Regulators’ Advice Can Make a Difference: European Medicines Agency Approval of Zynteglo for Beta Thalassemia

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This commentary aims to demonstrate how frequent interactions between a medicines developer, regulators, Health Technology Assessment (HTA) bodies, and patients during the development can result in accelerated access by patients to an innovative product, in this case, a gene therapy medicinal product for beta-thalassemia. The majority of patients, who needed at least eight transfusions per year in the last two years before treatment, remain transfusion independent over 12 months after Zynteglo (bluebird bio (Netherlands) B.V., Utrecht, The Netherlands) administration. Early approvals, albeit based on robust data, are only possible if a well thought-through postapproval commitment plan is put in place.

The recent European Union marketing authorization of Zynteglo (lentiglobin) illustrates how well planned and executed interactions among a medicines developer, regulators, HTA bodies, and patients can result in accelerated access by patients to an innovative product targeting an unmet medical need. Patients with transfusion-dependent beta-thalassemia require lifelong blood transfusions, leading to iron overload that impacts the patients’ quality of life. So far, the only curative treatment option is allogeneic hematopoietic stem-cell transplantation (HSCT), with related considerable morbidity. Mortality for patients with beta-thalassemia remains significantly increased compared with the general population.1,2

Zynteglo, a gene therapy medicinal product, represents a paradigm change in management—a treatment consisting of an autologous CD34+ cell enriched population that contains hematopoietic stem cells transduced with lentiviral vector encoding the β-globin gene.

Such innovative treatment modalities break new ground for patients and their clinicians as well as for developers and regulators, which can make generation of appropriate data to support licensing and, ultimately, access, a challenge. Preliminary clinical data for Zynteglo were promising, but important questions were identified early during clinical development. These were related to clinical trial design and sample size due to the nature of the clinical end point, the rarity of the condition, and difficulties in identifying a suitable comparator, type, and duration of postauthorization efficacy and safety follow-up, and to the impact of manufacturing changes on the interpretation of clinical data. Questions related to evidence generation for value assessment by HTA and reimbursement by healthcare payers also needed to be tackled, to facilitate patient access after marketing authorization.

Thus, Zynteglo was an ideal candidate for enhanced regulatory dialogue during development. It was included in a pilot project to explore the use of iterative development and real-world data collection, Adaptive Pathways,4 and then granted access to a European Medicines Agency scheme for priority medicines (PRIME),5 both schemes offering platforms for more frequent interactions during development.

Cell-based and gene therapy medicinal products are particularly sensitive to changes in their manufacturing conditions, and this can often lead to difficulties in the evaluation process because the commercial product may be produced by a modified process compared to that used preauthorization for clinical trials. In the case of Zynteglo, changes in the manufacturing site and processes like improvement of transduction efficiency in the commercial scale process were discussed with regard to their impact on the interpretation of clinical data. Other points were the timing of

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data submission and qualification of the apheresis collection centers.

Clinical issues were discussed together with patients and HTAs to help support subsequent patient access. Aspects included:

- The suitability of clinical data set (efficacy and safety) to support submission of a conditional marketing authorization application (a European Union procedure allowing licensing of a medicine to address an unmet medical need on the basis of less comprehensive data than normally required), including number of treated patients and their genotype.
- Discussion and agreement on the primary end point, “transfusion independence.”
- Extrapolation models for prediction of both long-term efficacy and for inclusion of children in the trials.
- Design of confirmatory trials and real-world data generation to assess long-term efficacy and safety following a conditional marketing authorization.
- Proposed pharmacovigilance and risk minimization plans.

Full details of the discussions and assessment can be found in the European Public Assessment Report available at the European Medicines Agency website (www.ema.europa.eu).

A series of scientific advice procedures took place between 2015 and 2017. This iterative engagement during development ensured that issues were addressed early to prevent delays in regulatory approval.

As the scientific advice process had allowed prediscussion of the more complex issues, and given the unmet need, the marketing authorization application, which was submitted in August 2018, was granted accelerated assessment. This reduced the timelines for the evaluation and final opinion of Zytelgo (in March 2019) by several months.

