EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 May 2023
EMA/267688/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004

Invented name: Adakveo

INN/active substance: crizanlizumab

Procedure number: EMEA/H/A-20/1525/C/4874/0013

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Information on the procedure

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. In order to confirm the efficacy and safety of Adakveo, the marketing authorisation holder (MAH) 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 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 the European Commission (EC) therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and requested the Committee for Medicinal Products for Human Use (CHMP) to assess the impact of the above concerns on the benefit-risk balance of Adakveo and to issue a recommendation on whether the relevant marketing authorisation should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Adakveo contains crizanlizumab (ATC code: B06AX01), a selective IgG2 kappa humanised monoclonal antibody (mAb) that binds to P-selectin with high affinity and blocks the interaction with its ligands, including P-selectin glycoprotein ligand 1 (PSGL-1). It is a centrally authorised product indicated for the prevention of recurrent VOCs in sickle cell disease (SCD) patients aged 16 years and older. It can be given as an add-on therapy to hydroxyurea/hydroxycarbamide (HU/HC) or as monotherapy in patients for whom HU/HC is inappropriate or inadequate. The recommended dose of crizanlizumab is 5 mg/kg administered over a period of 30 minutes by intravenous (IV) infusion at week 0, week 2, and every 4 weeks thereafter.

In patients with SCD, haemoglobin is altered causing deformation of erythrocytes and subsequent vaso-occlusive events and chronic haemolytic anaemia. The main manifestations of SCD include painful crises including chest, back and joints, organ damage and varying degrees of anaemia and related symptoms. In the chronic pro-inflammatory state associated with SCD, P-selectin is over-expressed. P-selectin is an adhesion molecule expressed on activated vascular endothelial cells and platelets and is a key molecule involved in the initiation of leukocyte extravasation to underlying tissues during inflammation. The binding to P-selectin is postulated to inhibit the P-selectin mediated cellular adhesive interactions that are a key factor in the pathogenesis of VOCs.

Adakveo was granted a CMA under Article 14-a of Regulation (EC) No 726/2004, valid throughout the EU, on 28 October 2020, based on primary analysis results of the phase II study (Study A2201, SUSTAIN). This was a phase II multicentre, randomized, placebo-controlled, double-blind, 12-month study to assess safety and efficacy of crizanlizumab with or without HU therapy in SCD patients with sickle cell-related pain crises. Patients with any SCD genotype (including HbSS, HbSC, HbSß0 thalassaemia and HbSß+ thalassaemia) and a history of 2-10 VOCs in the previous year were randomised in a 1:1:1 ratio to 5 mg/kg crizanlizumab, 2.5 mg/kg crizanlizumab or placebo.

Randomisation was stratified by HU use (yes, no) and the number of VOCs in the year preceding study start (2-4 or 5-10). The study consisted of a 30-day screening period, a 52-week treatment period and a follow-up evaluation phase for a maximum total duration of 58 weeks. The primary endpoint was the annual rate of sickle cell related pain crises (SCPC). The key secondary efficacy endpoint was the annual rate of days hospitalised. For consistency reasons, all crisis events identified by investigators were independently adjudicated by a central review committee (CRC) comprised of 3 independent haematologists to determine whether reported sickle cell crisis meet the criteria for the primary efficacy outcome.

In the original primary analysis of the SUSTAIN study, 5 mg/kg crizanlizumab treatment led to a 45% reduction of the annual rate of sickle cell related pain crises (CRC-adjudicated), considering the ratio of the standard median of 1.63 VOCs in 5 mg/kg crizanlizumab group (N=67) and 2.98 VOCs in the placebo group (N=65). The point estimate of the two-sample Hodges-Lehmann (HL) median annual rate of SCPC estimator was -1.01 (95% confidence interval (CI) [-2.00, 0.00], p=0.010). Some uncertainties were identified regarding the statistical methodology and the imputation methods. Following a GCP inspection, evaluation of the treatment effect of crizanlizumab based primarily on the CRC-adjudicated data was not considered sufficiently robust. As data collected at the study sites were considered credible, analyses using the investigator-based VOC rate were acceptable. Supplementary analyses taking into account the issues regarding statistical methodology and crisis adjudication showed a beneficial effect on the risk of SCPC occurrence in the 5 mg/kg crizanlizumab compared to placebo. The use of investigator reported VOCs instead of CRC-adjudicated VOCs affected the results only marginally. Under the most conservative imputation method, statistical significance could no longer be reached. However, all treatment effect estimates for the primary and secondary endpoints were systematically in favour of crizanlizumab and the observed favourable trends for the 5 mg/kg crizanlizumab dose were of a magnitude that was considered clinically relevant for SCD patients: a 26% reduction in VOC rate, a 28% reduction of the predicted number of days hospitalised due to VOC and an OR of 3 for patients being VOC-free during one year compared with placebo. From a safety perspective, only few concerns were identified in the SUSTAIN study and the majority of frequently observed safety signals were considered manageable.

Given the limited treatment options, a high unmet medical need in SCD patients, the debilitating nature of the disease, and despite the fact that the data package was not yet comprehensive, it was concluded that immediate availability of the drug would outweigh the risks inherent in the fact that additional data were still required. In summary, the benefit-risk balance of Adakveo was considered favourable for the prevention of recurrent VOCs in SCD patients aged 16 years and older based on the available evidence at that time and subject to additional confirmatory efficacy and safety data to be generated in the context of a CMA. In order to generate comprehensive data with Adakveo, the MAH was requested to submit the results of two studies by December 2025, as SOBs:

1. The results of the primary analysis of the phase III CSEG101A2301 study (study A2301, STAND) of crizanlizumab with or without HU/HC in adolescent and adult SCD patients with vaso-occlusive crises.
2. The final results of the phase II CSEG101A2202 study (study A2202) of crizanlizumab with or without hydroxyurea/hydroxycarbamide in SCD patients with vaso-occlusive crisis.

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

The EC thus triggered the present review in order for the CHMP to assess the above-mentioned concerns, and their impact on the benefit-risk balance of Adakveo.

The CHMP considered all available data, including clinical data (STAND study [**Error! Reference source not found.**], study A2202, and other clinical studies) and real-world data submitted by the MAH, as well as the views from patients and healthcare professionals (HCPs) representatives who attended the oral explanation by the MAH to CHMP. A summary of the most relevant information is included below.

