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Guideline on the clinical requirements for medicines intended for the treatment of thalassaemia

Draft

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Table of contents

Abbreviations

CRF: Case Report Forms

EC: European Commission

E-R: Exposure – Response

ESA: Erythropoiesis-Stimulating Agents

HbF: Foetal haemoglobin

HbH: Hemoglobin H

HRQoL: Health-Related Quality of Life

ICH: International Council for Harmonisation

PK: Pharmacokinetic

PD: Pharmacodynamics

POP PK: Population Pharmacokinetics

HLA: Human Leukocyte Antigen

HSCT: Haematopoietic Stem Cell Transplantation

MAA: Marketing Authorisation Application

MRI: Magnetic Resonance Imaging

NTDT: Non- Transfusion-Dependent-Thalassaemia

PA: Protocol Assistance

PAES: Post-Authorisation Efficacy Study

PASS: Post-Authorisation Safety Study

QoL: Quality of Life

RBC: Red Blood Cells

SA: Scientific Advice

TIF: Thalassaemia International Federation

TDT: Transfusion-Dependent-Thalassaemia

VTE: Venous Thromboembolic Events

1. Scope

This guideline aims at providing guidance on general principles of the clinical development programme of medicinal products for the treatment of α and β-thalassaemia. 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 medicines.

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
- 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)
- 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 E5 (R1) Ethnic Factors in the Acceptability of Foreign Clinical Data (CPMP/ICH/289/95).

3. Therapeutic context and treatment objectives

3.1. Therapeutic context

Thalassaemia is a rare inherited blood disorders worldwide and comprises a group of autosomal recessive diseases characterised by defective haemoglobin synthesis. The two principal forms, α-thalassaemia and β-thalassaemia, result from mutations affecting the production of α-globin and β-globin chains, respectively. These genetic defects lead to chronic anaemia, ineffective erythropoiesis and a range of clinical manifestations that vary considerably in severity. β-thalassaemia affects approximately 288,000 individuals globally and is caused by mutations in the β-globin gene (HBB), of which nearly 300 have been identified. Depending on the mutation, β-globin production may be completely absent (β^0 mutations) or significantly reduced (β^+ mutations), with disease severity generally increasing as β-globin production decreases.

Historically, β-thalassaemia was classified according to genotype and clinical severity; however, current practice increasingly focuses on transfusion requirements, reflecting their major impact on disease progression and management. Patients with transfusion-dependent thalassaemia (TDT) require lifelong, regular blood transfusions for survival, whereas those with non-transfusion-dependent thalassaemia (NTDT) require only occasional or intermittent transfusions. This classification is now widely used in clinical practice, treatment guidelines and clinical trial eligibility criteria.

Clinical presentation depends on disease severity. In β-thalassaemia major (typically associated with severe anaemia and subsequent regular transfusion requirements, when haemoglobin <7 g/dL), symptoms typically emerge between 6 and 24 months of age coinciding with the physiological transition from foetal haemoglobin (HbF) to adult haemoglobin (HbA). The severity of anaemia generally results in the need for regular red blood cell transfusions and a transfusion-dependent clinical course. Patients commonly develop severe anaemia, jaundice, hepatosplenomegaly, poor growth, feeding difficulties and recurrent infections. Without treatment, the condition is usually fatal in early childhood. In contrast, patients with β-thalassaemia intermedia or NTDT generally present later, often between two and six years of age, with milder anaemia. β-thalassaemia minor is usually asymptomatic or associated with only mild anaemia and carries an excellent prognosis.

Regular red blood cell transfusions remain the cornerstone of treatment for patients with TDT. The decision to initiate long-term transfusion therapy is based on the patient's clinical condition, including failure to thrive, persistent severe anaemia, evidence of ineffective erythropoiesis and the prevention of bone deformities. Although no universally accepted threshold exists, patients receiving six or more units of red blood cells within six months, or regular transfusions over one to three years, are generally considered transfusion-dependent. Transfusions inevitably lead to iron overload. Each transfused unit introduces a substantial amount of iron, which accumulates in the body and can damage the heart, liver and endocrine organs. Consequently, iron overload is a major cause of morbidity and requires regular monitoring through ferritin measurements and liver and cardiac imaging. Iron chelation therapy is therefore routinely combined with chronic transfusion programmes to remove excess iron. However, both transfusions and iron chelation therapies can cause adverse effects and are associated with risks such as alloimmunisation, infection and treatment burden.

