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Guideline on the clinical requirements for medicines intended for the treatment of sickle cell disease

Draft

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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

Guideline on the clinical requirements for medicines in sickle cell disease

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List of abbreviations

ACS: Acute Chest Syndrome

CNS: Central Nervous System

EC: European Commission

E-R: Exposure – Response

ICH: International Council for Harmonisation

HbF: Foetal Haemoglobin

HbH: Haemoglobin H

HLA: Human Leukocyte Antigen

HRQoL: Health-Related Quality of Life

HSCT: Haematopoietic Stem Cell Transplantation

MAA: Marketing Authorisation Application

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

PA: Protocol Assistance

PAES: Post-Authorisation Efficacy Study

PASS: Post-Authorisation Safety Study

PD: Pharmacodynamics

PK: Pharmacokinetic

POP PK: Population Pharmacokinetics

PROs: Patients Reported Outcomes

QoL: Quality of Life

SA: Scientific Advice

SAE: Serious Adverse Events

SCD: Sickle Cell Disease

SoC: Standard of Care

TEAE: Treatment emergent adverse events

TAMMV: time averaged maximum of the mean velocity

TDU: Transcranial Doppler ultrasound

TIF: Thalassemia International Federation

VOC: Veno-Occlusive Crises

1. Scope

This guideline aims at providing guidance on general principles of the clinical development programme of medicinal products for the treatment of sickle cell disease (SCD). This guideline focuses on the confirmatory phase 3 trials investigating safety and efficacy and serving as the main basis for benefit-risk assessment of these products.

2. Legal basis and relevant guidelines

This guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, as well as the Paediatric Regulation (EC) 1901/2006 as amended, the Orphan Regulation (EC) No 141/2000 and Regulation (EC) 847/2000, Regulation (EC) 1394/2007 and all other relevant EU and ICH guidelines. These include, but are not limited to:

- ICH E9 (R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (EMA/CHMP/ICH/436221/2017)
- ICH E6 Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)
- ICH M15 guideline on general principles for model-informed drug development (EMA/CHMP/ICH/496426/2024)
- ICH E8(R1) Note for Guidance on General Considerations for Clinical Trials (EMA/CHMP/ICH/544570/1998 Corr)
- Guideline on strategies to identify and mitigate risks for first-in human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07)
- Guideline on clinical trials in small populations (CHMP/EWP/83561/2005)
- ICH Topic E1 guideline on the Extent of Population Exposure to assess Clinical Safety (CPMP/ICH/375/95)
- ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population (EMA/CPMP/ICH/2711/1999)
- ICH E11A guideline on paediatric extrapolation (EMA/CHMP/ICH/205218/2022)
- ICH E21 Guideline on inclusion of pregnant and breastfeeding individuals in clinical trials (EMA/CHMP/ICH/149462/2025)
- Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products: (EMA/CAT/80183/2014)
- EMA guideline on registry-based studies (EMA/426390/2021)
- Draft guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products - Revision 1 (EMEA/149995/2008 rev.1)
- Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials (EMA/CAT/22473/2025)
- Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation application (EMA/CHMP/458061/2024)
- EMA Reflection Paper on the use of Health-Related Quality of Life (HRQoL) measures in the evaluation of medicinal products (EMA/CHMP/EWP/139391/2004).

- ICH Topic E 5 (R1) Ethnic Factors in the Acceptability of Foreign Clinical Data (CPMP/ICH/289/95).

3. Therapeutic context and treatment objectives

3.1. Therapeutic context

Sickle cell disease (SCD) is a rare inherited haemoglobinopathy caused by a mutation in the β-globin gene, resulting in sickle haemoglobin (HbS). SCD includes several genotypes, most commonly HbSS, HbSC, HbSβ+-thalassaemia and HbSβ0-thalassaemia, with HbSS and HbSβ0 generally associated with more severe disease. The disease is more prevalent in populations originating from malaria-endemic regions, including sub-Saharan Africa and South Asia. In Europe, prevalence has increased over recent decades due to migration from endemic regions.

The pathophysiology of SCD is mainly driven by HbS polymerisation under deoxygenated conditions, leading to red blood cell sickling, haemolysis, endothelial dysfunction, vasculopathy and vaso-occlusion. The main clinical consequences are chronic haemolytic anaemia and vaso-occlusive crises (VOCs), which contribute to acute pain episodes, tissue ischaemia-reperfusion injury, inflammation, progressive organ damage and increased mortality.

Clinical manifestations are heterogeneous and may vary by age, genotype, disease severity, comorbidities, background treatment, socioeconomic and environmental factors. This heterogeneity should be considered in clinical trial design. Trial populations should be representative of the intended target population and should reflect relevant sources of variability, including age, genotype, baseline disease severity and concomitant therapies.

From a drug development perspective, patient selection should primarily be guided by disease severity and the therapeutic objective of the investigational product. Relevant severity indicators may include annualised VOC rate, haemoglobin level, haemolysis markers, transfusion burden, organ involvement and other complications.

SCD symptoms usually begin in childhood as foetal haemoglobin declines. Paediatric development should therefore not be unnecessarily delayed, particularly to characterise pharmacokinetics, pharmacodynamics, exposure-response relationships and age-appropriate dosing. Older adults with SCD should also be considered in clinical development, as they may have chronic organ complications, comorbidities and polypharmacy that can affect benefit-risk assessment.

Current and emerging therapies target different mechanisms, including HbS polymerisation, modulation of haemoglobin subtypes, erythrocyte dehydration, oxygen affinity, cellular adhesion, endothelial dysfunction and inflammation. Available treatments remain limited and are primarily focused on alleviating the clinical manifestations, rather than being curative. Supportive care includes analgesics, antibiotics, oxygen therapy and transfusions. Allogeneic haematopoietic stem cell transplantation may be curative but is limited by donor availability and significant risks.

To be noted, measurements of haemoglobin are commonly presented as grams per decilitre (g/dL) or millimoles per litre (mmol/L). In this guideline, Hb values will be presented as g/dL.

To convert haemoglobin from g/dL to mmol/L, the value in g/dL should be multiplied by 0.6206. Pharmaceutical companies developing medicines for thalassaemia should provide both units in study reports and in SmPC.

3.2. Treatment objectives and efficacy criteria

The assessment of efficacy should be based on one or several of the treatment goals of SCD, which have as main objectives:

a) Reduction of vaso-occlusive crises (VOCs)

b) Improvement in haemolytic anaemia

c) Addressing transfusion reduction when applicable

d) Prevention of organ damage (kidneys, spleen, liver, lungs, heart, or central nervous system (CNS))

e) Prevention of long-term complications arising from long-term blood transfusions

f) Reduction in acute and chronic pain (reduction of VOC severity and the use of (chronic) pain medication)

g) Potential functional cure*

* In the context of gene therapy and gene editing approaches, functional cure refers to durable treatment effects. It should meet a defined set of criteria that includes clinical, laboratory biomarker and safety endpoints, while eliminating the need for conventional treatments to manage disease signs and symptoms and providing clinically meaningful improvements in quality of life.

3.3. Methods to assess efficacy

Methods to assess efficacy would vary depending on the treatment goals. Objective methods and criteria to measure effects should be used whenever feasible. With respect to endpoints based on VOC, blinded adjudication of severe VOC events is preferred. In addition, patient reported outcomes (PROs) (using intra-patients' comparison), and patient diaries could be used to collect data on VOC occurrence, severity and duration. The pre-study (baseline) transfusion burden should be documented using complete and reliable sources (e.g., transfusion medical records/registries). During the study, transfusions must be captured prospectively in CRFs with indication, timing, frequency and volume.

Standard laboratory measurements to assess haemoglobin or haemolysis response should be applied. For disease-modifying therapies, a combination of various measures covering the different dimensions of disease activity including VOC frequency, haemoglobin levels, markers of haemolysis (LDH, bilirubin, reticulocytes), transfusion requirements, organ function and patient-reported outcomes

4. Confirmatory studies

4.1. General design elements

Robust evidence is required to support a marketing authorisation. In SCD, the rarity of the condition and heterogeneity of the patient population introduce additional challenges; the following recommendations aim to mitigate these challenges.

4.1.1. Controlled studies

Randomised, double-blind study designs are preferred, although it is acknowledged that certain treatments may not be compatible with this approach. Placebo-controlled studies are recommended for evaluating the efficacy of treatments. Treatment should be administered on top of standard of care, which include prophylactic medications to prevent VOCs, supportive care for pain management and

chronic SCD complications, and acute interventions for VOCs when necessary. The studies should aim at demonstrating the superiority of the new agent over placebo when added to standard of care therapies.

