EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Oncology Working Party (ONCWP)

Overview of comments received on "Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia" (EMA/CHMP/153191/2013)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	EFPIA (Pär Tellner)
2	International Plasma Fractionation Association (IPFA)
3	NICE (Elisabeth George)
4	UCB (Diane Rickwood)
5	Maria Gabriella Mazzucconi
6	Francesco Rodeghiero
7	Miguel A. Sanz
8	Marc Michel
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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	**MAIN COMMENTS** We appreciate the opportunity to provide comments on the Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia released by the EMA for public consultation. We generally welcome the regulatory approach described in this document. However we have a few comments and suggestions, detailed with proposed changes in the second part of this template. The main comments are highlighted below: • Exclusion of patients with a positive Helicobacter pylori test: The rationale for excluding patients with a positive test for Helicobacter pylori is not clear. Depending on the mechanism of action of the treatment (e.g., immunological agents), the inclusion of both patients with positive tests and negative tests for Helicobacter pylori in exploratory studies such as Proof of Concept studies would be helpful as long as the study duration is short and no antibiotics are taken by research participants during the study. It may even be possible to stratify the randomization of patients by test results. This would help clarify the role of Helicobacter pylori in (chronic) ITP. In studies of longer duration, inclusion of positive Helicobacter pylori positive subjects should be allowed after they have been treated and have proven eradication of Helicobacter pylori provided there is no change in platelet counts. Furthermore, histological tests and urea-based biopsy tests could be also considered as alternatives to urea breath tests or stool antigen tests if they have been already performed and completed.	

	• <u>Stratification factors:</u> Stratification by ANA should not be considered especially as this covariant has no impact on efficacy. Furthermore as three stratifications factors are already required (baseline platelet counts, splenectomy, and concomitant ITP medication) it is not possible to add ANA as an additional stratification factor. ANA can be tested at baseline and used as a covariant in a supportive analysis of the primary endpoint if an imbalance is found across treatment groups. Stratification for APLA should not be considered either. The presence of ALPA is noted to not appear to affect treatment of ITP (line 144). In addition to the fact that there are already three stratification factors required, further stratification by ALPA would make the studies larger, which is problematic for a rare indication like ITP, especially when a randomized study is required. • <u>Bone marrow biopsies:</u> It is not feasible to do bone marrow biopsy during screening, and such a requirement may pose a problem for study enrolment. In addition this requirement is not in keeping with the current guidelines (ASH or International consensus guidelines). Bone marrow biopsies should only be required in those subjects who have not had them in the past and have a clinical reason for this test to be performed (e.g., unclear cases, or never responded to a prior ITP medication). If necessary, investigating effects on bone marrow reticulin might be accomplished in a sample of the Phase 3 study population.	See comment below. See comment below.
2	**<u>GENERAL COMMENT</u>**	

	The Guideline does not provide any comment on recommended method(s) for measuring platelet count. If no specific method(s) are preferred by the Expert Panel writing the guideline, it should be stated. In addition, the guideline should indicate if Sponsors/Applicants need to provide a rationale/justification for the method(s) used.	Not accepted. Platelet counts are generally performed by automated haematology systems, frequently using the coulter counter technology, with generally good precision. It is out of the scope of this guideline to recommend any specific method for measuring platelet counts. There is also wording in the text (lines 174 and 351) emphasising the importance of good quality controls in laboratories. It will be expected by the applicant to inform of the method use and confirm it is conducted according to good quality assurance.
3	This is a very useful document and should help any future HTA of drugs in the area of ITP. On a very general note, we would like to comment that we have, following feedback from patient organisations, changed the wording in our own documents where reference to patients is made to avoid the use of the words 'cases' or 'subjects', because patients have found those words derogatory. Also, we feel that it is not patients that who fail to respond but it is the treatment that fails. Again, patients prefer if it is not patients who relapse, are refractory or unresponsive, but it is the condition that relapses, is refractory or unresponsive.	The word "subjects" is sometimes used as it can refer to both, healthy volunteers and patients. Please note it is true the relapse/refractory/unresponsive terms relate to the disease itself but as the patients suffer from it expressions such as relapsed patients etc are commonly used in medical terms (see also text in provided literature references).
4	The draft Guideline for Chronic Primary Immune Thrombocytopenia is reflecting the experience with TPO-R agonists in this indication and focussed on efficacy and safety measures to the mode of action of this therapeutic class, which is the stimulation of platelet production to overcome the inhibition of megakaryopoieis by anti-platelet antibodies. The mode of action of other established therapies (IVIg, anti-D) is believed to act by reduction of platelet antibodies through blocking of the Fcγ-receptor of phagocytic macrophages within the mononuclear	Not accepted. The guideline has been targeted to the disease (chronic primary ITP) and not the mechanism of action by specific treatments. It has been written with the aim to help industry develop medicinal products to treat this condition, irrespective of the mechanism of action, and the text is not restricted to TPO-R agonists.