For patients with NTDT, the traditional approach has often been to avoid regular transfusions because many patients can tolerate chronic anaemia. However, untreated anaemia contributes to significant long-term complications, including thromboembolic disease, pulmonary hypertension, leg ulcers and extramedullary haematopoiesis.

α-thalassaemia is similarly common, with approximately 5% of the world's population carrying an α-thalassaemia mutation. More than 370 disease-causing mutations have been identified. Clinical

severity largely correlates with the number of affected α-globin genes, ranging from asymptomatic carrier states to severe disease. Clinically significant forms include haemoglobin H (HbH) disease and haemoglobin Bart's hydrops fetalis. HbH disease is characterised by chronic haemolytic anaemia resulting from excess β-globin tetramers and may range from mild anaemia to severe transfusion-dependent disease. Anaemia often worsens during periods of physiological stress such as infection, pregnancy or surgery. In patients with non-deletional HbH disease, disease severity is particularly variable and can extend from mild anaemia to severe foetal disease.

Management of clinically significant α-thalassaemia may include regular transfusions, particularly in children with severe anaemia, impaired growth, delayed puberty or significant splenomegaly. Adult patients with non-deletional HbH disease usually do not require chronic transfusions, although regular transfusion therapy may be considered in severe cases to prevent complications and improve quality of life. Management of transfusion-dependent α-thalassaemia follows principles similar to those applied in β-thalassaemia, with the aim of maintaining haemoglobin levels above 9 g/dL. Additional interventions may include splenectomy in selected patients with severe disease and cholecystectomy for symptomatic gallstones. Iron overload is also common in HbH disease, partly due to increased gastrointestinal iron absorption, and requires appropriate monitoring and management.

Allogeneic haematopoietic stem cell transplantation (HSCT) has long been used as potentially curative therapy for severe disease, but its use is constrained by donor availability and the risks associated with transplantation. More recently, gene therapy has emerged as a therapeutic option for selected patients with transfusion-dependent β-thalassaemia, although long-term experience remains limited and treatment requires intensive conditioning regimens. Other innovative approaches, including erythroid maturation agents and gene-based therapies, aim to reduce transfusion requirements and improve disease control. Nevertheless, current management remains largely centred on supportive care with blood transfusions and iron chelation therapy.

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 the product information.

3.2. Treatment objectives and efficacy criteria

Emerging therapies for thalassaemia can be divided into the following categories based on their pathological target:

(a) Addressing ineffective erythropoiesis and/or haemolysis
(b) New ways of modifying iron metabolism
(c) Altering globin gene expression
(d) Potential functional cure

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

Transfusion dependent thalassaemia:

- **Addressing the transfusion burden:**
  - Transfusion independence
  - Transfusion reduction
- **Reducing iron overload** [(ferritin, cardiac iron concentration (Magnetic Resonance Imaging (MRI)), liver iron concentration (MRI)]

- **Sustained Hb improvement supported by clinically meaningful effects** (e.g. transfusion burden, iron parameters). Health Related Quality of Life (HRQoL)/Patient Reported Outcomes (PROs) are encouraged as supportive evidence and should be validated in thalassaemia.
- **Long-term efficacy and safety**

Non–transfusion-dependent thalassaemias:

- **Sustained Hb improvement supported by clinically meaningful effects** (e.g. transfusion burden, iron parameters). Health Related Quality of Life (HRQoL)/Patient Reported Outcomes (PROs) are encouraged as supportive evidence and should be validated in thalassaemia.
- **Reducing iron overload**
- **Duration of erythroid response and reduction of erythroid mass (patients not starting transfusions)**
- **Long-term safety and efficacy (with particular focus on bone surveillance)**

In the context of gene therapy and gene editing approaches in TDT and NTDT, functional cure refers to durable transfusion independence with near/normal haemoglobin maintained over a prespecified period (e.g. ≥12 months), alongside sustained control of ineffective erythropoiesis and improvement in iron parameters. HRQoL/PROs are measures that may be considered as supportive to document patient-centred benefit and are not strictly required as primary endpoints. Given these considerations, any functional cure for β-thalassaemia should meet a defined set of criteria that includes clinical, laboratory biomarker and safety endpoints, while eliminating the need for conventional treatments, such as Red Blood Cells (RBC) transfusions or additional disease-modifying chronic therapy to manage disease signs and symptoms and providing clinically meaningful improvements in QoL.

