



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Report for the Application Evaluation Decision

**A Phase 3 Randomized Study
Comparing Ramantamig Plus
Daratumumab Versus Investigator's
Choice of Daratumumab, Bortezomib,
Lenalidomide, and Dexamethasone
(DVRd) or Daratumumab,
Lenalidomide, and Dexamethasone
(DRd) in Participants With Newly
Diagnosed Multiple Myeloma for Whom
Hematopoietic Stem Cell Transplant is
Not Planned as Initial Therapy.**

2026-526654-14-01

Decision

MSC:

Italy

Decision:

Authorised with conditions

Decision date:

17/09/2026

Tacit decision:

No

Application Part:**Conditions:****Condition 1:**

As study is multicentric, the Sponsor is asked to mention in the protocol amendment which is expected number of centres. This counts with possibility that number of centres can change in future. The Sponsor is asked to provide the protocol amendment as soon as possible but not longer than 6 months from official date of this request.

Condition 2:

The Sponsor states in section 10.11. Sample Size Determination that "The 3-year PFS rate in this trial population for the control arm is estimated to be 76.9% and an HR of 0.65 translates to a 3-year PFS rate on ramantamig-D of 84.3%." and that "Based on a Weibull distribution, median PFS is estimated to be approximately 88 months on IC (DVRd or DRd) and 129 months on ramantamig-D.". If Weibull distribution (WD) is assumed for calculation of median time of progression-free survival (PFS) in individual treatment groups, then the Sponsor is asked to mention in the protocol amendment which are corresponding values of scale parameter (SCP) and corresponding values of shape parameter (SHP) for WD. Moreover, the Sponsor is asked to support by literature references in the protocol amendment which is basis for value of SCP and value of SHP for WD. Further, the Sponsor is asked to mention in the protocol amendment whether methodology based on WD with SCP and SHP is considered in sample size calculation or methodology based on exponential distribution is used. Calculation of median time of PFS in individual treatment groups based on WD needs to be provided. Lastly, full title of reference "(Leleu 2024)" from response document needs to be provided by the Sponsor as this cannot be found among references in response document. Similarly, the Sponsor states in section 10.11. Sample Size Determination that "Based on a Weibull distribution, the median OS is estimated to be approximately 134 months on IC (DVRd or DRd) and 181 months on ramantamig-D, corresponding to an HR of 0.71." and that "Under these assumptions, the 5-year OS rate in this trial population is estimated to be 74.6% on IC (DVRd or DRd) and 81.1% on ramantamig-D, and the target of 284 OS events will be reached 8.5 years from first FPR, with a median follow-up duration of 7.5 years.". If Weibull distribution (WD) is assumed for calculation of median time of overall survival (OS) in individual treatment groups, then the Sponsor is asked to mention in the protocol amendment which are corresponding values of scale parameter (SCP) and corresponding values of shape parameter (SHP) for WD.

Moreover, the Sponsor is asked to support by literature references in the protocol amendment which is basis for value of SCP and value of SHP for WD. Further, the Sponsor is asked to mention in the protocol amendment whether methodology based on WD with SCP and SHP is considered in sample size calculation or methodology based on exponential distribution is used. Lastly, calculation of median time of OS in individual treatment groups based on WD needs to be provided. The Sponsor is asked to provide the protocol amendment as soon as possible but not longer than 6 months from official date of this request.

Condition 3:

The Sponsor states in section 10.3. Analyses of Demographics and Other Baseline Variables that "Demographic variables will be summarized by intervention group. Specific details will be provided in the SAP.". The Sponsor is asked to briefly describe in the protocol amendment which are these demographic variables and how are summarized by intervention group. Moreover, the Sponsor states in section 10.5.4.1. Statistical Analysis Method that "PROs are defined in Section 8.3.5 and further details will be described in the SAP.". The Sponsor is asked to briefly describe in the protocol amendment statistical methods for patient-reported outcomes (PROs) analyses. Further, the Sponsor states in section 10.6. Analyses Associated with the Exploratory Objective(s) that "Analysis details for additional tertiary/exploratory and other endpoints, if any, will be described in the SAP.". The Sponsor is asked to briefly describe in the protocol amendment statistical methods for additional tertiary/exploratory and other endpoints analyses. Lastly, the Sponsor states in section 10.8.1. Subgroup Analyses that "In general, subgroup analyses on pre-specified subgroups will be performed for the dual primary efficacy endpoints of 12-month MRD-negative CR and PFS.". The Sponsor is asked to briefly describe in the protocol amendment statistical methods for subgroup analyses. The Sponsor is asked to provide the protocol amendment as soon as possible but not longer than 6 months from official date of this request.

Condition 4:

The Sponsor states in section 10.10. Multiplicity Adjustments that "The multiplicity strategy will be applied to the 2 primary superiority hypotheses (PFS and 12-month MRD-negative CR) and 2 key secondary superiority hypotheses (OS, 24-month sustained MRD-negative CR) and follows the graphical approach for group sequential designs of Maurer (2013), which provides strong control of Type I error at the 1-sided 0.025 level." and that "The details of the testing procedure will be specified in the SAP.". The Sponsor is asked to more elaborate details of testing procedure in the protocol amendment.

Condition 5:

The Sponsor mentioned in response to why statistical analysis for dual primary endpoint given by 12-month minimal residual disease (MRD)-negative complete response (CR) rate is based on odds ratio (OR) and not on absolute difference (AD) between CR rates where AR is used for sample size calculation (SSC). Reasoning was that "it allows for consistent comparison with studies in a similar population (...) and other ongoing studies with Ramantamig-Dara in other MM populations (...) that also report the odds ratio as summary measure from the CMH test". This can be acceptable but then SSC needs to be based on assumption for OR and not for AD. The Sponsor is asked to provide the protocol amendment which either 1) changes statistical method which leads to AD with respect to dual primary endpoint given by 12-month MRD-negative CR rate in order to be consistent with methodology for SSC for this dual primary endpoint which is based on AR, or 2) changes methodology for SSC with respect to dual primary endpoint given by 12-month MRD-negative CR rate which is based on OR and not on AD in order to be consistent with OR which results from statistical method used for this dual primary endpoint.

Reason:
Justification:
Disagreement with Part I
Submission date: