Annex

Scientific conclusions and grounds for refusal of the variation presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation

The MAH for Avastin applied for an extension of indication to include Avastin in combination with radiotherapy and temozolomide for the treatment of adult patients with newly diagnosed glioblastoma.

- **Efficacy issues**

The demonstration of efficacy was based on a randomized, double-blind, placebo controlled, multicenter phase III trial (study BO21990, "AVAglio") of bevacizumab, temozolomide and radiotherapy (concomitant phase) followed by bevacizumab and temozolomide (maintenance phase) followed by bevacizumab (monotherapy phase) versus placebo, temozolomide (TMZ) and radiotherapy followed by placebo and temozolomide followed by placebo in patients with newly diagnosed glioblastoma (GBM).

Bevacizumab was administered at a dose of 10 mg/kg every two weeks in the concurrent phase and the maintenance phase, and at a dose of 15 mg/kg every three weeks in the monotherapy phase. Radiotherapy and TMZ were administered in line with standard regimens used in the setting of newly diagnosed glioblastoma (Stupp *et al.*, 2005).

Overall survival (OS) and progression-free survival (PFS) as assessed by the investigator were co-primary endpoints of the trial. Disease progression was assessed using adapted Macdonald criteria (Chinot *et al.,* 2013). The primary analysis of PFS showed a statistically significant difference in favour of bevacizumab (HR 0.64, 95%CI 0.55-0.74; p<0.0001). The median PFS was estimated to be 10.6 months in the bevacizumab arm and 6.2 months in the placebo arm. The analysis OS showed no statistically significant difference in survival time between the bevacizumab arm and the placebo arm (HR 0.89, 95% CI 0.75-1.07, p=0.2135).

The main efficacy issue was about the clinical relevance of the radiological endpoint PFS in the absence of a clinically relevant effect on OS. Antiangiogenic agents, especially those targeting vascular endothelial growth factor (VEGF), such as bevacizumab, can produce marked decrease in contrast enhancement and commonly result in high radiologic response rates. These apparent responses are not always necessarily indicative of a true antiglioma effect. Although standard response assessment criteria have been further developed (RANO criteria) aiming to minimise this issue and inform treatment decisions, validation of these criteria as clinical benefit endpoints is still ongoing (Wen *et al.,* 2010). Due to these reasons, the clinical relevance of the observed difference in the primary analysis of PFS is unknown. This is in agreement with the conclusions of the Scientific Advisory Group (SAG) consulted. The SAG also commented on the long survival observed for numerous patients with early progression and concluded that this finding was counterintuitive and possibly a further indication of the lack of clinical meaningfulness of the PFS adjudication criteria used in the study.

The analysis OS showed no statistically significant difference in survival time between the bevacizumab arm and the placebo arm. Arguably, one-way cross-over after progression may hamper the detection of a difference in OS. However, there are no established methods of analysis that can remedy this after cross-over has occurred.

The analyses of the secondary endpoint health-related quality of life (HRQoL) did not show an advantage of addition of bevacizumab to standard treatment. An effect was claimed based on analysis of the secondary endpoint time to definitive deterioration in HRQoL. However, in this analysis, progressive disease (which suffers of the limitations described above) was included as a deterioration event. Furthermore, it was unclear to what extent HRQoL data collection could have been influenced by knowledge of the response status. Similar limitations apply to the determination of performance status.

Other endpoints including corticosteroid use, and sign and symptoms of GMB also need special consideration in light of the nature of the mechanism of bevacizumab. Changes in corticosteroid use, normally considered indicative for disease progression are confounded by the overlapping physiological effects of corticosteroids and bevacizumab.

The observed efficacy results in study BO21990 were overall consistent with the results reported from another trial investigating the effect of bevacizumab in glioblastoma (RTOG0825), i.e., no effect on OS, no benefit in terms of HRQoL, and possibly even a detriment in neurocognitive functioning (as suggested in study RTOG0825).

Overall the conclusion on the efficacy of bevacizumab in this setting was that the clinical relevance of the observed effect on PFS cannot be determined and that a relevant effect has not been established on the basis of any other clinical relevant endpoint. Thus, with the evidence provided, the efficacy of bevacizumab has not been convincingly demonstrated.

- **Safety issues**

The most frequent toxicity associated with the bevacizumab treatment group were gastrointestinal (nausea, constipation, vomiting), alopecia, fatigue, thrombocytopenia, headache and hypertension. No new safety signals with bevacizumab were observed in study BO21990, but there was a higher incidence of Grade 3 and 4 AEs, SAEs, non-progression deaths, and discontinuations of treatment in the bevacizumab group. Arterial thromboembolic events, mainly ischaemic strokes, were observed at a slightly higher incidence rate in this trial (5.0%) than in previous bevacizumab trials (up to 3.8% in combination with different chemotherapies), and higher than in the placebo group (1.6%). Overall, the toxicity of bevacizumab in this regimen and combination did not, in itself, raise major concerns. However, in the absence of established efficacy, the toxicity of this regiment cannot be considered acceptable.

Therefore, the CHMP concluded on 22 May 2014 that the benefit/risk ratio of bevacizumab in combination with radiotherapy and temozolomide for the treatment of adult patients with newly diagnosed glioblastoma was negative.

Following the CHMP scientific conclusions adopted in 22 May 2014 that Avastin was not approvable in combination with radiotherapy and temozolomide for the treatment of adult patients with newly diagnosed glioblastoma on the basis of the following grounds for the refusal of the Marketing Authorisation:

- The efficacy of bevacizumab in combination with radiotherapy and temozolomide for the treatment of adult patients with newly diagnosed glioblastoma has not been sufficiently demonstrated;
- In the absence of established efficacy, a positive benefit-risk balance has not been

established.

