Annex I

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

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Overall summary of the scientific evaluation of Human IgG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech

Human IgG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech (MABp1) is a recombinant human IgG1 monoclonal antibody specific for human interleukin-1α (IL-1α). The aim of therapy with MABp1 in this application is to achieve reversal of tumour-related symptoms in terms of improvement or stabilisation of lean body mass (LBM), as well as improvement or stabilisation of quality of life (QoL) in patients with advanced colorectal cancer (CRC).

The MAA is based on one pivotal study (2014-PT026) which was a randomised, double-blind, placebo-controlled multi-centre study in advanced CRC patients (n=309, mITT) with ECOG status 1 or 2, who were refractory to two lines of standard of care therapies and also exhibited symptomatic disease. The primary efficacy endpoint was clinical response rate (CRR), a composite endpoint, which assessed change in LBM (based on dual energy X-ray absorptiometry scans) and change in QoL in terms of fatigue, pain, and appetite (based on EORTC QLQ-C30 Questionnaire) from baseline to Week 8. In order to be considered a responder, patients had to show: (i) stabilisation or improvement of LBM and (ii) improvement or no worsening on 2 of 3 QoL-symptoms.

- Quality issues

This application is not acceptable from a quality point of view due to concerns on the control of the active substance and finished product. A control strategy that would ensure consistent manufacture of a product with characteristics that are equivalent to the product used in pivotal clinical studies has not been provided.

- Efficacy issues

The primary efficacy analysis based on the composite endpoint of CRR demonstrated a statistically significant difference between the MABp1 and placebo arms (33% vs 19%, respectively; $p<0.01$). However, the analysis of the individual components of the composite endpoint did not demonstrate any clinically meaningful differences between the study arms, and hence it is not possible to ascertain how individual components might have contributed to the efficacy of MABp1. Whereas the only objective measure “change in LBM” resulted in no differences between the arms, i.e. mean LBM change was comparable for placebo-treated and MABp1-treated patients, 0.60±0.32 kg vs 0.53±0.22 kg, respectively ($p=0.87$). Also, the other individual component of the composite endpoint based on patient reported outcomes (i.e. change in the mean EORTC scores for pain, fatigue and appetite scales) showed no clinically or statistically significant changes from baseline and no differences between the arms. Therefore, there is lack of a clear evidence in support of beneficial effects of MABp1 on both components of the composite endpoint, and hence efficacy cannot be established based on the primary analysis.

Despite the fact that the composite endpoint measures clinically relevant disease aspects, patients were considered as having met the efficacy outcome although they might potentially have had a worsening in any one of the 3 QoL symptoms of pain, appetite or fatigue, according to the definition of the primary composite endpoint and the primary analysis. This in itself is considered contradictory from an efficacy point of view. Furthermore, in the absence of positive treatment effects on the components of the composite endpoint when analysed separately, the fact that there is a higher proportion of patients having met a favourable efficacy outcome (‘responders’) to treatment with MABp1 as measured by the composite endpoint gives rise to the question whether some patients could be detrimentally affected by treatment. However, the possibility of detrimental effects of the treatment has not been fully investigated and cannot be excluded. The lack of information on potential

detrimental effects hampers inherently the overall assessment of benefit/risk.

Although any degree of prior weight loss within last 6 months was a part of the main inclusion criteria as an evidence of metabolic dysregulation, no data were collected on the degree of patients' prior weight loss at baseline. Therefore, distribution of patients with different degrees of weight loss at baseline to the study arms remains unknown. In addition, ~33% of all patients were probably enrolled only based on IL-6 threshold of >10 pg/ml, which is not an acknowledged biomarker of metabolic dysregulation. Due to the above-mentioned shortcomings and uncertainties, it is difficult to evaluate the clinical relevance of the observed modest difference in the CRR (i.e. 14% in favour of MABp1) as the magnitude of any potential benefit cannot be put into context appropriately.

Regarding secondary endpoint analyses for change in IL-6 level or platelet count from baseline, the clinical relevance of the observed changes from baseline or any potential clinical benefit for the MABp1-treated patients remain unclear. The reliability of reported IL-6 levels is questionable as handling of outliers was not predefined and the outcome changed significantly when analysing with or without the outliers. Moreover, the mean IL-6 levels (excluding the outliers) were still >10 pg/ml in both arms at Week 8, indicating no clinically significant changes from baseline in the inflammation status. Mean platelet counts at baseline vs Week 8 were within normal range and comparable between the arms. Notably, the analysis of functional and global QoL scales of EORTC QLQ-C30 Questionnaire showed neither statistically significant nor clinically relevant changes from baseline in MABp1-treated patients compared to the placebo patients. Consequently, secondary analyses do not provide any additional evidence in support of efficacy.

