, it could induce a tumor. This has occurred in clinical trials for X-linked SCID patients, wherein hematopoietic stem cells were transduced with a corrective transgene using a retrovirus; this led to the development of T-cell leukemia in three (out of 20) patients.

Ethical and Social Considerations

Gene therapy is a powerful new technology that might have unforeseen risks; hence, scientists first develop proposed experiments, i.e., protocol, that incorporates strict guidelines. After approval from FDA, the organization continues to monitor the experiment. In the course of a clinical trial, researchers are required to report any harmful side-effects. Critics and proponents agree that risks of gene therapy must not be substantially larger than the potential benefit. Gene therapy poses ethical considerations for people. Some people are concerned about whether gene therapy is right and that it may not be used ethically. Some of the ethical considerations for gene therapy are as follows:

- *Deciding what is normal and what is a disability*
- *Deciding whether disabilities are diseases and whether they should be cured*
- *Deciding whether searching for a cure demeans the life of people who have disabilities*
- *Deciding whether somatic gene therapy is more or less ethical than germ line gene therapy*

Initial experiments using gene therapy have been conducted in patients for whom all other treatments have failed, so that the risks are small. Many people feel that because gene therapies use altered genes and potentially dangerous viruses, treatments should be tested more extensively.

Conclusion: Most scientists believe that the potential for gene therapy is the most exciting application of DNA science undertaken so far. How widely this therapy will be applied, depends on the simplification of the procedure. As gene therapy is increasing in the field of medicine, **scientists believe that after 20 years**, this will be the last cure of every genetic disease. Genes may ultimately be used as medicine as simple intravenous injection of gene transfer vehicle will seek target cells for stable, site-specific chromosomal integration and subsequent gene expression. Now that a draft of the human genome map is complete, research is focusing on the function of each gene and the role that a faulty gene plays in the disease.

I. Key Players with Gene Therapies in Clinical Development

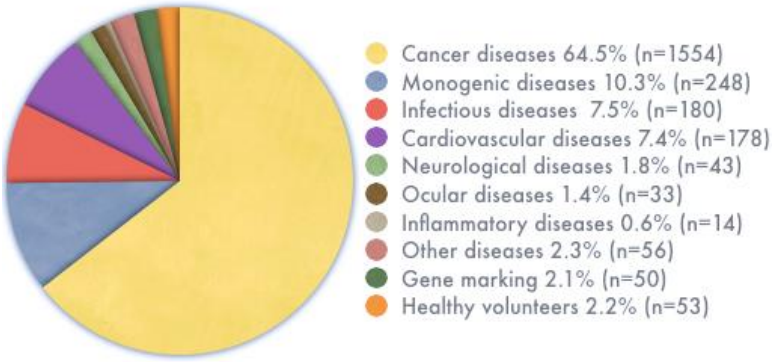
	Company	Gene Therapy/ Disease	Status
1	Uniqure	hF-IX gene/ Hemophilia B	Collaborator: Chiesi Farmaceutici (licensed from St. Jude Children's Research Hospital), Phase I/II
		NaGlu gene/ San Filipo B Syndrome	Collaborator: Institute Pasteur, Phase I/II
2	Oxford Biomedica	StarGen™ (Sanofi) / Stargardt Disease	Phase I/IIa trial ongoing
		UshStat® (Sanofi) / Usher Syndrome Type 1B	Phase I/IIa
		EncorStat® / Corneal Graft Rejection	Phase I/II trial preparation
		OXB-102 / ProSavin® / Parkinson's Disease	Phase I/II trial completed
		Retinostat®/ Wet AMD	Phase 1 trial ongoing
3	Bluebird Bio	Lenti-D/ Childhood Cerebral ALD	Phase II/III global study initiated
		LentiGlobin/ Beta Thalassemia, SCD	Beta thalassemia: Phase I/ II study initiated SCD: Phase I in US
4	Sangamo	SB-728/ HIV/AIDS	Phase II
		CERE-110/ Alzheimer's Disease	Phase II
5	AGTC	AATD / Alpha-1 Antitrypsin Deficiency	Phase IIb
		RS1 gene/ X-linked Juvenile Retinoschisis (XLRS)	IND filed; Phase I/II expected to start 2Q2015
6	Spark Therapeutics	SPK-RPE65/ Inherited Retinal Dystrophies due to RPE65 Gene Mutations	Phase III
		SPK-CHM / Choroideremia	Phase I/II
		SPK-FIX / Hemophilia B	Collaborator: Pfizer Phase I/II expected 1H2015
7	AnGes MG	Collategene™ Licensed from Vical (Also Known as Beperminogene Perplasmid, AMG0001)/ Critical Limb Ischemia	Phase III
		AMG0001/Primary Lymphedema	Phase I/II (Japan)
		AMG0001/ Ischemic Heart Disease	Phase I completed (US)
8	Taxus Cardium	Generx® (Alferminogene Tadenovec) [Ad5FGF-4]/Cardiac Microvascular Insufficiency (CMI) in patients with Myocardial Ischemia and Symptomatic Chronic Stable Angina Pectoris	Phase III
9	Genethon	WAS (Wiskott–Aldrich Syndrome)	Phase I/II
		X-Linked CGD Patients	Phase I/II
10	GSK	GSK2696273/ ADA Gene Transfer into Hematopoietic Stem/Progenitor Cells for the Treatment of ADA-SCID	Phase II
11	Viromed	Critical Limb Ischemia	Phase II completed
		Chronic Granulomatous Disease	Phase I/II (Korea)
		Painful Diabetic Neuropathy	Phase II
		Chronic Stable Angina	Phase I/ II
12	Voyager Therapeutics	VY-AADC01/ Parkinson's Disease	Collaborators: UCSF and Genzyme Phase I
13	Avalanche Biotechnologies	AVA101/ Wet AMD	Phase IIa
14	Celladon	MYDICAR® (SERCA 2A) / Systolic HF	Phase II/III
		MYDICAR® ((SERCA 2A) /Advanced HF with LVAD	Phase I/II

Source: Smart Analyst Analysis - Gene Therapies for Diseases Other Than Cancers

II. Phases of Gene Therapy Clinical Trials

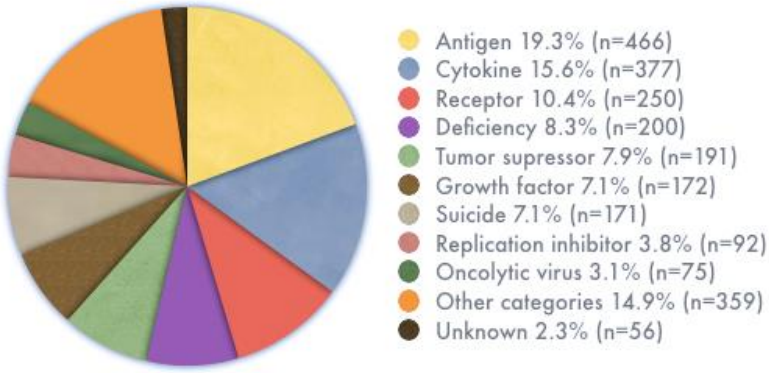
Source: The Journal of Gene Medicine, © 2016 John Wiley and Sons Ltd

III. Indications Addressed by Gene Therapy Clinical Trials



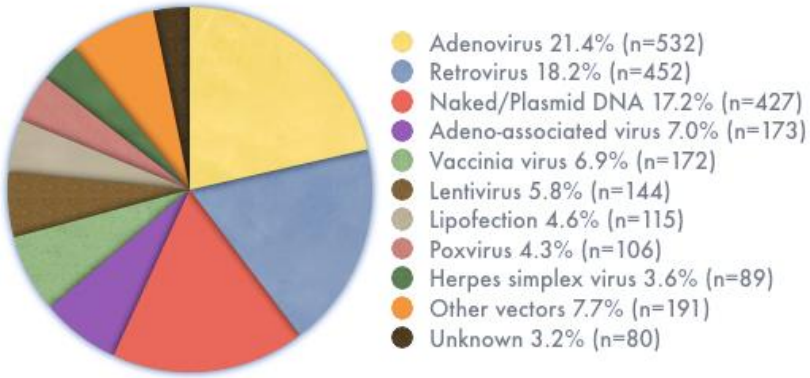
Source: The Journal of Gene Medicine, © 2016 John Wiley and Sons Ltd

IV. Gene Types Transferred in Gene Therapy Clinical Trials



Source: The Journal of Gene Medicine, © 2016 John Wiley and Sons Ltd

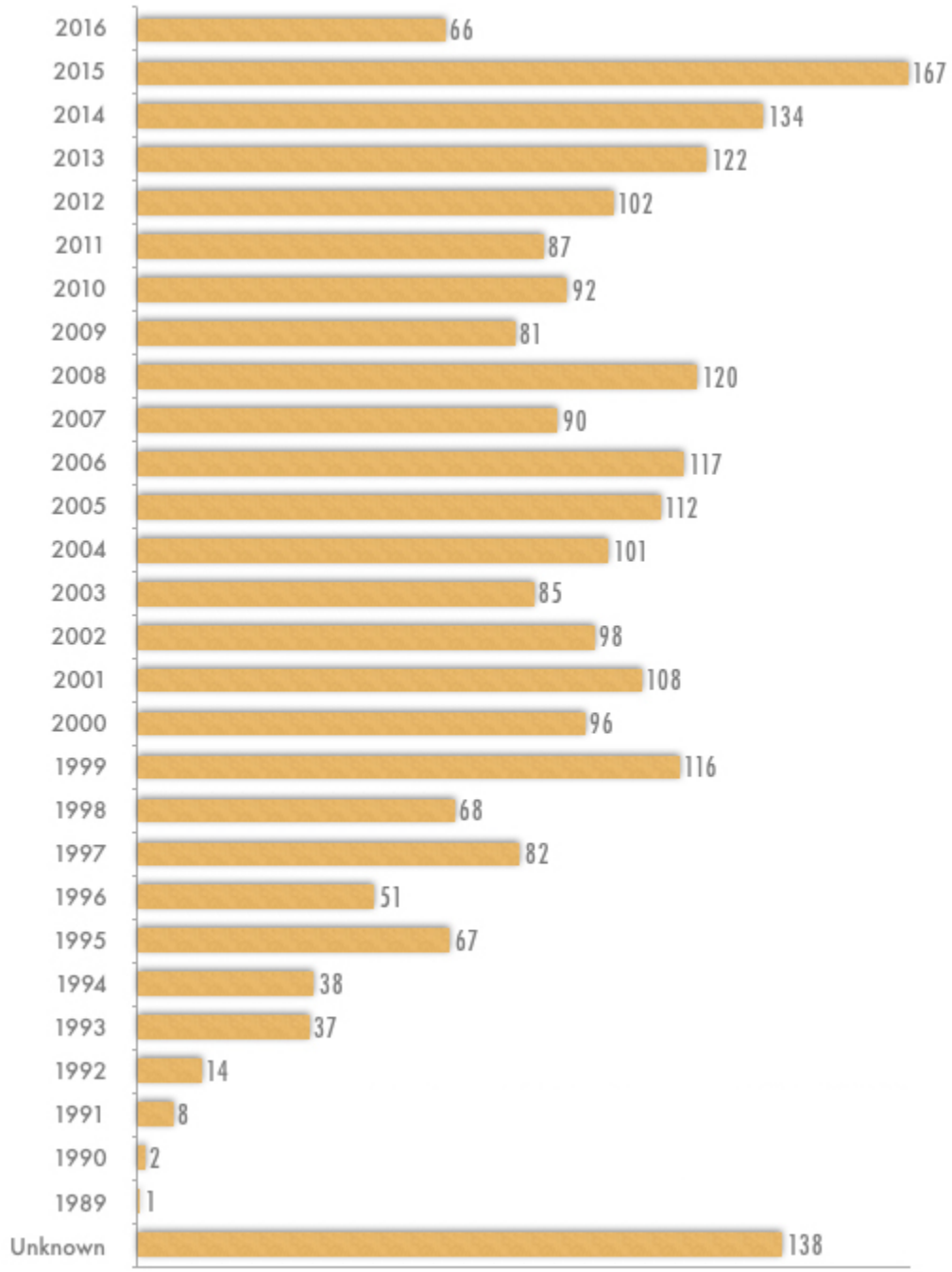
V. Vectors Used in Gene Therapy Clinical Trials



Source: The Journal of Gene Medicine, © 2016 John Wiley and Sons Ltd

VI. Number of Gene Therapy Clinical Trials Approved Worldwide 1989 – 2016

(Updated August 2016)



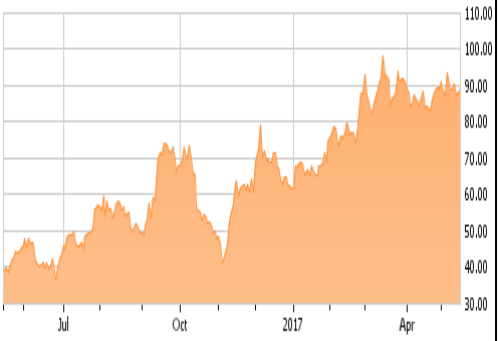
Source: The Journal of Gene Medicine, © 2016 John Wiley and Sons Ltd

Updated August 2016

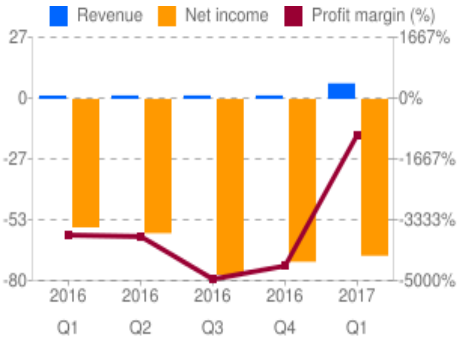
bluebird BLUE / Buy / 2019 price target: $110

Ticker	BLUE
Exchange	NASDAQ
Fiscal Year End	December 31
Market Cap	$3.22 billion
Shares Outstanding	40.95 million
Price 26-May-2017	$78.70
52 Week High / Low	$100.4 / $36.6
Average Daily Volume	600,000

Stock Performance



Net Revenue	$11.5 million
Institutions with > $250 mln stake	seven
Net Income/(Loss)	($275.9) million
Short Interest	$640 million
Total Cash	$634 million
Total Debt	$147 million



bluebirdbio

bluebird bio
Cambridge, MA 02141
www.bluebirdbio.com

bluebird bio (BLUE) is a **clinical-stage biotechnology company** that focuses on developing transformative gene therapies for severe genetic diseases and cancer. Its product candidates include **Lenti-D,** which is in phase II/III clinical studies for the treatment of cerebral adrenoleukodystrophy -- a rare hereditary neurological disorder -- and **LentiGlobin**, which is in four clinical studies for the treatment of transfusion-dependent beta-thalassemia and severe sickle cell disease. The company's lead product candidate is **bb2121,** a chimeric antigen receptor (CAR) T cell receptor (TCR) product candidate that is in phase I trial for the treatment of relapsed/refractory multiple myeloma.

