Vertex Pharmaceuticals, Inc. (Nasdaq: VRTX)

Rating: Buy

Price Target: $550.00
Share Price: $474.57

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Company Data	
Average Daily Volume (M)	1.18
52-Week Range	339.02-486.43
Shares Outstanding (M)	258.05
Market Cap (B)	122.46
Enterprise Value (B)	108.63
Total Cash (B), mrq	10.17
Total Debt (M)	721.3
Total Debt to Cap	3.74%

GAAP Estimates				
FYE: Dec		2023A	2024E	2025E
EPS	Q1	2.69	4.21	3.86
	Q2	3.52	3.69	3.90
	Q3	3.97	3.76	3.96
	Q4	3.71	3.98	4.06
	FY	13.89	15.63	15.79
P/E		34.2x	30.4x	30.1x
Rev	Q1	2,374.8	2,690.6	2,750.0
	Q2	2,493.2	2,660.0	2,790.0
	Q3	2,483.5	2,690.0	2,845.0
	Q4	2,517.7	2,730.0	2,920.0
	FY	9,869.2	10,770.6	11,305.0
EV/Sales		11.0x	10.1x	9.6x

One-Year Performance Chart

As of July 5, 2024. Source: E*Trade.

Biotech Company Known for Cutting-Edge Science Is Expanding Beyond Cystic Fibrosis

On Track to Meet the Global Medical Need for Effective Non-Opioid Pain Therapeutics; Initiate With a BUY

Summary

We initiate coverage of Vertex Pharmaceuticals with a BUY rating and $550 PT (based on 35.5x P/E). Vertex is a global biotechnology company focused on creating transformative medicines for patients with cystic fibrosis and other life-shortening diseases. The company currently has four cystic fibrosis (CF) therapies on the market, among them the blockbuster drug TRIKAFTA, which has a near-monopoly in the cystic fibrosis transmembrane receptor (CFTR) segment of the market. Vertex holds over 3,500 granted patents protecting its intellectual property in key geographies. The majority of the company's research centers are located in the U.S. and Germany.

Our rating is based on our view that Vertex has room to grow, with significant potential near- and medium-term upside, as its non-opioid pain drug Suzetrigine (VX-548) and its triple combination CF treatment are under regulatory review by the Food and Drug Administration (FDA), and other drug candidates for a variety of disease indications are progressing through clinical trials. At the 2023 price-to-earnings (P/E) ratio of 34.2x, Vertex trades at a premium to its competitor group median P/E of 17.0x, reflecting its market leadership in the cystic fibrosis space and its industry-wide reputation as a well-managed, research-based company. Key risks include clinical trials, regulatory, IP challenges, competition, and supply chain.

We believe that given Vertex's financial strength (with cash and short-term investments of $10.17 billion, current ratio of 3.5x, and last-twelve-months (LTM) interest coverage of 102.1x, as of March 31, 2024), deep pipeline, two drugs under FDA regulatory review, and two drug candidates in Phase 3 development for neuropathic pain and APOL1-mediated kidney disease, there is room for organic growth as drugs in the pipeline reach the market in 2025 and beyond. The foregoing is coupled with the company's ability to execute opportune acquisitions of innovative firms developing products or technologies capable of advancing Vertex's strategic goals.

Vertex is well-positioned to capitalize on its strong gross margin of 87% and net margin of 40%, as additional pipeline products come to market.

Key Points

- Vertex Pharmaceuticals is a market leader for cystic fibrosis therapies, with its blockbuster drug TRIKAFTA having posted year-over-year (YoY) revenue growth of 16% during FY23, to $8.94 billion.

- The company diversified its portfolio of marketed products in late 2023 and early 2024, when it secured regulatory approval for CASGEVY™, the first CRISPR/Cas9 gene-edited cell therapy for the treatment of sickle cell disease (SCD) and transfusion-dependent beta thalassemia in the United States, the European Union, the United Kingdom, the Kingdom of Saudi Arabia, and the Kingdom of Bahrain.

- A large pipeline of drug candidates in mid- to late-stage development is expected to further diversify the company's product portfolio and focus areas, providing significant potential increase of future revenue.

- Vertex has secured a strong financial position and is well-positioned to pursue both organic growth and growth by acquisition, in addition to being able to withstand potential market shocks.

- Vertex's May 2024 acquisition of Alpine Immune Sciences added protein engineering and immunotherapy capabilities to Vertex's arsenal of drug development tools. Alpine's clinical asset, povetacicept, has shown potential best-in-class efficacy in IgA nephropathy, a serious, progressive autoimmune disease of the kidney, and is ready to enter Phase 3 development. Povetacicept may also be developed for other disease indications.

- A share repurchase program, announced in February 2023 and without an expiration date, provides for the repurchase of up to $3.0 billion of VRTX common stock from time to time, subject to general business and market conditions and other investment opportunities. It has the potential to reduce the number of outstanding shares by approximately 3.5%, thus creating additional shareholder value. As of March 31, 2024, Vertex had $2.4 billion remaining authorization under this program.

Company Description

Founded in 1989, and headquartered in Boston, MA, and London, U.K., Vertex Pharmaceuticals, Inc., is a global biotechnology company focused on discovering, developing, manufacturing, and commercializing small molecule treatments for chronic and genetic diseases, for which there is acute medical need.

The firm's initial focus, and subject of ongoing research and development, is cystic fibrosis (CF), a genetic disease affecting the lungs and other organs. The Vertex portfolio of marketed CF medicines includes KALYDECO, ORKAMBI, SYMDEKO, and TRIKAFTA, which improve lung function and reduce hospitalizations in CF patients.

The company has also received regulatory approval for CASGEVY™, the first CRISPR/Cas9 gene editing therapy that treats the underlying causes of two chronic, life-shortening diseases: sickle cell disease and transfusion-dependent beta thalassemia.

Vertex has a robust clinical pipeline of investigational therapies for other debilitating diseases and conditions, including non-opioid treatment of acute and chronic pain, Type 1 diabetes, alpha-1 antitrypsin deficiency, kidney disease, Duchenne muscular dystrophy, and myotonic dystrophy type 1.

The company has research and development sites and commercial offices in the United States, Canada, Latin America, the Middle East, Japan, Australia, and several European countries.

Products

Cystic Fibrosis

Vertex Pharmaceuticals markets four therapies for the treatment of CF, targeting the underlying cause of the disease.

The drugs target the most common mutation in CF, F508del, which represents a deletion of three base pairs in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, resulting in the loss of the amino acid phenylalanine at position 508 of the CFTR protein. The CFTR protein is made up of 1,480 amino acids and under normal circumstances forms a stable three-dimensional shape that allows it to transport chloride ions across the cell membrane.

Without the phenylalanine building block at position 508, the CFTR protein cannot maintain its correct 3-D shape, thus the cell disposes of it via accelerated degradation by the proteasome. The defective CFTR protein is unable to regulate the movement of salt (chloride ions) and water across cell membranes, leading to the characteristic symptoms and complications of CF, such as persistent cough, wheezing, shortness of breath, and recurrent lung infections.

CFTR modulators such as those developed by Vertex Pharmaceuticals aim to correct the function of the defective CFTR protein and improve clinical outcomes for individuals with CF by enabling the defective CFTR protein to fold into a correct shape, stabilizing it, and activating the protein to allow more chloride ions to pass through. These products have revolutionized the treatment of CF, leading to substantial improvements in the lives of CF patients worldwide.

Figure 1: Cystic Fibrosis Marketed Products

Source: Vertex Pharmaceuticals.

Vertex's cystic fibrosis products are:

1. KALYDECO (ivacaftor): KALYDECO was the first CFTR modulator approved by the U.S. FDA for the treatment of CF. It is indicated for the treatment of CF in patients aged one month and older who have specific genetic mutations that result in a defective CFTR protein and are responsive to KALYDECO. KALYDECO helps improve CFTR protein function, leading to improved lung performance and other clinical benefits.
2. ORKAMBI (lumacaftor/ivacaftor): ORKAMBI is a combination therapy consisting of two active ingredients: lumacaftor and ivacaftor. It is indicated for the treatment of CF in patients aged one year and older who have two copies of the F508del mutation in the CFTR gene. ORKAMBI improves CFTR protein function and has been shown to improve lung performance and reduce exacerbations in patients with CF.
3. SYMDEKO/SYMKEVI (tezacaftor/ivacaftor): SYMDEKO (marketed as SYMKEVI in Europe) is another combination therapy containing tezacaftor and ivacaftor as active ingredients. It is approved for the treatment of CF in patients aged six years and older who have two copies of the F508del mutation in their CFTR gene or one copy of the F508del mutation and a residual function mutation. SYMDEKO/SYMKEVI helps improve CFTR protein function, leading to improved lung performance and other clinical benefits.
4. TRIKAFTA/KAFTRIO (elexacaftor/tezacaftor/ivacaftor): TRIKAFTA (marketed as KAFTRIO in Europe) is a triple combination therapy containing elexacaftor, tezacaftor, and ivacaftor as active ingredients. TRIKAFTA/KAFTRIO is approved for the treatment of CF patients aged two years and older who have at least one copy of the F508del mutation in the CFTR gene or at least one other mutation in the CFTR gene that is responsive to TRIKAFTA. It is the first therapy approved to treat the underlying cause of CF in this patient population, leading to significant improvements in lung function and other clinical indications.