Table 1. Overview of key data submitted (STAND study)

Study ID and design / reference	**Key objectives / endpoints**	**Population**	**Inclusion/ exclusion criteria**	**Treatment**	**Main results**
Therapeutic indication: *prevention of recurrent vaso-occlusive crises (VOCs) in sickle cell disease patients aged 16 years and older. It can be given as an add-on therapy to hydroxyurea/hydroxycarbamide (HU/HC) or as monotherapy in patients for whom HU/HC is inappropriate or inadequate*					
A phase III, multicenter, randomized, double-blind study to assess efficacy and safety of two doses of crizanlizumab versus placebo, with or without hydroxyurea/ hydroxycarbamide therapy, in adolescent and adult sickle cell disease patients with vaso-occlusive crises (STAND) Study identifiers: CSEG101A2301; A2301; STAND.	Primary endpoint: annualized rate of VOC events leading to a healthcare visit over the first year post randomization. Key secondary endpoint: annualized rate of all VOCs leading to healthcare visit and treated at home (based on documentation by health care provider following contact with participant) over the first-year post randomization.	Planned: 240 participants. Randomized: 252, 85 in placebo arm, 84 in crizanlizumab 5 mg/kg arm and 83 in crizanlizumab 7.5 mg/kg arm.	Main criteria for inclusion: SCD participants aged 12 years and older who had experienced at least 2 VOCs leading to a healthcare visit in the 12 months prior to screening visit, and who were not planning to initiate HU/HC or L-glutamine (local HA approved medicinal product) during the first year of investigational treatment. Diagnosis of SCD had to be confirmed by Hb electrophoresis or high performance liquid	Investigational arms: Crizanlizumab at 5.0 mg/kg Crizanlizumab at 7.5 mg/kg Placebo Dosage: 5 mg/kg or 7.5 mg/kg crizanlizumab or 0.5mL/kg (no active substance) placebo on Week 1 Day 1, Week 3 Day 1, and Day 1 of every 4-week cycle	Primary results: Mean (SD) annualized rates of VOC leading to health care visit (placebo, crizanlizumab 5 mg/kg and 7.5 mg/kg, respectively): 2.1 (2.81), 2.5 (2.98), 1.9 (2.30) Rate ratio (crizanlizumab 5.0 mg/kg): 1.08 (over placebo), 95% CI: (0.76, 1.55), adjusted p-value > 0.999 Rate ratio (crizanlizumab 7.5 mg/kg): 0.89 (over placebo), 95% CI: (0.62, 1.27), adjusted

			chromatography (HPLC) (performed locally). All SCD genotypes were eligible, genotyping was not required for study entry. Participants who were taking HU/HC or L-glutamine for at least 6 months at a stable dose for at least 3 months and planned to continue taking at the same dose and schedule until they had reached 1 year of investigational treatment were permitted.		p-value > 0.999 <u>Secondary results:</u> Annualized rates of VOC leading to health care visit (placebo, crizanlizumab 5 mg/kg and 7.5 mg/kg, respectively): 3.87, 4.70, 3.22 Rate ratio (crizanlizumab 5.0 mg/kg): 1,21, 95% CI: (0.87, 1.70) Rate ratio (crizanlizumab 7.5 mg/kg): 0.83, 95% CI: (0.59, 1.17)

2.2. Data on efficacy

2.2.1. STAND study

Study design and methodology

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, the latter being an unauthorized dose in the EU) versus placebo in adolescents and adults with SCD and a history of VOC leading to healthcare visit. The study included participants aged 12 years and older with confirmed diagnosis of SCD (any genotype) who had experienced at least 2 VOCs leading to healthcare visit in the 12 months prior to screening visit. Participants may had received HU/HC and/or L-glutamine as a standard of care at the time of enrolment. A total of 240 participants (including 48 adolescents) were planned to be randomized in a 1:1:1 ratio to either 5 mg/kg, 7.5 mg/kg of crizanlizumab or placebo. Randomized participants were stratified by concomitant HU/HC usage (yes/no) and baseline rate of VOCs leading to a healthcare visit in 12 months prior to screening visit (2-4 vs. ≥ 5 VOCs) at the time of enrolment.

Study endpoints

The primary endpoint was the annualized rate of VOC events leading to a healthcare visit over the first year post randomization. VOCs were reviewed and confirmed by an Adjudication Committee (AC) comprised of independent haematologists. The key secondary endpoint was the annualized rate of all VOCs leading to healthcare visit and treated at home over the first-year post randomization. The other secondary endpoints were: duration of VOCs leading to healthcare visit; number and percentage of subjects free from VOCs leading to healthcare visit; time to first and second VOC leading to healthcare visit; rate of visits to clinic, emergency room and hospitalizations, both overall and VOC-related; evolution of albuminuria and albumin creatinine ratio (ACR); pharmacokinetic (PK) profile of crizanlizumab (AUC, Cmax; Tmax; half-life); pharmacodynamic (PD) parameter (P-selectin inhibition); absolute change from baseline in haemoglobin; growth and sexual maturity assessment; measurement of anti-drug antibodies (ADA) to crizanlizumab.

Statistical methods

The scientific objective guiding the primary analysis was to estimate the treatment effect of crizanlizumab compared to placebo, for the target population on the annualized rate of VOC leading to a healthcare visit. The treatment effect of interest was defined as:

- on treatment over one year;
- without initiation or discontinuation of HU/HC or L-glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as Voxelotor and erythropoietin) over the first year post randomization;
- regardless of intake of analgesic (including opioids) or ad hoc transfusions administered temporarily.

The primary efficacy endpoint, annualized rate of VOC leading to a healthcare visit, was analysed according to the treatment arms and stratification factors that the participants were randomized to. The primary observation period was defined as the time from the date of the randomization to the minimum of (last dose date until treatment discontinuation + 27 days, date of initiation or discontinuation of HU/HC or L-Glutamine/other SCD therapies, date of randomization + 365 days).

A negative binomial regression model with treatment and randomization stratification factors as covariates was used for analysis, with the logarithm of observation time as offset. The estimates of annualized VOC rates ratios for treatment groups vs. placebo and 95% CI were provided.