The Company's gene therapy platform is based on viral vectors that utilize a non-replicating version of the Human Immunodeficiency Virus Type 1 (HIV-1). Its lentiviral vectors are used to introduce a functional copy of a gene to the patient's own isolated hematopoietic stem cells (HSCs) in the case of its LentiGlobin and Lenti-D product candidates, or the patient's own isolated white blood cells, which include T cells, in the case of its bb2121 product candidate.

BLUE has a strategic collaboration with **Celgene Corporation** (CELG) to discover, develop, and commercialize disease-altering gene therapies in oncology; with **Kite Pharma (KITE)** to develop and commercialize second generation T cell receptor (TCR) product candidates against an antigen related to certain cancers associated with the human papilloma virus; and with Medigene (Germany) for the research and development of TCR product candidates directed against approximately four antigens for the treatment of cancer indications. Founded in 1992 and headquartered in Cambridge, Massachusetts, the company was formerly known as Genetix Pharmaceuticals and later changed its name to bluebird bio (Incorporated) in September 2010.

$ in million, Except EPS	1Q2017	2016	2015	2014
Revenue	6.83	6.16	14.08	25.03
Operating Expenses	**75.31**	**269.89**	**180.25**	**85.80**
R&D	*55.03*	*204.78*	*134.04*	*62.57*
G&A	*20.28*	*65.12*	*46.21*	*23.23*
Loss from Operations	69.91	267.83	169.04	60.63
Net Loss	68.71	263.51	166.78	48.71

Source: Yahoo Finance

INVESTMENT THESIS

Integrated Product Platform with Broad Potential Application

With its lentiviral-based gene therapies, T-cell immunotherapy expertise, and gene-editing capabilities, BLUE has built an integrated product platform with broad potential application for severe genetic diseases and cancer. BLUE's approach to gene therapy is based on viral vectors that utilize the Human Immunodeficiency Virus Type 1 or HIV-1. The HIV-1 vector is stripped of all the components that allow it to self-replicate and infect additional cells. HIV-1 is part of the lentivirus family of viruses. The vectors are used to introduce a modified copy of a gene from the patient's own blood stem cells called hematopoietic stem cells (HSC), which reside in the patient's bone marrow. HSCs divide cells that allow for sustained expression of the modified gene.

The gene therapy platform is used for severe genetic and rare diseases, and in oncology. The company's pipeline of therapies based on its genetic modification techniques and lentivirus approach is as follows:

Product Candidates	Program Area	Preclinical	Phase 1/2	Phase 2/3	Rights/Partner
	CNS Diseases				
Lenti-D™ Drug Product	Cerebral ALD				Worldwide
	Rare Hemoglobinopathies				
LentiGlobin® Drug Product	Transfusion-Dependent ß-thalassemia*				Worldwide
	Severe Sickle Cell Disease				Worldwide
	Oncology				
bb2121 BCMA	Multiple Myeloma				Celgene
Next Gen BCMA	Multiple Myeloma				Celgene
Five Prime Target	Undisclosed				Worldwide
HPV-16 E6 TCR	HPV-associated Cancers				Kite Pharma
Viromed Target	Undisclosed				Worldwide excluding Korea
Other Programs	Undisclosed				Worldwide
	Research				
Early Pipeline	Undisclosed + Gene Editing				Worldwide

Lenti-D

Bluebird is developing the Lenti-D product candidate to treat patients with cerebral adrenoleukodystrophy (CALD). Adrenoleukodystrophy is a rare X-linked, metabolic disorder caused by mutations in the ABCD1 gene, which results in a deficiency in adrenoleukodystrophy protein, or ALDP, and subsequent accumulation of very long-chain fatty acids. Symptoms of CALD usually occur in early childhood and progress rapidly if untreated, leading to severe loss of neurological function and eventual death.

Completed non-interventional retrospective study (the ALD-101 Study)

CALD is a rare disease, and data on the natural history of the disease, as well as the efficacy and safety profile of allogeneic HSCT, is limited in scientific literature. To properly design clinical studies of Lenti-D and interpret the efficacy and safety results thereof, at the recommendation of the FDA, bluebird performed a non-interventional retrospective data collection study to assess the natural course of the disease in CALD patients that were left untreated in comparison with the efficacy and safety data obtained from patients that received allogeneic HSCT. For this study, data was collected from four US sites and one French site on a total of 137 subjects, 72 of whom were untreated and 65 were treated with allogeneic HSCT.

Starbeam Study (ALD-102) – Phase II/III clinical study in subjects with CALD

The company is currently conducting a phase II/III clinical study of Lenti-D product candidate in the US, referred to as the Starbeam Study (ALD-102), to examine the safety and efficacy of Lenti-D product candidate in subjects with CALD. The study was fully enrolled in May 2015; however, in December 2016, the company amended the protocol for this study to enroll up to an additional eight subjects in an effort to enable the first manufacture of Lenti-D product candidate in Europe and the subsequent treatment of subjects in Europe, and to bolster the overall clinical data package for potential future regulatory filings in the US and Europe. It intended to begin treating the additional patients in early 2017.

Study Design

- 15 patients (18 enrolled)
  - Age ≤ 17
  - Gad Positive
  - Loes Score 0.5 – 9
  - NFS ≤ 1
  - No HLA-matched sibling donor
- Primary endpoint: % of boys with MFDs at 24 months
- Secondary endpoints: NFS, Gad +/-, Loes score, safety

Update

- Eight additional patients to be enrolled
  - Same enrollment criteria
- Gain experience manufacturing and delivering Lenti-D in Europe
- Bolster data package for US and EU regulatory filings
- Enrollment planned to begin in early 2017

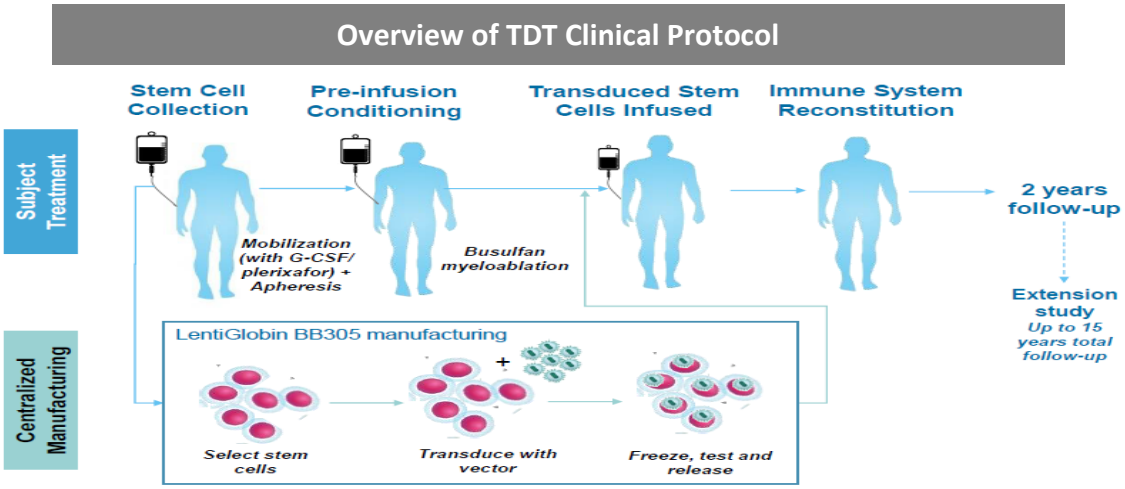
The ALD-103 (observational) study

bluebird is also conducting the ALD-103 study, an observational study of subjects with CALD treated by allogeneic HSCT. This study is ongoing and is designed to collect efficacy and safety outcomes data in subjects who have undergone allogeneic HSCT over a period that is contemporary with the Starbeam study.

LENTIGLOBIN PRODUCT

Transfusion-dependent β-thalassemia (TDT)

β-thalassemia is a rare hereditary blood disorder caused by a mutation in the β-globin gene, resulting in the production of defective red blood cells, or RBCs. Genetic mutations cause the absence or reduced production of beta chains of hemoglobin, or β-globin, preventing the proper formation of hemoglobin A, which normally accounts for more than 95% of the hemoglobin in the blood of adults.



Limitations of current treatment options

In geographies where treatment is available, patients with TDT receive chronic blood transfusion regimens. These regimens consist of regular infusions with units of packed RBC, or pRBC, usually every three to five weeks, to maintain hemoglobin levels and control symptoms of the disease.

The only potentially curative therapy for β-thalassemia today is allogeneic HSCT. However, complications of allogeneic HSCT include risk of engraftment failure in unrelated human-leukocyte-antigen, or HLA, matched patients, risk of life-threatening infection, and risk of GVHD -- a common complication in which donor immune cells (white blood cells in the graft) recognize the cells of the recipient (the host) as "foreign" and attack them. As a result of these challenges, allogeneic HSCT can lead to significantly high mortality rates, particularly in patients treated with cells from a donor who is not a matched sibling, and in older patients. Overall, TDT remains a devastating disease, with an unmet medical need.

The Northstar Study (HGB-204) – Phase I/II clinical study in subjects with TDT

The Northstar study is a single-dose, open-label, non-randomized, multi-site phase I/II clinical study in the US, Australia, and Thailand to evaluate the safety and efficacy of the LentiGlobin product candidate in increasing hemoglobin production and eliminating or reducing transfusion dependence following treatment. In March 2014, the first subject with TDT was treated in this study, and, in May 2016, the study was fully enrolled.

The study enrolled 18 adults and adolescents. To be eligible for enrollment, subjects had to be between 12 and 35 years of age, with a diagnosis of TDT, and received at least 100 mL/kg/year of pRBCs or more than or equal to eight transfusions of pRBCs per year in each of the two years preceding enrollment.

Efficacy will be evaluated primarily by the production of ≥2.0 g/dL of hemoglobin A containing βA-T87Q-globin for the six-month period between 18 and 24 months, post transplants. Exploratory efficacy endpoints include RBC transfusion requirements (measured in milliliters per kilogram) per month and per year, post transplants.

Patient and Drug Product Characteristics HGB-204
N=18 treated patients

	Genotype	
	β0/β0(n=8)	**Non-β0/β0**(n=10)
Genotype	8	10
βE/β0	-	6
Other(β+/β0, β+/β+,βx/β0)	-	4
Age at start of regular transfusions **Age at consent** *Median (range)years*	0 (0 –7) 23(12 -35)	6 (0 –26) 19.5 (16 –34)
Median (range) pre-study pRBC transfusion vol *annualized median(range) mL/kg/year*	184.9 (128.7 -261.3)	146.3 (117.0 –234.5)
Splenectomy	3	3
Drug Product Parameters	**Median (range)**	
Drug product VCN1	0.7 (range 0.3 -1.5)	0.8 (range 0.3 -1.1)
Drug product cell dose *CD34+ cells x106/kg*	11.0 (range 6.1-18.1)	7.1 (range 5.2-13.0)

The HGB-205 study – Phase I/II clinical study in subjects with TDT or with severe SCD

Bluebird is conducting the HGB-205 study, a phase I/II clinical study, in France to study the safety and efficacy of its LentiGlobin product candidate in the treatment of subjects with TDT and of subjects with severe SCD. In December 2013, the company said that the first subject with TDT had been treated in this study; in October 2014, Bluebird declared that the first subject with severe SCD had been treated in this study. By February 2017, the study had been fully enrolled.

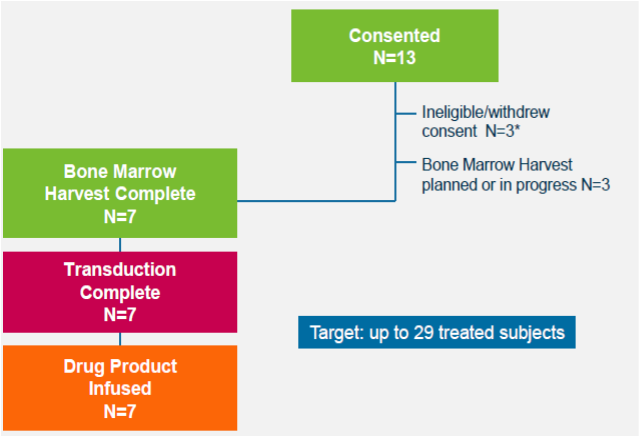
Patient and Drug Product Characteristics HGB-205

	1201	1202	1203	1204
Age at Enrollment(years)	18	16	19	17
Genotype	β0/βE	β0/βE	homozygous IVS1 nt110 G>A	β0/βE
Pre-Treatment pRBCTransfusions (mL/kg/year)1	139	188	176	197
VCN in DrugProduct2	1.5	2.1	0.8	1.1
CD34+ Cell Dose (x106/kg)	8.9	13.6	8.8	12.0
Busulfan AUC (average, uM/min)	4,967	5,212	4,670	4,930
Follow-up(months)	**33.5**	**30.3**	**14.6**	**11.6**

1mean pRBC requirement per year, over the past 2 years prior to consent; 2VCN = number of vector copies per diploid genome

In April 2017, BLUE met with the European Medicines Agency (EMA) regarding the regulatory path for LentiGlobin in TDT as part of its participation in the Adaptive Pathways Program. The company believes that it is possible to seek conditional approval for its LentiGlobin product candidate, with improved manufacturing process, for the treatment of patients with TDT and a non-β0/β0 genotype, based on the totality of the clinical data from the ongoing Northstar study in patients with TDT and supportive ongoing HGB-205 study, single-center study in patients with TDT and SCD, together with the data available from the ongoing Northstar-2 study in patients with TDT and non-β0/β0 genotypes at the time of filing.

