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Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia

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Executive summary

This guideline describes the information on the clinical development to be documented when an application for a marketing authorisation for a medicinal product is made for the treatment of chronic primary immune thrombocytopenia. The purpose of this guidance is to provide a harmonised regulatory approach that will lead to a consistent assessment of products by regulators and set clear standards for industry.

1. Introduction

Primary **i**mmune **t**hrombocyto**p**enia (ITP) is an acquired immune mediated disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count less than 100 x 10^9/L, and the absence of any underlying cause. Until recently, the abbreviation ITP stood for idiopathic thrombocytopenic purpura, but due to the current knowledge of the immune mediated mechanism of the disease, and the absence or minimal signs of bleeding in most cases have led to a revision of the terminology.

In Europe, adult ITP has an incidence of 1.6 to 3.9 cases per 100,000 per year with increasing incidence with older age and equal for the sexes except in the mid-adult years (30-60 years), when the disease is more prevalent in women. Childhood ITP has an incidence of between 1.9 and 6.4 per 100,000 per year with equal distribution between the sexes.

ITP is classified by duration into newly diagnosed, persistent (3-12 months' duration) and chronic (≥ 12 months' duration). Whereas ITP in adults typically has an insidious onset with no preceding viral or other illness and it normally follows a chronic course, ITP in children is usually short-lived with at least two-thirds recovering spontaneously within 6 months.

Signs and symptoms vary widely. Many patients have either no symptoms or minimal bruising, whereas others experience serious bleeding, which may include gastrointestinal haemorrhage, extensive skin and mucosal haemorrhage, or intracranial haemorrhage. The severity of thrombocytopenia correlates to some extent but not completely with the bleeding risk. Additional factors (e.g., age, lifestyle factors, uraemia) affect the risk and should be evaluated before the appropriate management is determined. Although haemorrhagic death is a major concern it has been reported that the estimated rate of fatal haemorrhage is around 0.02 to 0.04 cases per adult patient-year risk.

Diagnosis of ITP is one of exclusion, when the history, physical examination, complete blood count and examination of peripheral blood smear do not suggest other aetiology for the thrombocytopenia. Physical examination should be normal apart from bleeding signs. The peripheral blood count reveals isolated thrombocytopenia and normal red cell and white cell indices. If significant bleeding occurs there may be anaemia proportional to the degree of bleeding with possible iron deficiency. The peripheral blood smear reveals normal to large platelets in size and no abnormalities should be seen in red and white cell morphology. Bone marrow examination is currently not routinely conducted in patients with typical ITP presentations but reserved to selected cases such as those with an atypical presentation.

The major goal for treatment of ITP is to provide a platelet count that prevents major bleeding rather than correcting the platelet count to normal levels. The management of ITP should be tailored to the individual patient and it is rarely indicated in those with platelet counts above 50 x 10^9/L in the absence of bleeding, trauma, surgery or high risk factors (e.g. patients on anticoagulation therapy). The management of ITP varies widely. First line treatment options include corticosteroids, intravenous

immunoglobulin (IV Ig) and intravenous anti-D immunoglobulin (the latter only for non-splenectomised Rh(D)positive patients). Patients who fail to respond or who relapse face the options of treatment with second line drug therapy or splenectomy but there is no clear evidence to support the best approach. Splenectomy can provide long term efficacy in around 60% of cases. Second line drug therapies include high dose dexamethasone or methylprednisolone, high dose IV Ig or anti-D Ig, vinca alkaloids and danazol, the immunosuppressants cyclophosphamide, azathioprine and cyclosporine or mycophenolate mofetil, and the anti CD-20 monoclonal antibody rituximab.

ITP is a disease of increased platelet destruction but recent evidence suggests that suboptimal platelet production by suppression of megakaryocyte function also occurs. Thrombopoietin receptor (TPO-R) agonists activate the thrombopoietin receptor (c-Mpl) which is the primary factor that regulates platelet production. Treatment aimed at increasing the platelet production has become a potential treatment option and TPO-R agonists have been approved in the EU as second line therapy for the treatment of chronic ITP.

2. Scope

This guidance covers relevant aspects on the clinical studies to be conducted to assess the efficacy and safety of medicinal products intended for the treatment of chronic ITP.