	phagocytic system. The clinical development of IVIg for ITP was outlined in the CHMP Guideline on IVIg in 2010 (Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)). Therefore it is suggested that the proposed draft guideline could refer to TPO-R agonist in particular and not be applied for other therapies with a different mode of action (e.g. depletion of platelet antibodies) as aspects on PD and the study design will be different in this therapeutic class.	
4	Is it appropriate to reference management of ITP with specific medications or suggest specific medications as comparators if they do not have a licenced indication in ITP following controlled clinical studies and have not been used in established clinical use/ part of treatment algorithms?	Reference to medications used in ITP has been mentioned to be in line with the recommendations by up to date international guidelines (references 2 and 3). Note a sentence has now been included for clarity in the introduction. A specific non EU approved treatment may be acceptable as a comparator in a clinical trial if that has been fully justified. Reference has been made in the text to the guideline *Choice of Control Group in Clinical Trials – CPMP/ICH/364/96 (ICH E10),* where it says “the control should be a drug acceptable in the region to which the study will be submitted for the same indication at the dose being studied”. A sentence has been included in the text requiring full justification of the chosen control(s).
5	**GENERAL COMMENT** All the acronyms cited in the text should be clearly explained.	Accepted. All acronyms have been explained.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 55-56	1	**Comment:** The guideline defines chronic ITP as > 12months duration. It would be useful to note that the clinical trials for current TPO-R agonists indicated for chronic ITP used a definition of chronic ITP as > 6 months (Rodeghiero et al, (2009). Standardization of Terminology, Definitions and Outcome Criteria in Immune Thrombocytopenic Purpura (ITP) of Adults and Children: Report from an International Working Group. *Blood* **113** (11) 2386-2393).	Not accepted. The mentioned paper on standardization of terminology states the term "chronic ITP" should be reserved for patients with ITP lasting more than 12 months. The clinical trials that supported the marketing authorisation of current approved TPO-R agonists were conducted years before the mentioned standardization on the ITP terminology was agreed and published.
Lines 74-75	1	**Comment:** A goal of treatment is also to improve patients' quality of life. **Proposed change:** "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. ***A further goal of treatment of ITP is to improve the quality of life of patients.***"	Partially accepted. It is acknowledged that any treatment would ultimately be aimed to improve the quality of life of the patient and this point is not specific for ITP. Text not changed.
Lines 82-85	1	**Comment:** The guideline lists a number of second line therapies. Since there are approved TPO agonists these should be added to the list of second line drug therapies. **Proposed change:** "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, the anti CD-20 monoclonal	Partially accepted. It is agreed TPO agonists are considered second line therapies and as such a specific detailed paragraph is already included. Text not changed.

		antibody rituximab***, and thrombopoeitin receptor (TPO-R) agonists***.'	
4.1. Subject characteristics and selection (relevant target population) - Diagnosis of chronic ITP	1		
Line 136 - 139	1	**Comment**: The rationale for excluding patients with a positive test for Helicobacter pylori is not clear. Depending on the mechanism of action of the treatment (e.g., immunological agents), the inclusion of both patients with positive tests and negative tests for Helicobacter pylori in exploratory studies such as Proof of Concept studies would be helpful as long as the study duration is short and no antibiotics are taken by research participants during the study. It may even be possible to stratify the randomization of patients by test results. This would help clarify the role of Helicobacter pylori in (chronic) ITP. In studies of longer duration, inclusion of positive Helicobacter pylori positive subjects should be allowed after they have been treated and have proven eradication of Helicobacter pylori provided there is no change in platelet counts. Furthermore, histological tests and urea-based biopsy tests could be also considered as alternatives to urea breath tests or stool antigen tests if they have been already performed and completed. **Proposed change:** "~~Negative test for Helicobacter pylori will be required preferably by the urea breath test or still 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.~~ ***The mechanism of action of the treatment should be***	

		primarily considered for the decision to include/exclude patients with a positive test for Helicobacter pylori. Inclusion of patients with positive tests and negative tests for Helicobacter pylori in exploratory studies should be allowed if the study is short, mainly for new immunological active treatments other than TPO-R agonists. For trials of longer duration, Helicobacter pylori positive subjects should have their Helicobacter pylori infection eradicated prior to inclusion into the trial. ***Other tests for Helicobacter pylori, such as histological tests and urea-based biopsy tests, could be considered as alternatives to urea breath test or stool antigen test, if they have been already performed and completed."***	
Lines 140-147	1	**Comment:** Stratification by ANA should not be considered especially as this covariant has no impact on efficacy. Furthermore as three stratifications factors are already required (baseline platelet counts, splenectomy, and concomitant ITP medication) it is not possible to add ANA as an additional stratification factor. ANA can be tested at baseline and used as a covariant in a supportive analysis of the primary endpoint if an imbalance is found across treatment groups. Stratification for APLA should not be considered either. The presence of ALPA is noted to not appear to affect treatment of ITP (line 144). In addition to the fact that there are already three stratification factors required, further stratification by ALPA would make the studies larger, which is problematic for a rare indication like ITP, especially when a randomized study is required. **Proposed change:** "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, p~~Patient stratification ***by ANA or ALPA*** should ***not*** be considered ***as the covariants have no impact on efficacy. However ANA and ALPA can be tested at***	Accepted. Text amended to delete stratification by ANA/APLA status and included wording to use data on ANA/APLA status as a covariant supportive analysis.

		baseline and used as a covariant in a supportive analysis of the primary endpoint if an imbalance is found across treatment groups."	
Lines 148-152	1	**Comment:** It is not feasible to do bone marrow biopsy during screening, and such a requirement may pose a problem for study enrollment. In addition, this requirement is not in keeping with the current guidelines (ASH or International consensus guidelines). Bone marrow biopsies should only be required in those subjects who have not had them in the past and have a clinical reason for this test to be performed (e.g., unclear cases, or never responded to a prior ITP medication). If necessary, investigating effects on bone marrow reticulin might be accomplished in a sample of the Phase 3 study population. **Proposed change:** "Bone marrow examination (aspirate and a biopsy) at baseline will ***only*** be required for confirmation of diagnosis, ~~especially in older population or~~ **in** ~~those~~ patients ~~with non-typical presentation~~ ***who did not have them in the past and have a clinical reason for this test to be performed (e.g., unclear cases, or never responded to a prior ITP medication).*** In some situations bone marrow examination may also be required for other purposes; e.g. the use of TPO-R agonists has been associated with reports of an increase in bone marrow reticulin. ***This may be investigated in a sample of the Phase 3 study population."***	Accepted. Text has been amended.
Line 157 - 160	1	**Comment:** Systematic clotting screen at baseline may not be needed. Depending on the mechanism of action of the treatment, a clotting screen at baseline should be limited to patients at risk for thrombosis events. This could be based on medical history or presence of significant risk factors (e.g., other therapies like TPO-R agonists). **Proposed change:** "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.~~ ***A clotting screen at baseline should be limited to patients with***	Not accepted. Because the definition of response to treatment (CR/R/NR) includes bleeding assessment it is considered necessary for clinical studies to have a documented baseline normal clotting screen (normal PT/INR, APTT) and no history or significant risk factor for coagulopathy, e.g. family history of Factor V Leiden).

		risk factors, taking into account the mechanism of action of the new treatment."	
4.1. Subject characteristics and selection (relevant target population) - Entry platelet count	1		
Lines 166-167	1	**Comment:** The text states that the mean of three baseline platelet counts should be performed. It would be helpful to include guidance about the time-scale for the collection of these three baseline counts. **Proposed change:** Add time-scale e.g. "***within approximately 14 days***"; or "***within X to Y days" of the start of treatment.***"	Accepted. Time scale within approximately 14 to 7 days of the start of treatment included.
4.1. Subject characteristics and selection (relevant target population) - Previous treatments	1		
Line 180	1	**Comment:** It would be useful to define the expectations with regard to the prior treatment by inclusion of examples. **Proposed change:**	Not accepted. The proposed text is not considered necessary. Patients would have at least one

		"Patients with chronic ITP are expected to have received at least one previous treatment ***(e.g. first or second line therapy, or splenectomy)***."	therapy and it is expected the majority of enrolled patients would have ≥ 2 therapies with at least one first line therapy. Baseline disease characteristics would capture all data.
Lines 183-185	1	**Comment:** For more widely used first-line therapies, examples of the minimum period of time that should elapse between a prior therapy and study treatment would be useful. However, it may not feasible to run a study in ITP patients who have a platelet count of 30 x 10^9/L and are on no treatment. The vast majority of this patient population are on concomitant ITP medication, and it is unusual for this population to be on stable medication for 1 month as their ITP medication is often adjusted due to low platelet counts. This possibility should be addressed in the guidance.	Partially accepted. Examples for minimum time to be off first line treatment included (at least 2 weeks for IV immunoglobulin and at least 6 weeks for steroids). Patients on a stable ITP treatment for a month may be allowed to enter studies as mentioned under heading "concomitant treatment". This approach is not unusual as already reported in the registering studies of a current approved TPO-R agonist.
4.1. Subject characteristics and selection (relevant target population) - Concomitant treatments	1		
Lines 200-208	1	**Comment:** This section on 'Concomitant Medicines' may also usefully address the issue of Rescue Medications, and what considerations should be given to	Not accepted.

		trial design with regards use of such medications.	The "concomitant treatments" is addressed first under the subject selection heading for clinical trial and further down the guideline together with "rescue medication" in confirmatory studies.
Lines 202-204	1	**Comment:** ITP patients who have a platelet count of < 30 x 10^9/ L don't normally stay on stable medication for 1 month as their ITP is often severe and needs treatment. **Proposed change:** 'On entering clinical studies patients ***with platelet count above 30 x 10^9/L*** may be allowed concomitant specific anti-ITP medications provid**ed**~~ing~~ they have been on a stable treatment dose/schedule for at least one month prior to enrolment ***(excluding IVIG, anti-D and platelet transfusion)***. The use of concomitant treatments should be considered as a stratification factor.'	Not accepted. See previous comment.
4.2. Therapeutic goal	1		
Lines 211-212	1	**Comment:** We would suggest replacing the word 'safe', which is too vague, with 'sufficient'. **Proposed change:** "The major goal for treatment in primary ITP is to provide ***a sufficient*** ~~safe~~ platelet count to prevent or stop bleeding rather than correcting the platelet count to normal levels."	Accepted. Text has been amended.
Lines 214-217	1	**Comment:** The guidance should clarify if the parameters referred to (e.g., need for, or time to, more toxic treatments; corticosteroid exposure) should be secondary measures of treatment effect (expected versus optional).	Not accepted. The text refers to general aspects of the goal of ITP treatments to be considered but is not aimed at recommending specific study objectives.
4.3. Clinical	1	**Comment:** The example of "once only" as a duration of treatment is not applicable	Not accepted.