The HGB-206 study – *Phase I clinical study in subjects with severe SCD*



Enrollment criteria
- 18+ years of age
- History of symptomatic SCD
- Adequate organ function/performance status
- No previous HSCT or gene therapy

bluebird is conducting HGB-206 multi-site phase I clinical study in the US to evaluate the safety and efficacy of its LentiGlobin product candidate for the treatment of subjects with severe SCD. In October 2016, the company amended the protocol of its HGB-206 study to expand enrollment and incorporate several process changes, including updated drug product manufacturing process. Enrollment had begun under this amended protocol, and, in February 2017, the company treated the first subject under this amended protocol.

The Northstar-2 Study (HGB-207) – Phase III study in subjects with TDT and a non-β0/ β0 genotype

HGB-207
Non-β⁰/β⁰ genotypes

Phase 3, multi-center, global study

- N=15 adults and adolescents, and N=8 pediatric patients
- **Open and enrolling**

The Northstar-2 study is an ongoing single-dose, open-label, non-randomized, international, multi-site phase III clinical study to evaluate the safety and efficacy of the LentiGlobin product candidate to treat subjects with TDT and non-β0/β0 genotype. Approximately 23 subjects will be enrolled in the study, consisting of at least 15 adolescent and adult subjects between 12 and 50 years of age at enrollment, and at least 8 pediatric subjects less than 12 years of age at enrollment. In December 2016, the first subject had received treatment with the LentiGlobin product candidate.

The planned Northstar-3 Study (HGB-212) – Phase III Study for TDT in subjects with TDT and a β0/ β0 genotype

The company plans the initiation of HGB-212, a phase III clinical study of LentiGlobin in patients with TDT and the β0/β0 genotype in 2H FY2017.

HGB-212
β⁰/β⁰ genotypes

Phase 3, multi-center, global study

- N=15 adults, adolescents and pediatric patients
- **Initiation planned for 2017**

bluebird expects to enroll up to 15 adult, adolescent, and pediatric subjects. The company anticipates that the primary endpoint of the Northstar-3 study will be transfusion reduction, which is defined as a demonstration of a reduction in the volume of pRBC transfusion requirements in the post-treatment time period of 12-24 months, compared with the average annual transfusion requirement in the 24 months prior to enrollment.

Sickle Cell Disease (SCD)

SCD is an inherited disease that is caused by a mutation in the β-globin gene; this results in sickle-shaped red blood cells. The disease is characterized by anemia, vaso-occlusive crisis, infections, stroke, overall poor quality of life, and, sometimes, early death. Where adequate medical care is available, common treatments for patients with SCD largely revolves around the management and prevention of acute sickling episodes. Chronic management may include hydroxyurea and, in certain cases, chronic transfusions. Given the limitations of these treatments, there is no effective long-term treatment. The only advanced therapy for SCD is allogeneic hematopoietic stem cell transplantation (HSCT). Complications of allogeneic HSCT include a significant risk of treatment-related mortality, graft failure, graft-versus-host disease, and opportunistic infections -- particularly in patients who undergo non-sibling-matched allogeneic HSCT.

In March 2017, bluebird announced the Publication of the Case Study on the First Patient with Severe Sickle Cell Disease Treated with Gene Therapy in The New England Journal of Medicine. Patient 1204, a male patient with β^S/β^S genotype, was enrolled in May 2014 at 13 years of age into the HGB-205 clinical study. The patient underwent a regular transfusion regimen for four years prior to this study. Over 15 months since transplant, no SCD-related clinical events or hospitalizations occurred -- contrasting favorably with the period before the patient began regular transfusions. All medications were discontinued, including pain medication.

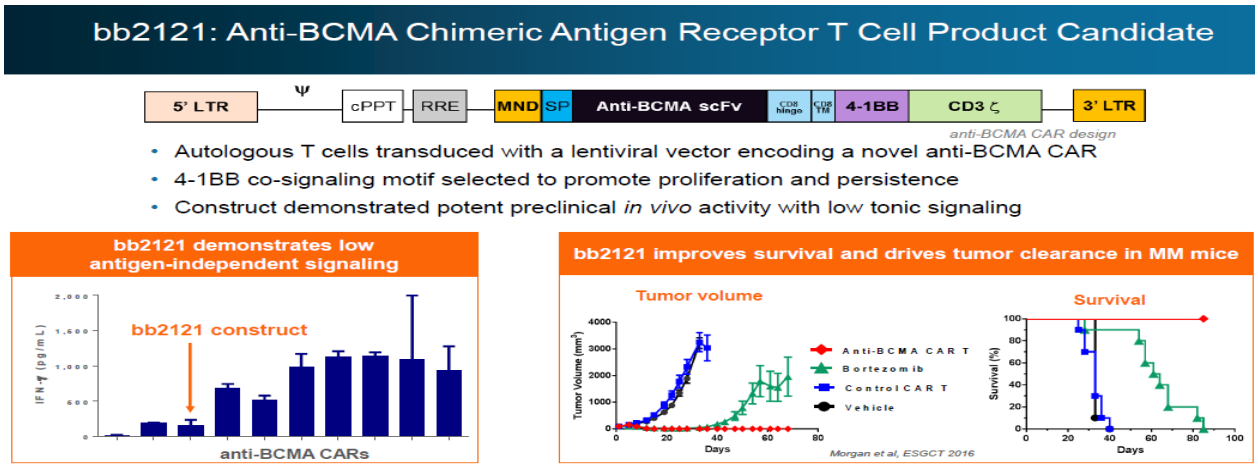
The successful outcome in Patient 1204 demonstrates the promise of treatment with LentiGlobin gene therapy in patients with severe SCD and serves as a guide to optimize outcomes in future patients.

Celgene Collaboration

In March 2013, BLUE entered into a strategic collaboration with **Celgene** to advance gene therapy in oncology (cancer), which was amended and restated in June 2015, and amended again in February 2016. The multi-year research and development collaboration focused on applying BLUE's expertise in gene therapy technology to CAR T cell-based therapies, to target and destroy cancer cells. The collaboration now focuses exclusively on anti- B-cell maturation antigen "BCMA" product candidates for a new three-year term.

Under the terms of the Amended Collaboration Agreement, for up to two product candidates selected for development under the collaboration, BLUE is responsible for conducting and funding all research and development activities performed up through completion of the initial phase I clinical study of such a product candidate.

In February 2016, Celgene exercised its option to obtain an exclusive worldwide license to develop and commercialize bb2121, the first product candidate under the Amended Collaboration Agreement, and paid the associated ($10 million) option fee. BLUE will share equally in all costs related to developing, commercializing, and manufacturing the product candidate within the US, if it elects to co-develop and co-promote bb2121 with Celgene. In case BLUE does not exercise its option to co-develop and co-promote bb2121, it will receive an additional fee (of $10 million).



In February 2016, BLUE initiated phase I clinical study of bb2121, the first anti-BCMA product candidate from this collaboration, and exclusively licensed Celgene the right to develop and commercialize bb2121.

The CRB-401 study – Phase I clinical study in subjects with relapsed/refractory multiple myeloma

CRB-401 study is a multisite phase I clinical study in the US to examine the safety and efficacy of the bb2121 product candidate in up to 50 subjects with relapsed/refractory multiple myeloma. Following screening, the enrolled subjects will undergo a leukapheresis procedure to collect autologous T-cells to manufacture the bb2121 drug product. The bb2121 drug product is produced from each subject's own blood cells, which are modified using a lentiviral vector encoding the anti-BCMA CAR.

Each subject will be followed for up to 24 months, post the treatment, and then will be enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond the 24-month period.

CRB-401 Open-label Phase 1 Clinical Study of bb2121

- Objectives: Determine preliminary safety and efficacy and recommended phase 2 dose
- N = 50 patients, standard 3+3 dose escalation + expansion cohort
- Eligibility
  - Relapsed / refractory MM with ≥ 3 prior lines of therapy (including PI and IMiD), or double refractory
  - Measurable disease
  - ≥ 50% BCMA expression
  - Adequate bone marrow, renal and hepatic function

9 U.S. Clinical Sites, 1 Centralized Manufacturing Site

In 2017, BLUE plans to initiate the CRB-402 study, a phase I clinical study of bb21217, next-generation anti-BCMA product candidate, for the treatment of subjects with relapsed/refractory multiple myeloma.

Broad Patent Portfolio Basket

BLUE has developed or in-licensed numerous patents and patent applications and possesses substantial know-how and trade secrets related to the development and commercialization of gene therapy products →

As of January 31, 2017, the company's patent portfolio includes the following:

- ✓ Approximately 222 patents or patent applications that bluebird owns or has exclusively in-licensed from third parties related to lentiviral vectors and vector systems
- ✓ Approximately 62 patents or patent applications that bluebird has non-exclusively in-licensed from third parties related to lentiviral vectors and vector systems
- ✓ Approximately 38 patents or patent applications that bluebird owns or has exclusively in-licensed from third parties, including eight that are co-owned with MIT, related to vector manufacturing or production
- ✓ Approximately 7 patents or patent applications that have been non-exclusively in-licensed from third parties related to vector manufacturing or production
- ✓ Approximately 58 patents or patent applications that BLUE owns or has exclusively or co-exclusively in-licensed from third parties related to therapeutic cellular product candidates
- ✓ Approximately 252 patents or patent applications that BLUE owns or has exclusively in-licensed or optioned from third parties related to oncology product candidates, including CAR T-cell vector systems and manufacturing, T-cell manufacturing, and therapeutic T cells
- ✓ Approximately 147 patents or patent applications that BLUE owns or has exclusively or co-exclusively in-licensed from third parties related to gene-editing compositions and methods
- ✓ Approximately 22 patent applications that it has non-exclusively in-licensed from third parties related to gene editing compositions and methods

The company's objective is to continue to expand its portfolio of patents and patent applications to protect the gene therapy product candidates' manufacturing processes.

Strong management team, with proven track record and established relationships

Led by a management team with extensive industry experience, BLUE is backed by top-tier life sciences investors. The management team at BLUE is composed of proven industry veterans, with vast experience in gene therapy, drug development, analytical characterization, and clinical-regulatory development. The company attributes its success, in a large measure, to its dynamic and rewarding organizational culture, which attracts the most highly talented, motivated, and productive team members in all of the biotechnology marketplace.

Members of the Leading BLUE Team Include Pioneers of the Industry

Name	Designation	Since	Prior Experience
Daniel S. Lynch	Independent Chairman of the Board	2011	Egenesis Inc., IVREA Pharmaceuticals, Nimbus Therapeutics, Third Rock Ventures
Nick Leschly	President and CEO	2010	Third Rock Ventures, L.P. , Millennium Pharmaceuticals, Agios Pharmaceuticals and Edimer Pharmaceuticals
Jason F. Cole, Esq.	Chief Legal Officer	2016	Zalicus Inc., Ropes & Gray LLP
David Davidson, M.D.	Chief Medical Officer	2012	Genzyme Corporation, GelTex Pharmaceuticals
Alison Finger	Head of Commercial	2015	Bristol-Myers Squibb, PM Connective
Philip D. Gregory, D. Phil.	Chief Scientific Officer	2015	Sangamo BioSciences
Susanna High	Chief Operating Officer	2016	Alnylam Pharmaceuticals, Inc, Millennium Pharmaceuticals
Andrew Obenshain	Head of Europe	2016	Shire, Genzyme and Sanofi
Manisha Pai	Senior Director, Investor Relations & Corporate Communications	2015	Epizyme, Inc., Pharmacyclics, Inc.
Jeffrey T. Walsh	Chief Financial and Strategy Officer	2011	SmithKline Beecham Corporation, Taligen Therapeutics, Inc.

Source: Company

In March 2017, BLUE appointed Derek Adams, PhD as its Chief Technology and Manufacturing Officer, and Joanne Smith-Farrell, PhD, as Senior Vice President, Corporate Development and Strategy.

Healthcare has been a very challenging sector to be invested in during the last year. Uncertainty with regards to whether or not the new administration will crack down on high drug prices is weighing on the sector. There is also the problem of investing in promising but speculative biotech names. The problem with investing in promising companies is that today they usually have an unreasonable valuation with market caps topping a billion dollars and no earnings to back up the market cap. It is easy to dismiss these names, but remember this is the way names like Amgen, Gilead, Celgene and Biogen were valued 20 years ago.

I always advise to have approximately 4%-8% of your portfolio in speculative biotech names where you do not allocate more than 1%-2% to any one of those names.

There are three drugs stocks in the cancer therapy industry that I have been talking about during the last two years: KITE, BLUE and JUNO. I have never (before today) put out an opinion or recommendation on bluebird -- I have put recommendations out on JUNO and KITE. Juno was initiated back in August of 2015 and closed out with a 58% gain on October 29, 2015. I reinstated Juno at $46 in December of 2015 and that second trade is currently minus 44% (against us). The stock collapsed last year after deaths on one of their trials. The deaths should not have come as such a surprise, and the market over-reacted, as these were patients that were receiving powerful therapies as a last resort (who more than likely would not have survived either way). Juno shares have since recovered somewhat and are now trading 40% off the crash point from last year. There was in fact insider buying there late last week ($500,000).

With Kite Pharma I have had more success. This is a name that I also initiated in August 2015. I have gone in-and-out of this name twice in the last two years and locked in gains of 35% each time. The stock was most recently closed out at $87 on March 13 and is currently trading at $73.

FINANCIAL ANALYSIS

No Commercial Product Revenue Yet / License Payments to Increase

BLUE has not generated any revenue from the commercial sale of its products to-date. All its revenue has been generated from collaboration arrangements, research fees, license fees, and grant revenues.

BLUE generates collaboration revenue exclusively from its collaboration arrangement with Celgene Corporation (CELG), a biotechnology company that discovers, develops, and commercializes drugs for cancer and inflammatory disorders. The terms of arrangement, amended in 2015, has multiple deliverables under the co-development and co-promotion agreement for the first-optioned product candidate under the license. The revenue from the Celgene arrangement associated with discovery, research and development services, joint steering committee services, and patent committee services are recognized ratably over the associated period of performance, which is initially three years. Research and license fee revenues are primarily generated through license, and research and development agreements with strategic partners and non-profit organizations for the development and commercialization of BLUE's product candidates.

BLUE's revenue over the last five years has been insignificant and dependent on milestones achieved, research and license fee services. The total revenue for the year-ended December 31, 2016, stood at $6.2 million, down from $14.1 million in 2015. This was attributed to the change in revenue recognition, on account of amendments to its Celgene collaboration agreement in 2015. For the first quarter-ended March 31, 2017, (1Q 2016) BLUE reported a total revenue of $6.8 million, up from $1.5 million in 1Q 2015. This was attributed to the commencement of revenue recognition for the "bb2121" license and manufacturing services under the Celgene agreement.

BLUE expects to recognize revenue of $17.3 million from the Celgene arrangement over the three years of associated period of performance from the date of agreement in June 2015. Further, the company expects to recognize approximately $77.6 million associated with the license to 'bb2121', and the manufacture of vector and associated payload for 'bb2121' following the initial phase I study. The revenue is expected to be recognized between 2017 and 2021, assuming the co-development and co-promotion agreement is executed and other revenue recognition criteria are met.

Research and Development Expenses Have Been Increasing to Constitute a Major Proportion of Total Expenses

BLUE's research and development (R&D) expenses have steadily increased over the years. The total R&D expenses increased by nearly 12X between 2012 and 2016. In 2016, the total R&D expenses increased by > 50% y/y to $204.8 million, up from $134 million in 2015. This was primarily attributed to the rise in headcount, in-licensing costs, clinical trial-related costs, and manufacturing-related expenses that were necessary to support the advancement of BLUE's product candidates. The trend continued in 1Q 2017, as R&D expenses increased by > 30% y/y to $55 million, up from $41.9 million in 1Q 2016. This was primarily due to the increase in headcount, manufacturing, and clinical trial-related expenses, as well as high facilities and information technology expenses.

Since its inception through December 31, 2016, BLUE incurred a total of ~$500 million in R&D expenses, which management estimates will increase in the near-term. This is primarily to advance the development of the 'Lenti-D', 'LentiGlobin', and 'bb2121' product candidates. The increase is also estimated due to continued research and development activities in oncology, including BLUE's strategic collaboration with Celgene and various other clinical trials in different phases in the US, Australia, Thailand, France and other locations.

BLUE's direct R&D expenses mainly comprise external costs, including fees paid to investigators, consultants, central laboratories, and clinical research organizations (CROs) in relation with the company's clinical studies. The expenses also include costs related to acquiring and manufacturing clinical study material.

General and Administrative Expenses Increase on the back of Increased R&D and Pre-Commercial Activities.

BLUE's general and administrative (G&A) expenses primarily consist of cost related to personnel, including stock compensation, facility-related costs, and professional fees for accounting, tax, legal, and consulting services, as well as directors' fee and expenses related to obtaining and maintaining patents. G&A expenses rose ~41% y/y to $65.1 million in 2016, up from $46.2 million in 2015. This was primarily due to an increase in employee-related and consulting costs.

For 1Q 2017, total G&A expenses increased 27% y/y to $20.3 million, up from $16 million in 1Q 2016. This was primarily on account of an increase in compensation and benefit expenses, due to a rise in headcount and facilities expenses, as well as expenses to support the company's pre-commercial efforts.

Management anticipates that its G&A expenses will increase in the future, in-line with the expected increase in headcount to support its continued R&D activities and potential commercialization of product candidates. Additionally, whenever the company approaches regulatory approval stage for any of its product candidates, it anticipates a sharp rise in payroll and related expenses in view of preparation for commercial operations -- especially sales and marketing activities.

Increase in Net Losses due to Lack of Commercial Product Revenue -- BLUE has been incurring R&D and G&A expenses in its effort to develop potential commercial products, but, to-date, lacks commercial product sale revenue. As its total operating expenses have continued to rise over the years, without any meaningful revenue, net losses at the company too have continued to rise. Total net losses for 2016 rose 58% y/y to ($263.5 million), up from ($166.8 million) in 2015. Net losses for 1Q 2017 rose 22% y/y to ($68.7 million), up from ($56.3 million) in 1Q 2016.

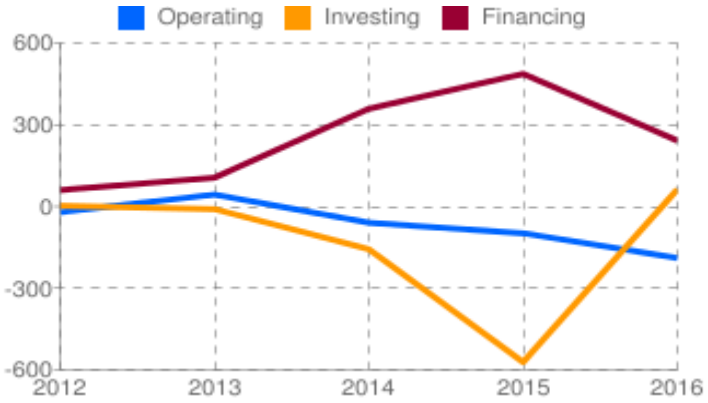
($ in '000)	1Q2017	1Q2016
LentiGlobin	20,509	15,200
Lenti-D	3,984	2,777
Bb2121	6,051	3,403
Pre-clinical programs	4,583	3,839
Total R&D Expenses	**35,127**	**25,219**

Net loss per share also increased and was ($7.07) per share for 2016, up from ($4.81) per share in 2015. For 1Q 2017, net loss per share was ($1.68), up from ($1.52) in 1Q 2016. The total accumulated deficit stood at ($646.9 million) as of March 31, 2017, up from ($577.7 million) in 2016 and ($314.2 million) in 2015.

Liquidity and Cash Flow -- BLUE's reported cash, cash equivalents, and marketable securities decreased to $800.0 million as of March 31, 2017, compared with $884.8 million as of December 31, 2017. Management believes that its current available cash, cash equivalents, and investments in marketable securities will fund the company's operations into the second half of 2019.

BLUE has reported losses and cumulative negative cash flow from operations since its inception in April 1992. As of March 31, 2017, the company had an accumulated deficit of $646.9 million, and management expects the company to continue to incur losses and negative cash flow from operations for the next several years.

Further, in the absence of any product revenue, the company is using cash for its operating activities rather than generating cash flow from operations. Cash used for operations by BLUE has been increasing over the years, in-line with the increase in its R&D and G&A expenses. The total cash used for operations for 2016 nearly doubled to $189.6 million, against $98.4 million in 2015. The trend continued in 1Q 2017 as well, and the total cash used for operations jumped to $75.3 million, from $36.7 million in 1Q 2016. The increase in cash used for operating activities was primarily due to the rise in net losses, as well as increase in working capital requirements.



BLUE has mainly funded its operations from the sale of common stock, preferred stock, and through the Celgene collaboration. The company has raised funds from several issuances of common stock in recent years. In June 2015, the company issued 2.9 million shares of common stock through an underwritten public offering, at a price of $170 per share for aggregate net proceeds of $477.2 million. Similarly, in December 2016, the company sold 3.3 million shares of common stock at a price of $76 per share, aggregating net proceeds of $234.7 million.

BLUE will continue to need additional capital to fund its operations through the next several years. The company may continue to raise funds through public or private equity and debt financing, strategic collaborations, or other available sources. BLUE currently has no credit facility or committed sources of capital, although the company may receive contingent payments under its collaboration agreements.

Management Team Members Have Been Selling Stock

Analysis of 4K filings by BLUE over the last 60 days (since March 1, 2017) establishes the sale of BLUE shares by senior members of the management team. Transactions have been in small numbers, as the average number of shares off-loaded was just over 2,000 shares per transaction; the largest transaction was of the sale of 13,800 shares. Most of the shares sold appear to be shares acquired as stock-based compensation from the company.

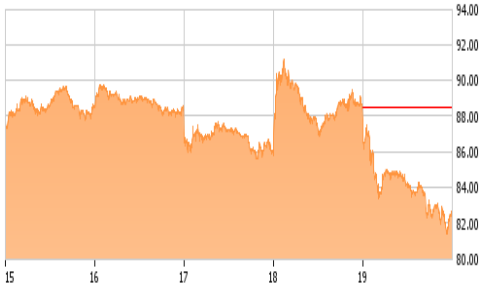
As per 4K filings from March 1, 2017 to May 3, 2017, the total number of shares acquired by senior members of the management stand at 57,524 shares, at an average price of $11.57 per share. The total number of shares sold during the same period by these members stood at 55,220 shares, at an average price of $90.04 per share, aggregating $4.97 million in total sales.

Source: Company 4K Filings

KITE PHARMA KITE Downgraded to Hold @ $87 on March 13

Ticker	KITE
Exchange	NASDAQ
Fiscal Year End	December 31
Market Cap	$4.1 billion
Shares Outstanding	56.55 million
Price 26-May-2017	$73.11
52 Week High/Low	$88.6 / $39.8
Average Daily Volume	1.8 million

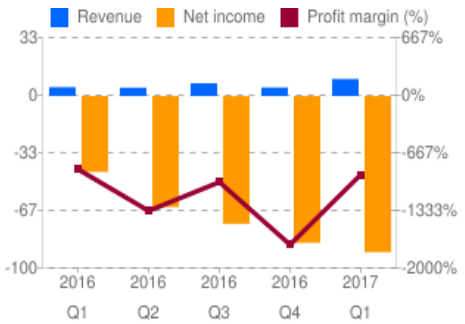
Stock Performance



Source: Seeking Alpha

Summary Financial (1Q 2017)

Net Revenue	$26.88 million
# of Institutions with > $175 mln stake	nine
Net Income (Loss)	($313 million)
Short Interest	$700 mln
Total Cash	$804 million
Total Debt	N/A



KITE PHARMA, INC.
2225 Colorado Avenue
Santa Monica, CA 90404
310-824-9999
http://www.kitepharma.com

In the last two years I went in-and-out of KITE twice and locked in gains of 35% both times. I most recently exited on March 13 @ $87 and have remained on the sidelines since then.

Founded in 2009, the Santa Monica, California headquartered Kite Pharma, Inc. (KITE), is a clinical stage biopharmaceutical company that focuses on the development and commercialization of novel cancer immunotherapy products. The company is developing a pipeline of engineered autologous cell therapy-based product candidates for the treatment of solid and hematological malignancies. Its lead product candidate is KTE-C19, a chimeric antigen receptor **CAR-based** therapy that is in phase II clinical trials for patients with relapsed or refractory aggressive diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma.

The company is also conducting a phase II clinical trial of KTE-C19 on patients with relapsed/refractory mantle cell lymphoma; phase I-II clinical trial of KTE-C19 on adult patients with relapsed/refractory acute lymphoblastic leukemia; and phase I-II clinical trial of KTE-C19 in pediatric patients with relapsed/refractory, as well as phase I(b)/II clinical trial of KTE-C19 in combination with Genentech's atezolizumab in patients with refractory DLBCL. In addition, it engages in developing T-cell receptor-based therapies, which target self-antigens, viral antigens, and neo-antigens.

The company has a research collaboration and license agreement with Amgen to develop and commercialize various CAR-based product candidates; cooperative research and development agreements with the US Department of Health and Human Services; a license agreement with Cabaret Biotech and National Institutes of Health; a license and research agreement with Alpine Immune Sciences; and a research collaboration and license agreement with Cell Design Labs.

KITE competes with Novartis, Juno Therapeutics, Celgene Corporation, bluebird, Lion Biotechnologies, Mustang Bio, ZIOPHARM Oncology, Takara Bio and Immunocore.

$ in million, Except EPS	1Q2017	2016	2015	2014
Revenue	9.84	22.17	17.26	-
Operating Expenses	**101.75**	**295.36**	**121.21**	**36.66**
R&D	*65.91*	*197.93*	*76.37*	*23.09*
G&A	*35.84*	*97.42*	*44.84*	*13.57*
Loss from Operations	91.91	273.19	103.95	36.66
Net Loss	90.46	267.07	101.65	42.77

KITE Reveals CAR-T Patient Death / Posts worse-than-expected Q1 Loss

During the pre-market on May 8, 2017, KITE filed its 10-Q for the quarter ended March 31, 2017, and disclosed the death of a cancer patient enrolled in a study evaluating axicabtagene ciloleucel, following treatment with the company's lead product candidate, KTE-C19, a CAR-based therapy that targets the CD19 antigen for treating aggressive non-Hodgkin lymphoma (NHL). KITE's 10-Q stated that in April 2017, one of its patients experienced multi-organ failure, and a neurologic event that subsequently progressed to a fatal grade 5 cerebral edema that was deemed related to axicabtagene ciloleucel.

KITE's reported revenue for 1Q 2017 was $9.8 million, and below the consensus estimate of $12.3 million, although it was up 92% y/y from $5.1 million in 1Q 2016. The increase in revenue was primarily due to $4.2 million revenue recognized under the Daiichi agreement. Net losses more than doubled to $90.4 million in 1Q 2017, compared with $43.9 million for 1Q 2016, primarily due to a rise in operating expenses -- which nearly doubled during the same period. R&D expenses increased nearly 92% y/y to $65.9 million on account of a rise in headcount to support increased clinical trials and clinical manufacturing activities, and higher facility and overhead expenses. General and administrative expenses were up 115% y/y to $35.8 million in 1Q 2017 due to a rise in headcount, increased pre-commercial activities, and higher consulting and other related costs.