This guideline does not cover primary immune (idiopathic) thrombocytopenia of less than 12 months duration or secondary thrombocytopenia (immune or non-immune) as the intended indications. Secondary immune thrombocytopenia (also known as secondary ITP) includes all forms of immune-mediated thrombocytopenia due to an underlying disease (e.g. HIV, systemic lupus erythematosus) or drugs (e.g. quinine, heparin) where the treatment is targeted toward the underlying medical condition not requiring the immunomodulation often used in primary ITP.

3. Legal basis and relevant guidelines

This document should be read in conjunction with Directive 2001/83/EC, as amended and relevant provisions of Regulation (EC) No 141/2000 on orphan medicinal products.

In addition, relevant CHMP guidelines should be taken into account. These include but are not limited to:

- Statistical Principles for Clinical Trials – CPMP/ICH/363/96 (ICH E9)
- Choice of Control Group in Clinical Trials – CPMP/ICH/364/96 (ICH E10)
- Points to consider on Missing data – CPMP/EWP/177/99
- Clinical investigation of medicinal products in the paediatric population – CPMP/ICH/2711/99 ICH11)
- Choice of the Non-Inferiority margin – EMEA/CPMP/EWP/2158/99
- Pharmacokinetic studies in man (EudraLex vol. 3C C3A)
- Note for Guidance on the Investigation of Drug Interactions - CPMP/EWP/560/95
- Dose Response Information to Support Drug Registration - CPMP/ICH/378/95 (ICH E4)
- Note for Guidance on Population Exposure: The Extent of Population Exposure to assess Clinical Safety - CHMP/ICH/375/95 (ICH E1)

- Guideline on good pharmacovigilance practices, Module V - Risk management systems (EMA/838713/2011)

4. Strategy and design of clinical trials

4.1. Subject characteristics and selection (relevant target population)

Diagnosis of chronic ITP

Patients should have confirmed primary chronic ITP (lasting > 12 months since diagnosis) and particular attention should be given to the following:

- A full blood count should be normal except for the isolated thrombocytopenia. However, if patients with bleeding symptoms are included in the clinical studies a low haemoglobin level may be acceptable but should be at least above 9 g/dL. If anaemia due to bleeding is recorded the reticulocyte count should be measured to exclude reduced erythropoiesis by bone marrow impairment and a negative direct antiglobulin test (DAT) be documented.
- Negative test for Helicobacter pylori will be required preferably by the urea breath test or stool antigen test. Serologic tests should be avoided because they are less sensitive and less specific than the other tests and they have also shown false positive results after the administration of IVIg.
- Screening for anti-nuclear antibodies (ANA) and anti-phospholipid antibodies (APLA) including anticardiolipin and lupus anticoagulant will be required. The co-existence of these types of antibodies in the absence of clinical manifestations suggestive of SLE and/or antiphospholipid syndrome, does not qualify these cases as secondary ITP. It has been reported that the presence of APLA do not appear to affect the treatment of ITP. Therefore, patients with a positive test can be included in the clinical studies providing they do not have any clinical manifestation of SLE or antiphospholipid syndrome. However, patient stratification should be considered.
- Bone marrow examination (aspirate and a biopsy) at baseline will be required for confirmation of diagnosis, especially in older population or those patients with non-typical presentation. In some situations bone marrow examination may also be required for other purpose; e.g. the use of TPO-R agonists has been associated with reports of an increase in bone marrow reticulin.

Exclusion criteria for entering clinical studies apply to all causes of secondary ITP (e.g viral infections, thyroid disease) or the presence of autoimmune haemolytic anaemia. Normal quantitative Ig levels and a negative test for thyroglobulin should be recorded at baseline.

Exclusion criteria also apply to clotting disorders including previous and recent history of thrombosis (arterial or venous), or the presence of significant risk factors for thrombosis because of the thrombotic risk associated with some therapies (e.g. TPO-R agonists, rituximab and IVIg). In general, a normal clotting screen at baseline will be required. However, patients with an isolated event of thrombosis that occurred more than 1 year before entering the study and without any other significant risk factors for thrombosis may be allowed to enter the studies.

Entry platelet count

In general the platelet count should be at least < 30 x 10^9/L. The mean of three baseline platelet counts should be performed and no individual platelet count should be above 35 x 10^9/L.

However, in specific clinical settings, patients on steroids or in patients with bleeding symptoms a platelet count < 50 x 10^9/L may be appropriate. If patients with platelet counts below 50 x 10^9/L are included in the study stratification by the level of thrombocytopenia (< 30 x 10^9/L and > 30 but < 50 x 10^9/L) is recommended.