Vertex is submitting regulatory filings globally for either geographic expansion, label expansion, or both for all of its marketed CF products.

Sickle Cell Disease and Beta Thalassemia

Vertex collaborated with CRISPR Therapeutics to develop CASGEVY™ (exagamglogene autotemcel, or exa-cel), a gene editing therapy that uses Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) technology to treat sickle cell disease (SCD) and beta thalassemia.

SCD is a genetic condition caused by a mutation in the beta globin genes, which results in expression of faulty hemoglobin protein. Hemoglobin is an iron-rich molecule in red blood cells that carries oxygen throughout the body. The mutated hemoglobin, called hemoglobin S (HbS), causes red blood cells to become rigid, sticky, and misshapen, forming a crescent or sickle shape. These sickled cells cannot move or bend as easily as normal red blood cells, which are round with a flattish, indented center, like doughnuts without a hole. As a result, sickled cells can block blood flow, depriving body tissues of oxygen and causing ischemic injury to organs. This elicits an inflammatory response.

In healthy humans, at or shortly after birth, a shift from γ-globin to β-globin gene expression underlies the switch from fetal hemoglobin production ($\alpha_2\gamma_2$; HbF), to adult hemoglobin production ($\alpha_2\beta_2$; HbA), so that by six months of age the majority hemoglobin in the body is HbA. HbA is better suited than HbF to oxygen transport needs after birth and throughout adult life. By contrast, in sickle cell disease patients the majority hemoglobin is HbS.

CASGEVY™ works by increasing the production of fetal hemoglobin and reducing the number of sickled red blood cells in the patient's body.

First, the patient's hematopoietic blood stem cells, which are precursors to all mature blood cell types, are extracted from the patient's own blood, collected, and sent to a laboratory for gene editing.

In the lab, inside the collected blood stem cells, CASGEVY™ suppresses expression of a protein that blocks fetal hemoglobin production. Removal of the block will allow the patient's bone marrow to produce more HbF and in turn help healthy blood cells outcompete sickled cells.

While the patient's blood stem cells are being modified, the patient undergoes chemotherapy to destroy defective hematopoietic stem cells in their bone marrow. This eliminates stem cells with the mutated HbS. Then the patient receives a one-time infusion of the lab-edited stem cells as part of a hematopoietic stem cell transplant. The edited stem cells migrate back to the bone marrow and begin producing HbF.

As the final result, the fetal hemoglobin generated following the CASGEVY™ gene editing procedure restores many of the natural properties of red blood cells, making it less likely that they will assume a sickle shape and obstruct blood flow.

In beta thalassemia patients, who have a reduced ability to produce β-globin and often suffer from anemia and reduced oxygen levels, increased production of HbF increases overall hemoglobin levels and improves the production and function of red blood cells. This can eliminate the need for regular blood transfusions.

CASGEVY™ is made for each patient. The therapy can eliminate vaso-occlusive crises in SCD, and the need for regular blood transfusions in beta thalassemia, and thus offers a functional cure for both diseases.

Figure 2: Sickle Cell Disease and Beta thalassemia Marketed Product

Source: Vertex Pharmaceuticals.

Between November 2023 and February 2024, CASGEVY™ was approved for treatment of both sickle cell disease and beta thalassemia in the U.S., Great Britain, the European Union (EU), the Kingdom of Saudi Arabia (KSA), and the Kingdom of Bahrain, making it the first CRISPR/Cas9 gene-edited therapy to be approved in those markets.

The treatment is indicated for patients aged 12 years and older with severe sickle cell disease characterized by recurrent vaso-occlusive crises, or for transfusion-dependent beta thalassemia, for whom hematopoietic stem cell (HSC) transplantation is appropriate, and a human leukocyte antigen matched related HSC donor is not available.

Vertex is submitting regulatory filings globally for geographic expansion. The company has completed submissions in Switzerland and Canada, and has signed multiple agreements with both commercial and government health insurance providers in the U.S. to provide access to CASGEVY™.

Product Pipeline

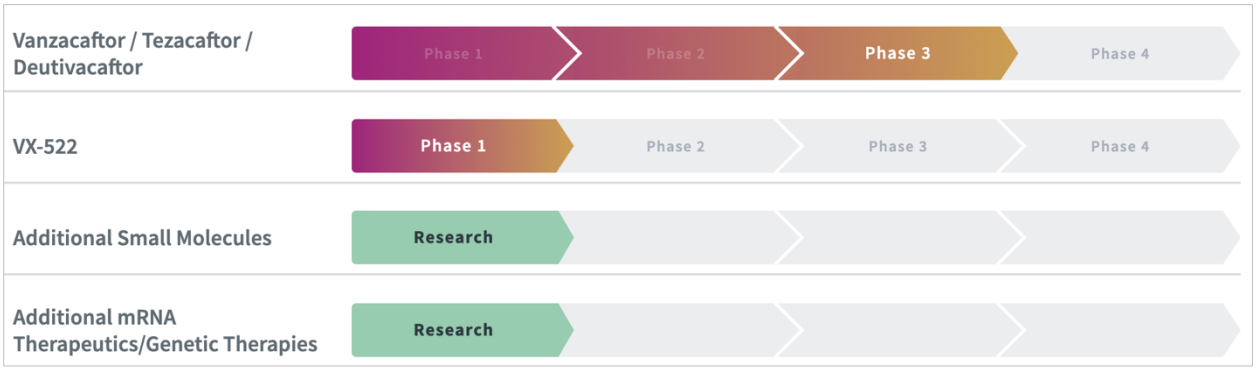
The primary focus of Vertex's pipeline programs is the discovery and development of therapies that address the underlying causes of genetic and autoimmune diseases. Focus areas include cystic fibrosis, sickle cell disease, beta thalassemia, alpha-1 antitrypsin deficiency, APOL1-mediated kidney disease, autosomal dominant polycystic kidney disease, Duchenne muscular dystrophy, myotonic dystrophy type 1, and type 1 diabetes. Vertex also develops medicines for acute and chronic pain, and has out-licensed three development programs for cancer.

Cystic Fibrosis

Cystic fibrosis (CF) is a rare, chronic, progressive, and life-shortening, genetic disease that affects the lungs, liver, gastrointestinal tract, pancreas, sinuses, sweat glands and reproductive tract. In the lungs, cystic fibrosis leads to the buildup of excessive thick, sticky mucus that can cause chronic lung infections and inflammation resulting in progressive lung damage and premature death in many CF patients. Other

complications can include malabsorption of food by the small intestine, and failure to thrive due to pancreatic disease, diabetes, liver disease, bone disease, or osteoporosis, depression, or anxiety.

Figure 3: Cystic Fibrosis Pipeline



Source: Vertex Pharmaceuticals.

The triple combination of vanzacaftor/tezacaftor/deutivacaftor (vanzacaftor triple) is being developed as an investigational once-daily treatment for CF patients with mutations in the CFTR gene that prevent proper folding of the CFTR protein, precluding it from acting as an ion channel on the cell surface.

Most CFTR mutations cause the abnormal CFTR protein to be degraded by the proteasome before it can reach the cell surface, resulting in a dearth of CFTR ion channels. The vanzacaftor and tezacaftor components of vanzacaftor triple are designed to increase the amount of mature protein at the cell surface by targeting the processing and trafficking defect of the mutated CFTR protein. Deutivacaftor is a potentiator designed to keep CFTR proteins at the cell surface open to enhance flow of salt and water across the cell membrane, which helps hydrate and clear mucus from the airways.

During Q1 2024, Vertex completed regulatory submissions for vanzacaftor triple as a once-daily treatment of CF patients six years and older to the FDA, using priority review, and to the European Medicines Agency (EMA). Two randomized studies in patients 12 years and older met their primary and all key secondary endpoints. The company intends to apply for regulatory clearance with the Medicines and Healthcare products Regulatory Agency (MHRA) in Great Britain, Health Canada, SwissMedic, the Australian Therapeutic Goods Administration (TGA) and the New Zealand Ministry of Health later this year.

VX-522 is a CFTR mRNA that can be delivered to the lung by lipid nanoparticles to address the underlying cause of CF lung disease in the approximately 5,000 patients with CF whose cells do not make any CFTR protein that would respond to a CFTR modulator therapy.

Vertex is also investigating a portfolio of other small molecules targeting the underlying cause of cystic fibrosis, aiming to achieve improved carrier levels of CFTR function. This includes CFTR potentiators, which improve the flow of salt and water across cell membranes, helping to hydrate and clear mucus from the airways, and small molecules that aid the movement of CFTR protein through the cell and to the cell surface.

To treat the approximately 10% of CF patients who do not make any CFTR protein and thus do not respond to CFTR modulators, Vertex, in collaboration with CRISPR Therapeutics, Arbor Biotechnologies, and Moderna, is developing alternative investigational technologies such as mRNA therapeutics, and genetic therapies.

Pain

The nervous system, through voltage-gated sodium channels (NaV), is responsible for how the body senses, transmits and interprets pain. These NaV channels are integral membrane proteins that enable the passage of selected inorganic ions across cell membranes, opening and closing in response to changes in transmembrane voltage. NaV channels play a key role in electrical signaling by excitable cells such as neurons. Some channels, like NaV1.7 and NaV1.8, which have been validated through human genetics research, play an important role in transmitting pain signals from peripheral sensory neurons to the central nervous system.

Poorly managed pain, whether chronic or acute, decreases quality of life and is often associated with side effects such as sleep interruption, immobility, inability to work, major depression, and addiction. Opioids are commonly prescribed for acute pain, but are often unsuitable for long-term use. Anti-inflammatory drugs can be used for both acute and chronic pain, but their use is limited due to side effects. A significant unmet medical need remains for new, non-opioid treatments effective for multiple types of pain.

Vertex is investigating an approach to treat both acute and chronic pain by targeting specific sodium channels in the NaV family to interrupt pain signals and prevent them from traveling from the sensory nerves to the brain.

Figure 4: Pain Pipeline

Source: Vertex Pharmaceuticals.

VX-548 is an oral NaV1.8 pain signal inhibitor that is highly selective for NaV1.8 compared to other NaV channels. NaV1.8 is a voltage-gated sodium channel that plays a critical role in pain signaling in the peripheral nervous system and is a genetically validated target for the treatment of pain. VX-548 has received FDA Breakthrough Therapy and Fast Track designations for moderate to severe acute pain.

Following three successful Phase 3 clinical trials, Vertex began a rolling New Drug Application (NDA) submission process to the FDA during Q2 2024, with the goal of achieving a broad label for VX-548 in moderate to severe acute pain. The molecule's benefit-risk profile positions it to potentially fill the gap

between medicines with good tolerability but limited efficacy, and opioids with therapeutic efficacy but known risks, including their addictive potential.

In addition to acute pain, Vertex also wants to secure a broad label for VX-548 in peripheral neuropathic pain. In December 2023, the company reported positive Phase 2 results in painful diabetic peripheral neuropathy (DPN), and plans to move the program forward to Phase 3 during the second half of 2024. VX-548 received FDA Breakthrough Therapy designation for the treatment of pain associated with DPN.

Vertex is continuing to enroll participants in its Phase 2 study of VX-548 for the treatment of lumbosacral radiculopathy (LSR), which is pain caused by impairment or injury to nerve roots in the area of the lumbar spine. The company is on track to complete enrollment by the end of 2024.

In line with its portfolio strategy, Vertex continues to advance preclinical and clinical development of additional NaV1.8 and NaV1.7 pain signal inhibitors for use alone or in combination, in acute and neuropathic pain.

Sickle Cell Disease

Sickle cell disease (SCD) is a rare, inherited blood disorder caused by a mutation in the beta-globin (HBB) gene. The HBB gene encodes for a key component of hemoglobin, the oxygen-carrying molecule in red blood cells. That mutation in the HBB gene causes the production of abnormal hemoglobin, called sickle hemoglobin (HbS). Because of this abnormal hemoglobin, red blood cells become rigid and misshapen, and block small blood vessels, resulting in a lack of oxygen being delivered to tissues. This can cause episodes of extreme pain and potential organ failure such as osteonecrosis (bone death).

Treatment is most often focused on pain management and minimizing organ damage, requiring medication, sometimes monthly blood transfusions, and frequent hospital visits. The only cures for SCD today are (i) a stem cell transplant from a matched donor, an option available to only a small fraction of people living with SCD, and (ii) CRISPR/Cas9-mediated gene editing using CASGEVY™. If these options are unavailable, SCD requires a lifetime of treatment and is often associated with a reduced life span.

Figure 5: Sickle Cell Disease Pipeline

Source: Vertex Pharmaceuticals.

In addition to having brought CASGEVY™ to market, Vertex conducts an internal research program exploring oral small molecule treatment options for people living with SCD, aimed at the underlying cause of SCD.

Beta Thalassemia

Beta thalassemia is a rare blood disorder affecting the blood protein hemoglobin. In beta thalassemia, inherited changes in the beta-globin (HBB) gene result in acute deficiencies of hemoglobin protein and severe anemia. Because of this anemia, people living with the disease may experience fatigue and shortness of breath, and infants may develop failure to thrive, jaundice, and feeding problems.

Treatment for beta thalassemia is personalized. Many patients require regular blood transfusions that deliver healthy donated blood to their bodies. The only cures for beta thalassemia today are (i) a stem cell transplant from a matched donor, an option available to only a small fraction of people living with beta thalassemia, and (ii) CRISPR/Cas9-mediated gene editing using CASGEVY™. If these options are unavailable, beta thalassemia requires a lifetime of treatment and can result in a reduced life expectancy.

Figure 6: Beta Thalassemia Pipeline

Source: Vertex Pharmaceuticals.

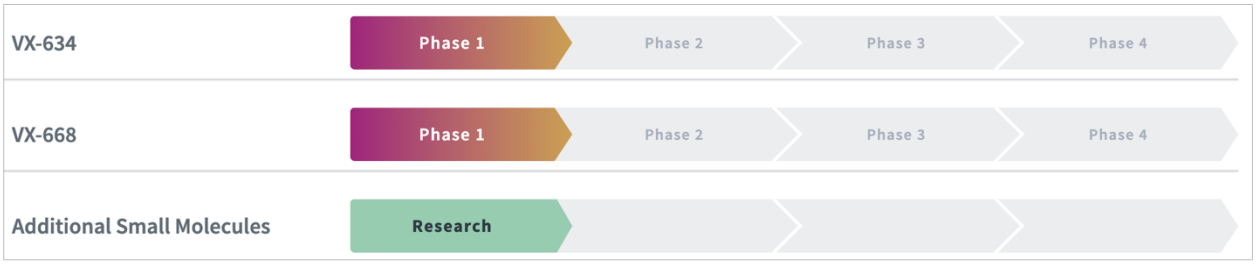
In addition to having brought CASGEVY™ to market, Vertex conducts an internal research program exploring oral small molecule treatment options for people living with transfusion-dependent beta thalassemia.

Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin deficiency (AATD) is an inherited disease that can cause significant damage to the lungs and liver. The primary manifestation of AATD in many patients is the development of lung disease characterized by symptoms such as wheezing or shortness of breath. These symptoms can worsen and progress to declining lung function, emphysema, and advanced lung disease that may require a lung transplant. The liver disease associated with AATD is often underrecognized, but can lead to severe damage such as cirrhosis and other debilitating complications. At present, there is no cure for AATD. Available treatments aim at alleviating symptoms and reducing the progression of lung disease. Even with treatment, people living with AATD experience recurring hospital visits and a shortened life expectancy.

AATD is caused by changes in the *SERPINA1* gene that encodes the AAT protein. In AATD's most common form, the changes to *SERPINA1* cause the body to produce misfolded AAT protein that gets trapped inside the liver, where most AAT is made. This results in low levels of AAT protein in the blood, preventing sufficient amounts of AAT from traveling to the lungs. Low AAT blood levels can cause inflammation and damage to healthy tissues, with the lungs being most often affected. The accumulation of misfolded AAT trapped in the liver is the cause of AATD-mediated liver disease.

Figure 7: Alpha-1 Antitrypsin Deficiency Pipeline



Source: Vertex Pharmaceuticals.

Vertex is focused on developing medicines to treat the underlying cause of AATD. The company's research and development efforts center on oral small molecules designed to target both the lung and liver manifestations of the disease associated with the most common form of AATD.

APOL1-Mediated Kidney Disease

APOL1-mediated kidney disease is a kidney disorder associated with certain *APOL1* genetic mutations carried by people of African ancestry. Having two mutations in the *APOL1* gene is associated with increased risk of kidney disease. In people living with two *APOL1* genetic mutations, an inflammatory exposure, such as an infection, can increase the toxic activity of the defective APOL1 protein in the kidney, which can lead to kidney cell injury, cell death, and damage to the glomeruli that filter blood in the kidney. This leads to abnormal amounts of protein in the urine and decreased kidney function, manifesting in symptoms that include fatigue, swelling in the legs and feet, and weight gain.

At present, there are no approved treatments addressing the underlying cause of APOL1-mediated kidney disease. High-dose steroids are often prescribed for short periods of time to help control blood pressure and fluid levels within the body, but their use is limited due to side effects. Even with treatment, people with APOL1-mediated kidney disease often progress to kidney failure. Kidney failure is treated with regular dialysis or a kidney transplant, both of which require lifelong treatment and follow-up care, and carry a high mortality risk.

Figure 8: APOL1-Mediated Kidney Disease Pipeline

Source: Vertex Pharmaceuticals.

Vertex's research and development efforts are aimed at treating the underlying cause of APOL1-mediated kidney disease. Research has shown that kidney disease progresses faster in patients with two *APOL1* genetic mutations than in patients with one mutation or none. Vertex is investigating inaxaplin and a portfolio of other small molecules aimed at inhibiting the function of the APOL1 protein in patients with high-risk variants of the *APOL1* gene.

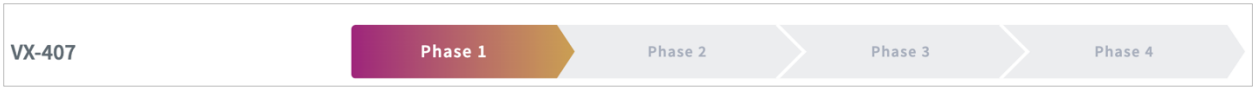
Inaxaplin is a first-in-class, investigational small molecule inhibitor of APOL1 that has been granted Rare Pediatric Disease (RDP) and Breakthrough Therapy designations by the FDA for APOL1-mediated focal segmental glomerulosclerosis, and Priority Medicines (PRIME) and Orphan Drug designations by the EMA for APOL1-mediated kidney disease.