Accordingly, the reported net loss per share increased to ($1.74) in 1Q 2017 compared with a net loss of ($0.90) per share in 1Q 2016. As of March 31, 2017, KITE reported cash, cash equivalents, and marketable securities of $804 million, up from $414.4 million as of December 31, 2016, as it generated approximately $409.7 million in gross proceeds from a follow-on public offering of its common stock. The company received a $50 million upfront payment related to its strategic collaboration with Daiichi Sankyo. Also, net cash used in operating activities was lower at $17.8 million in 1Q 2017 compared with $29.2 million in 1Q 2016, primarily on account of upfront payments from Daiichi. For 2017, KITE management guided the net cash burn to be $325-$340 million, assuming GAAP operating expenses to be $490-$515 mln, including approximately $135 mln in non-cash stock compensation. Of the total operating expenses, KITE expects R&D to account for nearly 60% and G&A for about 40%.

Law Firms Investigating KITE for Potential Securities Fraud

At least five national law firms have announced that they are investigating potential securities fraud at Kite Pharma. The investigation concerns whether KITE and some of its officers and/or directors violated Sections 10(b) and 20(a) of the Securities Exchange Act of 1934. The investigation focuses specifically on harm and losses that may have been caused to investors due to the significant decline in KITE's share prices on May 8, 2017. Pre-market on May 8, 2017, the company filed its 10-Q with SEC disclosing the death of a cancer patient following treatment with KITE's lead product candidate, KTE-C19, CAR-based therapy that targets the CD19 antigen. Shares of KITE declined on news of a patient's death, as cerebral edema was the same adverse event for which Juno Therapeutics (JUNO) phase II study on its most advanced pipeline candidate, JCAR015, for relapsed/refractory acute lymphoblastic leukemia (r/r ALL) was placed on clinical hold. JCAR015 ran into trouble last year when higher-than-expected severe neurotoxicity was observed in a study, along with the occurrence of live deaths due to cerebral edema. In March 2017, JUNO informed that it will discontinue the development of JCAR015. KITE dropped from $82 to $68 in early May but has rebounded to $75 (May 25).

Amid Investor Jitters, KTE-C19 Remains its Lead Product Candidate

KITE is advancing the Chimeric Antigen Receptors (CAR) and T-Cell Receptors (based) product candidates, including its lead product candidate, KTE-C19, a CAR-based therapy that targets the CD19 antigen, a protein expressed on the cell surface of B-cell lymphoma and leukemia. The company's other product candidates include KITE-718, a TCR-based therapy targeting a MAGE A3/A6 antigen for the treatment of MAGE A3/A6 positive cancers – including non-small cell lung cancer, or NSCLC, and bladder cancer.

KITE's CAR/TCR Pipeline

		TRIAL	AREA OF RESEARCH	PRE-IND / PHASE 1 / PHASE 2/3
Chimeric Antigen Receptor	axicabtagene ciloleucel	ZUMA 1	DLBCL, PMBCL & TFL	
	KTE-C19 (WAVE-1)	ZUMA 2 ZUMA 3 & 4	MCL Adult & Pediatric ALL	
	KTE-C19 (WAVE-2)	ZUMA-5 ZUMA-6 ZUMA-7 ZUMA-8	Indolent NHL DLBCL (PD-L1 mAb) DLBCL (2nd line) CLL	
	Human anti-CD19 (2nd Gen)	NCI	Heme Malignancies	
	Humanized anti-CD19 Control CAR (3rd Gen)		Heme Malignancies	
	KITE-585 (anti-BCMA)		MM	
	KITE-796 (anti-CLL-1 Control CAR)		AML	
T Cell Receptor	MAGE A3/A6	NCI	Solid Tumor	
	KITE-718 (MAGE A3/A6)		Solid Tumor	
	MAGE A3	NCI	Solid Tumor	
	HPV-16 E6 & E7	NCI	Cervical and HNC	
	KITE-439 (HPV-16 E7)		Cervical and HNC	
	KRAS	NCI	Solid Tumor	
	SSX-2	NCI	Solid Tumor	
	Neoantigens	NCI	Solid Tumor	

Source: Company Presentation, April 2017

Although the recent announcement by the company about a patient death during clinical trials of KTE-C19 has led to jitters in the market, especially among investors, the company remains optimistic about its lead product candidate. **It is particularly of concern for investors that the patient experienced brain swelling -- the same side-effect that derailed a similar treatment that was being tested and pursued by rival JUNO.** While unfortunate, the death is for now being treated as a non-event as only **one in 300** KTE-C19 patients has had cerebral edema and there is only a 2% death rate associated with the treatment. Some experts feel that relative to the efficacy benefit provided, these are **acceptable** numbers and should not impact the drug's opportunity.

KITE is still expected to be the first to market a treatment for diffusing large B-cell lymphoma and hopes are high of a market launch of its CAR-T therapy in 2017. There are some other early- to mid-stage trials starting, but these will not provide any solid information for quite some time, and the focus will be on lead drug applications and follow-up data from the ZUMA trials.

The company will also release preliminary 12-month follow-up data from ZUMA-1, which was for aggressive NHL, and the ZUMA-6 combination study pairing axicabtagene ciloleucel with Roche's checkpoint inhibitor Tecentriq. Kite expects to submit the MAA for its lead drug to the European Medicines Authority by 3Q 2017. KITE filed an investigational new drug application, or IND, to initiate phase I clinical trial of KITE-718 at end-2016 and plans to open clinical trial for patient enrollment in 1H 2017.

If there are any more fatalities, KITE may be forced in the same direction as JUNO -- another failure in the CAR-T space could take down other therapy developers as well. **While JUNO followers were relieved that when the company canned JCAR015, it already had advanced alternative assets -- JCAR017 -- to pivot to, and although it is still early days for KITE, investors are aware that KITE has no such luxury to fall back on.**

Launch and Pricing

KITE's Axicabtagene ciloleucel has already been granted Breakthrough Therapy Designation status for diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma (TFL), and primary mediastinal B-Cell lymphoma (PMBCL) by the US FDA and Priority Medicines (PRMIE) regulatory support for DLBCL in the EU.

The company has already opened a 43,500 square foot place near LAX Airport, and KITE expects the facility to enable it to treat 4,000-5,000 patients per year. KITE is also partnering with Vitruvian Networks for a software solution platform that will connect KITE, hospitals, physicians, and patients to streamline the logistics that form part of the process of providing patients with engineered T-cells. The company estimates the vein-to-vein time at approximately 16-18 days, including apheresis, manufacturing, transportation process, and infusion.

There is no certainty about the exact timeline for the market launch of the CAR-T treatment and pricing of the treatment is also equally uncertain. Estimates are that the process is most likely to be very expensive for the treatment provider. Looking at how aggressive NHL is treated now, KITE's therapy may probably be priced in the six-figure range, as per some market estimates, making it somewhat prohibitive for masses. Even though prohibitive pricing remains a minor risk to the company's expected revenue, uncertainties over market launch timing, or no launch at all, remains a bigger threat for KITE investors.

KITE Makes New Appointments to Strengthen its Board

In recent months, KITE has announced appointments to several senior management positions and to the board to broad-base and strengthen its management capabilities. In March 2017, the company appointed Owen N. Witte, MD, the founding director of the Eli and Edythe Board Centre of Regenerative Medicine and Stem Cell Research at the University of California Los Angeles (UCLA) and a renowned cancer researcher, to its Board of Directors. Dr. Witte will bring extensive scientific experience to the board, as Kite plans its future portfolio of chimeric antigen receptor (CAR) and T-cell receptor (TCR) therapies, including allogeneic cell therapy, TCRs targeting neoantigens, and other novel TCR approaches.

In March 2017, KITE named Richard L. Wang, PhD as the CEO of Fosun Kite Biotechnology Co., Ltd., KITE's 50:50 Joint Venture in China with Shanghai Fosun Pharmaceutical Co. Ltd., setup to develop, manufacture, and commercialize autologous T-cell therapies to treat cancer in China. Dr. Wang has extensive experience in the biopharmaceutical industry, including US- and China-based leadership roles at Procter & Gamble, Bristol-Myers Squibb, AstraZeneca, and GlaxoSmithKline. Most recently, he served as COO of Cellular Biomedicine Group, a US-listed clinical-stage immuno-oncology and cell therapy company with operations in China.

In January 2017, KITE announced that Ian T. Clark, former Chief Executive Officer, Head of Commercial Operations and a member of the Board of Directors of Genentech Inc., a Roche Group Company, was appointed to its Board of Directors as an independent director. Clark brings extensive commercialization experience to the board to help the company with potential approval and launch of its engineered CAR T-Cell therapy, axicabtagene ciloleucel, as a treatment for patients with refractory aggressive B-cell non-Hodgkin lymphoma (NHL) in the US. In addition to serving as Chairman to KITE's Commercialization Committee, Clark will join the company's Audit Committee.

In December 2016, the company appointed Dr. Jian Irish, PhD as the company's Senior Vice President of Supply Chain. She will be responsible for establishing and securing a reliable supply chain, including sourcing, logistics, inventory management, procurement, supply, and operations planning process -- further increasing the depth of an industry-leading cell therapy Supply Chain organization. She joins KITE from Sanofi, where she most recently served as Vice President of Biologics Strategic Supply, Sourcing and Partnerships. She also served as Vice President of Biologics Product Development Technology Transfer at Sanofi.

In October 2016, KITE announced the appointment of Chris Nowers as Head of Europe; he will be based in London. Nowers will oversee European commercial operations and build awareness of Kite's growing pipeline portfolio of CAR and TCR therapy product candidates in the region and prepare for the potential launch of the company's lead product candidate, KTE-C19. He is a seasoned executive with 30 years of commercial leadership experience in pharmaceuticals, biotech, and diagnostics companies, with a track record of successfully driving differentiated strategies for product commercialization across therapeutic areas in a competitive global landscape. Before joining KITE, Nowers held senior commercial leadership positions at Bristol-Myers Squibb, including Head of Immuno-oncology and Hematology in France, where he led the successful launch of Opdivo (nivolumab), and as Vice President of Global Commercialization for Yervoy (ipilimumab), where he led the global commercial launch.

In September 2016, KITE announced the appointment of Christine Cassiano as Senior Vice President of Corporate Communications and Investor Relations. She will also sit on the company's Executive Committee. Cassiano was most recently Head of Healthcare for the W2O Group, an integrated healthcare marketing and communications consulting firm. She previously co-founded ARC2 Communications & Media, a boutique agency that developed groundbreaking platforms for some of the largest companies in healthcare. Her more than 20-year career includes multiple product launches across various therapeutic areas.

GENE THERAPY – MARKET SIZE ESTIMATES

According to a report by RootsAnalysis, a business research and consulting firm, the Gene Therapy market is expected to be worth $11 billion by 2025, representing a healthy annual growth rate of 48.9%. Specific therapies such as Prostavac, ProstAtak and TroVax are likely to achieve blockbuster status.

As per statista.com, the global cell and gene therapy market is expected to quadruple between 2012 and 2020. The market size is expected to grow from approximately $3 billion in 2012 to $8 billion in 2018 and further to $12 billion in 2020. The global gene therapy pipeline by phase of trial, had a total of 144 gene therapy products in the pipeline, of which 54 were in Phase I, 74 were in Phase II and 16 in Phase III of the trials.

As per Global Market Insights, the cancer gene therapy market worth (US) $805.5 million in 2015, is anticipated to surpass (US) $4.3 billion by 2024, growing at a CAGR of 20.7% over the period of 2016-2024. The US cancer gene therapy market size worth $235 million in 2015, is predicted to grow at a CAGR of 20.9% over the 2012-2024 period. The gene induced immunotherapy segment contributed about 14% of the overall revenue share in 2015 and is projected to surpass $600 million by 2024.

The Regenerative medicine market, including cell therapy, gene therapy, tissue engineering, and immunotherapy, is expected to reach USD 38.70 Billion by 2021 from USD 13.41 Billion in 2016 at a CAGR of 23.6%.

The market is not estimated to grow that significantly in terms of revenue as the rise in these stocks' share prices project. Based on the limited info available on market size growth, it appears that the stocks are running ahead of the market at the moment but me indeed be undervalued if we look out 3-5 years (or more).

The concept of immunotherapies dates back to the 18th century; however, since inception, the field has evolved tremendously and is currently cited as one of the most rapidly growing segments of the pharmaceutical industry. Harnessing immune system components for developing therapeutic solutions has demonstrated significant clinical benefit for various diseases areas, specifically against a number of oncological indications. Immunotherapeutics have gradually gained a strong foothold in the pharmaceutical industry. Post the early success of immune checkpoint inhibitors, T-cell immunotherapy has emerged as another innovative and potent arm of this market.

Adoptive immunotherapy is an emerging concept that involves the passive transfer of immune cells, which may or may not be modified/genetically altered to express a desired set of traits and/or features. Characterized by key features such as target specificity, adaptability and the capability to retain immunologic memory, T-cells have been effectively used as therapeutic tools to mediate an artificial immune response. More specifically, T-cell immunotherapies are classified into three major segments, namely chimeric antigen receptor (CAR) T-cell, T-cell receptor (TCR) and tumor infiltrating lymphocyte (TIL) based therapies. Academicians across the globe have significantly contributed to this field by convening the initial research on potential product candidates; this has served as the intellectual framework for establishment of several start-ups and evolution of the product portfolios of established players in the industry.

The overall market is expected to witness significant growth in opportunities for a variety of stakeholders in the coming decade. It is important to highlight that various technology providers, aiming to develop and/or support the development of T-cell immunotherapy products with improved efficacy and safety, have designed and introduced advanced platforms for engineering of T-cells. Innovation in this domain, backed by lucrative rounds of venture capital (VC) funding, has led to the discovery of several novel molecular targets and strengthened the research pipelines of companies focused in this space. The capability to target diverse therapeutic areas is one of the most prominent growth drivers of this market.

Immuno-oncology has been gradually nurtured by researchers over the last several years and is now considered as the fourth major pillar of cancer therapy, after surgery, chemotherapy and radiotherapy. As indicated earlier, the T-cell therapy market has evolved significantly over the last few years, offering promising opportunities for a variety of stakeholders. The domain is characterized by a robust and opportunistic pipeline of product candidates focused on targeting hematological cancers and solid tumors.

However, with no marketed products, this emerging field is still in its infancy and share prices of the three speculative names highlighted in this report may have gotten ahead of themselves.