Storage of EDTA blood samples can produce artefacts in the analysis of several haematology parameters. Therefore local laboratories assessing platelet counts will be considered acceptable providing appropriate quality controls are in place. In particular, blood sampling conditions and time allowed between blood sampling and platelet measurement should be specified. All other laboratory assessments should be performed in central laboratories.

Previous treatments

Patients with chronic ITP are expected to have received at least one previous treatment. The type of previous treatment(s), dose/schedule, duration, response (if any), and interval of time since last administered should be documented.

Excluding studies which are evaluating an add-on treatment, patients should be off treatment for a time sufficient to exclude a late effect when entering the study. This amount of time will vary depending on the specific prior treatments.

Splenectomy will count as one type of previous treatment. Ideally clinical studies should try to enrol splenectomised as well as non-splenectomised patients. Patients who relapsed following an initial response to splenectomy should have an assessment for accessory spleen before entering the studies.

A distinction between refractory patients and patients unresponsive to one or more agents should be made and if both groups of patients are enrolled in the clinical study stratification is recommended.

a. Refractory ITP

Refractory ITP requires <u>all</u> the following criteria to be met:

- Failure to achieve a response (R or CR) after splenectomy or loss of response after splenectomy.

- Need of treatment(s) (including but not limited to low dose of corticosteroids) to reduce the risk of clinically significant bleeding. The need of on-demand or adjunctive therapy alone does not qualify the patient as refractory.

b. ITP unresponsive to one or more agents

Unsplenectomised patients who have not responded to previous treatment(s).

Concomitant treatments

On entering clinical studies patients may be allowed concomitant specific anti-ITP medications providing they have been on a stable treatment dose/schedule for at least one month prior to enrolment. The use of concomitant treatments should be considered as a stratification factor.

Concomitant medications that may be allowed include steroids, azathioprine, danazol, cyclosporin and mycophenolate mofetil. Details of the concomitant treatment such as type of treatment, dose or

duration will be required. Anticoagulants or drugs that affect the platelet function such as aspirin or NSAIDs will not be allowed.

4.2. Therapeutic goal

The major goal for treatment in primary ITP is to provide a safe platelet count to prevent or stop bleeding rather than correcting the platelet count to normal levels. Unnecessary treatment of asymptomatic patients with mild degrees of thrombocytopenia should be avoided.

In chronic ITP the goal of treatment is also to avoid or defer the risks of more toxic treatments (e.g. splenectomy or immunosuppression), reduce corticosteroid exposure to minimum levels and achieve long-lasting responses. On-demand treatment at the time of or in anticipation of high risk bleeding or surgical procedures is another approach that is often warranted.

4.3. Clinical pharmacology

Pharmacokinetics

The pharmacokinetics (PK) of the drug should be investigated following existing guidelines. Relevant studies according to the target population (e.g. refractory chronic ITP or un-splenectomised patients), proposed indication (e.g. emergency haemorrhage), duration of treatment (e.g. once only or chronic use) or medicinal product characteristics (e.g. biological) should be conducted.

Additionally, population PK studies are recommended in order to describe the PK characteristics of the drug and to identify potential covariates as predictors of drug exposure. It is particularly important for studies conducted in small populations that the collection of data on dosage, time of dosing and time of blood sampling is accurate. Consideration should be given to the quality and quantity of relevant data characterising the pharmacokinetics of the drug when designing the blood sampling protocol. Sparse blood sampling may not be adequately informative and more frequent sampling may be necessary.

Drug-drug interaction studies

In chronic ITP patients are often co-administered several therapies. Clinical implications of the use of pre-medication (e.g. steroids prior to anti-D Ig or IVIg), concomitant medication or rescue medication should be evaluated in accordance with current CHMP Note for Guidance on the Investigation of Drug Interactions.

Pharmacodynamics

Dosing will be based on the need to achieve a platelet count that is effective in the prevention of bleeding but safe against a thrombosis risk. Therefore, blood platelet count is considered a valid PD marker. A maximum level should be pre-defined as dosing stopping criteria (e.g. blood platelet count $>500 \times 10^9$/L) that may not correlate to the standard maximum tolerated dose approach.

The pharmacodynamic effects of the drug should be explored for both platelet count and function, including platelet adhesion, aggregation and activation.

In the case of biological medicinal products the risk for immunogenicity should be addressed, in particular the potential cross-reactivity seen in TPO-R agonists with endogenous thrombopoietin.

Studies designed to explore mechanisms of resistance to therapies, synergistic effects and cross resistance with other drugs and tolerability with repeat use are encouraged.

PK/PD model and simulation

Chronic ITP carries an orphan designation and the use of a PK/PD model is encouraged to describe the time course of drug activity leading to appropriate dosing recommendations. Clinical pharmacology studies able to describe a dose-exposure-response relationship can lead to establishing doses for further phase II/III trials.

Until recently thrombopoiesis was assumed to be similar in chronic ITP patients compared to healthy volunteers (HV) although platelets are destroyed earlier in ITP. Recent evidence suggests an impaired platelet production plays part in the pathogenesis of the disease. Baseline platelet counts will be higher in HV and the response to treatments and life span of platelets may be different compared to patients. Therefore, a combined population PK/PD analysis (exposure-response model) may be performed using the populations of HV and patients as covariates. If separate population PK/PD analyses are performed for HV and patients the same base structural model should be used to allow comparison of the model parameters and identification of differences between the healthy and disease populations. Covariates predictive of higher platelet counts based on PK or PD differences should be explored. A distinction should be made between predictors of plasma drug exposure and predictors of sensitivity to the drug.

Studies conducted in ITP patients should be stratified on the basis of current ITP medication (if any), prior splenectomy and baseline platelet counts. Randomised studies in healthy volunteers should be balanced to allow comparison data to studies in ITP patients. For example, as the prevalence of ITP is higher in female than male patients of mid adult age recruiting fewer female healthy volunteers than male may limit data comparison.

The duration of the studies should allow for sufficient follow-up assessments after discontinuation of medication and will depend on the predicted PK and PD characteristics of the individual drug. Time to initial response (when a response can be expected) and time to peak response (after which a response to the drug becomes less likely to occur) should be described when possible.

If patients are administered concomitant medication it should be included as a covariate and careful consideration should be given to the interpretation of the data.

Data arising from PK/PD model analyses will be expected to be in line with prior information based on in vitro studies, preclinical or literature data.

Based on the PK/PD analyses in patients and healthy volunteers a model based simulation for ITP patients could be done to estimate platelet response for different dosing regimens, subpopulations and dose modification recommendations based on platelet counts. This model simulation should aim to determine the impact of dose escalation, dose reduction and dose stopping.

Relevant covariates should be evaluated through simulations (e.g. gender, age, baseline platelet count, concomitant corticosteroid use etc). Ultimately, the estimation of any covariate effect should be discussed in relation to its clinical relevance.

The model qualification will be essential to allow extrapolation of the data generated and the report should be sufficiently detailed. Adherence should be measured as part of the study. A supporting narrative of the assumptions inherent in the modelling process, justification of these assumptions and sensitivity analysis aimed to identify the critical assumptions and consequent uncertainty in the simulation results will be expected.

How the final results from the PK/PD model simulation will be used should be well described in the report including, but not limited to, support the design of phase II /III confirmatory studies where additional PK/PD data may be collected to confirm any PK/PD assumption.

4.4. Therapeutic studies

4.4.1 Dose finding studies

Dose finding studies are required for new medicinal products with the objective of finding a starting dose, a response-guided titration guide and a stopping dose or response beyond which there is lack of further benefit or unacceptable undesirable effects.

Dose response data from studies conducted earlier in the development as part of the PK/PD profile of the drug are expected to contribute in identifying the selected study doses.

- The shape and location of a population dose response curve for desirable and undesirable effects and the observed PD and PK inter-subject variability will normally determine the starting dose with any adjustments (e.g. patient weight, race etc). Choosing a high starting dose that is well tolerated without exploring lower doses should be avoided especially if the treatment is intended for chronic use. The dosing interval should be justified by appropriate PK/PD data.
- Doses should be evaluated for a platelet target level and range. A target level of peak platelet count that has doubled from baseline but is within the range of 50-400 x 10^9/L without the need of rescue medication is appropriate.
- Studies are required to fully describe dose-dependency for platelet count so a dose titration regimen can be identified. Studies should also define a median time to target level (important in drugs intended for a very quick response) and when possible explore the durability of the response.
- A dose and response stopping criteria should be identified.

The choice of study design will depend on the target indication and the specific target population as well as any other specific drug characteristics, e.g. if given with concomitant medication. In general conducting randomized trials in patients with chronic ITP that have failed at least one prior treatment will be expected although additional studies in healthy volunteers may be of value. Platelet response on pre-specified timepoint(s) should in general be expected as the primary endpoint. However, the exact definition of the endpoint will also depend on the stage of the clinical development.