Active-controlled studies are currently challenging due to the limited treatment options. If an active control is used, it should be justified that the comparator is an adequate treatment option for the whole target population.

Randomisation should be stratified by the disease severity (e.g. adjudicated VOC rates in the 52 weeks prior to screening) and the current use of relevant active treatment(s). Additional stratification factors, such as region should also be considered.

Randomised clinical studies remain the core of clinical evidence in SCD. However, supporting information to contextualise the disease and trial outcomes may be useful. For instance, utilising registry data (e.g., national disease registries) could be considered as a platform to acquire data for natural history studies.

As commonly used endpoints cannot isolate treatment effect without a concurrent control, single arm studies are rarely suitable in this setting. If an applicant is considering conducting a single arm study, it is recommended to discuss such approach in scientific advice.

Open-label studies may be deemed acceptable upon the provision of adequate justification that blinding is not feasible. It should be noted that lack of blinding will increase the risk of bias and hence unblinded pivotal trials are considered to carry additional uncertainties. Even in partially open-label studies, blinding of endpoint assessors or study personnel should be implemented where feasible. Subjective outcome measures are generally not considered reliable in non-blinded studies. Deviations from the recommended approach may only be acceptable if adequately justified. It is encouraged to discuss such approach via scientific advice.

Baseline VOC rates. Reliable baseline data on VOC rates is considered crucial to assure proper stratification based on the disease severity and the ability to detect treatment effect during the trial. The completeness and quality of baseline data should be assured. The VOC definition to establish baseline rates should ideally be the same as the definition of VOC used on study. A 12-month baseline is recommended due to high fluctuations in VOC. Prospective data collection is always preferred and is necessary if intra-patient comparisons are used (patient-reported VOCs, VOC-related pain etc.). Intra-patient comparisons may be acceptable as supportive evidence when prospective, standardised data collection methods are used, and endpoint definitions are consistent over time.

4.1.2. Study duration

A sufficiently long evaluation period and follow-up are necessary to assess both the efficacy of the treatment and the sustainability of its effects, as well as long-term safety. Required duration of follow-up depends on the treatment goal, endpoints and safety profile of the product. A minimum 12-month main study phase to capture seasonal variability is recommended. Extension studies are strongly encouraged.

For gene therapy, study duration and long-term follow-up should be in line with EMA guideline on investigational medicinal products for gene therapy and EMA guideline on safety and efficacy and risk management for Advanced Therapy Medicinal Products (ATMPs).

Deviations from the recommended approach may only be acceptable if adequately justified. It is encouraged to discuss divergent approaches in scientific advice.

4.2. Patient selection/target population

For clinical development results to be generalisable, patients enrolled in clinical trials should represent and reflect the population affected by the condition for which the medicine will be used/intended for. In this context, inclusion of a diverse patient population reflecting variability in age, genotype, disease severity and geographic background is encouraged.

In general, haemoglobinopathies have a substantial genotypic and/or phenotypic heterogeneity. Moreover, the variability in phenotypic expression is only partially explained by genetics, as socioeconomic and environmental factors can also contribute to heterogeneity. This variability is evident both among patients with the same genetic variants and within individual patients over time. Given this variability, applicants must ensure that the population, included in the clinical trials and reflected in the indication, are representative across the most relevant factors.

4.2.1. Age

Patients as early as 6 months old begin to show clinical manifestations of SCD, as the protective effect of residual HbF no longer sufficiently prevents red blood cell sickling. Nevertheless, infants with SCD tend to experience milder and less frequent symptoms, largely because their deoxygenated red blood cells take longer to sickle compared to those in older children and adults. The staggered enrolment approach of paediatric patients is advised, including for infants. For paediatric populations, it is also essential to ensure the availability of age- and weight-appropriate formulations. The inclusion of paediatric patients in clinical studies should enable the characterisation of PK, PK/PD and exposure-response in all the different age categories. This approach can help optimize drug development timelines and facilitate timely access to medicines for patients of all ages, in line with the extrapolation principles outlined in ICH E11A. In general, preliminary safety and efficacy data on adults should be available before paediatric subjects could be enrolled in the trials. For gene therapy products, paediatric studies should start after at least 1 year safety and efficacy data are available in the adult population. Please see section 4.5.1. for more details on the studies in paediatric subjects.