pharmacology - Pharmacokinetics Lines 221-224		as the guideline pertains to the treatment of chronic ITP. Proposed change (if any): '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.'	Therapy for chronic ITP may be intended to be given once only (e.g. splenectomy), as a short course treatment or as a chronic therapy (continuous or intermittent). It is unknown if future new drug development will include a once only administration.
4.3. Clinical pharmacology - Pharmacodynamics Lines 237-238	1	**Comment:** The guideline seems to imply that it is possible to achieve a platelet count that is safe against a thrombosis risk. However no limit can be considered perfectly 'safe', we can only talk about limitation of the thrombosis risk. **Proposed change:** 'Dosing will be based on the need to achieve a platelet count that is effective in the prevention of bleeding but ~~safe against a~~ ***limits the*** thrombosis risk. ~~Therefore,~~ ***B***lood platelet count…'	Accepted.
4.3. Clinical pharmacology - PK/PD model and simulation Line 249	1	**Comment:** Orphan designation has to be applied for, therefore is not automatic and this should be clarified in the guidance. It is not clear what the relevance of this statement is in the PK/PD model and simulation section. Proposed change (if any): "***Based on the incidence data*** ~~C~~***c***hronic ITP ***meets the requirements for an application for*** ~~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."	Accepted. Text amended in line with EU orphan regulation requirement to "based on the ***prevalence*** in the EU chronic primary ITP meets the requirement for an application for an orphan designation….." The use of PK/PD modelling and simulation can provide answers on clinical pharmacology of new drugs faster than conventional studies and may lead to smaller number of studies needed for registration. PK/PD model can provide valuable data for further designing phase

			II/III trials. As primary chronic ITP has a low prevalence in EU it is anticipated large conventional randomized phase II/III studies are more difficult to conduct.
4.4. Therapeutic studies 4.4.2 Confirmatory studies 4.4.2.1 *General aspects of study design*	1		
Line 370	1	**Comment:** We are surprised that RITUXIMAB is specifically mentioned as a comparator because it is not authorised for ITP whereas other medicinal products are approved for the patient population in question. Clarification regarding why the latter approved products are not suitable comparators would be helpful.	Although rituximab has not been approved for chronic ITP, international guidelines (reference 2 and 3 of the guideline) recommend it as second line therapy. Rituximab is mentioned only as an example of a possible comparator, along other possible comparators like splenectomy and TPO-R agonists.
Lines 389-390	1	**Comment:** The word 'end point' is missing after 'surrogate'. **Proposed change (if any):** '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 ***end point*** in ITP because it measures treatment activity and is believed to be a reliable predictor of clinical benefit.'	Accepted. Text has been changed.
Line 409	1	**Comment:** Some may interpret the wording "....and further up to 6 months follow	Accepted.

		up....” to mean that patients are to be followed for 6 months <u>without</u> receiving any other treatment. For patients requiring further therapy this may put them at risk. **<u>Proposed change (if any):</u>** “.... including 6 months treatment and ~~further~~ ***a follow up period of*** up to 6 months ~~follow up~~ .....”	It is envisaged that patients off treatment and at high risk of bleeding may be administered a subsequent therapy and the trial protocol should have this issue addressed. For clarity the text will be amended to “6 months treatment plus up to 6 months follow up…” and a sentence regarding the use of subsequent therapy has been inserted in the text.
4.4. Therapeutic studies 4.4.2 Confirmatory studies 4.4.2.2 *Detailed study considerations in chronic ITP* *Quality of response*	1		
Lines 416-438	1	**<u>Comment:</u>** This section should include adjustments of concurrent medications during the study treatment period.	Not accepted. This section is intended to give clear definitions of quality of response and has been written in line with international guidelines (reference 1 of the guideline). The use of concomitant and rescue medication is addressed under a specific

			heading.
Lines 417-420	1	**Comment:** Requiring 2 screening platelet counts a week apart in subjects with platelet counts < 30 x 10^9/L is impractical and will result in these patients having to have low platelet counts for extended period. We would suggest 3 days instead of 1 week as this will allow more rapid screening and inclusion of patients into the study. **Proposed change:** "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 ***3*** ~~7~~ days apart when used to define CR/R or 1 day apart when used to define NR or loss of response."	Not accepted. The confirmation of the platelet counts in two separate occasions refers to the assessment of response to treatment, not the screening period. It should be confirmed at least 7 days apart for CR/R, or 1 day apart for NR or loss of response. This approach is recommended by international guideline (reference 1 of the guideline) and is not considered impractical in a clinical study setting, especially as patients are already used to have their platelet count monitored rather frequently. The criteria for platelet count to enter the study are addressed in section 4.1.
Line 433	1	**Comment:** The term "significant bleeding" should be defined as this could be subject to variable interpretation.	Accepted. The section of assessment of bleeding has been updated to reflect up to date standardization of bleeding assessment in ITP and a definition of clinically relevant or significant bleeding has been included (see also new reference 4).
4.4. Therapeutic studies 4.4.2 Confirmatory studies 4.4.2.2	1		

