Annex I

Scientific conclusions

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Adakveo was granted a conditional marketing authorisation (CMA) under Article 14-a of Regulation (EC) No. 726/2004, valid throughout the European Union (EU), on 28 October 2020. The authorisation based on primary analysis results of median annual rate of VOC leading to a healthcare visit of the pivotal phase II randomized, placebo-controlled, double-blind, 12-month study (Study A2201, SUSTAIN) assessing safety and efficacy of crizanlizumab with or without hydroxyurea therapy in sickle cell disease (SCD) patients with sickle cell-related pain crises. In order to confirm the efficacy and safety of Adakveo, the marketing authorisation holder was required to submit as a specific obligation (SOB) the results of the primary analysis of a phase III study (Study A2301, STAND).

In December 2022, the first interpretable results of the STAND study were communicated by the marketing authorisation holder (MAH) to the European Medicines Agency (EMA). The results showed that neither the primary nor the key secondary endpoint (i.e. annualized rates of vaso-occlusive crises [VOCs] leading to healthcare visit, or leading to healthcare visit, and treated at home combined) with crizanlizumab were met. These preliminary results of the STAND study showing a potential lack of efficacy raised uncertainty as to whether the benefit of crizanlizumab still outweighed its risks in its authorised indication.

On 26 January 2023, pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the opinion of the Agency on whether the marketing authorisation of Adakveo should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation

The STAND study was a phase III, multicentre, randomized, double-blind study to assess efficacy and safety of the two doses of crizanlizumab (5.0 mg/kg and 7.5 mg/kg) versus placebo in adolescents and adults with SCD and a history of VOC leading to healthcare visit. It was designed to confirm the efficacy and safety of Adakveo, previously characterised in the phase II study SUSTAIN, the main study supporting the conditional authorisation of Adakveo in the EU.

Overall, based on the provided study results, the STAND study failed to show an effect of crizanlizumab over placebo in the primary and key efficacy secondary endpoint. The study did not demonstrate superiority of crizanlizumab over placebo on its primary endpoint: the rate ratio of adjusted annualized VOC incidences leading to healthcare visit of the crizanlizumab 5 mg/kg arm vs. placebo arm was 1.08, 95% CI (0.76, 1.55), adjusted p-value> 0.999. There were no observable differences across arms in annualized rate of VOC leading to health care visit or mean rate of VOC leading to health care visit. The subgroup analyses by age (adolescents and adults) showed results similar to the overall population for the primary endpoint. The analysis of the key secondary endpoint (annualized rate of all VOCs managed at home and leading to healthcare visit) presented similar results as for the primary endpoint: the rate ratio of adjusted annualized VOC incidences managed at home and leading to healthcare visit of the crizanlizumab 5 mg/kg arm vs. placebo arm was 1.21 (placebo as a reference group), 95% CI (0.87, 1.70). A reduction in the free soluble P-selectin biomarker was observed, consistent with the postulated mode of action of crizanlizumab. However, this exploratory result was not followed by a clinical relevant effect as shown with the primary and key secondary results.

The overall safety profile of crizanlizumab in the STAND study was consistent with the known safety profile of crizanlizumab from previous studies. When comparing to the SUSTAIN study, however, the differences in the rates of grade ≥3 adverse events (AEs) (56.0% of patients in the crizanlizumab 5 mg/kg arm compared with 31.8% in the placebo arm) and serious adverse events (SAEs) (41.7% of patients in the crizanlizumab 5 mg/kg arm compared with 30.6% in the placebo arm) in the crizanlizumab group compared to the placebo group were more pronounced.

Concerning the STAND study, the CHMP considered that the study was adequately designed, conducted in the same target patient population and using the same efficacy endpoints as the phase II study SUSTAIN. Differences between the studies were hypothesized as contributing to the discrepant results between the two studies, including regarding study period vis-a-vis the COVID-19 pandemic, geographic location and study population. The CHMP acknowledged that the COVID-19 pandemic and respective lockdown and safety measures could have led to a reduction in VOCs in general due to a decrease in outside triggers and further to a reduction in healthcare visits due to fear of infection, potentially affecting the primary endpoint of the STAND trial. Nevertheless, this should have affected placebo and treatment arms equally, contrary to what is shown with the study results. Additionally, potential VOCs not treated via healthcare visits would have been treated at home, which would have been reflected in the key secondary endpoint results. This was also not observed. The other differences in the study populations are also not considered to have impacted the results. Overall, CHMP considered that none of the factors discussed above could explain the discrepant results between the studies, nor question the validity of the results of the STAND study. Lastly, the STAND study data presented by the MAH was considered sufficient to comprehensively evaluate the study results. The results of the primary and key secondary endpoint, as well as of the safety analysis were provided. The CHMP also considered that any additional analyses to be provided within a future final report would not change the observed results, specifically on the efficacy endpoints, and hence would not change the overall conclusions.

Additional data from single-arm or uncontrolled trials, including data from the other study defined as SOB, (study A2202), as well as real world data were presented. Favourable effects of crizanlizumab were observed in these studies. However, all of the studies presented were single–arm or uncontrolled, open-label with a limited number of subjects and presented efficacy data as change from baseline of event rates, consequently the results could suffer from many forms of biases. In addition to these uncertainties, the studies were performed during the COVID-19 pandemic, which is acknowledged to have a potential impact on the related efficacy parameters. Consequently, the reported results from these trials cannot be attributed to a treatment effect alone. Since all observed effects in these studies are rather modest, a relevant treatment effect of crizanlizumab cannot be assumed. As conclusion, the additional data derived from these studies are not considered robust enough to alleviate the concerns regarding a lack of efficacy of crizanlizumab raised by the STAND study results.

The MAH proposed to restrict the indication to patients who are currently responding to the treatment, possibly with 6-monthly reassessment of treatment response. However, no definition of treatment response was proposed. Based on the available data, no patient population could be identified by the CHMP for whom the benefit risk balance of Adakveo would be positive.

Overall, the results of the phase III STAND study are considered adequately mature and robust to draw the conclusion that Adakveo lacks therapeutic efficacy in its authorised indication. Additionally, any safety concerns associated with crizanlizumab render the benefit-risk balance of Adakveo negative in view of the lack of therapeutic efficacy observed in the study.

Whilst it is understood from the MAH that another phase III study aiming to provide further data on the safety and efficacy of crizanlizumab may be performed in the future, this has no bearing on the conclusion based on the data available at present.

Consequently, taking into account the totality of the data including the results of the STAND study imposed as a specific obligation, the conditional marketing authorisation for Adakveo should be revoked.

CHMP opinion

Whereas,

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Adakveo.
- The Committee reviewed the results of the STAND (A2301) study, in the context of all available data. This included the responses submitted by the marketing authorisation holder (MAH) in writing and during an oral explanation where representatives of HCPs and patients also expressed their views.
- The STAND (A2301) study was conducted to fulfil the specific obligation with a view to confirming a favourable benefit-risk balance for the conditional marketing authorisation for Adakveo, pursuant to Article 14-a of Regulation (EC) No 726/2004.
- The Committee noted that no benefit was observed from treatment with Adakveo in sickle cell disease (SCD) patients aged 16 years and older.
- The Committee, as a consequence, concluded that Adakveo lacks therapeutic efficacy and that the benefit-risk balance of Adakveo is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the revocation of the marketing authorisations for Adakveo.