To control the overall family-wise type I error rate (FWER) (to preserve the overall FWER at $\alpha = 5\%$ [two-sided]) an appropriate multiplicity adjustment procedure using a closed testing strategy was applied to the analyses of the primary and key secondary endpoints for the 2 doses comparisons to placebo.

Pairwise comparison of the 7.5 mg/kg and 5 mg/kg crizanlizumab annualized rate of VOC leading to a healthcare visit was performed against the placebo.

The primary statistical null hypotheses was:

- H_0 (7.5 mg/kg): there is no difference between crizanlizumab 7.5 mg/kg and placebo groups with respect to the annualized rate of VOCs leading to a healthcare visit over the first-year post randomization;

- H_0 (5 mg/kg): there is no difference between crizanlizumab 5 mg/kg and placebo groups with respect to the annualized rate of VOCs leading to a healthcare visit over the first-year post randomization.

These hypotheses were tested using the Wald test statistic within generalized linear model assuming a negative binomial distribution and compared 7.5 mg/kg and 5 mg/kg crizanlizumab versus placebo at the appropriate α-level adjusted considering multiple testing.

Results

A total of 252 participants were randomized, 84 participants to the crizanlizumab 5 mg/kg arm, 83 participants to the crizanlizumab 7.5 mg/kg arm and 85 participants to the placebo arm. The primary analysis, with a data cut-off (DCO) date of 31 August 2022, was performed when all 252 participants completed at least one year (52 weeks) of investigational treatment or discontinued within one year. The results of the primary and key secondary endpoint, as well as of the safety analysis were provided by the MAH. The results related with P-selectin exploratory biomarkers were also presented. The study data provided was considered sufficient to comprehensively evaluate the study results and draw conclusions as described in the sections below. The CHMP also considered that any additional analyses to be provided in the future with the final report would not impact the available results.

Treatment with crizanlizumab (5 mg/kg or 7.5 mg/kg) did not result in a statistically significant treatment difference compared with placebo in the annualized rate of VOCs leading to a healthcare visit over the first year post randomization. The adjusted annualized rates of VOC leading to healthcare visit over the first-year post randomization estimated via negative binomial regression were 2.49, 95% CI (1.90, 3.26) in crizanlizumab 5.0 mg/kg arm versus 2.30, 95% CI (1.75, 3.01) in the placebo arm. The median annualized rates of VOC leading to healthcare visit were 2.0 in crizanlizumab 5.0 mg/kg arm and 1.0 in the placebo arm. The incidence rate ratio of the crizanlizumab 5 mg/kg arm vs. placebo arm was 1.08, 95% CI (0.76, 1.55), adjusted p-value > 0.999, indicating no statistically significant difference compared to placebo arm. There were no observable differences across arms in annualized rate of VOC leading to healthcare visit or mean rate of VOC leading to healthcare visit. Additionally, in the 7.5 mg/kg treatment arm, no statistically significant treatment difference compared with placebo was observed (Figure 1).

				Between-treatment comparison			
Treatment	**n**	**Adjusted annualized rate of VOC**	**(95% CI)**	**Comparison**	**Rates ratio**	**(95% CI)**	**Adjusted P-value#**
Crizanlizumab 7.5 mg/kg	83	2.04	(1.56, 2.65)	vs Placebo	0.89	(0.62, 1.27)	> 0.999
Crizanlizumab 5.0 mg/kg	84	2.49	(1.90, 3.26)	vs Placebo	1.08	(0.76, 1.55)	> 0.999
Placebo	85	2.30	(1.75, 3.01)				

n: Total number of participants included in the analysis.
Obtained from fitting a negative binomial regression model with treatment and randomization stratification factors (baseline VOC and HU/HC) as covariates. The natural log of the observation period was used as offset.
Observation period = time from date of randomization to minimum of (last dose date until treatment discontinuation + 27 days, date of initiation or discontinuation of HU/HC or L-Glutamine (or other therapies such as Voxelotor and erythropoietin therapies to treat SCD and/or to prevent/reduce VOCs), date of randomization + 365 days).
#Adjusted p-values obtained from the closed testing procedure.
* Indicates statistical significance (2-sided) at the 0.05 level.

Figure 1 - Negative binomial regression treatment comparisons of VOC leading to healthcare visit (Full analysis set)

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 incidence rate ratio of the crizanlizumab 5 mg/kg arm vs. placebo arm was 1.21 (placebo as a reference group), 95% CI (0.87, 1.70) (Figure 2).

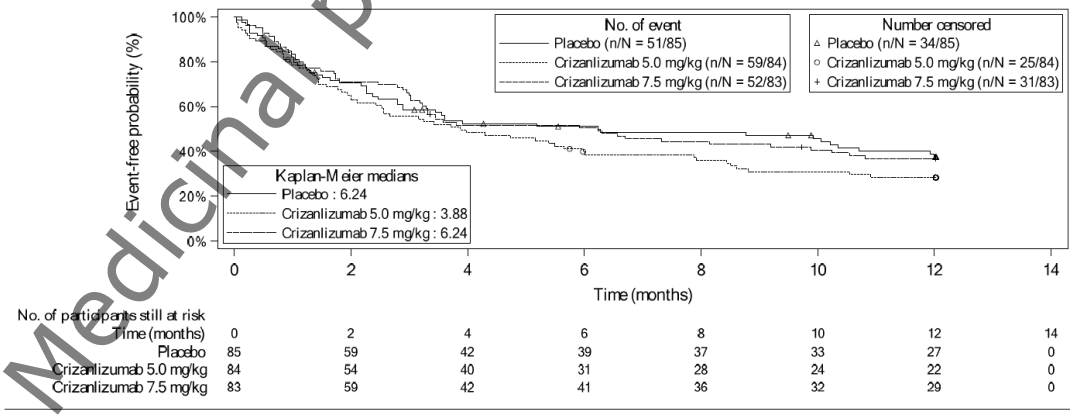
				Between-treatment comparison		
Treatment	**n**	**Adjusted annualized rate of VOC**	**(95% CI)**	**Comparison**	**Rates ratio**	**(95% CI)**
Crizanlizumab 7.5 mg/kg	83	3.22	(2.50, 4.13)	vs Placebo	0.83	(0.59, 1.17)
Crizanlizumab 5.0 mg/kg	84	4.70	(3.60, 6.14)	vs Placebo	1.21	(0.87, 1.70)
Placebo	85	3.87	(3.00, 5.01)			

n: Total number of participants included in the analysis.
Obtained from fitting a negative binomial regression model with treatment and randomization stratification factors (baseline VOC and HU/HC) as covariates. The natural log of the observation period was used as offset.
Observation period = time from date of randomization to minimum of (last dose date until treatment discontinuation + 27 days, date of initiation or discontinuation of HU/HC or L-Glutamine (or other therapies such as Voxelotor and erythropoietin therapies to treat SCD and/or to prevent/reduce VOCs), date of randomization + 365 days).

