

# Summary of risk management plan for Zynteglo (an autologous CD34<sup>+</sup> cell enriched population that contains haematopoietic stem cells transduced with lentiviral vector encoding the $\beta^{\text{A-T87Q}}$ -globin gene)

This is a summary of the risk management plan (RMP) for Zynteglo. The RMP details important risks of Zynteglo, how these risks can be minimised, and how more information will be obtained about Zynteglo's risks and uncertainties (missing information).

Zynteglo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Zynteglo should be used.

This summary of the RMP for Zynteglo should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to current concerns will be included in updates of Zynteglo's RMP.

## I. The medicine and what it is used for

Zynteglo is authorised for treatment of patients 12 years and older with transfusion-dependent  $\beta$ -thalassaemia (TDT) who do not have a  $\beta^0$  mutation at both alleles of the  $\beta$ -globin gene (see SmPC for the full indication). It contains an autologous CD34<sup>+</sup> cell enriched population that contains haematopoietic stem cells transduced with lentiviral vector encoding the  $\beta^{\text{A-T87Q}}$ -globin gene as the active substance and it is given by an intravenous route of administration.

Further information about the evaluation of Zynteglo's benefits can be found in Zynteglo's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <https://www.ema.europa.eu/en/medicines/human/EPAR/zynteglo>.

## II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Zynteglo, together with measures to minimise such risks and the proposed studies for learning more about Zynteglo's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Zynteglo, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Zynteglo is not yet available, it is listed under 'missing information' below.

## **II.A List of important risks and missing information**

Important risks of Zynteglo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Zynteglo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

| List of important risks and missing information |  |
|---|--|
| Important identified risks                      | Delayed platelet engraftment   |
| Important potential risks                       | Insertional oncogenesis<br>Production of replication-competent lentivirus<br>Loss of response to gene therapy<br>Neutrophil engraftment failure<br>Splenic rupture |
| Missing information                             | Long-term safety and efficacy<br>Use in patients over 35 years of age  |

## **II.B Summary of important risks**

| <b>Important identified risk 1: Delayed platelet engraftment</b> |  |
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| Evidence for linking the risk to the medicine                    | This risk is based on the safety analysis of data collected within the clinical development programme for Zynteglo which showed delayed time to platelet engraftment in TDT patients in comparison with data published for allogeneic haematopoietic stem cell transplant (HSCT) patients.<br><br>This delayed platelet engraftment was not correlated with an increased incidence of bleeding events in affected patients compared with patients with a faster time to platelet engraftment. However, delayed platelet engraftment bears a potential for development of bleeding events due to prolonged thrombocytopenia, which can be serious and lead to fatal outcomes. |
| Risk factors and risk groups                                     | Data analysis for risk factors was inconclusive because subject numbers were small and subjects had overlapping potential risk factors.  |
| Risk minimisation measures                                       | <u>Routine risk minimisation measures</u><br>– SmPC sections 4.4, and 4.8<br>– PL section 2  |

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|  | <p>Signs and symptoms of bleeding and recommendations if present included in PL section 2.</p> <p>Restricted prescription medicine</p> <p><u>Additional risk minimisation measures</u></p> <ul style="list-style-type: none"> <li>- Educational materials for healthcare professionals</li> <li>- Educational materials for patients</li> <li>- Patient alert cards</li> </ul>   |
| Additional pharmacovigilance activities                    | <p><u>Additional pharmacovigilance activities:</u></p> <ul style="list-style-type: none"> <li>- Study REG-501</li> <li>- Study HGB-207</li> <li>- Study HGB-212</li> </ul> <p>See section II.C of this summary for an overview of the post-authorisation development plan.</p>   |
| <b>Important potential risk 1: Insertional oncogenesis</b> |  |
| Evidence for linking the risk to the medicine              | <p>Lentiviral vectors integrate into host genomic DNA and have a potential for insertional oncogenesis. Gene transfer with <math>\gamma</math>-retroviral vectors (which were based on a different class of retroviruses than lentiviruses) led to development of lymphoma or leukaemia in some of the treated patients within 2-6 years post-therapy. Lentiviruses represent a class of retroviruses distinct from <math>\gamma</math>-retroviruses.</p> <p>Unlike the <math>\gamma</math>-retroviral vectors that led to leukaemia, self-inactivating lentiviral vectors lack the strong enhancer/promoter long terminal repeat sequences of <math>\gamma</math>-retroviral vectors and, unlike <math>\gamma</math>-retroviral vectors, do not preferentially integrate near gene promoter regions.</p> <p>BB305 lentiviral vector bears a significantly reduced risk of insertional oncogenesis; however, this risk cannot be fully excluded at this point. To date, there is no published evidence of lentiviral vector-mediated insertional oncogenesis in any nonclinical or clinical study of any ex vivo lentiviral vector gene-modified haematopoietic stem cell product.</p> |
| Risk factors and risk groups                               | No Zynteglo- or lentiviral vector-related risk factors/groups have been established.   |
| Risk minimisation measures                                 | <p><u>Routine risk minimisation measures</u></p> <ul style="list-style-type: none"> <li>- SmPC sections 4.4, and 5.3</li> <li>- PL section 2</li> </ul> <p>Recommendations for annual monitoring for leukaemia/lymphoma given in the SmPC section 4.4</p> <p>Collection of blood samples for testing if leukaemia/lymphoma is diagnosed given in SmPC section 4.4</p> <p>Restricted prescription medicine</p>  |