Older adults with SCD face a complex combination of chronic SCD complications and age-related health issues, impacting their QoL and requiring a multidisciplinary approach to care. They are at increased risk for complications like kidney and heart problems, avascular necrosis, and functional decline, often needing joint replacements and experiencing accelerated aging compared to the general population. There is a need for clinical trials focused on older adults with SCD to determine how to safely prescribe disease-modifying therapies and other medications in this population. Please see section 5.5.2. for more details on the studies in older subjects.

4.2.2. Pregnant and breastfeeding

In general, since individuals of childbearing potential are among the anticipated target population in SCD, the inclusion of pregnant and breastfeeding individuals in late-stage clinical trials should be considered in line with the ICH E21 guideline on inclusion of pregnant and breastfeeding individuals in clinical trials. Especially, pregnancy can exacerbate disease manifestations, leading to more frequent and severe VOCs and other complications. If feasible, it is important to generate data on safety, efficacy and dosing of the medicinal product during pregnancy and breastfeeding during medicine's development.

The risk of an impact on spermatogenesis in SCD treatment of boys and males should also be considered when developing novel treatments such as gene therapy, including measures needed before exposure.

4.2.3. Genotypes

The predominant SCD genotypes include Hb SS, Hb SC, Hb Sβ+-thalassemia, Hb Sβ0-thalassemia and haemoglobin SD disease. Other rare SCD genotype is haemoglobin SE, which usually presents with less clinical manifestations. Overall, HbSS and HbSβ0 are the most severe forms of SCD, given the highest fraction of pathological HbS in these populations, with HbSS being the most prevalent (approximately 75% worldwide).

Most therapies for SCD, based on their mechanism of action, are genotype non-specific, and therefore, efforts for the inclusion of patients with various genotypes in clinical studies are encouraged.

In this case, the severity of the disease, rather than genotype, should be the primary criterion for patient inclusion in clinical trials.

4.2.4. Severity

The clinical manifestations of SCD are diverse, including both acute and chronic complications that vary greatly among individuals. Patients should be stratified based on disease severity for inclusion in clinical studies. The indicator to define disease-severity may depend on the specific treatment goal.

Disease severity should be part of the inclusion criteria for clinical studies. The parameters used to define disease severity should be aligned with the specific therapeutic objectives of the study. Please see section 5.3 for more details on efficacy assessment. In line with the defined primary endpoint, the following indicators of severity should be considered:

Vaso-occlusive crises

The primary marker of disease severity is annualised rate of acute pain crises or VOCs. Especially if this endpoint is targeted, it is recommended to enrich the trial with patients with reliably reported, severe recurrent VOCs to enhance the possibilities of the study to detect a treatment effect, while also excluding individuals with chronic pain, whose disease aetiology may differ significantly from the frequent VOCs. Subgroup analysis by annualised VOCs will be required for more comprehensive data interpretation. Overall, it is important to ensure that enough patients in the extremes of the baseline VOC range are enrolled to be able to confirm efficacy in the different subgroups of patients and ensure generalisability of the study results. A clear definition of VOC should be provided in the study protocol.

Baseline VOC data should be comprehensive, use consistent definitions, cover 12 months, and preferably be collected prospectively to support assay sensitivity, patient stratification, and intra-patient comparisons.

Haemolytic anaemia

If the therapy targets aspects of the disease other than VOCs, such as haemolytic anaemia, clinical studies could be enriched based on haemoglobin levels and markers of haemolysis. Previously accepted thresholds were Hb ≥ 5.5 and ≤ 10.5 g/dL at screening. Somewhat lower threshold could be accepted in paediatric subjects (e.g. Hb ≥ 5.0 g/L at the screening visit) if justified.

Transcranial Doppler ultrasound

The inclusion criteria could include TCD velocity threshold or a threshold for the number of microbubbles observed during a TCD scan to be considered positive for emboli. Such thresholds need to be scientifically justified. In general, TCD time averaged maximum of the mean velocity (TAMMV) arterial cerebral blood flow ≥ 170 to 200cm/sec during the screening period) can be considered as an inclusion criterion. Children with abnormal TCD velocity (≥200cm/sec) are offered chronic transfusion for primary stroke prevention, according to the current standard of care.

Other indicators of disease severity

If the investigational medicinal product target other aspects of the disease, such as inflammation, overall prevention of organ damage, or prevention of long-term complications arising from long-term blood transfusions, it is advised to enrich the clinical studies accordingly. Some relevant aspects may be organ function (i.e., renal function, liver function), history of acute chest syndrome (ACS), or transfusions history. The specific parameters can be discussed on a case-by-case basis during Scientific advice and the Paediatric Investigation Plan (PIP).