- Safety issues

The safety database is currently limited, regarding both total number of patients treated and duration of treatment. The observed imbalance of infections (12.1% MABp1 vs 8.8% placebo) and severe infections (3% MABp1 vs 1% placebo) in disfavour of the MABp1 arm in the pivotal study is of concern, particularly in light of the claimed indication. In a palliative care setting for treatment of a frail and heavily pre-treated patient population, these risks are not considered acceptable, especially when potential risks cannot be outweighed by the questionable efficacy.

Based on the above-mentioned efficacy and safety concerns, the benefit/risk balance of MABp1 is considered negative.

Grounds for refusal

- A control strategy that would ensure consistent manufacture of a product with characteristics that are equivalent to the product used in pivotal clinical studies has not been provided.
- Robust evidence of therapeutic efficacy is insufficiently substantiated.
  - The robustness and meaningfulness of the observed differences of MABp1 compared to placebo in terms of the primary composite, clinical response rate (CRR), is questioned in the absence of positive treatment effects on symptoms and lean body mass separately. It is difficult to evaluate the clinical relevance of the observed potential efficacy in a sufficient context due to the lack of important baseline data regarding the degree of patients' prior weight loss as well as inclusion of substantial number of patients only based on the IL-6 threshold.
  - In the absence of positive treatment effects on the components of the composite endpoint when analysed separately, the fact that there are more patients having met a favourable efficacy outcome ('responders') to treatment with MABp1 as measured by the composite endpoint gives rise to the question whether some patients could be detrimentally affected by treatment.

However, the possibility of detrimental effects of the treatment has not been fully investigated and cannot be excluded.

  - Secondary endpoint analyses did not provide any additional evidence of clinically relevant efficacy. Importantly, there were no statistically significant or clinically relevant changes from baseline in the functional and global QoL scales based on EORTC QLQ-C30 assessments in MABp1-treated patients compared to the placebo patients.

- The observed increased risk of infections, including serious infections, is of concern in the context of the claimed indication. These risks, based on small numbers from a limited safety database, are not acceptable in a palliative care setting for treatment of a vulnerable and heavily pre-treated patient population, as these are not outweighed by the observed potential beneficial effects.

The CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the quality, safety, efficacy of the above mentioned medicinal product is not properly or sufficiently demonstrated.

Therefore, the CHMP has recommended the refusal of the granting of the marketing authorisation for Human IgG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech.

On 18 July 2017, the Applicant submitted its detailed grounds for the request for re-examination of the CHMP opinion recommending the refusal of the granting of the marketing authorisation.

Summary of the Applicant's grounds for re-examination:

The Applicant requested a re-examination of the CHMP's opinion on Human IgG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech, to re-assess the benefit/risk in the the control or relief of debilitating symptoms associated with advanced colorectal cancer. The Applicant submitted observations to the CHMP's concerns regarding quality, efficacy and safety.

The CHMP assessed the detailed grounds for re-examination and argumentation presented by the Applicant in writing and in an oral explanation on 12 September 2017 and agreed by consensus the following grounds for refusal.

Grounds for refusal

The CHMP considers that:

- A control strategy that would ensure consistent manufacture of a product with characteristics that are equivalent to the product used in pivotal clinical studies has not yet been provided.
- Robust evidence of therapeutic efficacy is insufficiently substantiated.
  - The robustness and meaningfulness of the observed differences of MABp1 compared to placebo in terms of the primary composite, clinical response rate (CRR), is questioned in the absence of positive treatment effects on symptoms and lean body mass separately. It is not possible to fully evaluate the clinical relevance of the observed potential efficacy in a sufficient context due to the lack of important baseline data regarding the degree of patients' prior weight loss as well as inclusion of substantial number of patients only based on the IL-6 threshold.
  - In the absence of positive treatment effects on the components of the composite endpoint when analysed separately, the fact that there are more patients having met a favourable efficacy outcome ('responders') to treatment with MABp1 as measured by the composite endpoint gives rise to the question whether some patients could be detrimentally affected by treatment. However, the possibility of detrimental effects of the treatment has not been fully investigated and cannot be excluded.

- Secondary endpoint analyses did not provide any additional evidence of clinically relevant efficacy. Importantly, there were no statistically significant or clinically relevant changes from baseline in the functional and global QoL scales based on EORTC QLQ-C30 assessments in MABp1-treated patients compared to the placebo patients.

The CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the quality and efficacy of the above mentioned medicinal product are not properly or sufficiently demonstrated.

Therefore, the CHMP has recommended the refusal of the granting of the marketing authorisation for Human IgG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech.