Zynteglo (beti-cel) gene therapy – A potential game-changer for bluebird bio

(If approved, Zynteglo will be the first ex-vivo hematopoietic stem cell gene therapy for β-thalassemia patients in the US)

The Institute for Clinical and Economic Review (ICER) has backed bluebird bio's beti-cel gene therapy, also known as Zynteglo (betibeglogene autotemcel), for transfusion-dependent β-thalassemia (TDT), by stating that its price tag of USD2.1 million is cost-effective. However, the opinion has been expressed in a draft report and could change as the evaluation process continues.

The USD2.1 million price tag has been debated strongly across payer communities in Europe and the US. The ICER's finalized recommendation of cost-effectiveness could revive bluebird bio's fortunes and potentially bring the company back into the reckoning as a premier gene therapy developer. Although the therapy was previously approved in the UK and the rest of Europe at a price tag of USD1.7 million, the company had to exit the markets, primarily due to 'hostile regulatory and reimbursement environments.'

bluebird bio is expecting to capitalize on the recent unanimous backing by the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee and the potential approval of Zynteglo in the US with a PDUFA date of August 19, 2022. To further secure its financial revival, the company is exploring multiple financing opportunities, including the sale of priority review vouchers, which the company will be eligible to receive upon approval of beti-cel for TDT and eli-cel for cerebral adrenoleukodystrophy.

bluebird bio's gene therapies

bluebird bio is conducting clinical studies with investigational gene therapy for three diseases:

- Zynteglo (beti-cel) for transfusion-dependent β-thalassemia
- LentiGlobin (lovo-cel) for sickle cell disease
- Eli-cel for cerebral adrenoleukodystrophy

Figure 1: Timeline of bluebird bio's gene therapy journey

Jun 19

bluebird bio receives conditional approval for beti-cel for TDT in the EU for patients aged 12 years+.

Oct 19

The EMA approves refined commercial drug product manufacturing specifications for beti-cel, licensed as ZYNTEGLO™, in the EU and the UK.

Jan 20

bluebird bio launches Zynteglo in Germany, accompanied by payment agreements with multiple statutory health insurers.

Jan 21

The company announces an intent to separate its severe genetic disease and oncology businesses into independent publicly traded companies, potentially to decrease operational challenges.

Feb 21

- The US FDA puts clinical hold on bluebird bio's gene therapy trials for LentiGlobin, as two patients develop acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).

Apr 21

- The company witnesses a failure of reimbursement negotiations in Germany after the first commercial infusion in Feb 21.
- It decides to recall Zynteglo from the German market, citing a failure to reach a pricing agreement with authorities.

Jun'21

- Investigators studying the development of AML and MDS in patients undergoing gene therapy trials for LentiGlobin declared that it was transfusion-dependent anaemia (and not MDS).
- The FDA lifts clinical hold on Phase 1/2 HGB-206 and Phase 3 HGB-210 studies of LentiGlobin and Phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies for Zynteglo.

Aug 21

The company plans to wind down its operations in Europe and starts looking for partners to out-license its gene therapies, after hitting reimbursement setbacks and challenges; bluebird bio leaves the EU market.

Dec 21

The FDA places bluebird bio's lovo-cel gene therapy (formerly LentiGlobin) on partial clinical hold for patients under 18 yrs, as an adolescent patient develops persistent anemia, leading to potential impact on BLA filing for LentiGlobin (expected in Q1 2023).

Jan 22

The FDA extends the review period for Zynteglo and eli-cel (revised PDUFA goal dates for Zynteglo and eli-cel announced as Aug 19, 2022 and Sep 16, 2022, respectively).

Mar 22

- bluebird states that its financial position poses doubts about its ability to continue and that it needs fresh funding.
- The FDA extends reviews for Zynteglo and eli-cel by three months (winding down business in EU delays programs in the US and exacerbates financial concerns).

Apr 22

bluebird bio initiates restructuring and workforce reduction to deliver cost-savings of up to USD160 million and to focus on near-term opportunities and potential launches in the US in 2022.