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is a life-shortening genetic kidney disease characterized by the growth of numerous kidney-enlarging cysts that impair kidney function. It can lead to kidney failure, requiring dialysis or kidney transplantation, or premature death. Kidney cysts can also cause acute abdominal pain, cyst infections, blood in the urine, and kidney stones. About half of patients with ADPKD experience kidney failure by age 60.

ADPKD is the most common inherited kidney disease, affecting about 250,000 people in the U.S. and Europe. In most cases, it is caused by variants of the *PKD1* or *PKD2* genes, which express proteins known as polycystins. About 80% of ADPKD patients have a variant of the *PKD1* gene that is associated with a loss of function of polycystin 1 (PC1). This results in the proliferation of kidney epithelial cells, increased fluid secretion, and the formation and expansion of fluid-filled cysts. Progressive cyst formation causes an increase in kidney size and decline in kidney function.

Figure 9: Autosomal Dominant Polycystic Kidney Disease Pipeline



Source: Vertex Pharmaceuticals.

Vertex is investigating VX-407, a small molecule designed to correct defective PC1 folding to restore function to the PC1 protein in patients with a subset of *PKD1* variants.

Duchenne Muscular Dystrophy

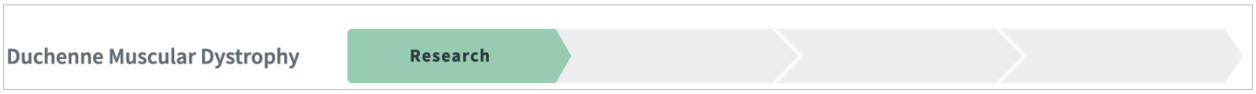
Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy in children. DMD is a genetic disease, more often seen in boys, that affects the skeletal muscles, breathing muscles, and the heart. Initially, the progressive muscle weakness and wasting leads to the inability to walk. As children with DMD grow older, heart problems, including cardiomyopathy develop. Breathing issues begin when the function of their breathing muscles begins to decrease. Most children with DMD are wheelchair-bound by ages 12-15 and have a significantly decreased life expectancy due to heart and respiratory issues.

DMD is a chromosomal X-linked recessive disorder caused by mutations in the dystrophin gene, which encodes dystrophin protein. Dystrophin is a key part of a protein complex that maintains muscle integrity during normal activity and exercise. Mutations to the dystrophin gene prevent the body from making

normal amounts of dystrophin. Lack of dystrophin causes progressive muscle weakness and muscle degeneration.

There is no cure for DMD. Treatments are focused on improving function and quality of life through steroids, and a multidisciplinary approach to anticipate, prevent, detect, and treat complications.

Figure 10: Duchenne Muscular Dystrophy Pipeline



Source: Vertex Pharmaceuticals.

Vertex is researching a novel approach to treating DMD through the delivery of CRISPR/Cas9 gene-editing technology to muscle cells with adeno-associated virus 9 (AAV9) to achieve precise changes in the targeted DNA sequence. The goal is to restore near-full-length dystrophin protein expression by targeting certain mutations in the dystrophin gene that cause the disease. Due to the number of mutations that can cause DMD, Vertex's research involves development of multiple gene-editing programs designed to address numerous disease-causing mutations.

Myotonic Dystrophy Type 1

Myotonic dystrophy type 1 (DM1) is a debilitating, multisystemic, genetic disease inherited in an autosomal dominant manner that presents with a spectrum of disease severity. When a trait is autosomal dominant, it means one parent needs to have a mutated gene to pass on the genetic condition. DM1 affects skeletal muscle, the heart, lungs, and several other body systems.

Muscle weakness, wasting, and myotonia (sustained muscle contraction and difficulty relaxing muscles), are distinguishing symptoms of the disease, which becomes more severe with each generation. DM1 is life-shortening with a median life expectancy of 55 years in adult DM1 patients. Leading causes of premature death are respiratory failure and cardiac abnormalities, consequences of the disease's impact on muscle cells.

DM1 is caused by an expanded trinucleotide repeat sequence in one allele of the DM1 protein kinase gene, which is then transcribed into an RNA with a toxic CUG repeat. Greater repeat length is correlated with early onset of illness, greater severity of symptoms, and shorter lifespan.

The CUG repeat RNA forms hairpin structures that sequester multiple proteins involved in gene splicing, including muscleblind-like protein 1 (MBNL1). Splicing is an important part of the cellular process required to generate functional proteins. Sequestration of MBNL1 results in mis-splicing, which leads to production of abnormal protein. Muscle is particularly affected since the proteins impacted by mis-splicing are important for aspects of normal muscle function, including contraction, relaxation, and maintenance of muscle mass.

DM1 is the most prevalent muscular dystrophy in adults, with about 110,000 people living with the disease in the U.S. and Europe. There are no approved treatments.

Figure 11: Myotonic Dystrophy Type 1 Pipeline

Source: Vertex Pharmaceuticals.

VX-670 is aimed at correcting splicing errors, and treating the underlying cause of DM1. It is a phosphorodiamidate morpholino oligonucleotide (PMO), a type of oligomer molecule used in molecular biology to modify gene expression. VX-670 is connected to a cyclic peptide, known as an endosomal escape vehicle, which contains a motif supporting effective delivery of VX-670 into cells, and its transfer to the nucleus where the CUG repeat sequence is located. The VX-670 oligonucleotide then engages the CUG repeat RNA and liberates bound splicing factors.

Type 1 Diabetes

Type 1 diabetes (T1D) is a metabolic, autoimmune disease that often develops in childhood or young adulthood. T1D is a disease in which the body's own immune system destroys the beta cells in the pancreas that produce insulin. Insulin is a hormone the body requires to metabolize glucose, a key source of energy. When beta cells function as they should, insulin is produced in response to increases in blood sugar, such as after eating, and glucose is moved from the blood into cells.

Insulin also signals the liver to store glucose as glycogen, which the liver then releases back into the bloodstream when blood sugar levels drop, thus maintaining normal blood sugar levels during sleep and between meals. Without sufficient beta cell function, proper insulin storage and use cannot occur, and blood sugar levels are not regulated. This leads to high glucose levels in the blood, known as hyperglycemia, with symptoms including increased thirst or hunger, frequent urination, and unexplained weight loss. Unable to use blood glucose for energy, the body attempts to compensate by breaking down muscle and fat, leading to long-term complications such as muscle wasting and the buildup of ketones in the blood, which become toxic.

Living with T1D requires lifelong treatment with insulin. People with T1D need to give themselves multiple injections of insulin per day, or use an insulin pump that is attached to the body. They must also check their blood sugar levels multiple times per day, and manage their diets and exercise. Proper insulin production and regulation is a delicate metabolic balance. Without enough insulin, uncontrolled high blood sugar can lead to complications such as kidney disease, eye disease, including blindness, nerve damage, or death. Too much insulin causes low blood sugar, which can lead to symptoms of severe hypoglycemia such as loss of consciousness, coma, or death.

Genetic and environmental factors are thought to play a role in the development of T1D, but the exact causes of autoimmune beta cell destruction are not known and may vary between people.

Figure 12: Type 1 Diabetes Pipeline

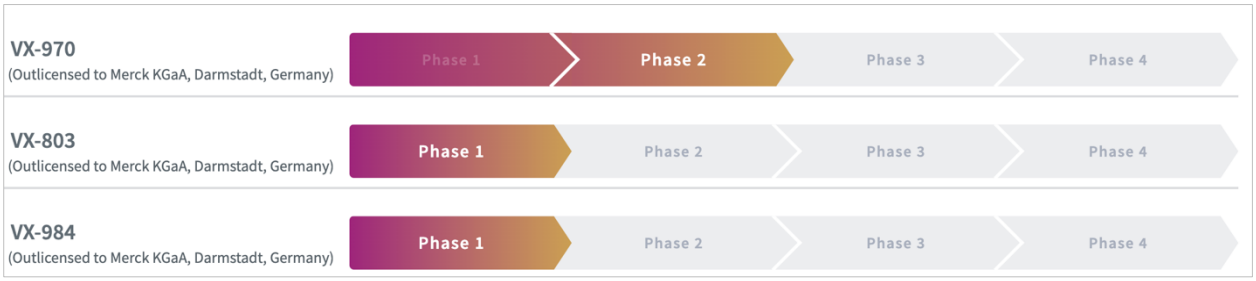
Source: Vertex Pharmaceuticals.

Vertex is advancing cell therapies intended to treat the absence of insulin-producing cells in the pancreas. The company is evaluating multiple approaches to deliver its proprietary, stem cell-derived, fully-differentiated, insulin-producing islet cells to replace cells destroyed by the body's immune system.

VX-880 is administered as an infusion into the hepatic portal vein, and requires immunosuppressive therapy to protect the islet cells from immune rejection. VX-264 therapy relies on encapsulating cells in a protective device to be surgically implanted in the body. VX-264 is being evaluated without the use of immunosuppressive therapy as the devices are designed to shield the cells from the body's immune system.

Cancer (Out-licensed)

Figure 13: Cancer Pipeline



Source: Vertex Pharmaceuticals.

In January 2017, Vertex entered a licensing agreement with Merck KGaA, Darmstadt, Germany for worldwide development and commercialization of four potential cancer treatments. Under the terms of the license, Merck undertook development of two clinical-stage programs from Vertex comprised of three compounds: VX-970, VX-803 and VX-984, targeting DNA damage and repair, plus two additional novel preclinical research programs.