3.3. Methods to assess efficacy

Methods to assess efficacy would vary depending on the treatment goals. Objective methods and criteria should be used whenever feasible. For therapies with curative intent, a predefined set of efficacy and safety endpoints should be prospectively collected to adequately characterise both the durability and the breadth of the treatment effect. When objective assessment is not possible, the use of subjective assessments (e.g. PROs) must be justified and supported by appropriate validation and collection procedure. The pre-study (baseline) transfusion burden should be documented from reliable sources (e.g. transfusion registries/medical records). During the study, transfusions must be captured prospectively in Case Report Forms (CRFs) (indication, timing, frequency, volume).

4. Therapeutic confirmatory studies

The regulatory considerations of interest for confirmatory trials for new treatments of thalassaemia are described below, followed by considerations on adequate study design.

4.1. General design elements

Robust evidence generated from pivotal clinical studies is required irrespective of the indication. In thalassaemia, the rarity in the EU and heterogeneity introduce additional challenges; the design recommendations below aim to mitigate these and support reliable efficacy and safety evaluation.

Benefit-risk considerations might differ between TDT and NTDT and paediatric and adult patients. These considerations should be taken into account in the design elements, if paediatric and adult patients are combined in a single study.

4.1.1. Controlled studies

Treatment should be administered on top of appropriate standard of care (e.g. transfusions in TDT; supportive/non-transfusion care in NTDT) and aim to demonstrate superiority versus placebo or superiority/non-inferiority versus active control, as justified. Additionally, double-blind study designs should be chosen whenever possible, although it is acknowledged that certain treatments may not be compatible with this approach.

Deviations from the recommended approach may only be acceptable if adequately justified (for example single-arm design with gene therapy). It is encouraged to discuss such approach in scientific advice.

Randomised clinical studies remain the core evidence. Registry-based natural history studies are encouraged (not mandatory) where they help contextualising outcomes (e.g. long-term complications, rare subgroups) or supports post-authorisation safety/effectiveness; necessity should be considered case-by-case.

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. A minimum of 6–12 months may be acceptable depending on the primary endpoint and disease context (e.g. transfusion cycles, iron dynamics). An open-label extension to follow participants who participated in the pivotal clinical trials is encouraged to assess durability and safety, but extension data are not mandatory at initial MAA as long as the pivotal evidence is of sufficient duration; post-authorisation commitments may instead be appropriate.

For gene therapy, study duration and long-term follow-up should be in line with EMA guideline on quality, non-clinical and clinical requirements for investigational medicinal products for investigational advanced therapy medicinal products in clinical trials and EMA guideline on safety and efficacy follow-up and risk management for advanced therapy medicinal product (ATMPs).

4.2. Patient selection /target population

For clinical development intended to support of registration, enrolled patients should reflect the intended use population to ensure generalisability of results. 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 (genotypes / phenotypes).

4.2.1. Age

Patients with most severe phenotypes of β-thalassaemia and α-thalassaemia, diagnosed by clinical and haematological criteria, will start on regular transfusion therapy within the first two years of life. Therefore, clinical studies in the paediatric population including infants will need to be conducted.

4.2.2. Pregnancy and breastfeeding

In general, since individuals of childbearing potential are among the anticipated user population in thalassemia, generation of pregnancy / breastfeeding data is encouraged although this is not a pre-approval requirement unless justified by the proposed indication and associated risk profile. Development should follow ICH E21; post-authorisation mechanisms may be used. Especially, pregnancy can exacerbate disease manifestations, leading to more frequent blood transfusions, higher risk of pre-eclampsia and venous thromboembolic events (VTE), especially in NTDT, 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 thalassaemia treatment of boys and males should also be considered when introducing novel treatments such as gene therapy medicinal products, including measures needed before exposure.