A wide range of doses should be explored and compared with placebo although in some cases the inclusion of an active control may be helpful for data assessment. To ensure an appropriate range of doses are tested an interim analysis should be planned with the possibility to broaden the study dose range.

In the end, data from all sources and not limited to specific studies should be analysed for dose response information and may include multivariate or other alternative approaches for dose related covariate effects.

4.4.2 Confirmatory studies

Confirmatory trials are necessary to provide evidence of efficacy and safety. This part of the guideline focuses in the efficacy aspects while safety evaluation is discussed in section 6.

As this guideline is intended for medicinal products for the treatment of chronic ITP and is not type class specific, a section with general recommendations is included first followed by a detailed section with clear definitions of some aspects to be considered in the study design.

4.4.2.1 *General aspects of study design*

In general, a parallel group *design* that includes the test drug at one or more doses, and one or more control treatments (placebo and/or active comparator) is appropriate although the use of other study designs may be acceptable depending on the objective of the trial.

A *multicentre* trial will be expected for accruing sufficient number of subjects. However, the inclusion of a wider population that can be representative of EU patient population and clinical practices should be ensured. Procedures should be standardised to reduce variability in evaluation criteria, for example training of personnel responsible for blood sample collection, with careful monitoring during the trial.

Randomisation will be required and stratification should be conducted taking into account its feasibility and subsequent calculated sample size together with the choice of stratification factors. Stratification factors to be considered may include splenectomy status, baseline platelet counts and the use of concomitant ITP treatment. A maximum number of three stratification factors is recommended and will ultimately depend on the target indication. Stratification factors will be expected to be taken into account in the analysis plan.

A double *blind* trial is the optimal approach but it may not be always feasible. During the study the investigators will require rapid laboratory results for dosing decisions and both investigators and subjects will be aware of the platelet count results. Blinding conditions may be compromised in a placebo controlled design. In such cases, single- blinding of relevant staff (e.g. laboratory personnel) should be considered.

The use of local *laboratories* for haematological blood counts and safety assessments is acceptable providing adequate quality controls are in place. Other assessments should be done in central laboratories.

Efficacy is normally better confirmed by demonstrating *superiority* to placebo and/or an active control. In some cases the use of a *non-inferiority* trial may be acceptable. There is currently a wide range of therapeutic options for patients with chronic ITP although only TPO-R agonists have been approved based on reasonably large randomised controlled studies and therefore provide a reliable basis for non-inferiority evaluation. Available second-line treatments in ITP can be categorized into those that are given once (or for only one course) and are intended to induce long term remission (e.g. splenectomy, rituximab), and those that require continued or chronic administration (e.g. corticosteroids, immunosuppression, TPO-R agonists).

The final study design and choice of *control* will depend on the nature of the product and the objectives of the trial, eg if the medicinal product is intended for the long term treatment of chronic ITP or only for short term control, in the context of available standard therapies and ethical considerations taking into account relevant guidelines *(Statistical Principles for Clinical Trials - CPMP/ICH/363/96 (ICH E9)* and *Choice of Control Group in Clinical Trials – CPMP/ICH/364/96 (ICH E10)*.

The inclusion of a placebo control with or without active comparator when possible is strongly encouraged. For example of active comparators, an experimental drug intended to be used in unsplenectomised patients as a short course treatment but with long term effect may be evaluated in a trial against splenectomy. However, if the target population is splenectomised patients but still intended to be given as short course treatment with long term effect a trial against rituximab may be considered. On the contrary, an experimental TPO-R agonist drug intended for chronic use may be studied in trial against another approved TPO-R agonist.

Because the type of trial depends on the objectives and chosen comparators the use of a superiority or non-inferiority design may both be acceptable. For example, an experimental TPO-R agonist drug intended for chronic use may be studied against an approved TPO-R agonist using a non-inferiority design . In this case the trial characteristics, in particular in the absence of a placebo control, should be the same or very similar to the study characteristics in which the active comparator (in this case the TPO-R agonist) demonstrated efficacy. This may provide assurance of assay sensitivity. Exclusion criteria should apply for subjects with a history of no response or poor response to the active comparator. The choice of non-inferiority margin should be clinically justified (reference is made to *Choice of the Non-Inferiority margin - CPMP/EWP/2158/99)*

Any dose titration guideline used in a confirmatory study should be pre specified and may be supported by data on medicinal products of the same therapeutic class/mechanism of action and any early phase I/II data.

