Annex IV

Scientific conclusions

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On 18 February 2021, pursuant to Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, the European Commission requested the opinion of the Agency on whether the marketing authorisation of Zynteglo should be maintained, varied, suspended or revoked.

Four events concerning 2 cases of myelodysplastic syndrome (MDS) and 2 of acute myeloid leukaemia (AML) have been reported in a clinical trial where the drug product bb1111 was administered to patients with sickle cell disease (SCD). Out of the 2 MDS cases, one was not confirmed, and one patient progressed to AML later on as such, 3 events in 2 patients were further assessed.

Since bb1111 contains the same lentiviral vector as Zynteglo (betibeglogene autotemcel or beti-cel) any conclusions on the association between treatment with bb1111 and development of AML might have had implications for the B-R balance of Zynteglo. Zynteglo is approved for the treatment of transfusion dependent thalassaemia in patients > 12 years with non-ß0/ß0-genotype and no matched HSC donor available, whereas bb1111 for SCD is currently not authorised in any country.

The PRAC, in close collaboration with the experts from the Committee for Advanced Therapies (CAT), reviewed all data available regarding the development of acute myeloid leukaemia (AML) in sickle cell disease patients that occurred with the drug product bb1111 containing the same lentiviral vector also included in Zynteglo (betibeglogene autotemcel, or beti-cel), the quality of the bb1111 product administered to the AML/MDS cases, as well as quality, non-clinical and clinical / post-marketing data on Zynteglo.

Overall summary of the scientific evaluation by the PRAC

Sickle cell disease population substantially differs from the ß-thalassaemia population in terms of disease characteristics and symptoms, conservative treatment options and long-term complications.

Based on the data and investigations provided through this referral a causal association of the oncogenic event with integration at the integration site VAMP4 of the lentiviral vector (LVV) and the direct role of VAMP4 in the development of AML in one of the SCD cases is considered unlikely. Thorough investigation of possible alternative routes of integration site involvement in AML development have been ruled out as far this is possible based on current scientific knowledge and methods.

On the other hand, several risk factors related to the treatment procedure (myeloablative conditioning, HSCT) and drug product (low dose of hematopoietic stem and progenitor cells (HSPCs), relatively low vector copy number (VCN)) potentially translating into lack of clinical effect seen may all have contributed to proliferative stress on HSPCs which may have all contributed to development of AML in two reported cases in SCD patients.

In terms of the quality of the bb1111 product received by the AML patients, all release specifications were met.

Data from 63 subjects in 4 clinical development studies for Zynteglo (HGB-204, HGB-205, HGB-207 and 212) were assessed. The data reflect a well-tolerated treatment with mostly non-serious adverse reactions. Fifty SAEs were reported from 29 subjects, of which 13 occurred prior to drug product infusion and were attributed to study procedures, mobilization and apheresis. The remaining 37 SAEs were treatment-emergent and occurred in 22 subjects. There have been no events of splenic rupture in beti-cel-treated subjects (potential risk). One serious adverse event of Grade 3 Thrombocytopenia occurred, 16 events of thrombocytopenia were non-serious and assessed as possibly related or related. Most other events attributed as related or possibly related to drug product were consistent with side

effects of the DMSO cryo-preservative used in beti-cel. Delayed platelet engraftment is captured in the safety concerns as an identified risk for Zynteglo and is closely monitored following treatment. Besides one event of epistaxis, no other serious bleeding events occurred so far in context with thrombocytopenia in patients treated with beti-cel.

The only patient treated with Zynteglo in the post-marketing setting took a favourable course with neutrophil engraftment on Day 27. The patient is currently free of transfusion requirements. Blood count revealed Hb at 11.2g/dl and platelets are stable at 29.000 / µl on Day 61 (12-Apr-2021-no platelet engraftment, which is defined as sustained >20.000pts/ µl).

Integration site analyses (ISA) performed in all ß-thalassaemia subjects continued to be inconspicuous for clonal predominance and no malignancy (leukaemia/MDS/lymphoma or other) occurred within a maximum follow-up time of 71.8 months following treatment (data obtained from 2nd renewal assessment).

Overall, there is no evidence that the vector integration is involved in the development of the two AML events. Other risk factors related to Busulfan use for myeloablative conditioning, underlying disease, as well as poor treatment response might have contributed to the development of AML in two SCD cases. The risk factors that are directly related to the bb1111 drug product (low dose of HSPC, relatively low VCN, lack of clinical effect) are considered low for Zynteglo and unlikely to substantially contribute to an increased risk of AML reported for TDT patients. The risk factors related to the transplantation procedure itself were already considered in the benefit-risk assessment at the time of the initial conditional approval.

Both subjects who developed AML following treatment with bb1111 received drug product made from bone marrow harvest with a low cell dose with compared to the current doses used in the Zynteglo trials as well as in post-marketing setting (product made from peripheral mobilized cells obtained by apheresis). If it can be assumed that the degree of proliferative stress increases with decreasing transplanted cell dose, then due to the higher cell dose and higher percentage of long-term engrafting cells (CD34hi/+) received by patients treated with Zynteglo, a risk of additional proliferative stress on the bone marrow is considered to be lower than for the two SCD patients who developed AML.