4.2.3. Genotypes

β-thalassaemia

Two subpopulations should be considered: subjects who do not have a β^0 mutation at both alleles of the β-globin gene (non-[β^0/β^0]), including subjects with HbE/β-thalassaemia and subjects who have a β^0 mutation at both alleles of the β-globin gene (β^0/β^0), also known as homozygotes. The β^0/β^0 β-thalassaemia genotype has the most severe clinical presentation. As thalassaemia genotype affects disease severity, a respective stratification based on disease genotype is expected.

α-thalassaemia

Two subpopulations should be considered: subjects with non-deletional HbH, and subjects with deletional HbH or other genotypes leading to regular transfusion therapy.

4.2.4. Severity

β-thalassaemia

The classification of disease severity, which has been used until recently, divided most patients with symptomatic disease into two groups: β- thalassaemia major and β- thalassaemia intermedia, with the former group being considered more severe, including patients who were started on regular transfusions soon after birth, and the latter being considered less severe, including patients started on regular transfusions later in childhood or those only requiring intermittent transfusions throughout life.

Per the 2025 Thalassaemia International Federation (TIF) Guidelines, the severity of disease for symptomatic patients is evaluated based on transfusion requirements. As such, patients with β-thalassaemia are classified either as transfusion-dependent (TDT) or as non-transfusion dependent (NTDT). These classifications for patients with β-thalassaemia (TDT and NTDT) are now commonly used for clinical trial eligibility.

α-thalassaemia

Similarly to β-thalassaemia, the severity of disease for symptomatic patients is evaluated based on transfusion requirements. As such, patients with α-thalassaemia are also classified either as transfusion-dependent (TDT) or as non-transfusion dependent (NTDT).

Similar to β-thalassaemiaa, applicants should also justify the inclusion strategy (TDT vs NTDT) and whether extrapolation across severities/genotypes is appropriate, supported by exposure–response, PK/PD, and clinical similarity.

4.2.5. Concomitant therapy

Potential drug-drug interactions and overlapping toxicities must be considered in the protocol and safety monitoring plan. In specific cases, such as if the mechanism of action of the investigational medicine 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 transfusion is recommended. Presentation across geographic regions may be warranted to account for care variation (e.g. transfusion/chelation practices). Sufficient representation of patients across clinically relevant characteristics, including but not limited to RBC transfusion requirements, is recommended. Representation across geographic regions may also be warranted to account for variations in clinical practice (e.g. transfusion and iron chelation strategies).

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.

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.

Endpoints for assessing a curative therapy in thalassaemia

Transfusion independence

The most important clinical endpoint is achieving a durable transfusion independence. This endpoint, therefore, should be measured as primary endpoint in trials of medicines aiming for cure of thalassaemia. Since patients with TDT typically receive transfusion support as often as every 2–5 weeks, a duration of 12 months or more without RBC transfusions and a weighted average total haemoglobin of ≥9 g/dL is sufficient to establish transfusion independence. Gene therapy (including gene editing therapies) typically involve long-term follow-up for up to 15 years after treatment, during which time transfusion independence will be monitored.

Iron chelation

Chronic iron overload in patients with TDT and NTDT, which persists even after any form of curative approach, perpetuates inflammation and continues to damage sensitive organs such as the liver. Therefore, discontinuation of iron chelation therapy and establishing a normal iron status are also important in defining a curative therapy. When assessing the need for iron chelation therapy, it is important to consider the baseline degree of iron overload and the additional transfusion support administered during the clinical trial. The normalisation iron status may require years; therefore, chelation discontinuation and organ iron improvement are long-term endpoints, typically captured in extension/post-authorisation studies rather than as pre-approval requirements.

Additional clinical endpoints

After establishing a normal or near-normal haemoglobin concentration without transfusions (e.g., ≥11 g/dL adults / age-adjusted in paediatrics), it is important to assess the trajectory of the end-organ disease. Assessments of organ function (cardiac, renal, hepatic, and endocrine) estimate a patient's physical health and whether stabilisation of end-organ damage associated with TDT/NTDT and long-

term RBC transfusions have occurred. Organ function in TDT/NTDT is influenced by tissue iron content, particularly in cardiac, hepatic, and endocrine organs where there is a predilection for iron overload to occur. These aspects could be considered for inclusion in the risk management plan and potentially further studied in registries. Monitoring paediatric patients with TDT might be particularly informative, with the expectation that organ function will return to normal (i.e. longitudinal cohorts).