Figure 2 - Negative binomial regression treatment comparisons of all VOC: managed at home and leading to healthcare visit (Full analysis set)

There were 29.8% event-free participants in the crizanlizumab 5 mg/kg group, 37.3% event-free participants in the crizanlizumab 7.5 mg/kg group and 40.0% event-free participants in the placebo group. The mean (SD) of duration of VOC leading to healthcare visit was 7.7 (6.93), 6.0 (4.54) and 6.6 (5.55) in the crizanlizumab 5 mg/kg, crizanlizumab 7.5 mg/kg group and in the placebo, respectively.

For the stratified Cox regression model for time to first occurrence of VOC leading to healthcare visit the hazard ratio was >1 for both crizanlizumab groups: 1.34 with 95% CI (0.92, 1.97) for crizanlizumab 5 mg/kg and 1.07 with 95% CI (0.72, 1.58) for crizanlizumab 7.5 mg/kg. The Kaplan-Meier plot of time to first occurrence of VOC leading to healthcare visit showed that the hazard of an event was always highest/the event-free probability lowest for the 5mg/kg crizanlizumab group. The event-free probability curve of the 7.5 mg/kg crizanlizumab group was higher than the placebo curve until month 4 and from month 6 onward the placebo curve had the highest probability of being event-free (Figure 3).

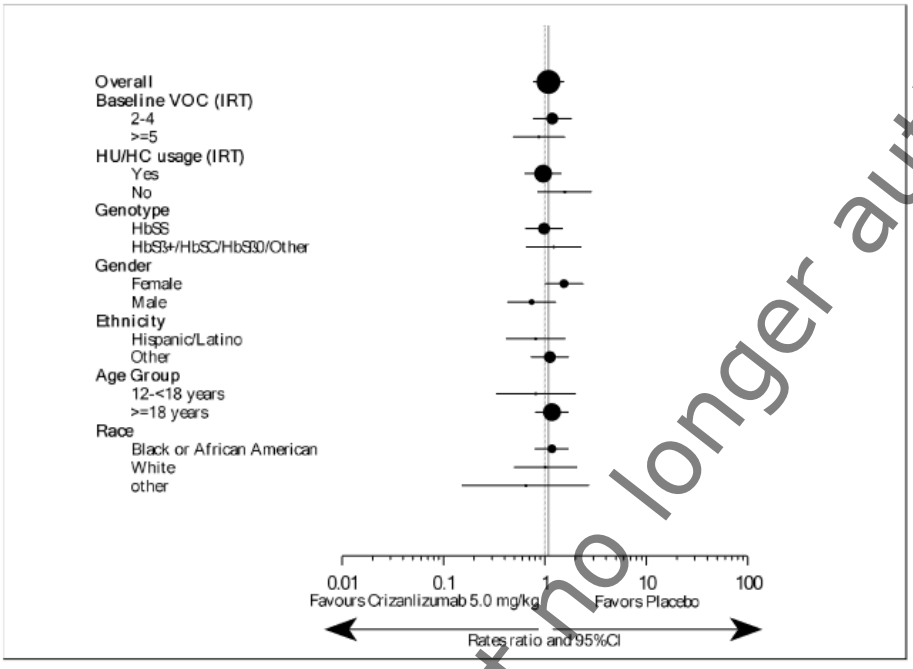


Observation period = time from date of randomization to minimum of (last dose date until treatment discontinuation + 27 days, date of initiation or discontinuation of HU/HC or L-Glutamine (or other therapies such as Voxelotor and erythropoietin therapies to treat SCD and/or to prevent/reduce VOCs), date of randomization + 365 days).

Figure 3 – Kaplan-Meier plot of time to first occurrence of VOC leading to healthcare visit (Full analysis set)

Subgroup analyses

Subgroup analyses were performed for baseline VOC (2-4, <=5), HU/HC usage (yes/no), genotype (HbSS vs HbSC, HbSβ^0/HbSC/HbSβ$^+$/Other), gender (male, female), ethnicity (Hispanic/Latino, Other), age group (12-<18 years, <=18) and race (Black or African American, White, other). The treatment effect in these subgroups seemed to be consistent with the overall population. Only slight differences were observed with baseline number of VOCs, gender and HU/HC use. None of the subgroup results showed clinically meaningful differences (Figure 4).



Dotted line shows no effect point, and (new) bold line shows overall treatment effect point.
Rates ratio from negative binomial regression.
Observation period = time from date of randomization to minimum of (last dose date until treatment discontinuation + 27 days, date of initiation or discontinuation of HU/HC or L-Glutamine (or other therapies such as Voxelotor and erythropoietin therapies to treat SCD and/or to prevent/reduce VOCs), date of randomization + 365 days).

Figure 4 – Forest plot of rates of VOC leading to healthcare visit from subgroup analysis (Full analysis set)

Sensitivity analyses of primary endpoint

Several sensitivity analyses were performed. The primary observation period included only data before study treatment discontinuation and before initiation or discontinuation of HU/HC or L-glutamine (or other therapies, such as Voxelotor and erythropoietin, to treat SCD and or to prevent/reduce VOCs) and only within a year after randomisation. The missing data of these patients was then imputed using the intrinsic assumption that the frequency of VOCs before treatment discontinuation would have been observed also for the entire first year of treatment.