Detailed study considerations in chronic ITP Assessment of bleeding			
Line 468	1	**Comment:** For clarity, we suggest a sentence be added to state that assessment of bleeding via adverse event (AE) reports is not acceptable (assuming this is what is being suggested via the prospective use of the referred to bleeding scales). **Proposed change:** End of line 468 "***The use of AE reports to assess bleeding is not advised."***	See previous comment. Assessment of bleeding for efficacy purpose has been described. It will be acceptable to also have bleeding AE recorded in order to evaluate the safety profile of a drug. No change of the text is considered necessary.
Lines 469-472	1	**Comment:** With respect to product labelling, is the inference that use of IBLS, or another valid scale, would support incorporation of data showing reduction of bleeding in the SmPC? **Proposed change (if any):** End of Line 472 ***".... and support the inclusion of data showing a reduction of bleeding into product labelling***".	Product labelling will ultimately depend on the final data collected. This point is not specific for this guideline. No change of the text is considered necessary.
5. Studies in special populations ***5.1. Paediatrics***	1		
Line 504	1	**Comment:** The sentence "Diagnosis is as for adults one of exclusion. " is unclear. **Proposed change:** "~~Diagnosis is as for adults one of exclusion.~~ ***As for adult ITP, a***	Accepted. Text has been changed.

		diagnosis of ITP in children is based on a process of exclusion [of other causative factors]."	
Line 507	1	**Comment:** The criterion for defining an area of "high prevalence" of Helicobacter pylori should be added.	Not accepted. This criterion is out of the scope of this guideline.
Line 548	1	**Comment:** Twelve months of data is a long time period and may discourage the development of new therapy for this orphan condition. The guideline would be better served by noting that <12 months data should be justified, and/or addressed in scientific advice.	Partially accepted. 12 months of safety data is not considered such long period of time for this chronic disease. However, a sentence has been included to address acceptability of less than 12 month's data.
6. Safety ***6.2 Specific adverse events***	1		
Lines 557-559	1	**Comment:** Please define what unacceptably high platelet counts are (e.g., >400 x 10^9 /L).	Partially accepted. Text has been included with limit of > 450 x 10^9 /L as some laboratories may have the upper limit of 450 x 10^9 /L instead of the more conventional upper limit of 400 x 10^9 /L.
Line 564-565	1	**Comment:** The addition of a 'reference' to support the statement that TPO-R agonists are associated with increased BM reticulin is warranted; this could be an EPAR or labelling or medical literature.	Not accepted. Reference is already included (ref No 2 at the end of the guideline).
Lines 567-570	1	**Comment:** It is impractical to do bone marrow assessments for all patients in the studies. Section 4.1 (lines 148-152, as revised) specifies when these would be particularly appropriate.	Accepted. The wording for bone marrow assessments was intended for TPO-R agonists that have

		Proposed change: 'It is ***sometimes*** recommended to perform bone marrow assessments at baseline and at different time points in ***certain*** patients included in the pivotal trial(s) ***(see section 4.1)***. Bone marrow assessments should be conducted in central laboratories by an independent expert reviewer.'	been associated with the risk of increased marrow reticulin. Text has been changed for clarity.
Lines 571-573	1	**Comment:** No recommendation is given for assessment/investigation of worsened thrombocytopenia. It would be helpful to have further clarity around the expectation for this assessment. Historically the following criteria is used to define worsening thrombocytopenia after discontinuation of treatment: 'a platelet count of < 10 x 10^9/L and 10 x 10^9/L less than baseline count within 30 days of discontinuation'. **Proposed change:** "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 below 10 x 10^9/L and 10 x 10^9/L less than baseline count within 30 days of discontinuation***. Platelet count normally recovers to pre-treatment levels after several weeks."	Accepted. As platelet count at entry will vary amongst patients it is considered the criteria for worsened rebound thrombocytopaenia to be ≥10 x 10^9/L less than baseline count within 30 days of discontinuation study treatment. The text has been amended.
EDITORIAL COMMENTS			
4.3. Clinical pharmacology - Drug-drug interaction studies Line 233	1	**Comment:** We would suggest 'corticosteroids' (rather than 'steroids')	Accepted. Text has been changed.
4.4. Therapeutic studies 4.4.2 Confirmatory studies	1	**Comment:** A grammatical error needs to be corrected after 'focuses'. **Proposed change:** 'Confirmatory trials are necessary to provide evidence of efficacy and safety. This part of the guideline focuses ~~in~~ ***on*** the efficacy aspects while safety evaluation is discussed in section 6.'	Accepted. Text has been corrected.

Lines 326-327			
4.4. Therapeutic studies 4.4.2 Confirmatory studies - 4.4.2.2 *Detailed study considerations in chronic ITP* (Quality of response) Lines 437-438	1	**<u>Comment</u>:** The word 'a' is missing between 'perform' and 'procedure'. **<u>Proposed change:</u>** 'Achievement of a platelet count sufficient to perform ***a*** procedure or minimize bleeding from trauma (in most cases platelet count 50-70 x109/L).'	Accepted. Text has been corrected.
4.4. Therapeutic studies 4.4.2 Confirmatory studies - 4.4.2.2 *Detailed study considerations in chronic ITP* (Duration response)	1	**<u>Comment</u>**: As mentioned in line 448 this subsection is about 'duration of response'. The word 'of' is missing in the title of the subsection between 'duration' and 'response'. **<u>Proposed change:</u>** 'Duration **of** response.'	Accepted. Text has been corrected.