The choice of the primary and secondary *endpoints* will also ultimately depend on the objectives of the trial.

The *primary endpoint* is expected to be the variable able to provide the most clinically relevant evidence of efficacy related to the primary objective. The platelet blood count is generally used as a valid surrogate in ITP because it measures treatment activity and is believed to be a reliable predictor of clinical benefit.

The increase in blood platelet count (CR or R) should be considered as primary endpoint. However, depending on the nature of the product and the study design it may be appropriate to use a composite or multiple variable as primary endpoint if clinically meaningful and validated (e.g. increase in platelet count of a pre-specified minimum time duration with the absence of bleeding symptoms). The primary endpoint should be well defined in the protocol with a justification of the clinical relevance and the validity of the measurement procedures.

For example, a trial against splenectomy may include as the primary endpoint response in platelet increase with the absence of bleeding for at least one year without the use of concomitant treatment (see also definition of quality of response section 4.4.2.2).

Secondary endpoints should also have an explanation on their clinical relevance and their role in the interpretation of the results. Relevant variables in chronic ITP include bleeding signs/symptoms, time to response, duration of response, concomitant treatment reduction, need for rescue treatment and safety (e.g. rebound thrombocytopenia or a predefined exceedingly high platelet count may be considered an AE).

Further details on the definitions of endpoints are given in section 4.4.2.2.

The *duration* of a confirmatory clinical study will also depend on the nature of the experimental drug and the objectives of the trial. For example, in a non inferiority study comparing a new TPO-R agonist versus an approved TPO-R agonist a study duration of approximate one year, including 6 months treatment and further up to 6 months follow up may be acceptable. On the contrary, a study comparing a new drug versus splenectomy will require a longer duration as up to 20% of patients that respond to splenectomy may relapse months after the procedure.

4.4.2.2 *Detailed study considerations in chronic ITP*

The following are clinically meaningful definitions to be considered in the study design and to help in the definition of study endpoints.

Quality of response

The platelet count is a useful measure of response that is objective, clinically relevant and easily compared. Baseline platelet count refers to platelet count at the time of starting the experimental drug. Platelet counts should be confirmed on at least two separate occasions, at least 7 days apart when used to define CR/R or 1 day apart when used to define NR or loss of response. The definition of response also requires concurrent resolution of bleeding symptoms.

- Complete response (CR): any platelet count $\geq 100 \times 10^9$/L and absence of bleeding
- Response (R): any platelet count between 30 and 100×10^9/L and at least doubling of the baseline count and absence of bleeding
- No Response (NR): any platelet count $< 30 \times 10^9$/L or less than doubling of the baseline count or bleeding
- Time to response: time from starting treatment to time to reach CR or R. A late response (CR/R) not attributable to the experimental drug can not be defined as CR or R
- Loss of CR: platelet count $< 100 \times 10^9$/L or bleeding
- Loss of R: platelet count $< 30 \times 10^9$/L or less than doubling of the baseline count or bleeding

CR or R with or without concomitant administration of investigational drug should be documented.

- Response in Refractory ITP: ability to maintain a platelet count sufficient to prevent clinically significant bleeding. Decrease in the use of other treatments (e.g. steroids) should be reported.
- Response to on-demand therapy:

  Control of bleeding in a specific situation

  Achievement of a platelet count sufficient to perform procedure or minimize bleeding from trauma (in most cases platelet count 50-70 $x10^9$/L)

Timing of assessment of response

The frequency of monitoring platelet counts and the timing of assessment of response depends on the pharmacodynamics of the experimental drug and comparator(s). It should also take into account the expected time to initial response and time to peak response.

- Time to initial response or when a response is expected
- Time to peak response after which a response is less likely to occur

Duration response

The assessment of duration of response may vary depending of the objectives of the study, especially if the study drug is intended as a short term treatment, such as to cover a period of increased risk (e.g. surgery), or for continuous therapy.

- Measured from the achievement of CR or R to loss of CR or R. This approach may be used if the experimental drug is intended to be used as a short course treatment aimed at inducing prolonged remission of the disease. It could be calculated using a time-dependent analysis such as Kaplan-Meier.

- Proportion of the cumulative time spent in CR or R during study period as well as total time from which the proportion is derived. This approach is suitable for continuous or intermittent repeated administration of experimental drugs that require dose adjustments with anticipated temporary losses of CR or R (e.g. more appropriate for TPO agonists). An upper limit of acceptable platelet count may be predefined and the cumulative time spent within a therapeutic window may be more suitable.