For supportive analysis 1, all VOC leading to healthcare visit collected over one year post randomization were included in the analyses (including VOC leading to healthcare visit after treatment discontinuation and VOC leading to healthcare visit after initiation or discontinuation of HU/HC, L-glutamine or other SCD therapies). The number of initiation or discontinuation of HU/HC or L-glutamine (or other SCD therapy) is only minor: one in the crizanlizumab 5 mg/kg group, one in the crizanlizumab 7.5 mg/kg group and 3 in the placebo group (Figure 5).

Treatment	n	Adjusted annualized rate of VOC	(95% CI)	Between-treatment comparison			
				Comparison	Rates ratio	(95% CI)	P-value
Crizanlizumab 7.5 mg/kg	83	1.97	(1.51, 2.57)	vs Placebo	0.96	(0.67, 1.37)	0.805
Crizanlizumab 5.0 mg/kg	84	2.18	(1.67, 2.85)	vs Placebo	1.06	(0.74, 1.51)	0.758
Placebo	85	2.06	(1.57, 2.71)				

Figure 5 – Negative binomial regression treatment comparisons of VOC leading to healthcare visit: supportive 1 (Full analysis set)
Observation period = time from date of randomization to minimum of (end of study date, date of randomization + 365 days)

The results of supportive analysis 2 with different imputation methods for different reasons for treatment discontinuation and other events mentioned above were not presented. For supportive analysis 3, all the VOCs leading to healthcare visits collected until the primary analysis cut-off and before treatment discontinuation and initiation or discontinuation of HU/HC or L-glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as Voxelotor and erythropoietin) were included (Figure 6).

Treatment	n	Adjusted annualized rate of VOC	(95% CI)	Between-treatment comparison			
				Comparison	Rates ratio	(95% CI)	P-value
Crizanlizumab 7.5 mg/kg	83	1.86	(1.42, 2.44)	vs Placebo	0.87	(0.60, 1.26)	0.470
Crizanlizumab 5.0 mg/kg	84	2.23	(1.68, 2.96)	vs Placebo	1.05	(0.72, 1.51)	0.815
Placebo	85	2.13	(1.61, 2.83)				

Figure 6 - Negative binomial regression treatment comparisons of VOC leading to healthcare visit: supportive 3 (Full analysis set)
Observation period = time from date of randomization to minimum of (last dose date until treatment discontinuation + 27 days, date of initiation or discontinuation of HU/HC or L-glutamine (or other therapies such as Voxelotor and erythropoietin therapies to treat SCD and/or to prevent/reduce VOCs), primary analysis cut-off).

Sensitivity analysis 1 and 3 showed lower adjusted annualized rates of VOC, but the same pattern between arms and the between-treatment comparison only marginally changed.

Discontinuations

Overall, in the STAND study the discontinuation rate was markedly higher for the placebo than for the crizanlizumab arms (placebo: 31.8%; 5 mg/kg crizanlizumab: 21.4%; 7.5 mg/kg crizanlizumab: 18.1%). The MAH implemented measures to reduce drop-out rates. These might have contributed to the lower rates observed in both treatment arms but in theory would have been effective in the placebo arm as well. In all three arms, the majority of discontinuations was reported as by subject or physician decision and the observed disbalance between arms is also observed in these categories. While both could hint to an unsatisfactory treatment effect, it seems that in the placebo arm, mainly patients without a VOC event leading to healthcare visit discontinued (Figure 7). However, reliable reasons for discontinuation are difficult to ascertain and any potential unblinding issue has not been further investigated. Possible reasons for the higher discontinuation rate in the placebo group were not explored. The discontinuation rates cannot explain the results under non-informative censoring: the applied Poisson model already considered the different observation periods and the Cox regression analyses for the time to first event showed a similar pattern as the primary analyses.

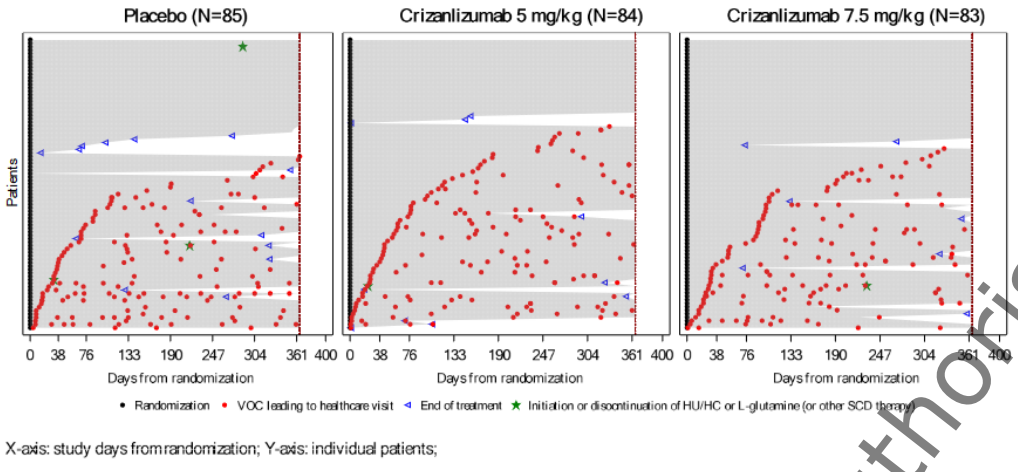


Figure 7 – Time to VOCs leading to healthcare visit (Full analysis set)

P-selectin biomarkers

Two soluble P-selectin exploratory biomarkers were assessed in the STAND study before and during treatment: free soluble P-selectin (free sPsel) and total soluble P-selectin (total sPsel). During treatment, total sPsel relative change from baseline remained close to zero percent for participants on placebo at different study visits, while an increase was observed for participants receiving crizanlizumab 5 mg/kg or 7.5 mg/kg. Free sPsel was reduced in the crizanlizumab 5 mg/kg and 7.5 mg/kg treatment arms, while no reduction was observed in the placebo arm. The relative change from baseline was similar across the crizanlizumab 5 mg/kg and 7.5 mg treatment arms and across study visits. Individual free sPsel concentration–time profiles suggested that free sPsel concentration remains very low for participants receiving crizanlizumab 5 mg/kg and 7.5 mg/kg over the first year of treatment, while free sPsel concentration remains at baseline level for participants on placebo. When the dose was interrupted or delayed, free sPsel concentration increased. These exploratory results were however not followed by a clinical relevant effect as described above in the primary and key secondary results.