The two clinical-stage programs represent first-in-class approaches to inhibit the DNA repair pathways fundamental to the survival and proliferation of certain cancers: (i) an ataxia telangiectasia and Rad3 related (ATR) protein kinase inhibitor program comprised of two compounds, VX-970 and VX-803, and (ii) a DNA-dependent protein kinase (DNA-PK) inhibitor program involving VX-984.

The preclinical programs are described by Vertex as an immuno-oncology program against an attractive target with first-in-class potential, and a program against a completely novel target. For both of

these programs, Vertex says research has demonstrated efficacy in relevant preclinical models, as well as combination potential with immune checkpoint inhibitors for the immuno-oncology program.

Market Opportunity

Cystic Fibrosis

According to a 2024 report by Research and Markets, the global cystic fibrosis therapeutics market size was valued at $17.5 billion in 2023 and is projected to reach $46.8 billion by 2030, growing at a CAGR of 15.1% during the forecast period. The U.S. segment of the market was $4.5 billion in 2023.

The CF therapeutics market encompasses the following drug classes: CFTR modulators, which account for the largest share of the total CF therapeutics market, followed by anti-infectives, mucolytic agents, pancreatic enzyme replacement therapies (PERTs), and bronchodilators.

Growth drivers in the CF market are increasing prevalence of the disease, increasing awareness and diagnosis of the disease, availability of innovative therapies that target underlying causes of the disease, and favorable reimbursement policies in many regions. Emergence of new treatments, such as Vertex's CFTR modulators, has improved quality of life and life expectancy for CF patients. These improvements have increased demand for these therapies, as the overall number of CF patients has simultaneously increased.

Factors such as the high cost of treatment and limited availability of medicine for all CF-related mutations are expected to restrain growth in certain markets. For example, the list price for Vertex's TRIKAFTA is $311,503 per year, while SYMDECO's price tag is $290,000.

Worldwide, over 75,000 people are affected by CF. The U.S. is one of the largest markets for CF therapies due to high prevalence of the disease. According to the Cystic Fibrosis Foundation, there are currently over 30,000 people in the U.S. living with CF.

Vertex Pharmaceuticals is a major player in the U.S. CF market, having a near-monopoly in the CFTR modulator market segment and having driven market growth following FDA approval of its CFTR modulators KALYDECO, ORKAMBI, SYMDEKO, and TRIKAFTA.

Sickle Cell Disease

According to analyses by Brainy Insights, BioSpace, and Grand View Research, the global sickle cell disease treatment market was valued at $2.75 billion in 2023, and is expected to grow at a CAGR of 15-20% from 2024 to 2030, to $7-10 billion. North America is now the largest global sickle cell disease treatment market, with a 37% market revenue share in 2022. The Asia Pacific market is expected to grow fastest over the forecast period.

Segments of the sickle cell disease treatment market include blood transfusions, which dominated the market with a 40-50% share in 2022, pharmacotherapy, bone marrow/hematopoietic stem cell transplant, and gene therapy.

Market growth drivers are:

- Increasing prevalence of the disease; for example, migration and global movement of the SCD population across regions and countries can introduce SCD into populations where it was previously less common
- Increasing awareness of SCD and its treatments
- Accessibility to healthcare services that improve the chances of early-stage diagnosis, such as newborn screening and genetic counselling
- Global health initiatives aimed at enhancing treatment accessibility and healthcare infrastructure
- Government initiatives, healthcare policies, and collaborations between pharmaceutical firms and research institutions that foster innovation and therapy development
- Advances in genetic research and technology
- Increased investments in R&D, and growing emphasis on developing curative treatments such as gene editing, leading to an increase in the number of clinical trials and research participation
- Innovations identifying novel therapies, such as gene therapy and gene editing, and optimizing existing treatments
- A large pipeline of innovative therapies driving regulatory approvals for novel treatments
- Increased focus on personalized therapy creating a trend toward designing treatment plans based on patient genetic profiles and illness severity, and tailoring medications based on particular genetic traits
- Increasing prescription rate of pharmaceutical SCD drugs
- Multi-disciplinary care being delivered by specialized SCD clinics

Restraints to market growth are:

- Lack of awareness about treatment options or access to treatment
- Cost of access to treatment
- Inadequate healthcare infrastructure in developing regions
- Reimbursement mechanisms
- Limited long-term safety and efficacy data for some of the emerging treatments
- Side-effects of SCD treatment, such as hair loss and gastrointestinal problems, which may decrease compliance with treatment regimens
- Increased susceptibility to infections caused by certain treatments
- Challenges associated with bone marrow transplants, which involve complex procedures, and difficulty finding suitable donors

In 2023, the Institute of Health Metrics and Evaluation published that the number of SCD patients globally increased by 41.8% between 2000 and 2021, from 5.46 million to 7.74 million. Part of the increase in patient numbers is attributable to the greater longevity of SCD patients due to availability of successful therapies developed over the past two decades.

Beta Thalassemia

According to Transparency Market Research, Spherical Insights, and Global Market Insights, the global market for beta thalassemia treatment was valued at $2.2 billion in 2023. It is predicted to grow at a CAGR of 7.4% to reach $4.2 billion in 2032. The beta thalassemia market share in North America was the largest geographic market segment, valued at $874 million in 2023. It is predicted to grow at a CAGR of 6.9% per year to $1.5 billion by 2032. The Asia Pacific market is expected to exhibit the fastest growth.

Based on treatment type, the market is segmented into red blood cell transfusions at 2-4-week intervals, iron chelation therapy for removing excess iron from the bloodstream, bone marrow transplantation, folic acid supplements, and other treatment types. Stem cell therapy is gaining traction, especially for severe cases, as is gene-editing therapy for the treatment of transfusion-dependent beta thalassemia (TDT) in patients 12 years and older.

Market growth drivers are similar to those of Sickle Cell Disease and include:

- Rising prevalence of the condition
- Increase in genetic testing and genetic counselling, leading to earlier disease detection
- Growing awareness of thalassemia
- A surge in R&D investments in potential therapies
- Emerging treatments like gene therapy, that aim to address genetic mutations causing thalassemia
- Stem cell therapy, particularly hematopoietic stem cell transplantation, a potentially curative treatment for thalassemia
- Technological advancements
- Government support for emerging therapies
- High demand for multidisciplinary thalassemia care that includes medical management, supportive therapies, and, in some cases, curative interventions
- A surge in healthcare infrastructure investments

Restraints to market growth include:

- High treatment costs
- Stringent regulatory requirements and guidelines

Beta thalassemia is most prevalent in the Middle East, Mediterranean, South Asia, Africa, and India. According to Boston Children's Hospital, nearly 300 million individuals worldwide carry a genetic beta thalassemia trait. These individuals are at a higher risk of having children with thalassemia, which affects approximately 4.4 out of every 10,000 live births throughout the world.

Boston Children's further stated that more than 1 million people worldwide have non-transfusion-dependent thalassemia, while more than 100,000 people have transfusion-dependent thalassemia (TDT). Though TDT is not common in the United States, it is thought that 1.25 million people, or 0.4% of the population, are carriers, and more than 1,200 people are affected by the disease. As the number of

individuals affected by thalassemia rises, there will be a corresponding increase in demand for effective treatment options.

Competitive Landscape

Vertex's competitive landscape for cystic fibrosis, sickle cell disease, and beta thalassemia includes diversified global biopharmaceutical companies Bristol Myers Squibb (BMY), Genentech/Roche Holding AG (ROG), and Novartis AG (NOVN). Other competitors include smaller, more specialized biotechnology firms Agios Pharmaceuticals (AGIO), bluebird bio (BLUE), CRISPR Therapeutics (CRSP), and Editas Medicine (EDIT), which compete in specific disease indications.

In terms of its enterprise value, Vertex falls between the global biopharmaceutical companies and the specialized biotechnology companies, which are at least one, if not several orders of magnitude smaller than Vertex, and may become acquisition targets.

Table 1: Vertex Pharmaceuticals Competitors

			Market Data			Balance Sheet Data ($)		P&L Data ($)		
Company Name	Ticker	Fiscal Period	Price	Market Cap (M)	Enterprise Value (M)	Cash & ST Investments (M)	Total Debt (M)	LTM Revenue (M)	LTM EBIT (M)	LTM Net Income (M)
Genentech/Roche Holding AG*	SWX:ROG	2023-12-31	243.30	196,774.94	221,061.94	10,511.00	30,850.00	60,441.00	17,779.00	11,498.00
Novartis AG*	SWX: NOVN	2023-12-31	96.61	197,123.66	213,055.67	8,707.90	24,485.80	42,837.50	12,823.50	13,681.50
Bristol Myers Squibb Co.	BMY	2023-12-31	39.66	80,394.79	127,872.79	9,670.00	57,457.00	45,534.00	8,334.00	(6,148.00)
Vertex Pharmaceuticals	VRTX	2023-12-31	474.57	122,464.40	108,633.00	10,171.30	721.30	10,185.00	4,399.50	4,019.40
CRISPR Therapeutics AG	CRSP	2023-12-31	53.10	4,509.15	2,635.95	2,108.13	234.93	271.71	(298.64)	(217.14)
Agios Pharmaceuticals, Inc.	AGIO	2023-12-31	42.65	2,421.37	1,775.42	597.99	68.35	29.40	(392.95)	(352.62)
bluebird bio, Inc.	BLUE	2023-12-31	0.92	177.96	307.37	174.29	303.71	21.73	(136.15)	(91.17)
Editas Medicine, Inc.	EDIT	2023-12-31	4.59	377.47	34.84	296.17	34.14	69.41	(185.21)	(166.13)

* In Swiss Francs. As of July 5, 2024 (Market Data), March 31, 2024 (Balance Sheet Data), or last four quarters (P&L Data).
Source: S&P Capital IQ.