When response duration includes time receiving treatment, this should be specified, and CR or R with or without concomitant treatment should be calculated and reported separately.

Assessment of bleeding

A standardised bleeding assessment tool will aid to examine the relationship between the surrogate laboratory parameter of platelet count and bleeding. However, a validated method for objective quantification of bleeding symptoms in ITP has not been established although several bleeding scales are available including TIMI, GUSTO, WHO and the ITP bleeding scale (IBLS).

The IBLS is the only scale with 11 site specific distinct grades and incorporates both history and physical examination to improve detection of fluctuating signs and symptoms which are a characteristic of ITP. Other scales may also be acceptable providing a discussion on their validity is submitted.

Concomitant and rescue medication

Corticosteroid dependence is defined as the need for ongoing or repeated doses administration of corticosteroids for at least 2 months in order to maintain a platelet count $\geq 30 \times 10^9$/L and/or avoid bleeding.

When concomitant and rescue medication specific for ITP (e.g. steroids) is given during trial in addition to the experimental drug full details should be provided including time of its discontinuation. The selected rescue medication should be justified and may include several therapy alternatives.

Corticosteroid dependent or other treatment dependent patients excluding the experimental drug will be considered as non-responders. Associated reduced doses or frequency of corticosteroids or other treatment dependence should be recorded as partial effect/activity of the experimental drug, even if below the level required to achieve CR or R.

5. Studies in special populations

5.1. Paediatrics

In general, other sections of this guideline still apply for studies required in the paediatric population and the guideline on *Clinical Investigation of medicinal products in the paediatric population -CPMP/ICH/2711/99 (ICH11)* should be followed but some further specific recommendations are included here for consideration.

Although presentation of ITP in children is generally acute and in around 60% of cases has a history of previous infection, bruising and purpura may develop slowly over weeks or months suggesting a chronic course. ITP in children is usually of short duration with at least two thirds

recovering spontaneously within 6 months. Older children are more likely to have a chronic disease. A waiver for children under 1 year of age is applicable. Because of the very low incidence of chronic ITP in those under 3 years of age it is normally acceptable to conduct clinical studies according to the following age cohorts:

≥ 1 year to < 6 years
6 years to <12 years
12 years to < 18 years

Severe bleeding tends to occur when the platelet count falls below 10 x 10^9/L and the incidence of intracranial haemorrhage in children with ITP has been reported to approximately 0.1% to 0.5%. Diagnosis is as for adults one of exclusion. However, mild splenomegaly may be found on examination in some younger patients.

The following points should be considered prior to entering clinical studies:

- Testing for Helicobacter pylori is not recommended in children except in high-prevalence areas. A negative test will be required in these areas.
- Screening for antinuclear antibodies (ANA) should be conducted because a positive test has been associated with chronicity in childhood ITP. If ANA positive patients are included in the studies stratification should be considered.
- Diagnosis of familial inherited thrombocytopenia should be excluded

The management of children with chronic ITP is the same as those with newly diagnosed ITP. In general the aim of treatment is to maintain a haemostatic platelet count with a first line therapy (e.g. IV Immunoglobulins) and to minimize the use of prolonged corticosteroid therapy. For those patients who fail to respond to first line treatment further options include dexamethasone, high dose methylprednisolone, rituximab, splenectomy and immunosuppression or immunomodulation (eg ciclosporin) as single or combination therapies. Unlike adults with chronic ITP, splenectomy is rarely recommended in children because the risk of death from ITP is very low compared to the risk of sepsis and it is normally delayed for at least 12 months. Therefore, the definition of refractory chronic ITP that is used for adults may not apply for children. As for adults, the choice of study design would depend on the objectives of the trial.

Efficacy should be shown in controlled clinical trials in children. Studies well characterising the long-term safety and the PK/PD relationship in children and in relation to adults, may be acceptable for authorisation in case of a strong rationale for extrapolation of efficacy from adults, availability of relevant data in the adult population and absence of paediatric-specific safety concerns. Extrapolation methods should be pre-defined for the paediatric development and before pivotal paediatric studies.

Clinical classification of children with ITP by severity of bleeding[2] (Table 1) is useful to guide management and may be considered when designing a confirmatory study. The severity of mucocutaneous bleeding does not predict the risk for life-threatening bleeding and patients should be treated taking into account other factors such as the platelet count, activity profile and psychosocial issues.