2.2.2. Additional studies

Additional data from study A2202 (Jun-2022, N=57), the second study defined as SOB, as well as data from study B2201 (SOLACE-kids) in the 12-18 years old age group (crizanlizumab 5 mg/kg in group 1, N=50), study AUS05 (SPARTAN) in priapism (N=24), a Managed access program (MAP) (N=188, with 87 patients treated for more than a year), a temporary authorization cohort in France (CSEG1011FR01M, N=26), and real-word studies, were presented. In general, it was unclear how missing data were treated as dropout rates were quite high. In case of complete case analyses and informative missingness, i.e. patients with a worse outcome discontinue the study and are left out, the studies would be biased in favour of treatment for a comparison against baseline. Only descriptive analyses showing the median (min-max) and no inferential statistics, i.e. tests or 95% CIs, were presented.

Study A2202 was an uncontrolled and open-label phase II study specifically designed to assess PK and PD of crizanlizumab and safety in SCD subjects. As secondary objective, the study aimed to assess the

efficacy, safety and tolerability of Adakveo. The study was ongoing at the time of the CMA and the submission of its results was defined as a SOB. Interim results were provided by the MAH for this procedure. In summary, the 5.0 mg/kg dose group showed a median (min-max) annualized rate of VOCs of 4.00 (1.0-25.0) at baseline and 2.75 (0.0-17.7) when on treatment, with a median absolute reduction from baseline of -0.76 (-12.7-8.4). This change was considered rather modest and lower than the treatment effect observed in the SUSTAIN study.

In study B2201 (SOLACE-kids), the observed median absolute reduction in annualized rate of VOCs was slightly higher with −1.50 (−12.0-8.0) (median (min-max) at baseline was 3.00 (1.0-26.0) and 2.00 (0-14.0) after one year of treatment).

In study AUS05 (SPARTAN), a reduction in priapic events was shown in 17 of 24 patients (70.8%) receiving crizanlizumab by Week 26. The median (IQR) percent reduction from baseline in priapic events per patient was −53.1% (−73.4% to 9.3%). This was an open-label single-arm trial in a different indication. Consequently, the applicability of these results to the authorized indication is very limited.

In patients with SCD participating in the crizanlizumab MAP, reductions in the median annualized rates of home- and healthcare-managed VOCs and the use of opioids were observed. At baseline, 100% (n=87) and 93% (n=81) of patients had ≥1 home- and ≥1 healthcare-managed VOC, respectively, vs. 79% and 63% of patients, respectively, after ≥12 months of crizanlizumab treatment. Overall, the median (IQR) absolute reduction from baseline was −3.0 (−6.0 to −1.0) for home-managed and −2.0 (−4.0 to 0) for healthcare-managed VOCs. Opioids were taken for VOC-related pain relief by 95% of patients (n=83/87) at baseline and by 69% (n=60/87) in the 12 months after start of crizanlizumab treatment.

Further, crizanlizumab treatment was initiated in 26 SCD patients as part of the temporary authorisation for use protocol (CSEG1011FR01M) in France. During the 12 months before crizanlizumab initiation, the patients experienced a median of 6.0 VOCs. Since treatment initiation, the median number of VOCs leading to healthcare visit decreased to 1.0 among 17 patients with reported data, 11 patients had at least 1 VOC, 3 patients had at least 1 acute chest syndrome and 1 patient had several priapism crises.

In addition, real world data from a National Alliance of Sickle Cell Centers (NASCC)-sponsored retrospective study conducted in the United Sates (Kanter, 2021)[1] were provided. The authors of this study found that most patients (68%) who initiated crizanlizumab remained on therapy throughout the study. Furthermore, over half (55%) of the patients who received ≥ 12 infusions had significant reductions in hospitalizations and emergency department use. Among the 32 patients (55%) who received at least 12 doses, there was a 61.2% reduction in hospital stays and emergency department visits, from 10.7 visits in the 12 months prior to starting crizanlizumab, to 4.1 visits during the 12 months of crizanlizumab treatment ($p<0.01$).

In a retrospective study including 18 patients (all genotypes, ≥16 years old) with SCD who received at least 2 consecutive doses of crizanlizumab 5 mg/kg, the median duration of exposure to crizanlizumab was 53.6 weeks, and 16 patients (89%) received crizanlizumab for ≥ 26 weeks (Chan et al 2022)[2]. The authors reported improvement in patients' subjective responses with crizanlizumab infusion. The median Patients' Global Impression of Change (PGIC) score of patients was 5, signifying 'moderately

[1] Kanter, J, Hellemann, G., Cohen, A. J., Manwani, D., Idowu, M.; Guarino, S., Saif Ur Rehman, S., Treadwell, M., Clay, E. L. J., Owusu-Ansah, A., Little, J. A., Desai, P., Madisetti, M., Lanzkron, S. M., 'Early Evaluation of the Use of Crizanlizumab in Sickle Cell Disease: A National Alliance of Sickle Cell Centers Study', Blood, Vol 138 (Supplement 1), 2021, p. 3113.
[2] Chan, Kok Hoe, Buddharaju, Ruhi, Chang, Shandel L., Lane, John S., Idowu, Modupe, 'Real-World Experience of Patients with Sickle Cell Disease Treated with Crizanlizumab: A Single Comprehensive Sickle Cell Center Retrospective Cohort Analysis', Blood, Vol 140 (Supplement 1), 2022, p. 8288–8289.

better with noticeable changes, although slight'. Twelve (12) patients (67%) provided a score of ≥ 4, which signified feeling better with changes. The authors concluded that crizanlizumab was associated with improvements in patient response that were both directly and indirectly related to the reduction of VOCs.

