EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 March 2021
EMA/PRAC/104560/2021

PRAC List of questions

To be addressed by the marketing authorisation holder for ZYNTEGLO

Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Procedure number: EMEA/H/A-20/1504/C/003691/0023

Marketing authorisation holder(s): bluebird bio (Netherlands) B.V.

Active substance: betibeglogene autotemcel

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1. Background

On 18 February EC triggered a procedure under Article 20 of Regulation (EC) 726/2004 due to concerns over a case of acute myeloid leukaemia (AML) in a patient with sickle cell disorder (SCD) patient treated 5.5 years earlier in a clinical study with an investigational medicinal product (bb1111) for treatment of SCD, which uses the same lentiviral vector as Zynteglo to transduce CD34+ cells.

Some of the characteristics of the patient's adverse event (time to onset, presence of lentiviral integration in AML blast cells) occurring after exposure to bb1111 raise concerns regarding a possible causal association between the lentiviral vector or other aspects related to the therapy and the event. In addition, two cases of myelodysplastic syndrome (MDS) after use of bb1111 also occurred in the same study.

On 11 March the PRAC adopted the below questions to the MAH.

2. Questions

The marketing authorisation holder (MAH) is requested to address the following questions:

Question 1

Clinical trial

Please provide a line listing of all serious adverse reactions from all clinical trials using the same lentiviral vector (LentiGlobin BB305 LVV/bb1111).

Post-marketing

Please provide patient details, treatment course, response to treatment, and current condition of the single patient treated in the post-marketing setting.

Please also provide results of cytogenetic investigations of this patient if available (in particular screening results for high-risk mutations).

Question 2

Please provide all available safety data relevant to evaluate the risk of AML and MDS with Zynteglo and products manufactured using the same or comparable viral vector (including bb1111), and an analysis of this data in each of their approved or studied indications, respectively . This should include:

a. Non-clinical and clinical trial data from both MAH sponsored and, if available, non-sponsored studies

b. Published literature

c. Case analysis with focus on all cases reporting clonal predominance and on cases reporting MDS, AML, or any other haematological malignancy. For all AML and MDS cases in-depth analysis of possible risk factors (including use of conditioning agent busulfan, mobilisation agent plerixafor and use of hydroxyurea prior or post treatment), patient history including previous treatment(s), family history, concomitant treatment (including growth factors post-treatment e.g. GCSF, TPO, EPO), time to onset (TTO) and treatment dose should be presented, separated by indication.

d. Detailed information on all cytogenetic or molecular diagnostic (mutations) work-up/investigations done in the last patient concerned following her diagnosis of AML including data about the insertion site of the LVV in the leukemic cells. For the two MDS patients cytogenetic diagnostics on possible mutations should be performed also, though no LVV integration has been identified so far.

Question 3

Please provide and discuss data and information on possible mechanisms, which may have potentially contributed to the development of haematological malignancy in the three cases concerned. This should include:

- Certificate of analysis of the drug product batch infused.
- Dose of cells received (total number and number of transduced cells).
- Data on VCN in the drug product and in the patient over time.
- Integration site analysis (ISA) in the drug product and in the patient over time.
- Integration analysis in AML/MDS blast cells, analysis of a possible relationship of the integration site with oncogenesis. Potential for interaction between vector integration and AML/MDS mutations/rearrangements should be discussed.
- Effect of ISA on gene expression profile (in particular for nearby genes, i.e. MYOC, EEF1AKNMT/METTL13 and DNM3). Quantification of mRNA levels of the gene at or in close proximity to the integration site. Are there any regulatory elements between exon 4 and 5 of VAMP4 close to the insertion site?
- Analysis of other causes of oncogenesis including the presence of somatic mutations and rearrangement associated with AML/MDS in the leukemic clone.
- Has the LVV integration seen in the case of AML, been found in other patients (understanding that ISA analysis is ongoing), the number of patients which this may concern and what the frequency of the integration over time has been in these patients?
- Can factors during the transduction process possibly promote a risk of leukaemia / MDS including incubation of CD34+ enriched cells with cytokines and growth factors?
- Differences in the properties of the drug substance and specifications of drug substance/drug product used in SCD (bb1111) compared to Beta thalassaemia (bb305).
- Differences in manufacturing process between drug products used in SCD (bb1111) and Beta thalassaemia (bb305).
- Results of release testing of drug substance /drug product batches, which all patients have received and any differences in the product which patients who developed AML, MDS, dysplastic changes in the bone marrow or any other bone marrow disorder received.
- To identify if some of the alterations found in the AML patient were pre-existing in the patient's bone marrow before infusion of the drug product.
- Information on bone marrow karyotype performed before treatment with bb1111 in the AML and MDS cases, on retention samples.
- Comparative analyses of the genetic findings in AML with pre-treatment genomic data (i.e. WGS on retained samples collected before exposure to bb1111).

Question 4

Please elaborate on the background incidence of haematologic malignancies in sickle cell disease and ß-thalassaemia populations and compare to the risk for haematologic malignancies of the same population following treatment with LentiGlobin drug product (Zynteglo or bb1111).

Please consider also ethnicity as a possible risk factor for development of leukaemic malignancy in your discussion since all affected patients have African-American origin (though confounded due to higher prevalence of SCD in this population).

Question 5

Please provide available information on the treatment and management of the patient with AML and the 2 patients with MDS after the use of bb1111 and the outcome of any treatments.

Question 6

Discuss the potential for insertional oncogenesis/mutagenesis in general and of products manufactured by bluebird bio with the same or comparable lentiviral vectors.

Question 7

Provide a full benefit-risk balance assessment of Zynteglo in the currently approved indication. This should include an assessment of the impact of occurrence of AML and MDS with products manufactured using the same viral vector on the benefit-risk balance of Zynteglo. Consider if/how the benefit-risk balance may differ in the approved age ranges or depending on concomitant treatment.

Question 8

Please provide proposals and justifications for any risk minimisation measures (including changes to the SmPC/PL) which may improve the benefit-risk balance of Zynteglo and how their effectiveness should be monitored.

Please elaborate if bone marrow karyotyping analyses performed before gene therapy could help in identifying patients at higher risk of developing leukemia/MDS.