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A Tale of Two Companies:

Observations from Back-to-Back Gene Therapy Approvals in Sickle Cell Disease and Implications for Future Innovators

Introduction

The end of 2023 marked a historic moment for gene therapies—two approvals in one day for sickle cell disease (SCD), a rare genetic disorder that affects approximately 100,000 patients in the US and over seven million worldwide.[1-2] Prior to December 2023, this disease had no curative treatment options outside of bone marrow transplants in which patients often faced challenges with identifying sufficient matches. On December 8th, Vertex Pharmaceuticals/CRISPR Therapeutics and Bluebird Bio gained FDA approval for their products, Casgevy and Lyfgenia, respectively. Moreover, Casgevy was previously granted conditional marketing authorization by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and more recently has gained a positive opinion from the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP), paving the way for full European approval in 2024. Both Casgevy and Lyfgenia will ultimately help to alter the treatment paradigm for patients and revolutionize the impact of gene therapies in the future. While Casgevy and Lyfgenia share some similarities in therapeutic modality and launch timing, the path to market and subsequent commercial strategy has differed across the two programs. This white paper explores the similarities and differences between Vertex's and Bluebird's approach to the commercialization of a sickle cell disease gene therapy in a "tale of two companies".

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The Approvals

Both Casgevy and Lyfgenia are ex vivo gene therapies, though each product achieves its therapeutic effect through different mechanisms. With Casgevy, Vertex Pharmaceuticals, in collaboration with CRISPR Therapeutics, received the first ever approval of an ex vivo CRISPR/Cas9 genome-edited cellular therapy (Figure 1). The one-time treatment involves a transplant of autologous, gene-edited CD34+ hematopoietic stem and progenitor cells (HSPCs) with reduced expression of BCL11A, ultimately leading to an increase in fetal hemoglobin (HbF) production. In the phase 2/3 CLIMB-SCD-121 study, treatment with Casgevy led to a reduction or complete elimination of vaso-occlusive crises (VOCs) which are directly associated with the pain crises for SCD patients (i.e., over 90% [29/31] of patients did not experience a VOC event for at least one year post-treatment).[3] The significant results of the trial led Vertex to pursue approval worldwide just five years after initiation of its phase 1/2 (Figure 2). Importantly, the success and expediency of Casgevy's path to approval signals the increasing feasibility and applicability of using CRISPR/Cas9 gene editing technology to develop novel therapeutics.

Similar to Casgevy, Bluebird Bio's Lyfgenia is a one-time ex vivo gene therapy for SCD, though its mechanism involves the addition of a functional β-globin gene to patients' own hematopoietic (blood) stem cells (HSCs) via a lentiviral vector. The resulting increase in β-globin production limits sickling of red blood cells which ultimately reduces the potential of vaso-occlusive events (VOEs) (Figure 2). The approval is based on results from a phase 1/2 HGB-206 study, which demonstrated elimination of VOEs in 88% (28/32) of patients between six and 18 months after infusion, with 94% (30/32) experiencing resolution of severe crises.[4] Furthermore, Lyfgenia has been able to show durable responses with all patients maintaining a stable production of anti-sickling adult hemoglobin and elimination or reduction in VOEs five years post-treatment.[4] The long-term follow-up data for Lyfgenia is seen as an advantage for Bluebird and something that is currently limited for Casgevy and has recently caused the National Institute for Health and Care Excellence (NICE) in the UK to not yet recommend Casgevy until more data is collected on its effectiveness.[5] Ultimately, the approval of Lyfgenia marked Bluebird's third gene therapy approval in under two years, reinforcing the company as a leader in gene therapy.

Figure 1.

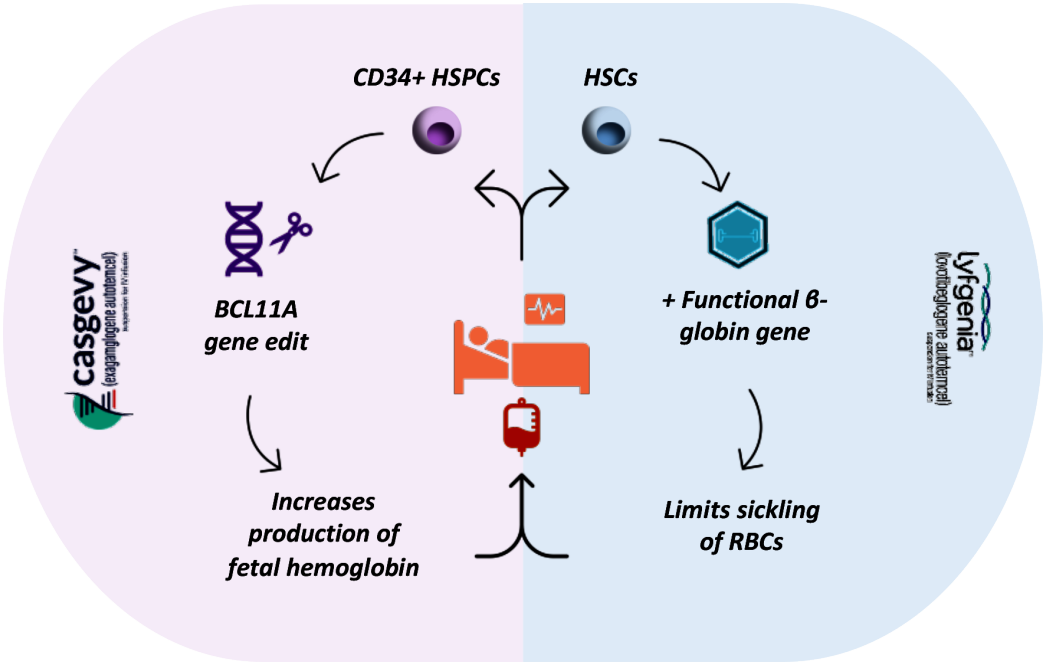

Figure 1. Mechanism of Action Comparison of Casgevy and Lyfgenia. Casgevy and Lyfgenia feature unique gene therapy modifications which contribute to different MOAs to treat SCD

HSPCs: Hematopoietic Stem and Progenitor Cells; HSCs: Hematopoietic Stem Cells; RBCs: Red Blood Cells

Source: Company Websites, accessed April 2024

While Casgevy and Lyfgenia have demonstrated strong efficacy data, they are coupled with potential safety concerns that differ between the two products. Lyfgenia comes with an additional black box warning which is attributed to two patients dying in clinical trials after initiation of treatment due to developing acute myeloid leukemia, causing Bluebird to temporarily pause trials in 2021.[6] Bluebird has stated that the underlying cause of death may have been attributed to the manufacturing process and transplant, both of which have been refined since then. Given the seriousness of the adverse event, the FDA issued a black box warning for Lyfgenia and requires patients to be monitored for cancer through complete blood count tests every six months for at least 15 years as well as bi-yearly viral vector integration site analysis. Such adverse events and monitoring have caused some to consider whether Lyfgenia can truly be characterized as a "one-time" therapy compared to Casgevy, which has no black box warning or monitoring requirements. On the other hand, it remains to be seen if there are safety concerns for a CRISPR/Cas9 gene therapy given the possibility of off-target effects (a possibility acknowledged in the "Warning and Precautions" section of Casgevy's label).

The Pricing and Market Access Strategies

Vertex and Bluebird have taken different approaches to pricing and access for Casgevy and Lyfgenia, respectively (Figure 3). Since the announcement of their approvals, Vertex has stated that their list price for Casgevy is $2.2M whereas Lyfgenia's is $3.1M, a 40% increase compared to Casgevy. The price differential has sparked some concerns regarding the rationale of Bluebird's price, given that both products have similar efficacy. Moreover, Casgevy was also recently approved for transfusion-dependent beta thalassemia (TDT) on January 16th, 2024, and the $2.2M list price is also lower than Zynteglo, Bluebird's $2.8M gene therapy for TDT that was launched in 2022 and leverages the same vector and gene payload as Lyfgenia. However, Lyfgenia's price point may be justified given Bluebird has long-term durability data on the product as well as "real world" vector safety and tolerability data through Zynteglo.

Figure 2.

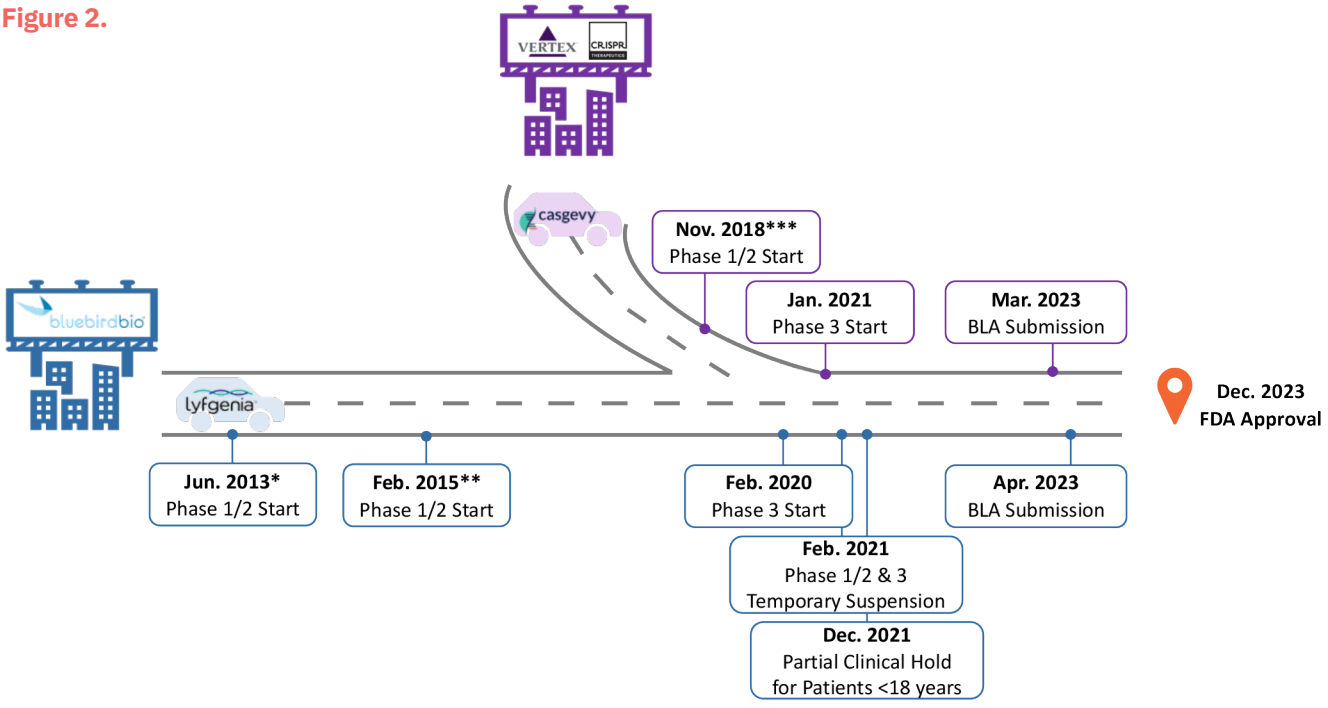

Figure 2. Clinical Development Timeline of Casgevy and Lyfgenia. Despite Casgevy starting clinical trials five years after the initiation of Lyfgenia's Phase 1/2 trial, Vertex was granted FDA approval on the same day as Bluebird Bio.

*Trial was conducted in Paris, France with N=7 participants; **Trial was conducted in the US with N=50 participants;***For Casgevy, developmental timeline is focused exclusively on sickle cell disease (i.e., does not include development dates for β-Thalassemia) in order to appropriately compare to Lyfgenia

Source: Company Websites, Pharma Projects, accessed April 2024

Since the start of the year, both Vertex and Bluebird have been working with payers to obtain coverage for their one-time gene therapies. Specifically, both companies have publicly announced negotiated outcomes-based/risk sharing agreements with Blue Cross' Synergies Medication Collective which covers 100 million people in the US.[7] Ultimately, these agreements will tie patient outcomes to the price payers will have to pay (i.e., if a patient is hospitalized because of vaso-occlusive events, payers will not be required to pay the full price). Bluebird has also announced an additional outcomes-based agreement with an undisclosed organization, totaling the current coverage of Lyfgenia to 200 million in the US. Bluebird has also stated the company is in advanced discussions with over 15 Medicaid agencies as well as additional commercial payers, which together are likely to represent approximately 80% of patients with SCD in the US today.[8] Just this March, Bluebird has signed its first Medicaid outcomes-based agreement for Lyfgenia with the state of Michigan.[9] Furthermore, Bluebird has also engaged with and continues to collaborate with the Center for Medicare and Medicaid Innovation (CMMI) on its Cell and Gene Therapy Access Model (see our previous whitepaper titled "The Race for Innovation: Regulatory Initiatives to Bolster Cell and Gene Therapy Development" for further details on the Cell and Gene Therapy Access Model). Bluebird has continued to assert that while Lyfgenia is priced higher than its competitor, the company is offering innovative contracts in which treatment centers can either pay for Lyfgenia upfront or Bluebird can aid in mitigating the payment risk. Thus, the price difference between Lyfgenia and Casgevy may not significantly impact access to these treatments in the near term given the flexibility offered in reimbursement mechanisms.

The Commercial Experience

As with any gene therapy approved to date, both Casgevy and Lyfgenia will require extensive infrastructure and resources to ensure commercial success. With an already established presence in transfusion-dependent beta thalassemia (TDT), Bluebird plans to leverage their existing commercial infrastructure to accelerate the launch of Lyfgenia with their established Qualified Treatment Center (QTC) network currently in place for Zynteglo. As of early January 2024, 48 centers are currently activated for Zynteglo of which 35 are ready to receive referrals for Lyfgenia. Bluebird has stated by the end of Q1 2024, all centers will be ready to treat with both Zynteglo and Lyfgenia.[8]

Figure 3.

	Casgevy	Lyfgenia
Manufacturer	VERTEX / CRISPR THERAPEUTICS	bluebirdbio
Gene Therapy Delivery Technology	CRISPR/Cas9	Lentiviral Vector
Label	12+ years old with recurrent VOCs	12+ years old with history of VOEs
Efficacy	90%+ of patients did not experience VOC for at least one-year post-treatment	88% of patients did not experience VOE between six- and 18-months post-treatment
Black Box Warning	-	✓
List Price	$2.2M	$3.1M
Treatment Centers (as of April 2024)	9	35

Figure 3. Comparison of Key Characteristics of Casgevy and Lyfgenia. While Casgevy and Lyfgenia have relatively similar efficacy, Lyfgenia is priced 40% higher and comes with a black box warning label.

Source: Company Websites, accessed April 2024

While new to the space, Vertex aims to apply their existing rare disease commercial experience amassed through years of supporting their cystic fibrosis franchise while building capabilities to support SCD and TDT. Vertex has already partnered with Charles River Laboratories and RoslinCT to aid in the manufacturing of Casgevy and currently has nine authorized treatment centers to administer the gene therapy with the target of 50 sites by the end of this year.[10] Both companies offer comprehensive patient services that include disease and product education, benefits verification and authorization support, treatment center identification and logistical assistance, as well as financial support for eligible patients. Given their longstanding experience in rare disease and commitment to patients, it is not a surprise that both companies are providing world-class patient services to support their products.

Conclusion and Future Implications

Vertex and Bluebird have both brought two valuable medicines to sickle cell disease market, providing optionality to patients with this life-altering disease. Given their differences in technology, pricing and reimbursement, and commercial footprint, it remains to be seen which product ultimately prevails as the market leader. Vertex offers a one-time gene therapy that is priced lower than its competitor and does not come with a black box warning. However, it remains unknown whether any long-term safety effects will emerge given the nascency of the technology. Lyfgenia is priced higher than Casgevy and comes with an additional black box warning that requires long-term monitoring. However, Bluebird already has a strong commercial infrastructure in place given the prior launch of Zynteglo and has secured numerous coverage agreements to ensure access to Lyfgenia. Differences aside, the ability for Vertex and Bluebird to separately advance two complex technologies for a condition with high unmet need represents the "best of times" in biopharma and reinforces continued success in the new era of personalized medicine.

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