Line 447			
5. Studies in special populations ***5.1. Paediatrics*** Lines 502-503	1	**<u>Comment</u>:** The word 'be' is missing between 'has been reported to' and 'approximately'. **<u>Proposed change:</u>** 'Severe bleeding tends to occur when the platelet count falls below 10 x 109/L and the incidence of intracranial haemorrhage in children with ITP has been reported to **be** approximately 0.1% to 0.5%.'	Accepted. Text has been corrected.
63-64	3	Comment: 'fatal haemorrhage is around 0.02 to 0.04 cases per adult patient year risk'. This is different from the incidence figures (which are given per 100,000) Proposed change (if any): please be consistent in how these are referred to.	The figures have been written as published in the literature. No change is considered necessary.
180-182	3	Comment: Should patients be stratified according to the previous treatments? (as indicated in line 189/190)	Line 189/190 refers to disease status stratification (refractory versus unresponsive) and not to type/number of prior treatment(s). Stratification is in general recommended according to current treatment (if any), prior splenectomy and baseline platelet counts. Because stratifications factors need to be limited (~max 3) no recommendation is made according to previous treatments, except for splenectomy.
183/4	3	Comment: There is some inconsistency (or a possibility for misunderstanding) to lines below 202/4 232 Proposed change (if any): please clarify	Comment not clearly understood. Lines 232 refer to drug interaction studies.
188	3	Comment: Not clear what this means: response to splenectomy should have an assessment for accessory spleen	An accessory spleen is a small nodule of splenic tissue found apart from the main body of the spleen that occurs in around 10% of the population. If splenectomy is

		Proposed change (if any): provide clarity	performed in ITP, failure to remove the accessory spleen (if present) may result in failure to respond to treatment.
191-198	3	Very helpful and clear definitions	N/A
202-204	3	Comment: Sounds inconsistent with line 183-184 (patients should be off treatment for a time sufficient to exclude a late effect when entering the study.' Proposed change (if any): maybe a clarification is needed to lines 183-184	Only specific types of concomitant treatments are allowed and they have been described separately from more general criteria as in lines 184-184. No change in the text is considered necessary.
232	3	Comment: As above (line 202-204)	See previous comment.
263	3	Comment: Current medication – stratification (is this consistent with the fact that they should not have any? (see comment related to lines 183/4)	See previous comment.
300-301	3	Comment: Not clear why one should choose a dose that is too high '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. ' Proposed change (if any): provide clarity	Sometimes dose finding studies do not explore a sufficient wide range of doses that will lead to find the most suitable efficacious and better tolerated dosing regimen.
311	3	Comment: Not clear what this (' A dose and response stopping criteria should be identified. ') means. Proposed change (if any): Maybe there are just a couple of words accidentally missing	These refer to stopping rules clinical studies should have defined in their protocol. No change in the text is considered necessary.
314	3	Comment: How about people with chronic ITP who have not had other treatments? Is it not envisaged to ever develop a new 1st line treatment?	This guideline is intended for the treatment of chronic primary ITP and in this group of patients it is anticipated they will have received at least one prior treatment.
328	3	Comment: 'and is not type class specific' Proposed change (if any): Is this a typo?	It refers to drug type classification (e.g. by chemical characteristics, mechanism of action etc). No change considered necessary.
366	3	Comment: This sentence 'The inclusion of a placebo control with or	As many different options of control may be

		without active comparator when possible is strongly encouraged.' does not give clear guidance, because it appears to include all options. Proposed change (if any): Be clearer about if the inclusion of an active control is encouraged.	acceptable only few examples are provided. A sentence for clarity has been included for the requirement of justification of the chosen comparator(s).
373-5	3	Comment: Some repetition with previous page 371-72	The first paragraph (lines 366-372) refers more to the choice of comparator whilst the second part (lines 373-381) refers to the design of the study (superiority/non-inferiority).
422 onwards	3	Comment: Very helpful definitions	N/A
427	3	Comment: Does 'late response' need defining?	Not considered necessary.
445	3	Comment: What is 'peak response'? The text suggests that there is no response after the peak? Could it not also be a plateau or slightly diminished response after the peak? Proposed change (if any): please clarify	Peak response is the maximum response to a given treatment.
447	3	Proposed change (if any): Duration **of** response	Accepted. Text amended.
497	3	Comment: What does this mean 'A waiver for children under 1 year of age is applicable'? Proposed change (if any): It is not expected to have children under 1 year of age in a trial?	The definition of chronic primary immune thrombocytopaenia requires for the condition to last at least one year. Therefore it cannot be diagnosed in children < 12 months of age. No change to the text.
504	3	Comment: What does this mean 'Diagnosis is as for adults one of exclusion'? Proposed change (if any): please clarify	For clarity the text has been changed to "*as for adults, a diagnosis of ITP in children is based on a process of exclusion of any potential cause"*.
524-9	3	Comment: Wording complex and difficult to follow Proposed change (if any): please clarify	The text refers to the acceptability of extrapolation of data from studies