The Zytelgo approval provides an example of the advantages resulting from iterative scientific advice. First, the discussions ensured that the studied patient population did meet the intended labeling claim (i.e., patients 12 years and older with transfusion-dependent β-thalassemia who do not have a β0 mutation at both alleles of the β-globin gene (i.e., patients with a non-β0/β0 genotype), for whom HSCT is appropriate but a human leukocyte antigen (HLA)-matched related HSCT donor is not available).

Second, although the number of subjects included in the marketing authorization application was only 19 and the follow-up time relatively limited (12 months), the data presented showed robust results by achieving transfusion independence in 15 of 19 patients. Because these patients had consistently required eight or more transfusions per year in the last 2 years preceding enrollment, it was considered that transfusion independence in the majority of patients is extremely unlikely to be a result of disease fluctuation or a chance finding, but demonstrated an effect that is both patient-relevant and of high magnitude. The safety profile included the expected adverse events related to mobilization, apheresis, and myeloablative conditions. This was deemed acceptable in light of the clear beneficial effect.

During the clinical studies, the drug manufacturing process was changed and optimized. At the time of approval, only three patients with the β0/β0 genotype had been treated with product manufactured by the commercial process. A comparability exercise between the previous process used for clinical trial material and the commercial manufacturing processes at the quality level had been extensively discussed before the evaluation. Given the well-known sensitivity of gene therapies to changes in the manufacturing process, and resulting uncertainties regarding their impact on drug product potency and clinical outcome, these changes might have contributed to a negative regulatory decision. However, in this particular case, pharmacodynamic parameters and efficacy results were consistent across studies. To address these uncertainties, the Agency decided to impose the following obligations: (i) tight control of the finished product potency attributes and (ii) reevaluation of the acceptance criteria for attributes related to the drug product potency tests using batch release data and clinical results after 6 months follow-up of 20 patients treated with commercial batches. It is up to the company to resolve the issues speedily and launch the product.

As consequence of the limited data base at marketing authorization, additional safety and efficacy data need to be collected during ongoing clinical development, such as in patients 12 years and older who do not have a β0/β0 genotype. In addition, all patients treated with Zytelgo need to be followed up to assess the duration of efficacy and to further specify the safety of the product. This includes the assessment of a theoretical risk for insertional mutagenesis that is common for CD34+ genetically modified cells. Although this risk has been minimized by the design of the lentiviral construct and through the manufacturing process and no evidence of such risk was observed at the time of the marketing authorization, all patients need to be monitored for development of leukemia or lymphoma until 15 years posttreatment with Zytelgo.

To comply with the requirements for long-term follow-up, a product registry has been set up for patients treated with Zytelgo and patients treated with transfusions or HLA-matched allogenic HSCT-treated patients. All of these topics had been considered in the earlier interactions with the company and helped to facilitate the definition of postapproval commitments.

This marketing authorization procedure and the preceding intensified regulatory support have also shown how regulatory advice with involvement of reimbursement bodies, up to the time of market authorization, can help to foster patient access. HTA bodies expressed their data needs to ensure that—once the product received regulatory approval—they would have the tools to swiftly make a value assessment informing pricing and reimbursement decisions. In addition, HTA bodies and payers could be given reasonable assurance that treated patients would be monitored for efficacy and safety as a result of the well-defined postmarketing commitments agreed on with the manufacturer. The Zytelgo experience highlights the value of European regulatory tools for early access (i.e., conditional marketing authorization and accelerated assessment), when the nature of the data required for the authorization and postapproval to confirm the initial opinion have been discussed upfront. It underlines the importance of setting up processes that enable such early interactions without compromising impartiality when assessing the results generated by the experiment.

The required effort on all sides is high and such resource-intensive support
should be reserved for products that are highly likely to offer true advancements for patients. In our experience, there is specific value for innovative and first-in-class medicines for patients with rare diseases and high unmet medical need. Due to their overall complexity and novelty, gene and cell therapy medicinal products particularly benefit from this enhanced support.

We believe that this is an important avenue to pursue to ensure robust data are collected in the most efficient way and genuinely innovative products reach patients with unmet needs without undue delays.

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CONFLICT OF INTEREST
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