4.2.5. Concomitant therapy

The enrolment of patients who are using disease targeting (e.g., hydroxyurea) or symptomatic medication (e.g., pain medication, antibiotics, iron chelation, etc) for SCD is appropriate, as this reflects current standard of care practices and it ensures the study adheres to ethical principles. Nevertheless, several considerations need to be addressed.

The study design should account for background therapy to allow isolation of the therapeutic effect of the investigational product. Concomitant treatments, including hydroxyurea, transfusions, pain medication, antibiotics and iron chelation, may introduce heterogeneity and confounding in clinical trials. Their use should be pre-specified, stabilised where appropriate, and considered in stratification, analysis and interpretation of efficacy and safety results.

For disease targeting medications, patients will need to be under stable treatment regimen during the run-in period for at least 6 months prior to treatment initiation. In some cases, longer period on stable doses of standard of care (SoC) medications might be required, while for paediatric patients a shorter duration may be justified. This helps to minimise any potential confounding effects from changes in background therapies just before or during the study and ensures that the observed treatment effects can be attributed to the investigational treatment alone. Stratification or adjustment for background therapy in the analysis (e.g., subgroup analysis or covariate adjustment) should be pre-defined. The indication should be in alignment with the hypothesis tested (e.g., add-on to standard of care or monotherapy). Potential drug-drug interactions and overlapping toxicities must be evaluated in the protocol and safety monitoring plan. In specific cases, such as if the mechanism of action of the investigational drug overlaps significantly with the background therapy, exceptional approaches may be considered.

4.2.6. Other factors

Sufficient representation of patients regarding other relevant factors, which include but are not limited to the need of RBC transfusions, ethnicity or region is necessary. Stratification or addition of the relevant covariates to the primary analysis is warranted. The specific relevant factors may be discussed and justified in a case-by-case basis, depending, for instance, on the treatment goals.

Geographical region stratification should be chosen to characterise the effect across areas with regional care variations.

4.3. Efficacy assessment

4.3.1. *Choice of endpoints*

The choice of endpoints will vary depending on the mechanism of action and treatment goals of the medicinal product under development.

Reduction (Prevention) of vaso-occlusive crises (VOC)s

Given the complex pathogenesis of VOCs as well as the difficulty in accurately quantifying these episodes, a stringent definition to discern the occurrence and severity of VOCs (e.g., VOC pain vs non-VOC pain) is necessary. The variable for the primary endpoint should be the annualised rate of (severe) VOCs. Severe VOCs are defined as either i) an acute pain event requiring medical contact and administration of pain medications (opioids or intravenous non-steroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions) where other causes for acute pain have been excluded, ii) acute chest syndrome, iii) priapism lasting > 2 hours and requiring a visit to a medical facility, or iv) splenic sequestration. Additional elements, such as stroke, can be considered. The counting and discrimination of events for the analysis of annualised rate of VOCs should be well defined *a priori* with regards to their duration, and how individual events occurring in close proximity to each other can be discriminated. Additionally, VOCs that do not require medical contact should ideally also be recorded, and the rate of any VOC (requiring or not medical contact) should be provided as supportive evidence.

To ensure that the primary endpoint is assessed objectively, an independent and blinded endpoint adjudication committee (EAC) consisting of experts in SCD should adjudicate presumptive VOCs identified by investigators. Any discrepancies between investigator-reported events and EAC-adjudicated events should be reported and discussed.

Efficacy information could be supplemented by intra-patients' comparison i.e. comparing each subject's annualised VOCs at baseline vs at the end of the main study phase if the same endpoint definition and data collection methods have been used. Considerations on minimal clinically important differences should apply to both within patient and between group comparisons. The average change in annualised VOC rate and the difference in percentage of patients achieving the threshold for a minimal clinically meaningful within patient change should be pre-defined and justified in the study protocol. The majority of SCD-related signs and symptoms are self-managed, and it would be valuable to enable a more comprehensive picture on disease manifestations, not limiting assessment to those VOCs where medical intervention is sought. Development of methods to reliably capture non-severe/home-managed VOCs is encouraged. Validation of the method is required, and discussion on definitions of relevant endpoints and clinically relevant treatment effects should be provided. Any novel tools and endpoint definitions should be discussed in scientific advice.