Finally, for TDT patients, treatment with Zynteglo offers those patients, who in principal would be eligible for HSCT, but do not have a matched (-related) donor, a causative treatment option with expected life-long effect. Since Zynteglo is based on transduced autologous haematopoietic stem cells no life-long immune suppressive therapy is warranted, which is considered an additional advantage over conventional allo-HSCT treatment, in particular with respect to adolescent patients.

In view of patient follow-up, maintaining for longer a 6-month frequency of ISA for possible clonal predominance is implemented in the follow-up study LTF-303, given the interventional nature of the study. It is further proposed to strengthen the information on haematologic work-up in the SmPC by stating that this should occur at least annually, to allow for more frequent follow-up schedules.

Based on the information provided through this referral it can be concluded that:

- Vector insertion site VAMP4 does not seem to be associated with oncogenicity
- Post-treatment mutations detected in both patients who developed AML are most likely to be related to the myeloablative conditioning and to an underlying risk of haematological malignancy in patients with SCD
- The SCD population has an increased baseline risk for haematologic malignancies
- The SCD population substantially differs from the ß-thalassaemia (TDT) population in terms of characteristics and symptoms of the underlying disease, conservative treatment options and long-term complications

- The TDT population and the SCD population share the risk associated with the myeloablative treatment due to the same pre-conditioning requirements for Zynteglo as for bb1111. This risk was already considered during the conditional marketing authorisation (CMA) assessment of Zynteglo and is covered in the SmPC.
- Both subjects who developed AML following treatment with bb1111 received drug product made from bone marrow harvest with a low cell dose compared to the current doses used in the Zynteglo trials as well as in post-marketing setting (product made from peripheral mobilized cells obtained by apheresis). Due to the higher cell dose and higher percentage of long-term engrafting cells (CD34hi/+) received by patients treated with Zynteglo, a risk of additional proliferative stress on the bone marrow is considered to be lower than for the two SCD patients who developed AML.

Taking into consideration all of the data discussed above and that no case of haematological malignancy occurred in the clinical trial TDT-population with beti-cel over a follow-up time of 7 years, PRAC, in close collaboration with the experts from the CAT, concluded that the benefit-risk-balance for Zynteglo remains positive but recommended amendments to the product information and risk management plan to

- add that patients should also be monitored for myelodysplasia in addition to leukaemia or lymphoma,
- clarify that monitoring of patients should occur at least annually over the period of 15 years
- better inform patients on the risks of the myeloablative conditioning through the educational material
- reflect also that monitoring of patients should occur at least annually also in the registry study REG-501 and extend 6-monthly monitoring in the long-term follow up study LTF-303 up to 5 years, (thereafter monitoring will be carried out on an annual basis).

Grounds for PRAC recommendation

Whereas

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for Zynteglo.
- PRAC considered the totality of the data submitted during the referral, regarding the development of acute myeloid leukaemia (AML) in a clinical trial in two sickle cell disease patients treated with the investigational drug product bb1111 transduced with the same lentiviral vector as Zynteglo (betibeglogene autotemcel, or beti-cel), including the responses submitted by the marketing authorisation holder in writing. The PRAC also considered the views expressed by experts of the CAT.
- PRAC noted that based on the extensive review of available information on the integration site found in one of the reported cases of AML the VAMP4 gene is not known to be associated with oncogenicity, therefore a causal association of the oncogenic event with the integration of the lentiviral vector at the VAMP4 site is considered unlikely.
- PRAC also concluded that post-treatment mutations detected in a second AML patient treated with bb1111 in whom the leukaemic cells did not contain the lentiviral vector, are most likely to be related to the myeloablative conditioning. PRAC also considered based on the scientific knowledge about proliferative stress and its impact on patients that increased bone marrow

stress due to the low cell number administered and lack of clinical response may have contributed to the development of AML in the reported cases.

- Available non-clinical and quality data also did not point toward an increased tumorigenic risk through transduction of cells with the lentiviral vector used in Zynteglo and bb111.
- PRAC concluded that overall, there is no evidence that the vector integration is involved in the development of the AML events reported with the bb1111, and as such, the risk of AML associated with Zynteglo remains unchanged. As for other gene therapies, insertional oncogenesis remains an important potential risk also for Zynteglo and PRAC recommended that patients should be monitored at least annually also for myelodysplasia in addition to leukaemia or lymphoma (including a complete blood count). Amendments to strengthen the product information in this respect were recommended accordingly.
- PRAC also agreed on revised key messages for the educational materials to strengthen the information on the risks associated with myeloablative conditioning and further emphasize the periodic monitoring of patients for malignancies post treatment with Zynteglo. PRAC also recommended amendments to the risk management plan to reflect these measures and clarify the frequencies for integration site analysis in long-term follow-up studies.

In view of the above, the Committee considers that the benefit-risk balance Zynteglo remains favourable subject to the agreed conditions to the marketing authorisation and agreed amendments to the product information and other risk minimisation measures.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisation for Zynteglo

CAT draft opinion

Having reviewed the PRAC recommendation, the CAT agrees with the PRAC overall conclusions and grounds for recommendation.

CHMP opinion

Having reviewed the PRAC recommendation and the draft CHMP opinion prepared by the CAT, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.