All of the additional clinical studies presented, including study A2202 (defined as SOB), were open-label and uncontrolled including a limited number of subjects. The efficacy data of these studies was shown as change from baseline of event rates. Consequently the quality of evidence is considered less than for randomized controlled clinical trials (such as the SUSTAIN and STAND studies) as the results could suffer from many forms of biases. These might include within-patient variability (random fluctuation over time), differences in reporting for baseline values or the natural course of a disease over time in a patient (systematic change over time). Further, a common phenomenon possible in these patients is 'regression to the mean' where the measurements of the same patients will have a tendency to vary from extremes values to mean/lower values at a later point in time, irrespective of being treated with an effective treatment or not. Also, in the SUSTAIN study, a reduction compared to baseline in the placebo group has been observed (-0.34). Similarly in the STAND study, in the placebo group the median number of VOCs leading to healthcare visit in the last 12 months was 3.0 and a VOC rate of 2.3 was observed within the study. This shows that the observed treatment effects were lying within the range of possible fluctuation.

In addition to all uncertainties pertaining to single-arm trials and the use of comparison to baseline as estimate to efficacy, these studies were performed during the COVID-19 pandemic. It was hypothesized that the COVID-19 pandemic may have reduced environmental triggers for VOCs through lockdown and change in life-style (e.g. reduced infections) and reduced accessibility to healthcare facilities or reduction in healthcare visits due to fear of infection (SCD patients are a reported high-risk COVID-19 population). This could mean a reduction in reporting of VOCs or related efficacy parameter inevitably leading to a reduction compared to a pre-pandemic baseline as described for the STAND study where this was brought up as a possible explanation for the negative results. As the STAND study was a randomised trial with treatment and control arm being affected equally, the COVID-19 pandemic should only have impacted the results of the single-arm trials which could have been biased in favour of treatment. Consequently, CHMP is of the view that the reported results might not be attributed to a treatment effect alone. Additionally, since all observed effects are rather modest, a relevant treatment effect of crizanlizumab cannot be assumed.

Lastly, the additional real-world data presented is considered to provide only limited supportive evidence. Furthermore, it is unclear how the data from real-world studies was chosen (selection bias) by the MAH, which could additionally suffer from publication bias. Moreover, in the NASCC-sponsored retrospective study, out of the 238 patients, only 32 patients received 12 doses and were included in the efficacy analysis. Only data on hospitalizations was presented. It is noted that in this study, crizanlizumab was prescribed at 11 NASCC centres from November 2019 to 30 June 2021, and thus the efficacy assessment period overlaps with the COVID-19 pandemic and the same considerations as described above may apply.

2.3. Data on safety

2.3.1. STAND study

The mean exposure in the crizanlizumab arms was longer (89.8 and 89.6 weeks in the 5 mg/kg and 7.5 mg/kg) compared to the placebo arm (80.9 weeks) due to the observed higher discontinuation rate in the placebo group. Two (2) participants (2.4%) in each group discontinued due to AEs.

Although the overall frequency of participants with at least one adverse event (AE) was comparable between the placebo (90.6%) and the 5 mg/kg (88.1%) group, the frequency of AES with grade 3/4 severity were higher in the 5 mg/kg arm (56.0%) when compared to the 7.5 mg/kg (38.6%) and the frequencies in both crizanlizumab groups were higher compared to the placebo group (31.8%) (Table 2).

The number of serious adverse events (SAEs) was also higher for the 5 mg/kg (41.7%) compared to the 7.5 mg/kg (26.5%) group and the placebo (30.6%) group. In both crizanlizumab groups, SAEs with an expected relation to study treatment were reported (3 participants with pain, abscess neck and pulmonary embolism in the 5mg/kg group and 2 participants with sickle cell anaemia with crisis and hypersensitivity in the 7.5mh/kg group) whereas no such event was reported in the placebo group. On-treatment death was reported for 2 participants (2.4%) in each arm, none reported to be related to the study treatment. In the placebo arm, 1 participant died due to inflammatory bowel disease and 1 participant due to acute chest syndrome. In the crizanlizumab 5 mg/kg arm, 1 participant died due to myocardial infarction and 1 participant due to sepsis. In the crizanlizumab 7.5 mg/kg arm, 1 participant died due to intracranial haemorrhage and 1 participant due to pulmonary embolism.

Table 2. Overview of adverse events in STAND study (Safety Set)

	Placebo		**5.0 mg/kg**		**7.5 mg/kg**	
	N=85		N=84		N=83	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
AEs	77 (90.6)	27 (31.8)	74 (88.1)	47 (56.0)	77 (92.8)	32 (38.6)
Treatment-related	21 (24.7)	2 (2.4)	25 (29.8)	7 (8.3)	22 (26.5)	6 (7.2)
SAEs	26 (30.6)	16 (18.8)	35 (41.7)	29 (34.5)	22 (26.5)	18 (21.7)
Treatment-related	0	0	3 (3.6)	3 (3.6)	2 (2.4)	2 (2.4)
Fatal SAEs	2 (2.4)	2 (2.4)	2 (2.4)	2 (2.4)	2 (2.4)	2 (2.4)
Treatment-related	0	0	0	0	0	0
AEs leading to discontinuation	2 (2.4)	2 (2.4)	2 (2.4)	2 (2.4)	2 (2.4)	1 (1.2)
Treatment-related	0	0	2 (2.4)	2 (2.4)	1 (1.2)	1 (1.2)
AEs leading to dose interruption/ reduction	14 (16.5)	4 (4.7)	17 (20.2)	9 (10.7)	19 (22.9)	6 (7.2)
AEs requiring additional therapy	69 (81.2)	23 (27.1)	64 (76.2)	35 (41.7)	67 (80.7)	26 (31.3)

The safety set included all participants who received at least one dose of study treatment.
Numbers (n) represent counts of participants.
A participant with multiple severity grades for an AE is only counted under the maximum grade.
CTCAE version 5.0; A2301 MedDRA version 25.1; A2201 MedDRA version 21.1

2.4. Comparison between phase II SUSTAIN and phase III STAND studies

The SUSTAIN (N=198) and the STAND (N=252) studies were similar with respect to design, including the choice of primary efficacy endpoint (i.e. annualized rate of VOCs leading to a healthcare visit over the first year of treatment). Both were randomized, blinded, placebo-controlled studies with randomization stratified by the baseline number of VOCs (i.e. in the 12 months prior to screening) and HU/HC use. Treatment duration at the time of the primary analysis was similar (approximately 1 year) and the standard of care (i.e. HU/HC as a concomitant medication) was essentially the same during the conduct of both studies. Both studies utilized adjudication of VOCs by an external adjudication committee comprised of independent haematologists specialized in the treatment of SCD.