Table 2: Vertex Pharmaceuticals Solvency, Valuation, and Profitability Metrics versus Competitors

		Solvency	Valuation					Profitability	
Company Name	Ticker	Interest Coverage, 12 Months Ending 12/31/23	P/E Before Extra Items, 12 Months Ending 12/31/23	P/E 2024 E (Consensus)	P/E 2025 E (Consensus)	EV/Revenue, 12 Months Ending 12/31/23	EV/EBIT, 12 Months Ending 12/31/23	Gross Margin, 12 Months Ending 12/31/23	Net Margin, 12 Months Ending 12/31/23
Genentech/Roche Holding AG	SWX:ROG	21.5x	17.0x	13.7x	12.5x	3.7x	NA	74.2%	19.0%
Novartis AG	SWX:NOVN	14.8x	26.3x	24.5x	14.7x	5.0x	18.4x	74.2%	31.8%
Bristol Myers Squibb Co.	BMY	7.5x	10.3x	70.7x	5.7x	2.4x	12.7x	76.6%	17.8%
CRISPR Therapeutics AG	CRSP	-	-	-	-	8.2x	NM	NM	NM
Agios Pharmaceuticals, Inc.	AGIO	-	-	39.8x	-	62.9x	NM	NM	NM
bluebird bio, Inc.	BLUE	-	-	-	-	8.3x	NM	NM	NM
Editas Medicine, Inc.	EDIT	-	-	-	-	NM	NM	NM	NM
Median		14.8x	17.0x	32.2x	12.5x	6.6x	15.6x	74.2%	19.0%
Vertex Pharmaceuticals	VRTX	97.7x	34.2x	30.8x	27.8x	11.1x	25.4x	87.2%	36.7%

NA: not available; NM: not material. Source: S&P Capital IQ.

Vertex's market leadership and near-monopoly in the CFTR modulator segment of the cystic fibrosis space, solid financial position, and innovative product pipeline are reflected in its valuation, which is justifiably rich compared to the competitor group median.

Agios Pharmaceuticals, Inc. is a biopharmaceutical company engaged in the discovery and development of medicines for metabolic and rare diseases. Its lead product, mitapivat, is a pyruvate kinase (PK) activator approved in the U.S., EU, and Great Britain for adult PK deficiency. Agios Pharmaceuticals was incorporated in 2007, and is headquartered in Cambridge, MA.

Agios competes with Vertex in the thalassemia and sickle cell disease indications, where mitapivat is in late-stage clinical development.

bluebird bio is a clinical stage biotechnology company engaged in researching, developing, and commercializing transformative gene therapies for severe genetic diseases. bluebird bio was incorporated in 1992 and is headquartered in Somerville, MA. The company was formerly known as Genetix Pharmaceuticals, Inc. and changed its name to bluebird bio, Inc. in September 2010.

bluebird bio competes with Vertex in the beta thalassemia and sickle cell disease indications. Its gene therapy products include ZYNTEGLO (betibeglogene autotemcel, or beti-cel) for treatment of transfusion-dependent beta thalassemia, and LYFGENIA (lovotibeglogene autotemcel, or lovo-cel) for treatment of SCD. The company's clinical development programs include HGB-206, in Phase 3, and HGB-210, in Phase 1/2, for treatment of patients with SCD.

Bristol Myers Squibb, **Inc.** is a global biopharmaceutical company engaged in the discovery, development, licensing, manufacture, marketing, distribution, and commercialization of biopharmaceutical products. Its focus areas are hematology, oncology, cardiovascular disease, immunology, fibrotic disease, and neuroscience diseases. The company offers small molecules, biologics, and chimeric antigen receptor (CAR) T-cell therapies. It sells products to wholesalers, distributors, pharmacies, retailers, hospitals, clinics, and government agencies. Bristol Myers Squibb was incorporated in 1887 and is headquartered in Princeton, NJ.

Bristol Myers competes with Vertex in the cystic fibrosis, beta thalassemia, and sickle cell disease indications. The company's CF Center at the Bristol Myers Squibb Children's Hospital is fully accredited by the National Cystic Fibrosis Foundation, and ranks among the top ten U.S. centers for patient outcomes. Its investigational lysophosphatidic acid receptor 1 (LPA1) antagonist is in late-stage clinical development for idiopathic pulmonary fibrosis. Bristol Myers also pursues development programs in beta thalassemia and SCD.

CRISPR Therapeutics AG is a gene editing company engaged in the development of gene-based medicines for diseases deriving from genetic mutations, using its proprietary CRISPR/Cas9 platform. CRISPR/Cas9 is a gene editing technology that allows precise, directed changes to genomic DNA. The firm offers a portfolio of therapeutic programs across a range of disease areas, including hemoglobinopathies, immuno-oncology, autoimmune diseases, *in vivo* DNA or RNA delivery, regenerative medicine, and

CRISPR-X next generation gene editing and delivery modalities. The company was incorporated in 2013 and is headquartered in Zug, Switzerland.

CRISPR Therapeutics collaborated with Vertex on the development of gene therapies for SCD and beta thalassemia, but also partners with some of Vertex's competitors. In collaboration with Vertex Pharmaceuticals, CRISPR Therapeutics developed CASGEVY™, the first ever autologous, *ex vivo* CRISPR/Cas9-based therapy to be approved for SCD and beta thalassemia in multiple countries.

Editas Medicine is a clinical stage genome editing company engaged in the development and commercialization of CRISPR/Cas9-based medicines to treat a range of diseases. The company has a partnership with Bristol Myers Squibb for R&D of alpha-beta T cell medicines for the treatment of cancer and autoimmune diseases, encompassing thirteen development programs. Editas Medicine was incorporated in 2013 and is headquartered in Cambridge, MA. The company was formerly known as Gengine, and changed its name to Editas Medicine in November 2013.

Editas Medicine competes with Vertex in the beta thalassemia and SCD indications. Its drug candidate renizgamglogene autogedtemcel (reni-cel), in late-stage clinical testing for SCD and in early-stage clinical testing for TDT, was developed on the company's proprietary gene editing platform. Editas Medicine's *in vivo* hematopoietic stem cell (HSC) editing technology is in preclinical development.

Genentech is a biotechnology company engaged in the discovery and development of medicines for people with chronic and/or life-threatening diseases. Considered the world's first biotechnology company, its transformational discoveries include the first targeted antibody for cancer and the first medicine for primary progressive multiple sclerosis. Genentech merged with the Roche Group in March of 2009, and operates as a separate business unit within Roche. Genentech's South San Francisco campus serves as the headquarters for Roche pharmaceutical operations in the U.S. Genentech's target therapeutic areas are oncology, immunology, infectious disease, neuroscience, and ophthalmology. The company's stated goal is to develop first-in-class or best-in-class therapeutics in each category. The company was founded in 1976.

Genentech competes with Vertex in the cystic fibrosis indication. The company is developing four compounds for the treatment of cystic fibrosis, idiopathic pulmonary fibrosis, and myelofibrosis.

Novartis AG is a global pharmaceutical holding company engaged in the research, development, manufacture, and marketing of healthcare products internationally. It operates through three segments: Innovative Medicines, Sandoz, and Corporate. The Innovative Medicines segment pursues research, distribution, and sale of patented pharmaceuticals. Its therapeutic focus areas are cardiovascular, renal and metabolic, immunology, neuroscience, oncology, ophthalmology, and hematology. The Sandoz segment focuses on marketing finished-dosage-form medicines, and intermediary products including active pharmaceutical ingredients (APIs). The Corporate segment is involved in group management and central services. The company was founded in 1996 and is headquartered in Basel, Switzerland. Its medicines reach more than 250 million people worldwide.

Novartis competes with Vertex in the cystic fibrosis, beta thalassemia, and SCD indications. The company markets the TOBI Podhaler, a prescription inhaler dispensing the antibacterial medicine tobramycin in dry powder form, used to treat CF patients with a Pseudomonas aeruginosa bacterial infection. In 2021, Novartis entered into a grant agreement with the Bill & Melinda Gates Foundation to develop a potential single-administration *in vivo* gene therapy for SCD that would be accessible in resource-constrained countries where SCD is most prevalent. Novartis is also collaborating with Precision BioSciences on developing a curative gene therapy for SCD and beta thalassemia.

Table 3: Competitor Products and Product Candidates

Disease Indication	AGIO	BLUE	BMY	CRSP	EDIT	RHHBY	NVS	VRTX
Cystic Fibrosis								
Products							TOBI Podhaler	KALYDECO, ORKAMBI, SYMDEKO, TRIKAFTA
Product Candidates			LPA1			✓		Vanzacaftor /Tezacaftor /Deutivacaftor, VX-522
Sickle Cell Disease								
Products		LYFGENIA		CASGEVY				CASGEVY
Product Candidates	Mitapivat, AG-946	HGB-206, HGB-210	✓		reni-cel		✓	
Beta Thalassemia								
Products		ZYNTEGLO		CASGEVY				CASGEVY
Product Candidates	Mitapivat		✓		reni-cel		✓	

Sources: Company websites. ✓= Development program(s) in progress.