Treatment of haemolytic anaemia due to SCD

Haemolytic anaemia is prevalent in the majority of SCD patients, and it is associated with complications such as cerebrovascular disease, kidney disease, pulmonary vasculopathy, and increased mortality. Generally, haemoglobin increase of >1 g/dL (10 g/L, 0.62 mmol/L) from baseline is considered clinically meaningful. However recent experience suggests that increasing haemoglobin levels does not consistently correlate with clinical benefit in SCD. Therefore, achieving haemoglobin response only is not considered sufficient to establish a relevant clinical benefit in SCD and other clinically relevant endpoints, such as decreased RBC transfusion requirements or improvements in validated in SCD QoL measures, would be required to confirm the benefit of a new medicine. These secondary endpoints should be prespecified in the protocol and should be included in the confirmatory multiple- testing strategy/alpha controlled.

Transcranial Doppler (TCD) ultrasound

TCD is a screening tool since a velocity of blood flow of at least 200 cm/s in the middle cerebral artery is associated with an augmented risk of stroke in children with SCD. If increased TCD velocity is detected, chronic RBC transfusions are standard practice to prevent organ damage and the occurrence of stroke in these patients. The use of these endpoints, particularly when these are associated with

additional clinical outcomes, may be considered informative in clinical studies. Increased TCD velocity, however, is not a prognostic or predictive risk factor in adult patients.

Surrogate endpoints

Exploring other endpoints to investigate their value as targets for drug development is encouraged. While multiple laboratory biomarkers are described for SCD, most of them have not proven sufficient clinical value. Further assessment in prospective studies to validate their predictive value before they are acceptable as surrogate endpoints is still necessary. This is a prerequisite for their use as primary endpoints.

Applicants are encouraged to request scientific advice to discuss potential alternative to the above-described acceptable endpoints.

Additional endpoints

Supportive data should be collected through secondary endpoints.

Relevant secondary endpoints include hospital admission rate, length of hospital stay, VOC-related hospital or acute care facility admission rate after initial VOC discharge, annualised rate of home-managed VOCs, total consumption of pain medication (as defined in the primary endpoint and stratified by drug class), proportion of subjects with ≥30% pain reduction by NRS score within 4 hours after start of medication, proportion of subjects experiencing ACS, acute kidney injury (AKI) or stroke, RBC transfusion activity, occurrence of infections, change in baseline haemoglobin, severe anaemic episodes (Hb<5.5 g/dL) , haemolysis markers (e.g., unconjugated bilirubin, reticulocyte percentage, absolute reticulocytes, and LDH), reduction of RBC transfusions, or mortality.

Effect on long-term complications are highly relevant and should be collected in the SCD studies. Long-term complications related to SCD include organ damage, ACS, ischaemic stroke, chronic kidney disease, priapism, pulmonary hypertension, leg ulcers, spleen infarction, or bone disease. Given that these events usually occur at a lower frequency than acute pain episodes or haemolytic anaemia, it is acknowledged that studying such endpoints in isolation will require larger number of study subjects and/or longer study duration. Nevertheless, efforts should be made to collect information on these events during clinical studies. For instance, multiple treatment studies have been performed using stroke (overt and silent stroke) as the clinical endpoint in SCD, confirming that the use of such clinical endpoints is feasible. Further, longer follow-up of patients in the registries to assess organ damage are encouraged.

Other secondary endpoints highly relevant to SCD patients are validated and pre-specified health-related quality of life (HRQoL) and functional capacity. The use of both generic QoL instruments covering each age-subset (e.g. EQ-5D in adults, EQ-5D-Y-3L and PedsQL in children) and SCD-specific instruments (e.g. ASCQ-Me in adults and the PedsQL Sickle Cell Disease Module in paediatric populations) is encouraged. Functional capacity, measured by, for instance, exercise capacity is also considered relevant for SCD patients. Decreased exercise capacity, possibly due to anaemia, cardiac disease, restrictive and obstructive lung disease, pulmonary vascular disease, as well as bone and muscle abnormalities, is commonly observed in SCD. Measures such as the 6-min walk test are considered meaningful for this population when adequately contextualised. For both endpoints, efforts to ensure the validity of the instrument/measure and sufficient information to establish minimal clinically important differences in the population under study are necessary to allow the interpretation of the results. Such parameters should be pre-specified in the study protocol.