			conducted in adults to children. No change of the text considered necessary.
575	3	Comment: What does this mean ‘ be expected to address the likely risks and knowledge of the product’? Proposed change (if any): please clarify	Risk management plans should address potential and identified risks of a product. No change of the text considered necessary.
544 onwards	3	Comment: The safety section is very brief. I would have expected more about a comparison particularly with the safety concerns with other active treatments.	The safety section is considered to include relevant aspects to this guideline. Please note reference to other relevant guidelines is included in section 3.
Section 4.1 Lines 157-159	4	Comment: Would the clotting disorder exclusion still apply if the drug under test had a different mechanism of action and preclinical evidence that a thrombotic risk was not anticipated? i.e. is it automatically an exclusion criterion and would otherwise need justification? Proposed change (if any): 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). *Omitting the thrombosis exclusion criteria for therapies with a different mechanism of action would need to be justified.*	Not accepted. The clotting disorder (any type) exclusion is intended to apply to all drugs even if there was no evidence of thrombotic risk at pre-clinical phase. The lack of a thrombotic risk at pre-clinical stage does not guarantee a non risk at clinical level. No change to the text has been made.

Lines 257-261	4	Comment: It may be necessary to include some new elements in the model other than covariates if you find the HV model does not describe patients data and a miss-specification related to the model structure, for instance elements related to the disease. Proposed change (if any): If separate population PK/PD analyses are performed for HV and patients the same base structural model should be *initially* used to allow comparison of the model parameters and identification of differences between the healthy and disease populations.	Accepted. Text has been changed.
Lines 319-321	4	Comment: Appropriate range of doses may not always need interim analysis Proposed change (if any): To ensure an appropriate range of doses are tested an interim analysis ~~should~~ *may* be planned with the possibility to broaden the study dose range.	Accepted. Text has been changed.
Section 4.4.2.1 Lines 369-371	4	Comment: Is it appropriate that rituximab is specifically mentioned here even though it is not yet licenced for ITP? Also it may be difficult to include as a comparator in a clinical trial application if it is not licenced. Does appearing in a guideline as a recommended comparator endorse its use? Proposed change (if any): delete reference to “rituximab” as comparator. ~~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.~~	Not accepted. See previous comment.

Section 4.4.2.2 Lines 417-438	4	Comment: The Guidance on clinical investigation of IVIg mentions statistical considerations for presenting platelet data. Should the same be mentioned in the ITP Guidance? Proposed change (if any): Add: *Statistical considerations:* *Wherever possible, platelet parameters should be provided as mean (and standard deviation) and median (and minimum and maximum) values for each patient, as well as for summary data.*	Accepted. Text has been included.
Section 4.4.2.2 Line 427 Definitions Line 578	4	Comment: Would it be useful to explain the term “late response” here? With reference to line 184, some studies will avoid a late response effect because patients are off treatment for a sufficient time before starting the study. Proposed change (if any): Suggest to add to Definitions section something such as mentioned in Rodeghiero et al, 2009: *Late Response* *A response that may be attributable to a specific prior treatment*	Not accepted. A late response may be due to a prior treatment or the investigational treatment. In the former case the late response cannot be defined as CR/R. However, if it can be attributed to the investigational treatment a definition of CR/R can be used. Text has not been changed.
Section 4.4.2.2 Line 437	4	Comment: Re the term “procedure”; although it may be generally understood, would it be helpful to be clarified as “invasive procedure”? Rodeghiero et al, 2009, page 2390 refers in the text to invasive procedure. Proposed change (if any): Achievement of a platelet count sufficient to perform *an invasive* procedure or minimize bleeding from trauma (in most cases platelet count 50-70 $x10^9$/L).	Accepted. Text has been changed.

Line 468/Line 605	4	Comment: In addition to the Page et al reference for IBLS, should references be given for the other bleeding scales mentioned in the text? TIMI, GUSTO? Proposed change (if any): Suggest to add appropriate references for TIMI & GUSTO	The section of "assessment of bleeding" has been updated to reflect up to date standardization of bleeding assessment in ITP and a definition of clinically relevant or significant bleeding has been included (see also new reference 4). All previous references for bleeding scales have been deleted.
Line 538/605	4	Comment: Should the author reference for the Kids' ITP Tools (KIT) be added? Proposed change (if any): Add to References the following: *Validity, reliability, and responsiveness of a new measure of health-related quality of life in children with immune thrombocytopenic purpura: the Kids' ITP Tools. R.J. Klaassen et al, J Pediatr. 2007;150:510-515.*	Accepted. The reference has been included in the text.
Lines 541-542	5	**Comment:** I have not agreed on what was stated in section 5.2. In fact, the pITP in the elderly is not a rare occurrence, although the differential diagnosis with other hematologic disorders should always be done carefully (e.g .MDS)	Accepted. The text has been reworded. The reference to incidence/prevalence has been deleted and emphasis on data requirement from this subgroup of patients has been included.
Lines 464-472	6	**Comment:** For the bleeding assessment, of course the recent consensus paper (Rodeghiero et al, Blood 2013; 121 (14):2596-606) should be adopted. It has been approved for both children and adults and developed particularly for clinical trials. Incorporating a careful and reliable bleeding assessment would allow to move the principal outcome of treatment from platelet count increase to bleeding prevention. Platelet count is still a surrogate endpoint. See criticism from the Cochrane review (Zeng Y, Duan X, Xu J, Ni X. TPO receptor agonist for chronic idiopathic thrombocytopenic purpura, Cochrane Database Syst Rev. 2011(7):CD008235.), that we commented in the American Journal of	Accepted. The assessment of bleeding has been amended accordingly to the mentioned consensus paper and the reference has been included at the end of the document.