Patient-reported outcomes (PROs) on HRQoL

The effect of the curative therapy on quality-of-life should also be assessed. There are validated tools to measure health status and QoL in adults and children with TDT/NTDT across these domains.

Laboratory and radiological endpoints

Improvements in total haemoglobin (including normalisation) above RBC transfusion thresholds (generally ≥9 g/dL) support the clinical endpoint of transfusion independence, although ideally a normal or near normal haemoglobin could be targeted.

Laboratory biomarkers that directly measure the proportion of genetically targeted cells should include the level and persistence of allelic editing at the intended locus (gene editing approaches) or vector copy number (viral vector approaches). These measurements in peripheral blood and bone marrow over time will prove essential data for demonstrating the long-term treatment efficacy of therapy with curative intent. The persistence of gene-edited alleles and the impact of gene insertion using lentiviral vectors should be also assessed in long-term follow-up studies to evaluate the durability of the treatment effect.

In paediatric patients, in addition to the above-mentioned considerations, the focus should be on the improvement in several endocrine aspects (hypogonadism, diabetes) and growth (including bone disease).

Endpoints for assessing a non-curative therapy in thalassaemia

Clinical endpoints in TDT

Transfusion dependency is defined as 6 to 20 RBC units transfused and a ≤6-week transfusion-free period during the 24-week period before randomisation.

The primary endpoint should focus on the reduction of transfusion requirement in a population where most participants have high transfusion frequency (>12 RBC Units in the 24-week pre-randomisation, i.e. approximately one transfusion every 2 weeks). Enrichment for high transfusion frequency (e.g. >12 units/24 weeks) enhances assay sensitivity to detect clinically meaningful transfusion reduction.

An increased threshold of 50% reduction in transfusion burden is recommended to reflect clinically meaningful benefit. The choice could be made for a fixed total or 12-weeks period or rolling 12-weeks period, representing the proportion of patients who benefit from the treatment at any time. However, rolling period comes with methodological challenge that the chance of false positive findings increases due to several rolling windows of 12 weeks over a period of 24 weeks. When a rolling period approach is used, the reasons for that should be justified and also appropriate measures should be taken to prevent an increase in Type I error. Use of rolling period makes it also difficult to prespecify an estimand with all attributes. Careful consideration is needed when rolling period is used. Importantly, the same strategy (fixed or rolling window) should be used in pre-treatment period if intra-patient comparisons are performed.

The secondary endpoints should include both responder analysis (with different thresholds of transfusion reduction) and continuous variables (mean change) which allows a better assessment of the treatment effect, rather than relying on responder outcomes only.

Secondary endpoints could also include change in haemoglobin (continuous) and proportion achieving prespecified Hb thresholds, biological parameters with iron metabolism assessment, markers of haemolysis and erythropoiesis and PK/PD measures and clinical parameters with percent reduction in RBC transfusion burden and evaluation of transfusion independence.

Among secondary or exploratory endpoints, HRQOL measures should be included as well as relevant age-specific PROs.

Clinical endpoints in NTDT

The targeted population should be anaemic but not transfusion-dependent and this could be defined as administration of ≤5 RBC units during the 24-week period before randomisation and no RBC transfusions ≤8 weeks before providing informed consent and during the Screening Period.

In NTDT, a binary Hb responder endpoint (e.g. ≥1.0 g/dL increase over the whole study period or Weeks 12–24) is acceptable and aligns with prior precedents; continuous Hb change may be provided as supportive. Inclusion of the whole treatment study period in the analysis is preferred. Applicants should justify the clinical meaningfulness of the chosen metric and specify handling of intercurrent events.

Of particular relevance to support the results from the primary endpoint with documented clinical benefit will be the secondary endpoints. In this scenario, HRQOL and patient-related outcomes (PRO)s are particularly relevant. Indeed, the impact of the Hb change on the clinical symptoms of anaemia could be supported by participant self-reported fatigue outcomes. However, the interpretation of PROs could be subject to multiple biases. Generally, a PRO tool to be used as confirmatory evidence should be age specific appropriately validated in the target thalassaemia population. See section on PRO on HRQoL below for additional information.

Transfusion reduction, as pre-specified in the protocol, and clinically relevant should be also considered.

