Input from manufacturer on the 2nd draft assessment "ELIVALDOGENE AUTOTEMCEL (ELI-CEL) FOR TREATMENT OF CEREBRAL ADRENOLEUKODYSTROPHY (CALD)"

Project ID: PTJA17

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

The objective of this reviewer form is to standardise the process of the factual accuracy check of the rapid relative effectiveness assessments.

The 2nd version of the Rapid Assessment of Elivaldogene autotemcel (eli-cel) for the treatment of cerebral adrenoleukodystrophy (CALD) was open to review by the manufacturer bluebird bio between **02/08/2021 and 06/08/2021**.

Comments received from:

Market Authorisation Holder
bluebird bio

All received comments are formally responded in this combined document, to be published on the EUnetHTA website, name of organisation/institution (or individual names of the reviewers/affiliations) disclosed.

Page	Line	Comment	Character of comment[i]	Reply from author
Throughout		Company name is mentioned incorrectly on several occasions. The correct spelling is bluebird bio (without capital letters).	3	Done.
Page 11, Page 56, Page 64 respectively	Line 27 Line 1, Appendix 3-Table A1 respectively	Correction of text. The report states 'PAES-study REG-502... ' which is as such categorized in the RMP, but also as PASS. As condition to the license it is only categorized as PASS [ref. EPAR pg 25]. Therefore, bluebird bio requests for the study to be categorized as PASS and PAES in this report. Please note that PASS (Post Authorisation Safety Study) should also be added to the list of abbreviations on page 5.	2	Changed to post authorisation efficacy/safety study.
Page 7	Line 11	Correction of text. The report states: *'There is currently no treatment approved for CALD anywhere in the world ...'*. For clarification, elivaldogene autotemcel is authorised in the EU for the treatment of children under 18 years of age with early CALD. Text should be updated to read: 'There is currently one treatment approved for CALD; elivaldogene autotemcel is authorised in the EU for the treatment of children under 18 years of age with early CALD'.	2	Done.
Page 7	Line 21	*"Unfortunately, according to EBMT registry more than 70% of transplants for CALD involve unrelated donors"* This should read "more than 80%", according to the recent EBMT report referred to in the submission dossier and provided as pdf with the original submission (84% had no MSD) [ref 1].	2	Information is added.
Page 7	Line 25	*These data are expected from study ALD-102 (expected completion in May 2021),* ALD-102 completion date has occurred in March [not May]; final analysis and reporting remains ongoing.	3	We have extracted this date from the submission dossier. We have slightly changed the wording regarding completion date to *"according to submission dossier study completion was expected in May 2021"*.

Page	Line	Comment	Character of comment[i]	Reply from author
P10	Line 15	*All adverse events recorded in ALD-103 study were grade 3 or higher treatment-emergent AEs. Data for overall AEs and SAE related to Allo-HSCT treatment are not available* SAEs were collected in ALD-103 (see Table 4-3 of the PTJA17 assessment report v0.2). bluebird bio therefore requests to remove "SAEs" from this statement.	2	Thank you, we clarified this in the text and table accordingly.
Page 11 Page 56	Line 37 – 42 Line 13 – 18	*"Treatment can be given only at specialised care centres. Significant distance between the manufacturing site and treatment centres may influence the rate of successfully infused patients (and has impact on costs, especially as specific storage conditions are required). For further research it is important to gather data on reasons for non-infusion of the product, that may be both clinical (e.g. unsuccessful conditioning) and practical (e.g. various problems during manufacturing or transport) or other."* The conclusion that any distance between de manufacturing center and the treatment centers would impact the rate of infused patients seems to be a hypothetical statement, as there are no data available to support this statement. bluebird bio therefore requests removing this statement. Since costs are being mentioned, bluebird bio requests to mention other relevant aspects as well, e.g. having multiple manufacturing sites for eli-cel would increase production cost. Moreover, from the language used it seems like a limited number of specialized centers is only viewed negatively; however given the very low incidence rate of CALD it makes sense as it allows HCPs to get sufficient experience and expertise with eli-cel, even though patient numbers are this small.	1	The MAH was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check.
Page 11 Page 56	Line 29 – 30 Line 3 – 4	*"the comparison was accepted conditionally by the EMA"* elivaldogene autotemcel received full marketing authorization by	2	Conditionally is deleted.

Page	Line	Comment	Character of comment[i]	Reply from author
		16 July 2021. At time of dossier compilation for EUnetHTA, the EU MAA procedure was ongoing at D120. During D120 EMA raised questions to the applicant to further substantiate a full MAA to which the sponsor responded on 25 Feb 21. CAT and CHMP subsequently endorsed a positive opinion for FULL Marketing Authorization. The applicant therefore requests removal of term "conditional"		
Page 9	Line 27	*"230 x 106 cells/mL"* Hyphen is missing between "2" and "30" Text should be updated to: "2-30 x 10^6 cells/mL"	2	Thank you, changed.
Page 10 Page 49	Line 23 Line 18	*"5 out of 51 patients (9.8%) in TP-102/104 experienced AEs that were potentially related to eli-cel, 21 of which 3 (5.9%) were serious adverse events: BK-mediated viral cystitis (TP-102) and two cases 22 of pancytopenia (TP-103)."* Text "TP-103" should be changed to "TP-104". Two cases of pancytopenia were from TP-104.	2	Thank you, changed.
Page 46	Line 8	*Comment from "Met opmerkingen [HVM74]: @Bluebird Bio, could you provide us the CI?"* CI is (75.3, 100.0) [ref 2]	2	Thank you.
Page 46	Table 4.10	*Comment from "Met opmerkingen [HM75]: @Bluebird Bio, could you provide the CI?"* CI for Subjects who were GdE- at M24 for TPES is 13/13 (75.3, 100.0) and for TP is 24/24 (85.8, 100.0) [ref 2]	2	Thank you, is added.
Page 7	Line 39	Abbreviation 'MAH' is not defined in the text yet. Do we want to define it here? E.g., "Market Authorization Holder (MAH)	3	Thank you, MAH is defined here.
Page 38	Line 3	Missing data for Ethnicity for ALD-104, LTF-304 and ALD-101 study	2	Complete data were not provided.

[i] Character of comment
- 'major'=1
- 'minor'= 2
- 'linguistic'=3

References

1. bluebird bio Inc. EBMT Registry CALD allo-HSCT 2015-2020. *Data on file* (2021)
2. ALD-103 CSR table 14.2.3.1