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|   | <p><u>Additional risk minimisation measures</u></p> <ul style="list-style-type: none"> <li>- Educational materials for healthcare professionals</li> <li>- Educational materials for patients</li> </ul>  |
| Additional pharmacovigilance activities   | <p><u>Additional pharmacovigilance activities:</u></p> <ul style="list-style-type: none"> <li>- Study REG-501</li> <li>- Study HGB-207</li> <li>- Study HGB-212</li> <li>- Study LTF-303</li> </ul> <p>See section II.C of this summary for an overview of the post-authorisation development plan.</p>   |
| <b>Important potential risk 2: Production of replication-competent lentivirus</b> |   |
| Evidence for linking the risk to the medicine                                     | <p>This risk of Zynteglo is based on a theoretical possibility as this lentiviral vector was significantly modified to minimise any remaining potential for production of replication-competent lentivirus. No Zynteglo-induced replication-competent lentivirus has been detected in any subject of the clinical development programme.</p> <p>No replication-competent lentiviruses have been detected to date in any material generated with third-generation vector systems, based on literature sources.</p> |
| Risk factors and risk groups  | <p>The use of cells of patients infected with HIV-1/-2 or human T-lymphotropic virus type 1, or type 2 (HTLV-1/-2) may theoretically increase the risk of replication-competent lentivirus if such cells are used for manufacturing of Zynteglo.</p> <p>The design of third-generation lentiviral vectors suggests that the risk of replication-competent lentivirus is significantly lower than that of <math>\gamma</math>-retrovirus-based vectors.</p>  |
| Risk minimisation measures  | <p><u>Routine risk minimisation measures</u></p> <ul style="list-style-type: none"> <li>- SmPC sections 4.3 and 4.4</li> <li>- PL section 2</li> </ul> <p>The need for screening for the presence of HIV/HTLV prior treatment stated in the SmPC section 4.4</p> <p>Restricted prescription medicine</p> <p><u>Additional risk minimisation measures</u></p> <ul style="list-style-type: none"> <li>- Educational materials for healthcare professionals</li> <li>- Educational materials for patients</li> </ul> |
| Additional pharmacovigilance activities   | <p><u>Additional pharmacovigilance activities:</u></p> <ul style="list-style-type: none"> <li>- Study REG-501</li> <li>- Study HGB-207</li> <li>- Study HGB-212</li> <li>- Study LTF-303</li> </ul>   |

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|   | See section II.C of this summary for an overview of the post-authorisation development plan.  |
| <b>Important potential risk 3: Loss of response to gene therapy</b> |   |
| Evidence for linking the risk to the medicine                       | Loss of response to gene therapy is a theoretical risk potentially associated with all gene therapies and as such, it is a potential risk of Zynteglo.  |
| Risk factors and risk groups  | Not yet established   |
| Risk minimisation measures  | <u>Routine risk minimisation measures</u><br>Restricted prescription medicine<br><u>Additional risk minimisation measures</u> <ul style="list-style-type: none"> <li>- Educational materials for healthcare professionals</li> <li>- Educational materials for patients</li> </ul>  |
| Additional pharmacovigilance activities                             | <u>Additional pharmacovigilance activities:</u> <ul style="list-style-type: none"> <li>- Study REG-501</li> <li>- Study HGB-207</li> <li>- Study HGB-212</li> <li>- Study LTF-303</li> </ul> See section II.C of this summary for an overview of the post-authorisation development plan.   |
| <b>Important potential risk 4: Neutrophil engraftment failure</b>   |   |
| Evidence for linking the risk to the medicine                       | Data available indicate that administration of Zynteglo is not associated with neutrophil engraftment failure. However, any transplant procedure is associated with a potential risk of such failure, which is more common for allogeneic haematopoietic stem cell transplants than for autologous. Considering the potential implications for patients, this risk represents a safety concern of Zynteglo. |
| Risk factors and risk groups  | Not yet established   |
| Risk minimisation measures  | <u>Routine risk minimisation measures</u> <ul style="list-style-type: none"> <li>- SmPC section 4.4</li> <li>- PL sections 2 and 3</li> </ul> Restricted prescription medicine<br><u>Additional risk minimisation measures</u> <ul style="list-style-type: none"> <li>- Educational materials for healthcare professionals</li> </ul>   |
| Additional pharmacovigilance activities                             | <u>Additional pharmacovigilance activities:</u> <ul style="list-style-type: none"> <li>- Study REG-501</li> <li>- Study HGB-207</li> <li>- Study HGB-212</li> </ul> See section II.C of this summary for an overview of the post-authorisation development plan.  |