Intellectual Property

Vertex Pharmaceuticals has filed over 8,000 patent applications globally, of which 3,591 have been granted, belonging to 1,429 unique patent families. The majority of Vertex's patents have been filed in the U.S., followed by Europe and Japan. Vertex's patent grant rate of 29.89% is in line with the pharmaceutical industry average in these key geographic regions.

Key intellectual property focus areas are detailed below:

Table 4: Vertex Pharmaceuticals Key Intellectual Property Focus Areas

Focus Area	Description	Aim	Patents Granted
Cystic Fibrosis (CF) Treatments	CFTR modulators, including correctors and potentiators	Improve function of the defective CFTR protein in CF patients	~50
Genetic Therapies	Gene-editing technologies using CRISPR/Cas9	Curative therapy correcting DNA mutations that are the cause of disease	~30
Pain Management	Sodium channel modulators	Non-opioid relief for chronic and acute pain	~40
Cell and Gene Therapy Manufacturing	Production of stem cells and their differentiation into specific cell types	Protect methods of manufacturing and stem cell use for therapeutic purposes	~25
Alpha-1 Antitrypsin Deficiency (AATD)	Chemical compounds and their pharmaceutical compositions	Develop new methods of treating the underlying cause of AATD	~20

Sources: Justia Patents, Pharmaceutical Technology magazine, MIT Technology Review, Wikipedia.

The company's intellectual property portfolio provides it with a competitive edge, market exclusivity, and the ability to protect its investments in research and development. Vertex's patents and overarching intellectual property strategy reflect the company's focus on addressing the underlying causes of rare or debilitating diseases through cutting edge technologies. This intellectual property strategy incentivizes innovation, attracts investment, and supports continued development of novel therapies.

Management

Reshma Kewalramani M.D., FASN – Chief Executive Officer and President

Dr. Kewalramani joined Vertex in 2017 and leads and executes the company's strategy and mission. Prior to taking on her role as CEO and President, she was the Chief Medical Officer and Executive Vice President of Global Medicines Development and Medical Affairs. Dr. Kewalramani has more than 15 years of experience developing new medicines.

She earned her medical degree with honors from the seven-year medicine program at the Boston University School of Medicine and completed the General Management Program at Harvard Business School. She completed her internship and residency in internal medicine at the Massachusetts General Hospital (MGH) and her fellowship in nephrology through the MGH and Brigham and Women's Hospital combined program.

With Dr. Kewalramani as CEO, Vertex was ranked number 2 on The Commonwealth Institute's Top Women-Led Businesses in Massachusetts in 2021.

David Altshuler M.D., Ph.D. – Executive Vice President and Chief Scientific Officer

Dr. Altshuler joined Vertex in 2015 and leads internal and external innovation, including research, preclinical and pharmaceutical sciences, corporate data strategy, technology, and engineering. He is responsible for Vertex's research strategy and pipeline. Before joining Vertex as Chief Scientific Officer, he served on the company's board of directors from 2012 to 2014.

He earned his bachelor's degree in life sciences from the Massachusetts Institute of Technology and his M.D. and Ph.D. in genetics from Harvard Medical School. He completed his clinical training at the MGH in internal medicine and endocrinology, diabetes, and metabolism. He is a Fellow of the American Academy of Arts and Sciences.

The Obama White House named him a Champion of Change for creating and leading the Global Alliance for Genomics and Health.

Stuart Arbuckle – Executive Vice President and Chief Operating Officer

Mr. Arbuckle joined Vertex in September 2012. As Vertex's Executive Vice President and Chief Operating Officer, Mr. Arbuckle oversees Vertex's global commercial team supporting the approved use of Vertex's marketed medicines around the world. He also leads program and portfolio management, commercial manufacturing, supply chain, human resources, and corporate communications functions.

He graduated with a degree in pharmacology and physiology from the University of Leeds in the U.K. Prior to Vertex, he held leadership roles at Amgen and GlaxoSmithKline (GSK) PLC.

E. Morrey Atkinson, Ph.D. – Executive Vice President and Chief Technical Operations Officer, Head of Biopharmaceutical Sciences and Manufacturing Operations

Dr. Atkinson joined Vertex in 2020 and serves on the Executive Committee as Chief Technical Operations Officer and Head of Biopharmaceutical Sciences and Manufacturing Operations. In this role, he oversees all aspects of Vertex's preclinical, clinical, and commercial biopharmaceutical sciences, manufacturing operations, and global supply chain functions. He is responsible for the development and commercialization of multiple modality therapeutics across all aspects of manufacturing, including small molecules, biologics, and cell therapies.

Prior to joining Vertex, Dr. Atkinson was the SVP of Global Manufacturing Operations at Bristol Myers Squibb (BMS), having joined BMS in 2012 as Vice President of Biologics Development and progressed through various roles. He held scientific and management roles at Eli Lilly, Cook Pharmica (now Catalent, Inc.), and Targeted Genetics Corporation before joining BMS. He currently serves on the board of 89bio.

Dr. Atkinson earned a bachelor's degree in biology from Indiana University and his doctoral degree in biological sciences from Stanford University.

Jonathan Biller – Executive Vice President and Chief Legal Officer

Mr. Biller joined Vertex in 2022, serves on the Executive Committee, and oversees all aspects of Vertex's global legal and compliance functions.

Before joining Vertex, Mr. Biller served in executive roles at Agios Pharmaceuticals including Chief Legal Officer and most recently Chief Financial Officer and Head of Corporate Affairs. He also served as Executive Vice President, General Counsel at Celgene, where he was responsible for its global legal functions, and before that as Senior Vice President, Tax and Treasury. Prior to Celgene, he served in leadership roles at Bunge Limited and Alcon, Inc.

He earned his bachelor's degree in history from Brown University and his law degree from Yale Law School. He began his legal career at Hopkins & Sutter, rising to partner, and was also a partner at Foley & Lardner after the firms merged.

Carmen Bozic M.D. – Executive Vice President, Global Medicines Development and Medical Affairs, and Chief Medical Officer

Dr. Bozic joined Vertex in 2019 and is responsible for clinical development programs, medical affairs, drug safety, global clinical operations, and biometrics. She has experience leading global clinical development programs across all phases of development, across multiple diseases and therapeutic modalities.

Dr. Bozic earned her medical degree from McGill University, where she also completed a residency in internal medicine, and served as Chief Resident. She completed a combined fellowship in pulmonary and critical care medicine at Brigham and Women's Hospital and Beth Israel Deaconess Medical Center.

Dr. Bozic was the industry representative to the U.S. Food and Drug Administration's Risk Communication Advisory Committee, and a member of PhRMA's Clinical and Preclinical Development Committee.

Amit K. Sachdev – Executive Vice President, Chief Patient and External Affairs Officer

Mr. Sachdev joined the company in 2007. During 17 years at the company, he has held leadership positions across the Vertex organization, including establishing the company's first international commercial operation in 2010. He leads Vertex's efforts to build relationships with patient communities globally across the disease treatments Vertex is pursuing.

He earned a B.S. from Carnegie Mellon University and a J.D. from Emory University. Before joining Vertex, he held roles with the Biotechnology Innovation Organization (BIO), the U.S. Food and Drug Administration and the U.S. House of Representatives.

Nia Tatsis, Ph.D. – Executive Vice President and Chief Regulatory and Quality Officer

Dr. Tatsis joined Vertex in 2017 with extensive experience in global regulatory affairs in the pharmaceutical industry. She provides global leadership and manages all regulatory interactions and quality assurance involving research and development, manufacturing, and commercialization of the company's medicines. As part of creating and executing the company's global regulatory strategy, Dr. Tatsis manages a worldwide team of regulatory professionals.

She graduated with a B.S. in biology from Temple University and a Ph.D. in cell and molecular biology from the University of Vermont. Before joining Vertex, she held positions of increasing responsibility at pharmaceutical companies such as Sanofi, Stemnion, Pfizer, and Wyeth.

Charles Wagner – Executive Vice President and Chief Financial Officer

Mr. Wagner joined Vertex in 2019 and oversees the accounting, finance, internal audit, investor relations, business development transactions, and alliance management, as well as global security and facilities functions. His corporate finance and health care experience includes more than a decade of Chief Financial Officer roles in public and private companies.

He holds a B.S. in accounting from Boston College and an M.B.A. from Harvard Business School. Before joining the Vertex leadership team, he held leadership roles at Ortho Clinical Diagnostics, Bruker Corporation, Progress Software Corporation, and Millipore Corporation.

Financial Resources and Strategic Execution

Vertex relies on existing cash reserves, marketable securities, and product revenue as its primary sources of liquidity. With over $10 billion of cash and short-term investments as of March 31, 2024, Vertex is in a strong financial position. In our view, this allows the company to weather clinical setbacks or adverse market conditions, while providing management with the flexibility to execute their business plan, including strategic acquisitions and tactical opportunities.