Jun 22

- bluebird bio receives unanimous backing from the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee for both Zynteglo and eli-cel stating that the benefits outweigh the risks of the therapies.
- Zynteglo and eli-cel all set for PDUFA goal dates of Aug 19, 2022 and Sep 16, 2022, respectively.

Zynteglo – a high-potential emerging gene therapy

Zynteglo is a one-time gene therapy for TDT. bluebird submitted the biologics license application (BLA) for Zynteglo to the FDA (for patients with β-thalassemia who require RBC transfusions) in Sep 2021, based on data from its Phase 3 and phase 1/2 Northstar studies. The FDA had previously granted the 'orphan drug' status, 'breakthrough therapy' designation, and 'rare pediatric disease' designation to Zynteglo for TDT.

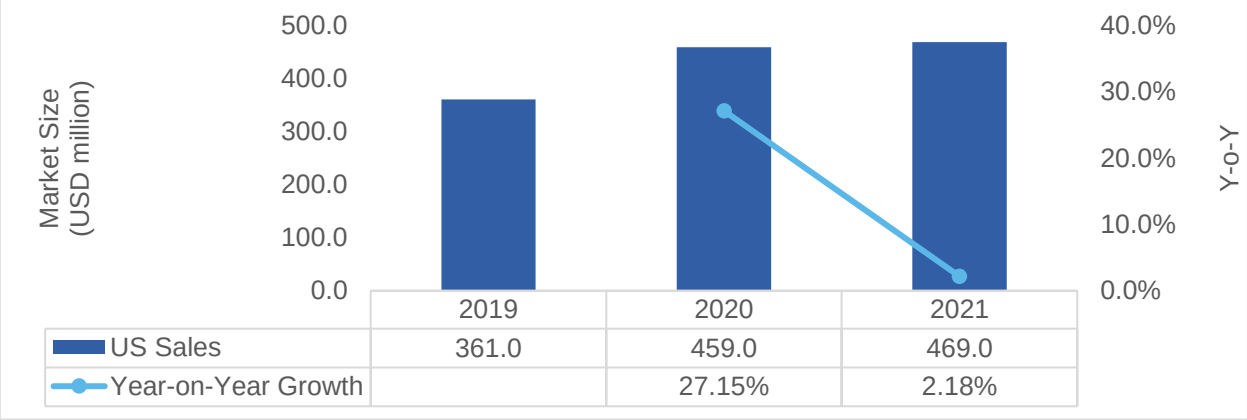
Table 1: Zynteglo's trial status

Study	Indication	Phase
Northstar-2 (**HGB-207**)	Transfusion-dependent β-thalassemia	3
Northstar-3 (HGB-212)	Transfusion-dependent β-thalassemia	3
Northstar (HGB-204)	β-Thalassemia Major (Transfusion-dependent β-thalassemia)	1/2
LTF-303	Transfusion-dependent β-thalassemia	Long-term follow-up study for safety and efficacy

bluebird bio has potential to achieve significant Zynteglo sales in the US and similar adoption as Zolgensma, due to the country's higher addressable β-thalassemia patient population of 1,000–1,500. Zolgensma is an approved one-time gene therapy for spinal muscular atrophy, a significantly rare disease that affects ~1 in 6,000–10,000 children in the US. It provides a functional copy of the SMN1 gene to a very specific patient population of children up to the age of two years. The therapy's manufacturer, Avexis, was acquired by Novartis in 2018, right before the approval of the therapy in the US in May 2019.

Priced at USD2.125 million in the US, Zolgensma is currently the world's most expensive therapy and has exhibited successful growth in the US market. Zolgensma witnessed significant sales growth in the US, from USD361 million in 2019 to USD469 million in 2021. However, its growth has been significantly staggered at 2.18% between 2020 and 2021, compared with 27.15% between 2019 and 2020.