| <b>Important potential risk 5: Splenic rupture</b>                 |   |
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| Evidence for linking the risk to the medicine                      | <p>Splenic rupture is a risk associated with the use of G-CSF and G-CSF/plerixafor.</p> <p>To date, there have been no cases of splenic rupture in LentiGlobin BB305 Drug Product treated patients.</p> <p>Considering the known effects of TDT on the spleen, the potential risk of splenic rupture in the target population of LentiGlobin BB305 Drug Product cannot be excluded.</p> |
| Risk factors and risk groups                                       | Not yet established   |
| Risk minimisation measures   | <p><u>Routine risk minimisation measures</u></p> <ul style="list-style-type: none"> <li>- SmPC section 4.4</li> </ul> <p>Restricted prescription medicine</p> <p><u>Additional risk minimisation measures</u></p> <ul style="list-style-type: none"> <li>- Educational materials for healthcare professionals</li> </ul>  |
| Additional pharmacovigilance activities                            | <p><u>Additional pharmacovigilance activities:</u></p> <ul style="list-style-type: none"> <li>- Study REG-501</li> <li>- Study HGB-207</li> <li>- Study HGB-212</li> </ul> <p>See section II.C of this summary for an overview of the post-authorisation development plan.</p>  |
| <b>Missing information 1: Long-term safety and efficacy</b>        |   |
| Risk minimisation measures   | <p><u>Routine risk minimisation measures</u></p> <ul style="list-style-type: none"> <li>- SmPC section 4.4</li> </ul> <p>Restricted prescription medicine</p> <p><u>Additional risk minimisation measures</u></p> <ul style="list-style-type: none"> <li>- Patient alert cards</li> <li>- Controlled distribution</li> </ul>  |
| Additional pharmacovigilance activities                            | <p><u>Additional pharmacovigilance activities:</u></p> <ul style="list-style-type: none"> <li>- Study REG-501</li> <li>- Study HGB-207</li> <li>- Study HGB-212</li> <li>- Study LTF-303</li> </ul> <p>See section II.C of this summary for an overview of the post-authorisation development plan.</p>   |
| <b>Missing information 2: Use in patients over 35 years of age</b> |   |
| Risk minimisation measures   | <p><u>Routine risk minimisation measures</u></p> <p>Restricted prescription medicine</p>  |

## **II.C Post-authorisation development plan**

### **II.C.1 Studies which are conditions of the marketing authorisation**

The following studies are conditions of the marketing authorisation:

#### **Long-term observational registry study**

In order to further characterise and contextualise the long-term safety and efficacy of Zynteglo in patients 12 years and older with transfusion-dependent  $\beta$ -thalassaemia (TDT) who do not have a  $\beta^0/\beta^0$  genotype, the MAH should conduct and submit the results of a study based on data from a product registry (REG-501) and use data on patients treated with transfusions and/or HLA-matched allogeneic HSCT treated patients from an established European registry as a comparator group.

Purpose of the REG-501 product registry: This is an observational study to collect longitudinal data on the clinical outcomes of patients with TDT who have received treatment with Zynteglo in the post-marketing setting. The study will provide a long-term follow-up for patients treated with gene therapy drug products to monitor for serious AEs and AEs of interest as well as to assess the durability of clinical response. Patients treated with Zynteglo in the post-marketing setting will be followed in the Registry for 15 years after infusion with Zynteglo.

In addition, this longitudinal study will further characterise the established safety profile of the product and provide long-term safety data. Finally, the study will also evaluate the extent of patients' healthcare resource utilisation to characterise the amount of care and treatment they receive after administration of Zynteglo.

#### **Phase 3 efficacy and safety study HGB-207**

Purpose of the study: This is a Phase 3 efficacy and safety study with the primary objective to evaluate the efficacy of treatment with Zynteglo in subjects  $\leq 50$  years of age with TDT who do not have a  $\beta^0/\beta^0$  genotype at the  $\beta$ -globin gene. The secondary objective is to evaluate the safety of treatment with Zynteglo in the same TDT subjects.

The conditions of the marketing authorisation concern subjects  $\geq 12$  years of age.

#### **Phase 3 efficacy and safety study HGB-212**

Purpose of the study: This is a Phase 3 efficacy and safety study with the primary objective to evaluate the efficacy of treatment with Zynteglo in subjects  $\leq 50$  years of age with TDT who have a  $\beta^0/\beta^0$  genotype at the  $\beta$ -globin gene and the secondary objective to evaluate the safety of treatment with Zynteglo in the same study subjects.

The conditions of the marketing authorisation concern subjects  $\geq 12$  years of age with an IVS-I-110 genotype.

#### **Long-term follow-up study LTF-303**

Purpose of the study: This is a study to monitor the long-term safety and efficacy of the gene therapy drug product used in bluebird bio-sponsored clinical studies (i.e., the "parent studies") in treated subjects with hemoglobinopathies.

The conditions of the marketing authorisation concern subjects  $\geq 12$  years of age who do not have a  $\beta^0/\beta^0$  genotype.

### **II.C.2 Other studies in post-authorisation development plan**

There are no studies required for Zynteglo.