Iron overload

Evaluation of tissue iron content in the organs using non-invasive imaging approaches such as with T2* magnetic resonance imaging should be considered as supportive endpoints in assessing the impact of treatment on tissue iron concentrations. Improvements in liver and cardiac iron content are important correlations for the risk of end-organ damage. In addition, laboratory measures of iron overload, including serum ferritin, and markers of hemolysis should be included.

Patient-reported outcomes on HRQoL

Previously used tools to measure health status and QoL in adults with TDT across these domains. Patient-reported outcome tools utilised in HSCT studies include the EuroQol Quality of Life Scale (EQ-5D-5L) and the FACT-BMT, while the EQ-5D-Y and PedsQL Core are tools for measuring general well-being and overall health status in children and their caregivers. Reference is made to the 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) and to EMA Reflection paper on patient experience data (EMA/CHMP/PRAC/148869/2025).

4.3.2. Methodological considerations

The intercurrent events and their handling need 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. 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.

Transfusion, use/change of concomitant treatments, dose modifications, use of rescue medication and treatment discontinuation are of interest in the evaluation of assigned treatment and relevant intercurrent event.

The primary regulatory interest is in the outcome regardless of whether patients discontinue the treatment (treatment policy strategy). Correspondingly, the outcome after the discontinuation of treatment is relevant for the regulatory assessment and all efforts should be made to collect them. While certain intercurrent events (e.g. transfusion or major treatment change) may indicate lack of efficacy, reductions in such events may conversely reflect treatment benefit and should be interpreted accordingly. In the case there are other ICEs or other estimands of interest, they should be clearly prespecified.

The following subgroup analyses should be conducted and pre-specified in the study protocols, defining subgroups by:

- Transfusion burden (TDT/NTDT) (if combined populations (TDT and NTDT) are enrolled)

- Thalassaemia type (genotype), especially in TDT

- Previous splenectomy (prior splenectomy may impact transfusion needs, iron handling and haemolysis markers)

It should be considered to use the above listed factors for stratified randomisation. All relevant paediatric age groups should be addressed.

An adequate number of patients should be included to permit a meaningful evaluation of efficacy and safety. This applies especially to clinical trials in which patients with various genotypes, e.g. both β- and α-thalassaemia, are eligible. 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.

4.4. Safety aspects

4.4.1. *Specific effects*

The occurrence of a wide spectrum of adverse effects should be carefully monitored for any new agent to capture and document AEs related to mechanism of action and thalassaemia comorbidity (e.g. thromboembolic events) and collect post-discontinuation effects (e.g. exacerbation of anaemia/iron rebound). Special efforts should be made to capture potential adverse events that could be related to the mechanism of action and the pharmacodynamic properties of the medicine being investigated based on findings from non-clinical studies. Monitoring for occurrence of Venous Thromboembolic Events (VTEs) is of importance.

Specifically for gene therapies, the safety database should aim at identifying any adverse events linked to the transgene product and/or to the vector or the transduction mechanism, paying particular attention to the events mentioned 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 ICH E1 guideline, Guideline on the Extent of Population Exposure to assess Clinical Safety.

Given the rare nature of the disease in the EU 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 studies (PASS) and/or registry-based 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- and 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 be described and separated to distinguish disease-related events (e.g. anaemia severity, iron overload) from AEs. Disease manifestations should only be recorded as AEs when they meet TEAE/SAE definition.

4.5. Studies in special populations

4.5.1. Studies in paediatric patients

For characterisation of the medicines' effects 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 thalassaemia. Since the pathophysiology and current standard of care treatment for thalassaemia 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).

Except for gene therapy, inclusion of children ≥12 years of age together with adult patients in a phase 3 study is generally possible, depending on already available data, but a staggered enrolment approach might be needed (depending on phase 2 results, or eventually following a predefined interim analysis). Enough paediatric patients from 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. 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.

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.

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.

4.5.2. Studies in older patients

Similarly to the average older adults' population, older adults (65 years and older) with thalassaemia 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 pharmacokinetics, 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 on studies in support of special populations: geriatrics).

As with any other subpopulation, an adequate number of older adult patients should therefore be included in the Phase III studies, and inclusion or exclusion criteria in terms of age need to be adequately justified. A sub-group analysis should be considered. The results, as well as the lack of such data, are informative and will usually need to be mentioned in the SmPC.