Figure 2: US Sales of Zolgensma (2019-21)



Source: Novartis Annual Report

Zolgensma's staggered sales growth can be potentially attributed to its hefty price tag and the overall impact of COVID-19, which restricted patients' access to the therapy. However, Novartis is hopeful that Zolgensma sales will pick up in the years to come; Evaluate Pharma forecasts worldwide revenues of USD1.9 billion for the therapy in 2026. This figure is expected to increase significantly, given that Novartis recorded USD1.35 billion in worldwide sales for Zolgensma in 2021.

Zynteglo's potential approval in the US is expected to bring about a similar change in the therapeutic landscape for β-Thalassemia.

Challenges to market adoption of gene therapy

Despite their efficacy and impact, the adoption of gene therapies, including cell and gene therapies (CGTs) as a whole, is challenged by multiple factors. On the one hand, they are primarily targeted at a niche patient category, while on the other their high costs make them virtually inaccessible for a vast majority of patients. Apart from cost, complex supply chain issues, low manufacturing yields, and uncertain long-term benefits make gene therapies highly exclusive. While these challenges exist everywhere at the global level, Europe has presented multiple unique challenges to adoption, including a stringent reimbursement pathway.

Table 2: Overview of reimbursement schemes and key outcomes considered for CGT reimbursement in Europe

	France	Germany	Italy	Spain	UK
Reimbursement scheme	Coverage with evidence development	Outcomes-based rebates	Outcomes-based staged payments	Outcomes-based staged payments	Coverage with evidence development
Details	**Annual reassessments**: Long-term follow-up data from pivotal trials + regional patient-specific post-launch data	**Linked rebates**: Individual patient outcomes	**Linked payments (3 installments):** Individual patient outcomes	**Linked payments (2 installments):** Individual patient outcomes	**Future price reassessment**: Long-term follow-up data from pivotal trials + regional patient-specific post-launch data
Key outcomes	**Multiple**: Survival, remission status, disease progression, adverse events	**Survival**	-	**Complete response**	**Multiple**: Survival, remission status, disease progression, adverse events

Source: NCBI

In Europe, insurance plans available in the market lead to a significant short-term cost concentration that is difficult for healthcare systems to carry. For example, France and the UK use an evidence development (CED) approach based on national-level cohort data to determine pricing and payments, while Spain and Italy use an outcomes-based reimbursement (OBR) based on individual patient data (IPD). On the other hand, Germany has been using an OBR-based IPD for gene therapies, while imposing CED on certain cases.

On top of the insurance-related challenges, the pricing strategies adopted by companies add to the difficulties of healthcare systems. Most governments have a legal obligation and an ethical ambition to make therapies equally available to all patients. However, they face a dilemma when conducting a risk-benefit analysis of low-cost therapies for common conditions and high-cost therapies for rare conditions. While market access regulations are easier to establish (since therapies approved by the EMA can be marketed anywhere in Europe) reimbursement is a lengthy, complex, and costly process. In such a scenario, gene therapy manufacturers need to negotiate with each member country and, in some cases, with regional authorities within countries.

These challenges often impact the viability of companies across markets, as is evident in bluebird bio's decision to 'wind down' Zynteglo from the German market, citing a failure to reach a pricing agreement with the authorities. Although the company had planned an annual performance-based payment program (OBR-based on IPD), the therapy still seemed too expensive as a one-time treatment.

Long-term follow-up data is an inherent part of the ideal reimbursement process for gene therapies. However, both manufacturers and payers face challenges with respect to pricing reassessments and reliable long-term data collection. OBR-based IPDs can be significantly less burdening on payers, as they spread post-treatment reimbursement between manufacturers and payers.

Conclusion

The overall potential of gene therapies is enormous, and it is an exciting area for the biopharma industry at this moment as it moves forward towards personalized treatment. A positive decision on Zynteglo by the FDA, coupled with a favorable ICER assessment, could lead to a massive change in bluebird's fortunes. Additionally, being considered 'cost-effective' may offer bluebird a distinct advantage in its negotiations with payers.