The role of academic players and research institutes has been critical in this domain. Post the establishment of initial proof-of-concept, several industry players have entered into collaboration with non-industry participants to fund the clinical and commercial development of potential product candidates. Some late stage products that have emerged out of such collaborations include CTL-019 (Novartis and University of Pennsylvania), KTE-C19 and HPV-16 E6 TCR (Kite Pharma and National Cancer Institute), and LN-144 (Lion Biotechnologies and National Cancer Institute). As mentioned before, encouraging clinical results have significantly accelerated the progress of these therapies.

Several technology providers, especially those with capabilities in genome editing, and viral and non-viral gene transfer, are also actively involved in this emerging market. Many of these players have entered into partnerships with therapy developers in order to assist in designing novel features to enhance the efficacy and potency of existing T-cell therapies. A prominent example of such a technology is safety switches; these are innovative molecular tools designed to manage known side effects, such as cytokine release syndrome and B-cell aplasia, by allowing control over the expression of certain genes in the engineered cell population.

One of the key objectives of the study was to review and quantify the future opportunities associated with the ongoing programs of both small and big pharmaceutical firms in this domain. It is worth mentioning that there is a lot of hope pinned on multiple start-ups, which have received significant backing by several strategic investors and venture capital firms.

There are currently ~ 280 T-cell therapies being evaluated across various phases of development. Among these, CAR-T cell products are the most common (67%), followed by TCR (23%) and TIL (10%) based therapies. Overall, 29% of the pipeline therapies are being evaluated in phase II / phase III clinical trials; on the other hand, 38% of the therapies are in the preclinical / discovery stage of development. Examples of promising late-stage therapies include CTL-019 (Novartis), JCAR015 (Juno Therapeutics), KTE-C19 and HPV-16 E6 TCR (Kite Pharma), NY-ESO-1 TCR (Adaptimmune / GSK), LN-144 (Lion Biotechnologies), ALT801 (Altor BioScience) and IMCgp100 (Immunocore).

Academic institutions are the leading innovators in this domain. Many universities and research institutes have made significant contributions by investing time and building expertise in the design and development of novel CAR-Ts, TCRs and TILs. We observed that non-industry players are involved in the development of ~50% of all the therapies currently in the pipeline. The most active non-industry players, based upon the number of therapies under development, include the National Cancer Institute, MD Anderson Cancer Center, Baylor College of Medicine, University of Pennsylvania, Chinese PLA General Hospital, Southwest Hospital, Fred Hutchinson Cancer Research Center, Fuda Cancer Hospital, Memorial Sloan Kettering Cancer Center, Uppsala University and City of Hope Medical Center.

The market is highly fragmented and characterized by the presence of several start-ups, small pharma and big pharma firms. The key players involved in development of T-cell therapies, based upon the number of candidate therapies in their respective product pipelines, include Juno Therapeutics, Shanghai Genechem, Kite Pharma, Cellular Biomedicine Group, Lion Biotechnologies, Takara Bio, Celgene, Adaptimmune and ZIOPHARM Oncology. AURORA BioPharma, Beijing Doing Biomedical, Bellicum Pharmaceuticals, CARsgen Therapeutics, iCarTABBioMed, Intrexon, Mustang Bio, Novartis, Sinobioway Cell Therapy, Unum Therapeutics and Shionogi are other players that have more than one clinical stage therapies.

In addition to some of the companies outlined above, there are several other start-ups that are focused in this domain; these include: Altor BioScience, Autolus, Adicet Bio, Catapult Therapy TCR, Chimeric Therapeutics, Formula Pharmaceuticals, Gadeta, Immatics US, JW Biotechnology, Lion TCR, Leucid Bio, Mustang Therapeutics, Poseida Therapeutics, TILT Biotherapeutics, TNK Therapeutics, Tmunity Therapeutics and Vor Biopharma.

Stakeholders have forged synergistic partnerships in order to exploit the commercial potential of their respective assets. Overall, there are more than 135 partnerships that have been inked in the T-cell immunotherapy field over the period 2005-2016. Most common forms of partnerships were related to research (20%), followed by technology licensing (15%), product discovery, development and commercialization (12%), manufacturing (11%), clinical trials (7%) and acquisitions (7%).

Amid several challenges, including the complexities associated with manufacturing cell-based products, and competition from existing drug / therapy classes, such as monoclonal antibodies, bi-specific antibodies and immune checkpoint inhibitors, therapy developers are engaged in extensive research in order to effectively deal with these issues. Several contract manufacturing organizations with advanced capabilities have emerged to provide manufacturing services for the personalized T-cell based therapies. Examples of the CMOs providing manufacturing services for T-cell therapies include apcethBiopharma, Atlantic Bio GMP, Cell and Gene Therapy Catapult, Cell Therapies, CELLforCURE, Cellular Therapeutics, MolMed and PCT (a Caladrius company).

A number of technological advancements have taken place in order to support the development of these therapies; engineered CAR-Ts with switch technologies are among the latest additions to next-generation T-cell immunotherapies. Funding from VC firms and strategic investors has been a key enabler to the market's growth. Notably, close to (US) $5 billion has been invested in this domain over the past few years. Several big ticket investments have recently taken place. For instance, Immunocore raised $320 million in July 2015, Kite Pharma raised $288 million in December 2015 and Cellectis raised $228 million in March 2015.

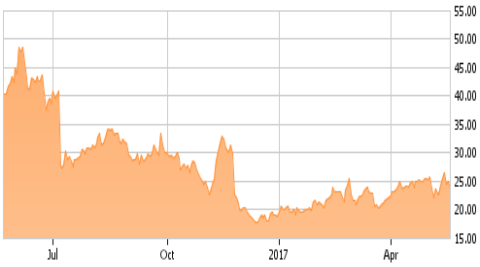
A variety of novel types of immunotherapies, other than CAR-T, TCR and TIL, are expected to emerge in the mid-long term. Companies such as TxCell, Caladrius Biosciences, TRACT Therapeutics, Green Cross Cell and Tmunity Therapeutics, are developing T-regulatory cell based therapies. Other players, namely Opexa Therapeutics, TVAX and Immunovative Therapies, are developing T-cell based vaccines for treating autoimmune disorders and various forms of cancer. Further, Atara Biotherapeutics, Cell Medica and Tessa Therapeutics are working on the development of virus-driven T-cell therapies. A number of companies have developed unique technology platforms based on T-cells. Examples include Targazyme (Fucosylated T-cells), Triumvira (TAC-T cells), Chengdu MedGenCell (PD-1 Knockout Engineered T-cells) and GammaCell Bio-Technologies (γδ T-cells).

It is estimated that the T-cell therapy market is likely to be worth USD 25 billion by **2030**, expanding at a very high annualized growth rate over this time period, albeit off a small base. Specifically, by 2030, the markets for CAR-T and TCR therapies market are likely to be worth over USD 11 billion each. Product candidates, such as KTE-C19, CTL019, NY-ESO-1 TCR, ALT 801 and JCAR017, are expected to emerge as potential blockbusters in the long term.

Juno Therapeutics JUNO / Buy Recommendation / 2019 price target: $32

Ticker	JUNO
Exchange	NASDAQ
Fiscal Year End	December 31
Market Cap	$2.47 billion
Shares Outstanding	106 million
Price 26-May-2017	$23.30
52 Week High / Low	$49.8 / $17.5
Average Daily Volume	1,500,000

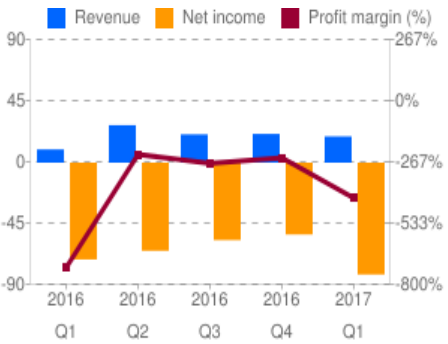
Stock Performance



Source: Seeking Alpha

Statistics & Financials

Net Revenue	$88.9 million
Short Interest	$400 million
Net Income (Loss)	($256.6) million
Float	62 mln shares
Total Cash	$722 million
# of Institutions with > $150 mln stake	two



JUNO THERAPEUTICS, INC.
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Juno Therapeutics (JUNO) is a biopharmaceutical company that focuses on developing cellular immunotherapies for the treatment of cancer. The company develops cell-based cancer immunotherapies based on its chimeric antigen receptor (CAR) and T-cell receptor (TCR) technologies to genetically engineer T-cells to recognize and kill cancer cells.

Its product candidates are **JCAR017, JCAR014,** and JCAR015 (discontinued). In March 2017, the company halted the development of an experimental leukemia treatment, following the deaths of five patients in its trials, as well as an additional early stage product candidate incorporating a fully human binding domain, leverage CAR technology to target CD19, a protein expressed on the surface of almost all B-cell leukemia and lymphoma. Its CAR product candidate JCAR018 targets CD22, a different protein commonly expressed on the surface of B-cell leukemia and lymphoma.

Its MUC-16 -directed product candidate is an armored CAR that secretes the cytokine interleukin 12 (IL-12), which may help overcome the inhibitory effects that the tumor microenvironment can have on T-cell activity.

Juno has collaboration agreements with Celgene, Fate Therapeutics, Editas Medicine, MedImmune, and Memorial Sloan Kettering Cancer Center. The company was formerly known as FC Therapeutics and changed its name to Juno Therapeutics, Inc. in October 2013. Founded in 2013, Juno is headquartered in Seattle, Washington.

Juno competes with Novartis, Kite, Amgen, National Cancer Institute, Cellectis, Servier, Johnson & Johnson, Transposagen Biopharmaceuticals, bluebird bio, Bellicum, Celyad, Cell Design Labs, NantKwest, Intrexon, ZIOPHARM, MD Anderson Cancer Center, Unum Therapeutics, Adaptimmune, ImmunoCellular Therapeutics, Adicet Bio, Autolus, Bristol-Myers, Incyte, Merck, Regeneron, Corvus, and Macrogenics.

$ in million, Except EPS	1Q2017	2016	2015	2014
Revenue	19.33	79.36	18.21	-
Operating Expenses	**103.65**	**340.45**	**262.31**	**232.76**
R&D	*82.92*	*264.29*	*205.16*	*204.51*
G&A	*20.73*	*70.67*	*51.13*	*19.53*
Loss from Operations	84.32	261.09	244.10	232.76
Net Loss	82.20	245.58	239.38	310.87

JUNO Reports First Quarter 2017 Results

JUNO reported its first quarter (ending March 31, 2017) earnings results after close of market on May 4, 2017. The total revenue in 1Q 2017 nearly doubled y/y to $19.3 million, compared with $9.8 million during the corresponding period in the previous fiscal year. This was primarily due to revenue recognized in connection with the company's collaboration with Celgene, and the CD19 license for partial reimbursement by Celgene for research and development cost incurred by JUNO in 1Q 2017. In April 2016, Celgene exercised its option to develop and commercialize JUNO's CD19 program, for which, JUNO was paid $50 million and shares for the program development cost.

JUNO's total operating expenses in 1Q 2017 was up 15.6% y/y to $103.65 million, compared with $89.7 million in 1Q 2016 -- as both R&D and G&A expenses increased during the quarter. R&D expenses rose 12.5% y/y to $82.9 million for 1Q 2017, primarily due to a $20.7 million increase in the cost to execute JUNO's clinical development strategy, manufacture its product candidates, and expand its overall R&D capabilities.

G&A expenses increased 28.1% y/y in 1Q 2017 to $20.7 million on account of a rise in consulting and costs related to the commercial readiness, and increase in headcount to support the business -- including stock-based compensation. JUNO recorded a lower income tax benefit of $1.3 million in 1Q 2017, against $7.4 million in 1Q 2016.

JUNO's reported GAAP net loss for 1Q 2017 stood at 15.6% y/y to $82.2 million or ($0.79) per share, compared with a net loss of $71.1 million or ($0.72) per share in 1Q 2016, primarily due to a rise in operating expenses during the quarter. Non-GAAP net loss, which incorporated non-GAAP R&D expenses as well, was lower at $73.7 million or ($0.71) per share in 1Q 2017, compared with $77.5 million or ($0.78) per share in 1Q 2016. The improvement was primarily due a change in the estimated fair value of the success payment obligations owed to Memorial Sloan Kettering Cancer Center and the Fred Hutchinson Cancer Research Center.

JUNO reported cash, cash equivalents, and marketable securities totaling $850.7 million as of March 31, 2017, down from $922.3 million as of December 31, 2016. This should see the company through for the next ~three years. The company's cash burn in 1Q 2017, excluding cash inflows and outflows from business development activities, was $75.3 million, against $61 million recorded in the prior-year period. The increase stemmed from general growth in the company's clinical, manufacturing, and research operations (including purchase of manufacturing equipment), as well as additional cost to build Juno's planned headquarters facility.

The management has reaffirmed its 2017 cash burn, excluding cash inflows or outflows from upfront payments related to business development activities, to be $270-$300 million. Capital expenditure, net of tenant improvement allowances, is estimated to be $22-$27 million, a majority of which is related to one-time infrastructure build-outs.

JUNO Closes Down the Development of JCAR015 -- Lead Product Candidate

JUNO's JCAR015 was an experimental drug based on the Chimeric Antigen Receptor (CAR) T-Cell therapy and was being evaluated for treating adult patients suffering from relapsed acute lymphoblastic leukemia (ALL), a rare and fatal form of blood cancer. The drug belonged to an ambitious CAR-T technology that involves extracting T-cells from human body's immune system, fabricating them to make them competent to attack and destroy cancer cells, and re-infusing them into the body.

Phase I trial results for JCAR looked impressive, as it seemed to have spurred remission in > 90% of the patients, a nine-fold increase in the natural remission rate of 10%. However, the company reported **three** patient deaths in July 2016 during trials of its genetically-engineered JCAR015. The company attributed these deaths to the chemotherapy agent fludarabine being added to the pre-conditioning regimen. This was a major setback, with FDA placing a clinical hold on the company's phase II study (ROCKET) on JCAR015 in adult patients with Relapsed/Refractory (R/R) B-Cell Acute Lymphocytic Leukemia (ALL). Around the same time, the Novartis (NVS) decision to dismantle its dedicated CAR-T research unit led to further doubts about the sustainability of the CAR-T technology.