Despite these similarities, the efficacy and safety results from the two studies differ as reported above. In the SUSTAIN study, treatment effect estimates for the primary and secondary endpoints were systematically in favour of crizanlizumab and the observed favourable trends for the 5 mg/kg crizanlizumab dose were of a magnitude that was considered clinically relevant for SCD patients and hence supportive for the granting of the CMA of Adakveo in the EU. However, in the STAND study, neither the primary nor the key secondary endpoints were met. Additionally, in terms of safety, the rates of Grade ≥3 AE and SAEs (in the crizanlizumab group compared to placebo) observed were higher when compared to the safety results in the SUSTAIN study.

There were identified differences between the studies, including differences in the studies periods vis-à-vis the COVID-19 pandemic, differences in the geographic location and differences in study population. The contribution of these differences as possible factors to the discrepant results between the two studies as presented by the MAH was considered by CHMP.

Firstly, on the COVID-19 impact, it was hypothesised that effects of the COVID-19 pandemic may have caused a masking effect/reduction in reporting of VOCs in the STAND study including reduced environmental triggers for VOCs through lockdown and change in life-style (e.g. reduced infections) and reduced accessibility to healthcare facilities or reduction in healthcare visits due to fear of infection (SCD patients are a reported high-risk COVID-19 population). While it is agreed that a certain effect on triggers and VOCs is likely, this effect should have impacted placebo and treatment study arms equally, contrary to the study results described above. Further, potential VOCs not treated via healthcare visits would have been treated at home and this would be reflected in the key secondary endpoint of the STAND study that included VOCs treated at home. However, no effect in this endpoint was also observed.

A further possible explanation to the impact to the placebo group and less so to the treatment groups was a supposed 'floor effect' (i.e. VOCs in each group would score near the lowest possible value, likely making it impossible to compare the average VOCs between each treatment group and placebo to determine if the active treatments made any difference), thereby eliminating the treatment effect. However, the VOC rates were 2.3 in the placebo arm, 2.49 in the crizanlizumab 5 mg/kg arm and 2.04 in the crizanlizumab 7.5 mg/kg arm in the STAND study vs. 3.75 in the placebo arm, 2.43 in the crizanlizumab 5 mg/kg arm and 2.69 in the crizanlizumab 2.5 mg/kg arm in the SUSTAIN study. In the STAND study, the number of VOC leading to healthcare visit in the last 12 months had a mean of 3.8 in the placebo and a mean of 3.6 in the crizanlizumab 5 mg/kg arm. As the trial was stratified for the number of VOC at baseline, balance in this baseline variable could be expected. It is not understood why there should only be a reduction to a VOC rate of approximately 2, when the minimum VOC rate is 0. No rational for this plateau effect which is higher than the floor at 0 was provided. The impact of the "floor effect", with loss of low treatment effect when the number of events approaches zero, cannot be assessed in this study. Therefore, the proposed explanation based on a floor effect is not considered suitable to explain the observed results of crizanlizumab versus placebo in the STAND study.

It was also argued that differences in geographic location of study centres could have played a role in lack of efficacy given the differences in healthcare utilization. Patients were located primarily in the USA in the SUSTAIN study, while there was a global dispersion of patients in the STAND study. Additionally, the SUSTAIN study had a higher proportion of patients who described themselves as Black or African American (91.9% vs. 48.8% in STAND study). While these differences are acknowledged, this argument could raise uncertainties about the applicability of the SUSTAIN data (primarily from USA) to the EU population in general.

Regarding the differences in the study population, the SUSTAIN study patients had higher number of VOCs leading to a healthcare visit in the 12 months prior to screening. While this is correct based on the two applied categories (0-5 and ≥5 VOCs; 34.8% of participants with ≥5 VOCs in SUSTAIN study

vs. 28.2% of participants in STAND study), the actual number of VOCs at baseline (in the period prior to screening) was balanced between arms in both studies and consequently this is no obvious reason for the lack of observable difference in the annualized rates of VOCs between arms in the STAND study. A higher treatment effect in the more severely affected population might have attenuated the effect seen in the STAND study, as this population was less represented in this study. Nevertheless, this would question the effectiveness in the overall population and this slight difference in number of VOCs cannot explain the large reduction in treatment effect observed.

Lastly, it was reported that the VOC rate in the placebo arm of the STAND study was considerably lower than expected and lower than the rate in the SUSTAIN study. As observed in the SUSTAIN study, there is fluctuation in VOC rates over time, potential regression to mean in groups with high VOC rate at baseline, among others, and therefore small differences over time, or between treatment groups, are difficult to interpret. For the SUSTAIN study, the median number of VOCs leading to healthcare visit in the last 12 months in the placebo group was 4.00 and a VOC rate of 2.98 was observed in the placebo group within the study. Similarly, in the STAND study, the median number of VOCs leading to healthcare visit in the last 12 months in the placebo group was 3.0 and a VOC rate of 2.3 was observed within the study. This could be seen as a potential regression to mean effect and shows that the observed treatment effect in the SUSTAIN study was lying within the range of possible fluctuation assuming that the comparison to baseline is unbiased. In any case, the observed changes in the placebo group make any results based on single-arm trials questionable.

Overall, the discussed arguments do not explain the discrepant results between the SUSTAIN and the STAND studies. It is acknowledged that the COVID-19 pandemic and linked safety measures have probably led to a reduction in VOCs in general. Nevertheless, this would have affected all arms equally. The other differences in the study populations are also not considered to impact the results. Therefore, none of the identified differences between studies were considered as possible explanation for the discrepant results. No further limitations or uncertainties were identified impairing the validity of the STAND study results.

3. Benefit-risk balance

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 AEs (56.0% of patients in the crizanlizumab 5 mg/kg arm compared with 31.8% in the placebo arm) and 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.

4. Direct Healthcare Professional Communications and Communication plan

The Committee adopted the wording of a direct healthcare professional communication (DHPC), to inform HCPs of the conclusions of the review and upcoming unavailability of Adakveo. The Committee also agreed on a communication plan.

5. Grounds for 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.