4.3.2. Methodological considerations

Randomised, double-blind study designs are preferred, although it is acknowledged that certain treatments may not be compatible with this approach. Open-label studies may be deemed acceptable upon the provision of adequate justification that blinding is not feasible. It should be noted that lack of blinding will increase the risk of bias and hence unblinded pivotal trials are considered to carry additional uncertainties.

The handling of intercurrent events needs to be defined in the study protocol, together with a definition of the primary (and secondary) estimand(s).

The frequencies and pattern of the occurrence of the relevant intercurrent events can be informative about the new treatment in itself and should be reported per study arm. Additionally, within the same overview, information should be included on the occurrence of missing data and whether data became missing after the respective intercurrent events.

Relevant intercurrent events include but are not limited to the change in SCD background therapy, transfusion, use of concomitant treatments, and discontinuation of study treatment.

The primary regulatory interest is in the outcome, regardless of whether patients discontinue the study treatment (treatment policy strategy).

The regulatory preferred handling of the intercurrent event "initiation or intensification of background / additional therapy" differs between haemoglobin-based responder endpoints and VOC related endpoints. Generally, it is expected that fewer patients in the investigational treatment arm initiate or intensify their background / additional therapy. This should be confirmed by descriptive analyses comparing the proportions of patients initiating or intensifying their background / additional therapy at relevant timepoints during the trial. This analysis should be presented separately by type of background / additional therapy.

For responder endpoints based on the haemoglobin increase, such as achievement of a haemoglobin increase of >1 g/dL, the initiation or intensification of background/additional treatment (particularly the use of transfusions) should be interpreted as treatment failure in the primary estimand (composite strategy). Additionally, for contextualisation, the initiation or intensification of background therapy other than transfusion should be handled with a treatment policy strategy in an additional estimand while the initiation or intensification if transfusion is still handled as treatment failure / non-response (composite strategy).

For VOC related endpoints, the initiation or intensification of background/additional therapy should be handled with a treatment policy strategy in the primary estimand. In an additional estimand, the use a hypothetical strategy for these intercurrent events, estimating the effect in a scenario where the background / additional treatment would not be initiated or intensified, could provide valuable contextualising information about the investigational treatment. In this scenario, it should not be assumed that the cause for initiating or intensifying the background / additional treatment was not there (e.g. worsened disease status), but only that the background / additional therapy would not be initiated / intensified.

Alternative approaches for handling the above listed intercurrent events might also be valuable depending on the clinical context. Whenever these are planned to be used for the primary estimand, it is recommended to discuss the proposals at EMA scientific advice.

Importantly, the outcome after the discontinuation of study treatment or the initiation or intensification of background / additional therapy is relevant for the regulatory assessment and all efforts should be made to collect them. If some patients have missing values after discontinuation of study treatment or the initiation or intensification of background / additional therapy, those need to be imputed under

plausible and sufficiently conservative assumptions that avoid an overestimation of the treatment effect or an underestimation of its variability.

Assumptions underlying the primary analysis should be examined through pre-specified and justified sensitivity analysis (e.g. tipping point analyses) addressing the same estimand.

An adequate number of patients should be included to permit a meaningful evaluation of efficacy and safety. Importantly, the sample size should not only be determined based on statistical considerations concerning the primary estimand but also ensure sufficient data on key secondary estimands and safety outcomes. Since high heterogeneity in the study population is anticipated, a sufficiently large size of clinically relevant subgroups should also be taken into consideration in sample size evaluation. All relevant paediatric age groups should be addressed.

4.4. Safety aspects

4.4.1. *Specific effects*

The occurrence of a broad spectrum of adverse events should be carefully monitored and thoroughly documented for any new investigational agent. Particular attention should be paid to capturing adverse events that may plausibly relate to the product's mechanism of action or pharmacodynamic properties. Furthermore, irrespective of the primary endpoint selected, detrimental effects on VOCs should be excluded. Monitoring for the occurrence of stroke, especially in paediatric studies, is also of critical importance. In addition, safety data should adequately capture effects following treatment discontinuation (e.g., exacerbation of VOCs or anaemia after treatment discontinuation).

For gene therapies specifically, the safety database should include all adverse events potentially associated with the transgene product and/or the vector or transduction mechanism. Special consideration should be given to the safety aspects highlighted in the Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014).

4.4.2. *Long-term effects*

The overall safety database must generally include data on a large and representative group of patients, as stated in the guideline ICH Topic E1, Guideline on the Extent of Population Exposure to assess Clinical Safety.

Given the rare nature of the disease and patient availability for clinical studies, it is expected that safety data will be limited pre-approval. Nevertheless, the best efforts to compile sufficient safety information are a requisite. Further, additional data may need to be collected post-marketing through dedicated Post-Authorisation Safety Study (PASS) and/or registry studies, in particular to document long-term benefits and risks in children, in which pre-authorisation clinical data may be more limited. The use of existing platforms, such as national disease registries, and any initiatives to set global registries that centralise and harmonise knowledge related to α/ β-thalassaemia are encouraged.

Specially for gene therapies, follow up should follow the principles laid down in the Guideline on follow-up of patients administered with gene therapy medicinal products (EMEA/CHMP/GTWP/60436/2007).

4.4.3. *Safety endpoints*

Safety endpoints should distinguish disease-related clinical endpoints (e.g., VOC, ACS, stroke) from adverse events. Companies are recommended to apply for scientific advice to discuss safety data collection plan in detail.

4.5. Studies in special populations

4.5.1. Studies in paediatric patients

For characterising the pharmacological effects of medicines in children, the use of model informed drug development (MIDD) approaches (POPPK, PKPD, DER) should always be envisaged given their high potential and ability to analyse the data more efficiently, to support optimisation of clinical trial design, to adequately inform dose selection and optimisation, extrapolation across populations and indications, ultimately facilitating a more efficient and timely paediatric drug development. General principles described in the ICH M15 guideline on general principles for model-informed drug development and ICH guideline E11A on paediatric extrapolation should be applied for this purpose.

The paediatric population faces a high unmet medical need for treatments for SCD. Since the pathophysiology and current stand of care treatment for SCD in adolescents are consistent with those in adults, their inclusion in clinical trials is recommended, as early as possible, following positive results in phase 2 in adults (EMA/CHMP/ICH/205218/2022), while adhering to the general guidelines for paediatric medicine development (EMA/CHMP/QWP/805880/2012 Rev. 2; EMA/CPMP/ICH/2711/1999).

In general, inclusion of children ≥12 years of age together with adult patients in a phase 3 study can be advisable, depending on already available data, but the staggered enrolment approach might be advised (depending on phase 2 results, or eventually following a predefined interim analysis). The general advice is that the clinical trial(s) in children <12 years of age should not start before sufficient experience has been gained in adults and patients ≥12 years of age. Specifically for gene therapy medicinal products, clinical studies in paediatric patients might need to be deferred until at least one year of safety and efficacy follow-up data is obtained based on the mechanism of action and expected safety profile of the concerned medicine.

Sufficient number of paediatric patients in all age (or/and bodyweights) ranges intended to be included in the clinical indication need to be represented in the clinical studies. Although the inclusion of adolescents together with adult patients could be acceptable if adequately justified, and efficacy and safety data from adults and adolescents can be combined, a separate analysis for these subgroups showing consistent effects is required.

Informative data must be collected across all relevant paediatric age groups (≥12, 6–<12, <6 years), including adequate PK, exposure–efficacy, exposure–safety and clinical data to support dose and benefit–risk assessment. In particular, sufficient PK information should be available for in each age group, for PK, PD, exposure-efficacy and exposure-safety, for dose recommendations and benefit/risk assessment.

4.5.2. Studies in older patients

Similarly to the average older adults' population, older adults (65 years and older) with SCD suffer from several comorbidities that need to be considered during clinical studies. Applicants should include older adult patients to enable meaningful benefit–risk assessment (with appropriate monitoring for comorbidities/polypharmacy). Baseline documentation supports interpretation but does not replace risk minimisation; risk should be mitigated via eligibility, monitoring and dose adjustments where appropriate.

The potential PK and/or PD interactions with other concomitant products frequently used in older adults due to comorbidities should be studied. Also, it is important to characterise the impact of aging to determine if the PK, behaviour and PK/PD and E-R relationships of the concerned medicine in older adults are different from that in younger adults (reference is made to the ICH E7 guideline).

As with any other subpopulation, an adequate number of older adult patients should be included in the Phase III studies, and inclusion or exclusion criteria based on age need to be justified. A sub-group analysis by age should be considered (e.g., <65 years, 65-74, ≥75 years). The results, as well as the lack of such data, are informative and should be mentioned in the SmPC.