Table 1. Grade of severity and management of paediatric patients with ITP[2]

Bleeding/Quality of life	Management
Grade 1 Minor bleeding Few petechiae (≤ 100) and/or ≤ 5 small bruises (≤ 3 cm in diameter) No mucosal bleeding	Observation
Grade 2 Mild bleeding Many petechiae (>100) and/or > 5 large bruises (> 3 cm in diameter) No mucosal bleeding	Observation
Grade 3 Moderate bleeding Overt mucosal bleeding Troublesome lifestyle	Intervention to reach grade 1/2 in selected children
Grade 4 Mucosal bleeding or suspected internal haemorrhage	Intervention

Patient-reported outcomes and health related quality of life measures may be useful for the evaluation of treatment. A disease specific tool for ITP, the **Ki**ds' **I**TP **T**ools (KIT), has been developed and can be used as a secondary outcome measure.

5.2 Elderly population

Primary ITP in the elderly is a very rare condition but the enrolment of elderly patients in clinical studies is strongly encouraged.

6. Safety

6.1 General considerations

Prior to approval the safety database should be sufficient to characterise the safety profile of the medicinal product but it is expected to reflect the orphan status of the disease. Due to the chronic nature of this disease a minimum of 12 month data in the target population will be expected but longer periods may be required. However, the extent of safety data will ultimately depend on the nature of the study drug and its intended use, long term therapy or only for short term control.

The use of rescue medication should be fully documented in a confirmatory trial but consideration should also be given to the potential adverse effects of the concomitant therapy.

If applicable, immunogenicity should be addressed.

6.2 Specific adverse events

Primary chronic ITP including recommended therapies, have been associated with an increased risk of infections, bleeding episodes requiring hospitalization, arterial and venous thromboembolism, haematological malignancies and mortality. The potential risk for rebound thrombocytopenia following cessation of treatment or an unacceptably high blood level of platelets should be investigated. Studies should be designed to capture all such relevant safety data.

A focus on specific adverse events known for the corresponding substance class should also be characterised. These adverse events might occur after drug discontinuation and should be evaluated and documented for an appropriate length of time.

For example, in the case of a TPO-R agonist the risk of increased bone marrow reticulin should be investigated. An increased bone marrow reticulin has been demonstrated with the use of TPO-R agonists and it appears to be reversible when treatment is discontinued. It is currently unknown if this finding represents a class effect and all efforts should be taken to obtain as much information as possible on bone marrow changes associated with the use of TPO-R agonists. It is recommended to perform bone marrow assessments at baseline and at different time points in all patients included in the pivotal trial(s), especially those patients on long-term treatment. Bone marrow assessments should be conducted in central laboratories by an independent expert reviewer.

Worsened thrombocytopenia after discontinuation of treatment with TPO-R agonist has also been reported in up to 10% of patients with an increased risk of bleeding during the first 4 weeks. Platelet count normally recovers to pre-treatment levels after several weeks.

6.3 Long term safety aspects

A detailed RMP will be expected to address the likely risks and knowledge of the product. The use of registries is encouraged. The collection of post marketing safety data in special populations (eg renal or hepatic impairment) should be included in the RMP.

Definitions

The following definitions have been designed to reflect clinical practice and to standardize clinical trial design.

Primary ITP

Immune disorder characterized by an isolated thrombocytopenia (peripheral blood platelet count < 100 x 10^9/L) in the absence of other causes or disorders that may be associated with thrombocytopenia.

Secondary ITP

All forms of immune-mediated thrombocytopenia except primary ITP (for example, lupus, drug-induced, HIV).

Newly diagnosed ITP

ITP within 3 months of diagnosis

Persistent ITP

ITP between 3 to 12 months from diagnosis. Includes patients not reaching spontaneous remission or not maintaining complete response off therapy

Chronic ITP

ITP lasting more than 12 months

Severe ITP

Presence of bleeding symptoms at presentation sufficient to require treatment, or occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose

On-demand therapy

Any therapy used to temporarily increase the platelet count sufficiently to safely perform invasive procedures or in case of major bleeding or trauma

Adjunctive therapy

Any non-ITP specific therapy that may decrease bleeding. It includes antifibrinolytic agents, hormones, DDAVP, fibrin sealants and platelet transfusion.

References

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4. The immune thrombocytopenic purpura (ITP) bleeding score: assessment of bleeding in patients with ITP. L. Page *et al*, British Journal of Haematology 138, 245-248 (2007)