PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Phase 3 Randomized Trial of Eltrombopag vs. Standard First-Line Pharmacologic Management for Newly Diagnosed Immune Thrombocytopenia (ITP) in Children: Study Protocol
AUTHORS	Shimano, Kristin; Grace, Rachael; Despotovic, Jenny; Neufeld, Ellis; Klaassen, R; Bennett, Carolyn; Ma, Clement; London, Wendy; Neunert, Cindy

VERSION 1 – REVIEW

REVIEWER	RUIZ-ARGÜELLES, Guillermo J. Centro de Hematología y Medicina Interna
REVIEW RETURNED	23-Nov-2020

GENERAL COMMENTS	No comments.

REVIEWER	Lee , Anselm Chi-Wai Mount Elizabeth Hospital, Children's Haematology and Cancer Centre
REVIEW RETURNED	25-Feb-2021

GENERAL COMMENTS	This is a well-designed clinical trial of randomized treatment with eltrombopag against current standard first-line treatments for childhood ITP. My major concern is that the design of the trial is heavily biased towards the favor of eltrombopag. First, it is the absence of a non-interventional group of patients for comparison. Children with ITP who stay away from pharmacologic interventions despite very low platelet numbers often come from families who can cope with stress and illness better and thus by nature have good quality of life. On the other hand, parents and/or clinicians who favor pharmacologic intervention tend to target platelet counts more than the actual bleeding symptoms. Thus, a sustained response after eltrombopag will easily fill in the gap and produce a dramatic improvement in the quality of life scores in a patient population who could not cope with a low platelet count after the diagnosis of ITP. Second, the design allows the use of eltrombopag continuously while the other comparative therapies are only used once in a limited period. Then, one can increase the dose of eltrombopag if there is no initial response. But you are not allowed to do something similar to the other treatments. It is a totally unfair match. My counter suggestion is to use eltrombopag at a fixed dose for 4 weeks and then monitor for the response like the other treatments. Third, the definition of platelet response, defined as >6 of 8 weeks with platelet > 50 e9/L during weeks 5-12 of therapy, is primarily set for eltrombopag. In prior studies using intravenous immunoglobulin, corticosteroid therapy, or anti-D globulin, we have never used such a

	criteria to assess response. Without looking at the data, I can imagine what the results will be like. I have two other concerns about the study design. First, it is about the rescue treatment. What are allowed and what are not? Would the protocol encourage the same first treatment the child has received, and thus produce a comparison population similar to the continuous treatment with eltrombopag? Second, the range of target platelet counts (50 – 200) for maintenance of eltrombopag treatment is too conservative and does not match real-life needs. A range of 50 – 100 is good enough to sustain normal life and activities. This range also allows the opportunity to catch spontaneous recovery early. This is especially relevant in this study population of whom spontaneously recovery will occur in the majority. Finally, because of all the above concerns, I worry the results from this study will promote treating platelet number as the primary objective in the management of childhood ITP. Although the study tries to separate platelet responses, bleeding symptoms, and quality of life as different outcomes, they are nevertheless inter-related. From our clinical experience, platelet number is often the major driving factor for pharmacologic intervention. It is likely that a study like this one where platelet response is the most obvious outcome indicator will in turn promote the treatment of ITP into treatment of thrombocytopenia.

REVIEWER	Kapur, Rick Sanquin Research
REVIEW RETURNED	02-Mar-2021

GENERAL COMMENTS	Shimano and colleagues report the study protocol of their phase 3 randomized trial of Eltrombopag vs. Standard first-line pharmacologic management for newly diagnosed ITP in children. This is an important and well-designed trial by experts in the field. I only have few minor comments. - The platelet response will be defined as ≥6 of 8 weeks with platelets >50 x109/L. Why was a platelet response of >100 x109/L not chosen? Thrombocytopenia is generally defined as a platelet count below 100 x109/L (Rodeghiero et al, Blood 2009). - Apart from just measuring the percentages of Tregs, the suppressive function of Tregs could also be determined in biological assays. - Will anti-platelet antibodies also be determined? It could be considered to also measure these, as it has been suggested in animal models that TPO-RA may reduce these anti-platelet antibody levels (Kapur et al, Platelets 2020).