For example, during May 2024 Vertex completed the acquisition of Alpine Immune Sciences, a clinical-stage publicly traded biotechnology company focused on the discovery and development of protein-based immunotherapies. Alpine's Phase-3-ready lead product candidate, povetacicept, demonstrated best-in-class potential in patients with IgA nephropathy, a form of kidney disease. Under the terms of the agreement, Vertex acquired Alpine for $65 per share or approximately $4.9 billion in cash. Alpine will add protein engineering, and immunotherapy capabilities to Vertex's arsenal of drug development tools.

Total long-term liabilities of $1.575 billion amount to less than 8.5% of equity and less than 6.6% of assets, and are easily serviced, as demonstrated by an interest coverage ratio of 97.7 times.

Total shareholder equity amounts to 77.5% of total assets, highlighting Vertex's solid overall financial position. Our financial estimates are in line with the majority of Wall Street opinions.

Valuation

As an established company in the cystic fibrosis space, Vertex leads its competitors across a spectrum of solvency, valuation, and profitability metrics, including having a 2023 P/E of 34.2x versus the competitor group median of 17.0x. The firm's 2023 enterprise value (EV)/Revenue was 11.1x versus its competitor group median of 6.6x. Vertex's 2023 EV/EBIT was 25.4x, versus its competitor group median of 15.6x. The company's 2023 gross margin was 87.2%, contrasted with its competitor group median of 74.2%, and its 2023 net margin was 36.7% against the competitor group median of 19.0%.

Combined with the above metrics, Vertex's rich valuation is, in our opinion, justified by its formidable cash resources, deep and broadening pipeline, historical successes in clinical trials, and the marketing of its drugs in key strategic regions.

We believe that additional shareholder value will be unlocked as Vertex's portfolio of approved products broadens. One example is the company's global launch of and reimbursement coverage for CASGEVY™, its gene therapy for SCD and beta thalassemia. Another near-term product launch opportunity is the vanzacaftor/tezacaftor/deutivacaftor triple oral small molecule combination for cystic fibrosis, which employs a similar mechanism of action as Vertex's blockbuster drug TRIKAFTA.

Vertex's non-opioid treatment for moderate to severe acute pain, Suzetrigine (VX-548), completed Phase 3 clinical trials in December 2023. It is now in regulatory review by the U.S. FDA. Non-opioid pain management is a significant, unmet medical need worldwide. It is possible that Suzetrigine could be approved within one calendar year, and capture a significant first mover share of the $80-90 billion global pain management market.

Based on our analysis of available clinical data, we expect regulatory approvals of the vanzacaftor triple combination and Suzetrigine in 2025, followed by accelerating revenue and EPS growth in 2026. We recommend investors begin accumulating shares of Vertex during the next 12-18 months. Our 12-month price target of $550.00 is based on next-twelve-months (NTM) projected earnings of $15.50 and a P/E multiple of 35.5x.

Investment Thesis

Vertex Pharmaceuticals is a market leader for cystic fibrosis therapies, with its blockbuster drug TRIKAFTA posting year-over-year revenue growth of sixteen percent during fiscal year 2023, to $8.9 billion. A robust pipeline of drug candidates in mid- to late-stage development has the potential to diversify the company's portfolio of marketed products. Vertex adding products to their portfolio will provide significant potential upside to revenue, while reducing overall investment risk.

Vertex's gene therapy for SCD and beta thalassemia, CASGEVY™, was approved by regulatory authorities in multiple key geographies in late 2023 and early 2024. FDA approval of Vertex's non-opioid pain management drug Suzetrigine (VX-548) for acute pain, expected in 2025, would be an important share price inflection point for investors, given the size of the pain market and unmet medical need for

effective non-opioid therapies. Data releases from clinical trials of Suzetrigine in both acute, and neuropathic pain have been followed closely and generated intense interest in the medical field.

Vertex has secured a strong financial position, has a wide moat of patent protection, and is thus able to withstand potential market shocks. The foregoing strengths enable the company's pursuit of organic growth and growth by acquisition. The company has an excellent industry-wide reputation and is led a management team with deep experience in drug development and commercialization.

Vertex Pharmaceuticals Financial Forecast											
	FY 23 A	MAR 24 A	JUN 24 E	SEP 24 E	DEC 24 E	FY 24 E	MAR 25 E	JUN 25 E	SEP 25 E	DEC 25 E	FY 25 E
Revenue	9,869.2	2,690.6	2,660.0	2,690.0	2,730.0	10,770.6	2,750.0	2,790.0	2,845.0	2,920.0	11,305.0
Cost of Sales	1,262.2	342.6	333.8	336.3	342.5	1,355.2	337.5	345.6	355.6	365.0	1,403.7
Gross Profit	8,607.0	**2,348.0**	**2,326.2**	**2,353.7**	**2,387.5**	9,415.4	**2,412.5**	**2,444.4**	**2,489.4**	**2,555.0**	**9,901.3**
Operating Expenses:											
R&D	3,162.9	789.1	798.0	860.8	873.6	3,321.5	935.0	948.6	967.3	992.8	3,843.7
Acquired in-process R&D	527.1	76.8	200.0	100.0	30.0	406.8	30.0	30.0	30.0	30.0	120.0
SG&A	1,136.6	342.7	345.8	349.7	354.9	1,393.1	357.5	362.7	369.9	379.6	1,469.7
Change in Fair Value of Contingent Consideration	-51.6	-0.1	-17.0	-30.0	-12.9	-60.0	-15.0	-15.0	-15.0	-15.0	-60.0
Total Operating Expenses	**4,775.0**	**1,208.5**	**1,326.8**	**1,280.5**	**1,245.6**	**5,061.4**	**1,307.5**	**1,326.3**	**1,352.2**	**1,387.4**	**5,373.4**
Operating Income	**3,832.0**	**1,139.5**	**999.4**	**1,073.2**	**1,141.9**	**4,354.0**	**1,105.0**	**1,118.1**	**1,137.3**	**1,167.6**	**4,528.0**
Interest Expense/Income, net	570.6	170.8	134.0	86.0	87.0	477.8	88.0	89.0	90.0	91.0	358.0
Other Income/Expense, net	-22.8	-31.2	-	-	-	-31.2	-	-	-	-	-
Earnings Before Tax	**4,379.8**	**1,279.1**	**1,133.4**	**1,159.2**	**1,228.9**	**4,800.6**	**1,193.0**	**1,207.1**	**1,227.3**	**1,258.6**	**4,886.0**
Income Tax Expense	760.2	179.5	170.0	173.9	184.3	707.7	179.0	181.1	184.1	188.8	732.9
Net Income	**3,619.6**	**1,099.6**	**963.4**	**985.3**	**1,044.6**	**4,092.9**	**1,014.1**	**1,026.0**	**1,043.2**	**1,069.8**	**4,153.1**
Weighted Average Basic Shares Outstanding	257.7	258.2	258.6	259.3	259.5	258.9	259.8	260.0	260.4	260.7	260.2
Weighted Average Diluted Shares Outstanding	260.5	261.1	261.4	262.1	262.5	261.8	262.9	263.0	263.2	263.6	263.1
Net Income per Share, GAAP, Basic	$14.05	$4.26	$3.73	$3.80	$4.03	$15.81	$3.90	$3.95	$4.01	$4.10	$15.96
Net Income per Share, GAAP, Diluted	$13.89	$4.21	$3.69	$3.76	$3.98	$15.63	$3.86	$3.90	$3.96	$4.06	$15.79
All figures in millions of U.S. Dollar except per share items.											

Sources: Capital IQ, Kingswood Capital Partners Estimates.

Risks to Our Price Target

Clinical trial setbacks: The success of Vertex's drug development pipeline depends on the outcomes of clinical trials, which are subject to risks and uncertainties, including unexpected safety issues, serious side effects, or lack of efficacy.

Regulatory: Vertex may face delays caused by, or rejections from regulatory agencies of its applications for regulatory clearance and marketing authorizations, which in turn would delay or prevent commercialization.

Pricing and reimbursement: Payers such as medical insurers or government-underwritten health systems may limit patient access, or decline to reimburse Vertex's therapies if Vertex's prices are deemed too high, or the efficacy of its therapies are deemed insufficient.

Dependence on a few key products: Vertex's revenue is heavily dependent on its cystic fibrosis products, and any setbacks or competition in this area could have a significant impact on the company's financial performance.

Intellectual property challenges: Vertex's patents may be challenged by competitors, declared invalid by the Patent Trial and Appeal Board, or in court, which could lead to loss of intellectual property or formulary exclusivity, and increased competition.

Competition: Vertex operates in a highly competitive industry, and its competitors may develop equivalent or superior therapies, thereby eroding its market share and revenue.

Supply chain disruptions: Vertex relies on a complex global supply chain to manufacture its therapies, and disruptions or quality issues could impact production, sales, as well as clinical trial timelines.

DISCLOSURES

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Buy - Buy-rated stocks are expected to have a total return of at least 15% over the following 12 months and are the most attractive stocks in the sector coverage area.

Hold - We believe this stock will perform in line with the average return of others in its industry over the following 12 months.

Sell - Sell-rated stocks are expected to have a negative total return of at least 15% over the following 12 months and are the least attractive stocks in the sector coverage area.

Company-Specific Disclosures

Distribution of Ratings
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			Investment Banking Services/Past 12 Months	
Rating	**Count**	**Percent**	**Count**	**Percent**
BUY	3	100.00	1	33.33
HOLD	0	0.00	0	0.00
SELL	0	0.00	0	0.00

As of July 2024.

Vertex Pharmaceuticals Rating History as of July 5, 2024

Source: E-Trade.

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