		Hematology (Am J Hematol. 2012;87(10):943-4).	
Lines 60-61	6	**Comment:** I would suggest to change the sentence into "Additional factors may increase the risk (e.g., advanced age, lifestyle factors, concomitant medications or congenital or acquired bleeding disorders) ... is determined". Indeed uraemia is very rare in ITP.	Accepted. The text has been changed as suggested.
Line 79	6	**Comment**: "Intravenous anti-D immunoglobulin": is anti-D available in Europe for ITP? I don't think so. Perhaps this should be specified.	Accepted. Anti-D Ig is currently not available in Europe for ITP. The text has been changed to specify that some drugs are recommended by international guidelines as treatment options in ITP although they are not currently approved in the EU for this indication. This text is relevant to several medicinal products (for example rituximab) and not only to anti-D Ig.
Lines 89-91	6	**Comment**: I would add the following at the end of the sentence: "... chronic ITP, in not splenectomized patients or in those with contraindication to splenectomy at risk of bleeding".	Partially accepted. The text has been changed to include the exact full current approved indications of TPO-R agonists in the EU.
Lines 157-162	6	**Comment**: I would rephrase the sentence as follows: “Exclusion criteria also apply to patients with 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, IVIg). 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 if the patient aged > 60 years at the time of episode or even	Partially accepted. The text has been amended as suggested. See also previous comment.

		younger if the episode was provoked by e.g. surgery or trauma." Indeed, a normal clotting screen is not appropriate for its low predictive value in asymptomatic patients. Furthermore, unprovoked thrombosis in young patients is almost invariably secondary to "thrombophilia" for venous episodes, or to significant vascular disease for arterial cases. All cases with myocardial infarction should also be excluded.	
Line 215	6	**Comment**: "… reduced corticosteroids exposure to minimum levels and for the shortest time and achieve…"	Accepted. The text has been changed as suggested.
Line 465	6	**Comment**: Specific encouragement should be made to adopt the recently published new bleeding assessment tool (Rodeghiero et al, Blood 2013; 121(14):2596-606). WHO, TIMI and GUSTO are not appropriate. WHO has been proposed for cancer patients undergoing chemotherapy.	Accepted. See previous comment.
Line 535	6	**Comment** Perhaps Table 1 is redundant and it has not been harmonized to the new bleeding assessment tool.	Accepted. The table and related previous paragraph (lines 530-534) have been deleted.
Lines 136-139	7	**Comment** I am particularly reluctant to include the text "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." This test will be positive in 70-80% of ITP patients as in normal population. Therefore, an eradication of H. pylori will be required in the vast majority of patients before the inclusion in a clinical trial. I fully disagree and it is not evidence-based.	Partially accepted. The comment is acknowledged and it will not be a requirement to conduct HP testing at study entry. However, to make progress in this field the text has been amended to encourage companies to study the role of HP. New text included "*The role of Helicobacter pylori (HP) infection in chronic ITP is currently unclear. Due to the high prevalence of the infection and variability amongst regions within the EU and across the world, testing for HP at study entry is*

			not required. However, in order to make progress in this field companies are encouraged to consider testing for HP status at study entry by a justified laboratory method, and either conduct appropriate protocol pre-specified subgroup analysis or allow study entry for patients who have persistent thrombocytopaenia following HP eradication."
Line 541	8	**Comment** The sentence « *Primary ITP in the elderly is a very rare condition but the enrolment of elderly patients in clinical studies is strongly encouraged"*(line 541) should be modified since ITP in elderly is far from being rare and some epidemiological studies have even shown that the risk of ITP increases with age (even if excluding an underlying MDS may be difficult)	Accepted. See previous comment.
Lines 469-472	8	**Comment** In term of assessing bleeding, I don't agree with the following statement: 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…." This score has not been validated and I suggest that the effort made by the IWG on ITP for setting up a Bleeding scale (taking into account both history and physical examination) should be rather mentioned and promote (even if it has not been validated yet throughout a clinical trial) => Rodeghiero F et al. Standardization of bleeding assessment in immune thrombocytopenia: report from the International Working Group.Blood. 2013 121: 2596-2606.	Accepted. See previous comment.
Lines 136-139	9	**Comment** In a recent study of H.pylori infection in our patient population in Los Angeles, submitted to ASH, the median age was over 50 years.	See previous comment.
Lines 136-139	10	**Comment** If tests on helicobacter are left in - at least - it should be clarified that after eradication and persistent ITP, patients can enter a study.	See previous comment.
Lines 140-147	10	**Comment** Stratification for a number of factors is suggested: pos/neg ANAs, pos/neg APLAS, SE yes/no, refractory/unresponsive yes no - this seems	Accepted.

		to be too much considering that the patients fulfilling in-exclusion criteria will be not high, even when multicenter studies are planned.	See previous comment.
Line 211	10	**Comment** On the one hand it is suggested to not include patients just on the basis of platelet count, on the other hand a "safe platelet count" - whatever that means - should be the goal. This is a little bit contradictory and not easy to solve, I agree.	Accepted. The word “safe” has been replaced by “sufficient”. See previous comment.
Line 11	11	**Comment** Thrombopoietin if incorrectly spelt as thromobopoietin.	Accepted. Typo error has been corrected.