Following the above CHMP opinion, the applicant requested re-examination and submitted on 22 July 2014 its detailed grounds for the request for re-examination of the CHMP opinion recommending the refusal of the granting of the marketing authorisation.

The applicant presented his rationale in writing and at an oral explanation.

Summary of the applicant's response to the grounds for re-examination:

Study methodology including imaging and disease assessment criteria: The applicant considered that the pivotal study (Avaglio) was designed using standard methodology in GBM for the assessment of tumour growth and followed the current clinical practice. While the applicant acknowledged that there is an on-going evolution of the criteria used to assess disease progression in brain tumours, they contended that the criteria used in Avaglio study represent the most advanced and accepted technology in line with expert recommendations. Several strategies were applied prospectively in Avaglio in order to minimize the possibility of incorrectly interpreting the MRI scan including implementation of an algorithm for the determination of pseudo-progression.

Reliability of PFS: The applicant considered that the robustness and reliability of the primary analysis of PFS was confirmed in a number of predefined and post-hoc sensitivity analyses. Key post-hoc sensitivity analyses that took into account the concerns raised by the CHMP on the reliability of the imaging technique to detect disease progression excluded patients 1) with potential or confirmed pseudo-progression, 2) with possible pseudo-progression in the PI+RT/T arm and possible pseudo-response in the Bv+RT/T arm and 3) with PFS < Day 93 to avoid any potential impact of pseudo-progression and post-radiation imaging changes at the first disease assessment. The applicant provided an additional post-hoc PFS analysis where all progressions exclusively based on non-index lesions were not regarded as a PFS event.

Finally, the applicant provided a *post-hoc* analysis in line with the RANO criteria (Wen *et al.,* 2010), which are the current standard used in clinical trials. According to this analysis, 84% of the PFS events could be considered unequivocal.

Clinical relevance of PFS: The applicant considered that Avaglio study used a variety of validated and reliable measures to assess the clinical status that captured the patient's perspective (health-related quality of life [HRQOL]), neurocognitive function (Mini Mental Status Examination [MMSE]), and functional status (Karnofsky Performance Status [KPS]). According to the applicant, the KPS results showed a delay in time to definitive deterioration in KPS in favour of bevacizumab irrespective of whether PD was included (pre-specified) or excluded (exploratory) as an event. At the time of disease progression, the data indicated a trend for deterioration in functional status and HRQoL compared to the assessments prior to progression, which underscores the clinical importance for the patients of delaying the time until disease progression. While the Applicant acknowledged that limited data was captured beyond the time of progression, they contended that this does not diminish the value of the data captured on study.

Absence of OS benefit: According to the applicant, the use of subsequent lines of therapy, that often included bevacizumab, may have confounded the result. The applicant concluded that

despite the obvious flaws and biases of the exploratory survival analyses these analyses indicated a beneficial effect of bevacizumab.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant.

Regarding the MRI evaluation of disease progression, the CHMP maintained the view that the impact of the use of adapted criteria in Study BO21990 remains unclear. The number of PD events may have been overestimated in the placebo arm and underestimated in the bevacizumab arm. The applicant did not convincingly show that the sensitivity analyses performed were able to mitigate the risk of systematic biases in the evaluation of PFS and were adequate to provide sufficient reassurance that bevacizumab produces a PFS increase of clinically important magnitude. In particular, the applicant did not clearly justify how the criteria chosen to exclude specific patients or events in the various sensitivity analyses were able to address the biases/uncertainties around the assessment of progression.

The results of the *post hoc* analysis according to the RANO criteria were not considered sufficiently robust to resolve the uncertainties around the PFS results. This analysis resulted in an estimated benefit of smaller magnitude, based on an analysis that, necessarily but problematically, introduces some informative censoring. All the additional analyses cannot exclude the possibility of important bias and the estimated effect is not regarded as sufficiently reliable to conclude that a clinically relevant therapeutic efficacy has been established.

Thus, the CHMP maintained the view that it was not possible to estimate with sufficient confidence the magnitude of the gain in tumour control provided by bevacizumab when added to standard of care.

Regarding clinical outcomes, the applicant proposed that only maintenance of QoL to the time of disease progression may be expected, and this can be accepted. However, the CHMP concluded that the positive effects claimed by the applicant are mainly driven by the inclusion of PD as an event in these analyses, and therefore, they cannot provide independent support or insight into the clinical benefits of delaying progression. Nominally, statistically significant results were retained for some parameters when PD was not counted as a deterioration event. These analyses should be interpreted with caution since relevant data were not collected systematically after disease progression and the consequent impact of (potentially informative) censoring on the results is unclear. In addition, some assessments may have been influenced by knowledge of progression status.

Concerning overall survival, the CHMP acknowledged that no OS benefit had been observed in Study BO21990, a finding consistent with the result of the RTOG 0825 trial. It has not been established that the most likely cause for the failure to demonstrate an OS benefit is confounded by post-progression treatments (including crossover to bevacizumab) rather than lack of an effect.

In conclusion, as the clinical relevance of the efficacy results is uncertain, and the benefit-risk balance of bevacizumab as an add-on therapy to standard of care for newly diagnosed glioblastoma is considered negative.

Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore maintains its recommendation for the refusal of the variation of the Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

- The efficacy of bevacizumab in combination with radiotherapy and temozolomide for the treatment of adult patients with newly diagnosed glioblastoma has not been sufficiently demonstrated;
- In the absence of established efficacy, a positive benefit-risk balance has not been established.

Therefore, the CHMP has recommended the refusal of the variation of the marketing authorisation for Avastin in the treatment of adult patients with newly diagnosed glioblastoma in combination with radiotherapy and temozolomide.