REVIEWER	Schifferli, Alexandra University Children's Hospital Basel
REVIEW RETURNED	05-Mar-2021

GENERAL COMMENTS	Interesting and challenging study in the field of pediatric ITP. 4 comments: - Do you recommend (or request) special initial diagnostic to exclude secondary forms? Only coombs test and HIV serology are mentioned in the exclusion criteria.

	- For patients in the eltrombopag arm: it is not clear what will be the treatment recommended to overcome the 1-2 weeks delay until the drug shows an effect. If the patients needs IVIG: dropout? - It is not clear if the percentage of the Tregs are calculated on total lymphocyte or CD4-Tcells, or something else. Please define this outcome. Will the FACS analysis be done only for Tregs? Or will you measure also B/T Subpopulation? -what is the amount of blood required at day 0 if you considere diagnostic tests+ study tests (iron, Tregs) + blood banking?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Guillermo J. RUIZ-ARGÜELLES, Centro de Hematología y Medicina Interna
Comments to the Author:
No comments.
Thank you to the reviewer for reading our manuscript.

Reviewer: 2
Dr. Anselm Chi-Wai Lee, Mount Elizabeth Hospital
Comments to the Author:
This is a well-designed clinical trial of randomized treatment with eltrombopag against current standard first-line treatments for childhood ITP. My major concern is that the design of the trial is heavily biased towards the favor of eltrombopag.
We appreciate the reviewer's concerns and suggestions below for alterations to the protocol design. As this manuscript is a report of a protocol for a registered study already approved by multiple regulatory bodies and currently under conduct we are not able to incorporate changes to the study design, but we have responded to the suggestions with the rationale we used in designing the trial. The study steering committee members had clinical equipoise with respect to the efficacy of both treatment arms.

First, it is the absence of a non-interventional group of patients for comparison. Children with ITP who stay away from pharmacologic interventions despite very low platelet numbers often come from families who can cope with stress and illness better and thus by nature have good quality of life. On the other hand, parents and/or clinicians who favor pharmacologic intervention tend to target platelet counts more than the actual bleeding symptoms. Thus, a sustained response after eltrombopag will easily fill in the gap and produce a dramatic improvement in the quality of life scores in a patient population who could not cope with a low platelet count after the diagnosis of ITP.
Thank you for raising this concern. We considered many different protocol schemas when designing the trial. While we would have loved to include an observation-only arm, randomization to a non-interventional arm would have not been practical for patients requiring treatment for bleeding symptoms, and we ultimately decided that given the study timeframe and budget limitations we would limit the comparison to those requiring pharmacologic intervention. The benefit of a randomized trial, however, is that the varied indications for treatment (whether bleeding symptoms or other) are expected to be equally distributed between the two study arms, so there should not be a biased response in quality of life scores in one treatment group over the other based on indication for treatment.

Second, the design allows the use of eltrombopag continuously while the other comparative therapies are only used once in a limited period. Then, one can increase the dose of eltrombopag if there is no initial response. But you are not allowed to do something similar to the other treatments. It is a totally unfair match. My counter suggestion is to use eltrombopag at a fixed dose for 4 weeks and then monitor for the response like the other treatments.
The dosages and dosing schedules for the standard therapies in the protocol are standard ITP doses (which are typically given with the initial intention of a one-time course in newly diagnosed ITP).

Similarly, the upward dose titration of eltrombopag if there is no response is based on the manufacturer-recommended starting dose and titration of this drug. One of the pitfalls of current first-line ITP therapies is indeed that the response is often transient, and that was a strong impetus for a trial of a TPO-RA in the newly diagnosed setting. It is not evident *a priori*, however, that this is an "unfair match," as this trial represents how these medications are used in clinical practice. For either arm, if there is a need for additional treatment beyond the protocol-prescribed therapy, patients are permitted to receive a rescue therapy, but they are then categorized as a non-responder for the purpose of the primary endpoint. In theory, one could also postulate that those in the eltrombopag arm are more likely to require a rescue therapy as there will be a longer onset to platelet count improvement and resolution of bleeding symptoms, which would be an "unfair match" biased toward standard therapy. The protocol classifies patients who receive rescue therapies as non-responders, a strategy which may address some of the concerns outlined above by the reviewer.