After the FDA hold was lifted a week later, the study was resumed under a revised protocol, whereby the company switched to the earlier regimen that excluded fludarabine. However, in November 2016, the company voluntarily placed on hold phase II clinical trial of JCAR015 in adult patients, after two patients suffered cerebral edema or swelling in the brain -- resulting in their deaths. The company notified the FDA of the voluntary hold and worked with the agency and the Data and Safety Monitoring Board to assess data from the cases and evaluate options regarding the JCAR015 program.

Finally, during its earnings call to announce the fourth quarter and full-year 2016 financial results, JUNO announced that it was discontinuing the development of JCAR015 for r/r ALL due to toxicity witnessed in the ROCKET trial, primarily cerebral edema, which results from brain trauma or from non-traumatic causes (such as ischemic stroke, cancer, or brain inflammation). The company redirected its freed-up resources for the development of programs of another product for r/r ALL, particularly the **JCAR017** therapy.

JUNO's hopes rest on its new CD19 lead product candidate – JCAR017

After JUNO's lead product candidate JCAR015 out to contention due to safety reasons, the company's hopes now rest largely on its other CD19 candidate, JCAR017. The company is evaluating JCAR017 in a phase I study for treatment in non-Hodgkin lymphoma, including large B-cell lymphoma (DLBCL) as well as chronic lymphocytic leukemia and acute lymphoblastic leukemia.

JUNO has shifted its focus and resources from JCAR015 to developing its new CD-19 product candidates, primarily **JCAR017 and JCAR014**. The company is conducting a Phase I trial with JCAR017 in adult relapsed or refractory (r/r) non-Hodgkin lymphoma (NHL), including r/r DLBCL. In December 2016, JUNO presented data at the American Society of Hematology meeting (ASH 2016) from an ongoing Phase I trial in patients with r/r NHL and reported that it had achieved a complete response in 12 of 20 patients, or 60%, with r/r aggressive NHL. The company is now planning to file an Investigational New Drug (IND) application in 2017 in support of a planned I/II trial with JCAR017. If the results of these trials are favorable, JUNO may be obtain US regulatory approval in r/r DLBCL as early as 2018 and in r/r CLL as early as 2019. JUNO intends to develop JCAR017 in both pediatric r/r ALL and adult r/r ALL and seek registration in relatively similar timeframe as r/r/ CLL.

JUNO is also continuing to enroll patients in an ongoing Phase I/II trial for JCAR014 in B-cell malignancies, and although the company does not plan to move JCAR014 into registration trials, it plans to use the trial to explore important questions that may improve its platform overall, including testing the combination of JCAR 014 and ibrutinib in r/r CLL patients. The company is also enrolling patients in a combination Phase Ib clinical trial combining JCAR014 with MedImmune's investigational PD-L1 immune checkpoint inhibitor, durvalumab for the treatment of r/r NHL.

Apart from CD-19, JUNO is conducting trials for seven additional product candidates that target different cancer-associated proteins in hematological and solid organ cancers, including a Phase I trial for a CAR T cell product candidate targeting BCMA in patients with multiple myeloma. Additionally, the company commenced a Phase I trial through its collaborator MSK of a CD19/4-1BBL "armored" CAR. It also has a number of other pre-clinical programs against other targets that should move into human testing over the next several years. With up to 20 ongoing trials by year end, JUNO expects to gain additional insights that may lead to product candidates that can deliver long-term durable remissions for patients in need.

JUNO and its partner Celgene believe that JCAR017 could be on the market as a treatment for non-Hodgkin lymphoma as early as next year. However, even if all goes well, it is possible that JUNO will not be the only CAR-T player in the market as competing companies like Novartis and Kite Pharma have already sent CAR-T product candidates off for regulatory review in disease states like acute lymphoblastic leukemia and non-Hodgkin lymphoma. If these competitors succeed in bringing these therapies to market first, then JUNO might find it hard for its product and therapy to gain traction in the market.

JUNO Adds Key Talent to Leadership Team

JUNO has added key talent and expertise to its leadership team, as well has to its Board of Directors. On April 19, 2017, JUNO announced the appointment of Dr. Rupert Vessey, President of Research and Early Development at Celgene Corporation, to its Board of Directors. He brings significant drug development capabilities to JUNO's board. Dr. Vessey has handled several roles of increasing responsibility in drug discovery, experimental medicine, and early clinical development of therapeutics for respiratory and immune diseases; he has significant experience in building an efficient, world-class research organization from his earlier associations with Merck and GlaxoSmithKline. He will serve as Celgene's designated appointee to the JUNO board, while Dr. Tom Daniel, who was appointed as Celgene-designated appointee in 2015 upon closing of the Celgene/JUNO collaboration agreement, has agreed to remain on the board as an independent director.

JUNO also announced the appointment of Sunil Agarwal, MD, as President of R&D, bringing the R&D function under one leader. He will be responsible for the execution of JUNO's drug development pipeline, integration of translational insights into ongoing programs, and prioritization of R&D initiatives. Dr. Sunil joins from Ultragenyx Pharma, where he was Chief Medical Officer and Executive Vice President. He has previously worked with Genentech. He has led global approvals of multiple therapies, and successfully built and led large global development organizations in multiple geographies.

In January 2017, the company appointed Dr. Corsee D. Sanders, PhD, as Executive Vice President and Head of Development Operations, responsible for the planning, management, execution, analysis and reporting of JUNO's clinical trials. Dr. Sanders joins from Roche Pharmaceuticals, where she was designated as Senior Vice President and Head of Global Clinical Operations and Industry Collaborations. Dr. Sanders has also worked in a number of senior leadership roles at Genentech, where her responsibilities included biostatistics, epidemiology, health economics and outcomes research, data management, medical writing, information technology, and biosample management, patient operations, and program and project management.

The drug companies engineering T-cells to recognize and kill cancer, otherwise known as chimeric antigen receptor T-cells, or CAR-Ts, will be busy at the American Society of Clinical Oncology (ASCO) annual meeting in June. Investors, however, won't find much new CAR-T data in the ASCO research abstracts released (beforehand).

Bluebird Bio (BLUE), **Juno Therapeutics** (JUNO) and **Kite Pharma** (KITE) submitted placeholder abstracts that largely rehash old data, choosing to wait for the actual meeting to provide significant updates.

Novartis' (NVS) CAR-T unit is sidestepping ASCO and will instead use the International Conference on Malignant Lymphoma (ICML) later in June to present the highly anticipated results from the JULIET study of CTL019 in patients with diffuse large B-cell lymphoma.

The ASCO abstract describing the Bluebird CAR-T known as BB2121 rehashes multiple myeloma data presented last October. Updated results from the BB2121 clinical trial -- more patients and longer follow up, are being presented at the ASCO meeting on June 5. Bluebird is developing BB2121 in partnership with **Celgene** (CELG).

Juno last presented in December an update on its JCAR017 TRANSCEND study in non-Hodgkin lymphoma. Wednesday's ASCO abstract doesn't shed new light on JCAR017. New data were preserved for presentation at the actual ASCO meeting, Juno said. JCAR017 is co-owned by Celgene.

Kite is waiting for the FDA to render an approval decision on KTE-C19 (axi-cel) in relapsed/refractory non-Hodgkin lymphoma, based on data from the ZUMA-1 study. At ASCO, Kite will be updating results from the ZUMA-3 study of KTE-C19 in adults with relapsed/refractory acute lymphoblastic leukemia (R/R ALL). Wednesday night's ASCO abstract contains data last seen in December.

One more intriguing abstract of note: **Nanjing Legend Biotech**, a Chinese drug company, snagged a late-breaker abstract and presentation for an anti-BCMA CAR-T targeting multiple myeloma. This is the same cancer-killing target and tumor type that Bluebird and Celgene are pursuing with BB2121. ASCO keeps late-breaker abstracts under wraps until the start of the meeting.

Here are the relevant ASCO abstracts (already) released:

Abstract # 7513 (Juno Therapeutics)

CR rates in relapsed/refractory (R/R) aggressive B-NHL treated with the CD19-directed CAR T-cell product JCAR017 (TRANSCEND NHL 001).

Background: JCAR017 is a second-generation, CD19-directed, 4-1BB CAR T cell product comprising CD8 and CD4 CAR T cells in a 1:1 ratio. A multi-center phase I trial of JCAR017 in R/R B-cell NHL (NCT02631044) is underway.

Methods: Patients with R/R DLBCL, PMBCL, FL grade 3B, or MCL and adequate organ function are eligible. There was no minimum ALC requirement for apheresis; no test expansion was required. Treatment includes lymphodepletion with fludarabine and cyclophosphamide, followed by JCAR017. Multiple dose levels (DLs)/administration schedules of JCAR017 are being evaluated. Study objectives include safety, PK, and antitumor response.

Results: As of November 23, 2016, 28 patients have been treated and are evaluable for safety and efficacy. Nineteen were male, 9 female; 25 DLBCL, 2 MCL, and 1 FL grade 3B. Median age was 63 years (range 37-79), median number of prior therapies was 4 (range 1-8), 23 (82%) were refractory to their last chemotherapy, and 16 (57%) had prior transplant. No severe cytokine release syndrome (sCRS) was observed; 10 patients had grade 1-2 CRS (one received tocilizumab). Five patients developed neurotoxicity, including 4 grade 3-4; all events resolved in the 4 patients who had adequate follow up. Median onset of CRS and neurotoxicity were 5 and 11 days, respectively.

Four deaths after disease progression occurred, none related to JCAR017. In 20 patients treated at DL1 (5107 cells), the RR was 80% with 60% achieving CR. One patient with secondary CNS involvement achieved CR without neurotoxicity. JCAR017 was detected at 3 and 6 months in responding patients, including some who relapsed; higher mean peak levels were detected in patients with durable response at 3 months.

Conclusions: Treatment with JCAR017 results in high CR rate in patients with heavily pretreated R/R DLBCL. Relapses can occur despite persistence of JCAR017, suggesting tumor immune evasion mechanisms may contribute to relapse. Observed toxicities are manageable and occurred at rates lower than those reported for other CD19-directed CAR T cell products.

Abstract # 3010 Bluebird, Celgene

First-in-human multicenter study of bb2121 anti-BCMA CAR T-cell therapy for relapsed/refractory multiple myeloma: Updated results.

Background: To test the safety and efficacy of the CAR T cell modality in relapsed/refractory multiple myeloma (MM), we have designed a second-generation CAR construct targeting B cell maturation antigen (BCMA) to redirect T cells to MM. bb2121 consists of autologous T cells transduced with a lentiviral vector encoding a novel CAR incorporating an anti-BCMA scFv, a 4-1BB costimulatory motif and a CD3-zeta T cell activation domain. We will report updated safety and efficacy following initial results (Berdeja et al, ENA 2016).

Methods: CRB-401 (NCT02658929) is a multi-center phase I dose escalation trial of bb2121 in patients with relapsed and/or refractory MM who have received ≥ 3 prior regimens, including a proteasome inhibitor and an immunomodulatory agent, or are double-refractory, and have ≥ 50% BCMA expression on plasma cells. Peripheral blood mononuclear cells are collected via leukapheresis. Patients undergo lymphodepletion with Flu (30 mg/m2) / Cy (300 mg/m2) daily for three days then receive one infusion of bb2121. The study follows a standard 3+3 design with planned dose levels of 5, 15, 45, 80 and 120 x 107 CAR+ T cells.

Results: As of November 18, 2016, 11 patients had been infused with bb2121 in the first 4 dose cohorts, and 9 patients had reached at least one month of follow-up. As of data cut-off, no dose-limiting toxicities and no > Grade 2 neurotoxicities or cytokine release syndrome (CRS) had been observed. Grade 1-2 CRS had been reported in 8/11 (73%) treated patients. All patients treated with doses of 15.0 x 107 or higher remained on study and the overall response rate (ORR) in the six patients at these doses was 100%, including two sCRs and two MRD-negative responses (one sC, one VGPR). CAR+ T cell expansion has been demonstrated consistently. An additional six months of follow up on previously reported results and initial data from an additional ~10 patients will be presented.

Conclusions: bb2121 shows promising efficacy at dose levels above 5 x 107 CAR+ T cells, including two sCRs and ongoing clinical responses at six months, with mild and manageable CRS to date. These initial data support the potential of CAR T therapy with bb2121 as a new treatment paradigm in MM. Study sponsored by bluebird bio.

Abstract # 3024 Kite Pharma

Updated results from ZUMA-3, a phase 1/2 study of KTE-C19 chimeric antigen receptor (CAR) T cell therapy, in adults with high-burden relapsed/refractory acute lymphoblastic leukemia (R/R ALL).

Background: Promising results have been observed with KTE-C19, an anti-CD19 CAR T cell therapy, in refractory aggressive NHL in the ZUMA-1 trial (Blood 2016;128:LBA-6). We present here updated results from the ZUMA-3 phase I trial of KTE-C19 in adult patients (pts) with R/R ALL.

Methods: Adult (≥18 y) pts with R/R ALL (Ph+ eligible), ≥25% bone marrow (BM) blasts, adequate organ function and ECOG status 0-1 received one (or two) 106 CAR T cells/kg after conditioning with cyclophosphamide + fludarabine. Phase I primary endpoint is incidence of dose-limiting toxicity (DLT). Secondary endpoints include efficacy outcomes and biomarker associations.

Results: As of Nov 1, 2016, 11 patients were enrolled; 10 received KTE-C19. One patient had a serious adverse event (SAE) prior to dosing and was not treated. KTE-C19 was successfully manufactured in all patients across a broad range of baseline absolute lymphocyte counts in six days in a centralized facility, with an approximate two-week turnaround time. Patients were 60% men with 1-4 prior lines of therapy and high disease burden (median, 70% BM blasts). No patient (0/3) experienced a DLT at the 2106 dose. Phase I was expanded to 6 patients at the same dose; 1 grade (Gr) 5 AE (multi-organ failure due to cytokine release syndrome) was observed. Subsequent patients (4) received 1106CAR T cells/kg. Overall, the most common Gr≥3 AEs were cytopenias (80%), febrile neutropenia (50%), pyrexia (40%), and transaminitis (40%). Gr≥3 CRS and neurologic events (NEs) were reported in 20% and 40% of patients, respectively. Cerebral edema was not observed. All CRS (except Gr5) and 5 of 6 NEs (one Gr3 ongoing at cut-off) resolved. Of the eight efficacy evaluable patients, six achieved an MRD-negative (MRD-) complete response (CR, or CR + partial or incomplete hematopoietic recovery). Updated results will include additional patient follow-up and biomarker data.

Conclusions: No DLTs were observed with KTE-C19 in adult patients with high BM disease burden; one patient had G5 CRS after the DLT cohort. Manufacturing was successful in all patients; most patients achieved an MRD- CR. Based on these results, ZUMA-3 continues to enroll patients with additional measures implemented to further enhance safety.

Abstract # LBA3001 Nanjing Legend Biotech

Durable remissions with BCMA-specific chimeric antigen receptor (CAR)-modified T cells in patients with refractory/relapsed multiple myeloma.

[Text of abstract not yet available.]

JUNO Therapeutics will present key clinical updates in partnership with its collaborators on its investigational products JCAR017 and JCAR014 at ASCO in **early June**. New data from the ongoing Phase I TRANSCEND NHL 001 trial (NCT02631044) evaluating JCAR017 in adult patients with relapsed or refractory aggressive NHL diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL), follicular lymphoma Grade 3B, and mantle cell lymphoma (MCL) will be presented, with increased patient numbers and longer duration of follow-up reported at two dose levels as compared to previous presentations. Updated safety data will also be presented from the ongoing Phase I trial (NCT01865617) evaluating JCAR014 in adult patients with relapsed or refractory ALL, NHL, or CLL. The JCAR014 presentation will also include data on clinical and laboratory biomarkers that may allow early identification of cytokine release syndrome (CRS) and neurotoxicity (NT).

May 26: FBR notes this morning, **KITE** announced that the FDA has accepted for priority review the Biologics License Application (BLA) for axicabtagene ciloleucel (axi-cel). The FDA has set a PDUFA target action date of November 29, 2017 for axi-cel. As a reminder, KITE reported an 82% objective response rate (ORR) recorded after a single infusion of axi-cel, including a 54% complete response (CR) from the ZUMA-1 trial. At a median follow-up of 8.7 months, 44% of the patients were in ongoing response, which included 39% CRs. In addition, the company indicated that it remains on track to submit a marketing authorization application (MAA) to the EMA for axi-cel in aggressive NHL in 3Q17. **Firm continues to expect a late 2017 launch of axi-cel, and they estimate sales will reach one billion dollars in 2023.**

May 26: Juno Therapeutics Director disclosed purchase of 20,000 shares worth approximately $500K with transaction dates of May 24-26, 2017.

May 11: Kite Pharma CFO disclosed purchase of 3,450 shares worth about $250K ($74.88, +$2.78)

May 10: Kite Pharma Director disclosed purchase of 1,400 shares worth about $97K ($73.48, +$1.38)

May 9: Kite Pharma CEO/Pres disclosed purchase of 17,000 shares worth more than $1 mln ($70.87, -$0.12)

May 8: Wedbush downgraded **KITE** to Underperform from Neutral and lowered their target to $54 from $60 as they see significant risk to KITE shares despite expected approval of axi-cel, with additional safety concerns raised by a reported cerebral edema death and the challenge of a complex product launch leading to downside to revisions and erosion of its first-mover advantage in r/r NHL. Firm sees increased risk to follow-on indications for axi-cel, and with the CD28 costimulatory domain incorporated into KITE's pipeline CAR-Ts, they are increasingly skeptical of its pipeline competitiveness going forward.

May 8: KITE shares dropped by 15% and weighed on immuno-oncology stocks after reporting patient death in its Phase II CAR-T trial treating NHL ($69.07, -$12.71)

May 2: **BLUE** enters into a worldwide license agreement around its proprietary lentiviral vector platform with Novartis (NVS). Under the terms of the agreement with Novartis, NVS will non-exclusively license certain bluebird patent rights related to lentiviral vector technology to develop and commercialize chimeric antigen receptor T cell (CAR T) therapies for oncology, including CTL019, Novartis's anti-CD19 CAR T investigational therapy. Financial terms of the agreement include an upfront payment to bluebird as well as milestone and royalty payments.

March 13: Kite Pharma downgraded to Hold from Buy at Standpoint Research ($87.06, +$3.08)

March 6: FBR notes the potential for tax reform and policy changes relative to the FDA could prime the pump for acquisitions of clinical-stage biotech companies by Big Pharma. With a likely increase in mergers, they believe certain companies including **JUNO & KITE** are prime targets.

March 3: Stifel downgraded **KITE** to Hold from Buy and set a target price at $74 based on valuation in front of a launch that seems unlikely to exceed expectations. Firm found recent data highly compelling with nearly a third of patients experiencing what appears to be life-saving treatment. Nonetheless, KITE now faces a unique launch with treatment centers that have not all used these cells before and are likely to move slowly. In addition, firm still awaits a pricing announcement that is likely to trigger the heel-dragging that payors (payers) are becoming comfortable with. Finally, until more data for JCAR017 are released, the stock will continue to be plagued by doubts that **JUNO** cells may be meaningfully better. Despite the high chances for approval, firm does **not** see the conventional counter argument that Kite could be acquired. Firm sees only a handful of companies as sophisticated enough to take Kite over, namely **Amgen** and **Roche/Genentech**, but both of those companies are highly involved with competing, non-cellular, technologies.

March 1: Juno Therapeutics discontinued development of JCAR015 in r/r adult ALL to focus on defined cell product in this setting ($25.31, +$1.27): *We continue to experience encouraging signs of clinical benefit in our trial addressing NHL, but we also recognize the unfortunate and unexpected toxicity we saw in our trial addressing ALL with JCAR015. We have decided not to move forward with the ROCKET trial or JCAR015 at this time, even though it generated important learnings for us and the immunotherapy field. We remain committed to developing better treatments for patients battling ALL and believe an approach using our defined cell technology is the best platform to pursue. We intend to begin a trial with a defined cell product candidate in adult ALL next year. We look forward to sharing detailed data supporting our learnings from the ROCKET trial at an upcoming scientific conference.*

Swiss major **Novartis** is still hoping to be first to market a pioneering new class of oncology medicine known as CAR-T after getting a priority review from the FDA last night for its blood cancer med CTL019. Novartis is gunning for its first license with CAR-T (more are in the pipeline) in kids and young adults with relapsed or refractory (R/R) pediatric and young adult patients with B-cell acute lymphoblastic leukemia (ALL). Last year, Novartis came out with new data from its Phase II test that saw 82% (41 out of 50 patients) achieve complete remission or complete remission with incomplete blood count recovery at three months after an infusion of its med CTL019 infusion in young R/R patients with B-cell ALL.

Big Pharma in a race with Kite Pharma, a specialist CAR-T biotech working on axicabtagene ciloleucel (KTE-C19), which has already kick-started a rolling submission with the FDA for a BLA of its med as a treatment for patients with R/R aggressive B-cell non-Hodgkin lymphoma who are ineligible for autologous stem cell transplant. The two will likely have a very close battle to go down in the history books as the first to market CAR-T; a priority review means that it could be on the market within six months.

If Novartis does turn victor, this will come as a major turnaround given that last year, it announced plans to cut back on its gene and cell therapy unit (which developed this drug) and saw the exodus of many of those who had helped create and nurture it. The drug originally came out of work out of the University of Pennsylvania, which Novartis teamed up with in 2012. *With CTL019, Novartis is at the forefront of the science and development of immuno-cellular therapy as a potential new innovative approach to treating certain cancers where there are limited options* -- said Vas Narasimhan, global head of drug development and CMO of Novartis. *The priority review and file acceptance of CTL019 by the FDA brings us one step closer to delivering this novel treatment option to children and young adults with r/r B-cell ALL in the United States*.

This was also good news for British biotech Oxford BioMedica, which produces the lentiviral vector expressing CTL019 and has a CAR-T partnership with Novartis. The news that the FDA has accepted the BLA for CTL019 and granted it priority review is an important development for Oxford BioMedica. We continue to work closely with Novartis in delivering the lentiviral vector expressing CTL019, a product described earlier this year by Novartis as having 'blockbuster' potential.

Its blockbuster potential will likely come with a blockbuster price: Analysts at Jefferies believe Kite's Axi-Cell, across all indications, could cost up to **$300,000** in the US, while in Europe, they are predicting a price tag of **$204,000**.

These prices have gone up by ~100,000 and ~$80,000 respectively in recent months (as new data have come in).

Another CAR-T biotech, Juno, had looked to be alongside Novartis and Kite in the race to market, but is now out of the running after a string of deaths from several studies last year saw it ditch its leading CAR-T med as it had to rely on JCAR017, a med further back in its pipeline.

Bluebird is a little further behind in regulatory terms than Novartis and Kite, posting some early but impressive data last year from a Phase I trial showing its anti-BCMA CAR-T cell product candidate, which was given to patients with R/R multiple myeloma and were heavily pre-treated, had an ORR rate of 78%, and with no dose-limiting toxicities and no grade 3 or higher neurotoxicities or CRS coming out of its test.

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The KITE market cap is $4.0 bln dollars and short interest is $650 mln ... the JUNO market cap is $2.7 bln and short interest is $400 mln … the BLUE market cap is $3.3 bln and short interest is $600 mln. The market is telling us that this trio is worth 10 billion dollars and that within 3-5 years there will be at least a few hundred million dollars in net profit to go around. In my opinion, and in the opinion of some of those who bet $1.65 billion against this group, it will take a bit longer in order for this group to generate a profit of a few hundred million dollars. There may be one winner and two losers here. Hard to get excited about any of these three names right now given their current valuations. If you are going to go into the space I would allocate no more than 3% portfolio to these names and divide the investment up between the three of them. I would put half of the 3% into BLUE. The only thing I can guarantee you is volatility. You don't want to have all your eggs in one basket, as any one of these names could disappoint on a trial and/or see deaths on a trial that will not be received well by the market. These are risky and speculative names that are not suitable for everyone. If you are looking for volatility and high-reward then you must take high-risk. If you are risk averse then you should go into low beta mega-cap names instead. Any one (or all) of these names could double or triple in the next 5-7 years but it will not be a smooth ride -- in the near-term, on any given day, these names with no EPS can look over-valued.

The stock market is a marathon not a sprint. Anyone looking for get rich quick schemes is going to be disappointed. I have mentioned **at least a dozen times** in my notes during the last year that you should try to avoid taking sector bets and you should not have more than 4%-8% of your money tied up in speculative biotech names (with no earnings) in a balanced portfolio. In my opinion you should have three or four speculative biotech names with no more than 1%-2% weight allocated to any one of those positions.

I believe in this cancer therapy space that I covered in this 45-page report. **That being said** -- this industry is in its **infancy** and it will take 3-5 years before you see how valuable these names will be (as many of them are still only in Phase I or Phase II of the process). There are **dozens** of companies fighting for a piece of what may be a $20 billion pie 3-5 years from now. The consensus is that there will be **a few** winners -- and **more losers than winners** in this fight and race. From my research it looks like **BLUE, KITE and JUNO** are three names that you can take a bet on. My recommendation is to split 3% of your portfolio across these three names with **half** of the money going into **BLUE** -- my favorite of the trio.

What I like about BLUE is that their therapy is **very** high margin and, conservative estimates say, they should/will **net** six figures on every patient that they treat -- maybe as much as $200,000 on each patient. They will have the capacity to treat **thousands** of patients a year and the demand should/will be there. We are looking out 3-5 five years, so you have a choice -- you can buy the stock now when it appears over-valued at $3.3 billion dollars with no earnings, or you can wait until you see light at the end of the (EPS) tunnel and the market cap is double what it is today. Several of the industry research reports that I read are making revenue projections that are **not** looking out three months, or a year, or two years -- the forecasts are for 3, 5, 7 and some cases 10 **years** out -- which is when we will know the true value of these companies operating in an industry in its infancy. Right now they are volatile and they look over-extended on a valuation basis, but the same could have been said about names like Amgen, Biogen, Gilead and Celgene 20 years ago.

Again, I stress, you should not have more than 1%-2% of your money in any of these names. Nothing goes up in a straight line -- especially names in this industry. It will be volatile. Two of these three names could end up dropping by 25%-50% (unlikely), but if one of these names does what I expect, that will more than offset the loss that you have on the one (or two) disappointment(s). The market is currently valuing this trio at **$10 billion** so there is more than likely something significant here. That being said, the trio does need to generate a few hundred million dollars in profit in order to justify this valuation. All we need to see here, in order to get a return on our investment in the next 3-5 years, is one of these three names coming up with a billion dollar (blockbuster) therapy. I also think each of these three names are possible takeover targets. In fact, each of them already has partnerships with mega-cap healthcare names. **Many mega-cap names in the healthcare sector -- Gilead is one example -- are struggling to grow and this may be one area where they look to for possible growth via acquisition.**

Credits

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Please assist here if you have not yet done so –
www.foodforthepoor.org/Moas
Launch Date: July 15, 2016 / Raised: $52,440 / # of Donations: 276

Food for the Poor Annual Report --

http://www.foodforthepoor.org/about-us/financial-info/files/annual-report-2015b.pdf

More than one billion dollars in humanitarian aid distributed in 2015 to 18 countries.

Administrative expenses were only 4%. Established in 1982, FFTP is a five-star charity headquartered in Coconut Creek, FL. 35% of the aid in 2015 went to Haiti. 25% went to Guatemala. Dominican Republic, El Salvador, Honduras, Jamaica and Nicaragua were the other countries who each received significant assistance of $50,000,000-$100,000,000. FFTP does not work with any country or port that taxes humanitarian aid and five officials must sign off on each expense. $200 pays for 800 pounds of rice and beans – enough to keep a single Mom and three starving children alive for a year. $7,200 pays for a double-unit concrete house (400-square feet) and takes a homeless family (of 6-8) off the street.

3,000,000 children under age five starve to death worldwide every year

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End of Report

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