Third, the definition of platelet response, defined as >6 of 8 weeks with platelet > 50 e9/L during weeks 5-12 of therapy, is primarily set for eltrombopag. In prior studies using intravenous immunoglobulin, corticosteroid therapy, or anti-D globulin, we have never used such a criteria to assess response. Without looking at the data, I can imagine what the results will be like.
We agree with the reviewer that many trials of standard treatments for newly diagnosed ITP have measured a single short-term platelet response. However, sustained response at more distal timepoints are also frequently considered as relevant outcomes (for instance, Heitink-Pollé et al, Blood 2018). One of the frustrations of treating with the current standard therapies is that responses are often transient and patients require multiple courses of therapy until the ITP spontaneously resolves. If a therapy could produce a sustained platelet response (and by extrapolation, a sustained period free from bleeding symptoms), this would potentially have great benefit for patients who require treatment for ITP. As eltrombopag has not previously been studied in the newly diagnosed setting in pediatric ITP, we feel it is speculative to make an assumption about the results.
Of note, since the original submission of this manuscript, the study DSMC recommended a change to the primary endpoint due to COVID-19 pandemic-related concerns. This is detailed on p.7 of the revised manuscript.

I have two other concerns about the study design.
First, it is about the rescue treatment. What are allowed and what are not? Would the protocol encourage the same first treatment the child has received, and thus produce a comparison population similar to the continuous treatment with eltrombopag?
We apologize that this was unclear in the original manuscript. For both the standard therapy arm and eltrombopag arm, patients are permitted to receive rescue therapies of IVIg, steroids, or anti-D globulin at protocol-prescribed doses if needed for significant bleeding or other indication. The choice of which of the 3 rescue therapies to use is at the discretion of the treating physician, and the initial treatment could be repeated as the rescue therapy if clinically appropriate. If a patient in either arm requires rescue therapy, he or she will be categorized as a non-responder for the purpose of the primary outcome. Clarification regarding the rescue therapies has been added to the manuscript (p.7).

Second, the range of target platelet counts (50 – 200) for maintenance of eltrombopag treatment is too conservative and does not match real-life needs. A range of 50 – 100 is good enough to sustain normal life and activities. This range also allows the opportunity to catch spontaneous recovery early. This is especially relevant in this study population of whom spontaneously recovery will occur in the majority.
We agree with the reviewer, and it is for this reason that we built more aggressive weaning parameters into the protocol for patients continuing on eltrombopag after week 12. While we adhered to the standard manufacturer-recommended platelet ranges for dose titration during weeks 1-12, the protocol calls for dose reduction for platelet counts between 100-200 $x10^9$/L after week 12 for the very relevant reasons the reviewer mentions. The dose titration is detailed in Supplementary Table 2.

Finally, because of all the above concerns, I worry the results from this study will promote treating platelet number as the primary objective in the management of childhood ITP. Although the study tries to separate platelet responses, bleeding symptoms, and quality of life as different outcomes, they are nevertheless inter-related. From our clinical experience, platelet number is often the major driving factor for pharmacologic intervention. It is likely that a study like this one where platelet response is the most obvious outcome indicator will in turn promote the treatment of ITP into treatment of thrombocytopenia.

This is an important point. We absolutely advocate for close observation as a management strategy (and based on our site pre-screening logs, there continues to be widespread practice of observation alone amongst our study investigators). While the primary endpoint is a platelet number objective, we agree that bleeding symptoms and quality of life are more clinically relevant, and we have therefore included multiple secondary outcomes to address these critical aspects of ITP management. Eligibility requirements for study enrollment include *need for pharmacologic treatment*, and that will remain our framework for interpretation and reporting of the study results.

Reviewer: 3
Dr. Rick Kapur, Sanquin Research
Comments to the Author:
Shimano and colleagues report the study protocol of their phase 3 randomized trial of Eltrombopag vs. Standard first-line pharmacologic management for newly diagnosed ITP in children. This is an important and well-designed trial by experts in the field. I only have few minor comments.

- The platelet response will be defined as ≥6 of 8 weeks with platelets >50 x109/L. Why was a platelet response of >100 x109/L not chosen? Thrombocytopenia is generally defined as a platelet count below 100 x109/L (Rodeghiero et al, Blood 2009).
Thank you for this question. The goal in defining a primary outcome for this study was to choose an endpoint that would be clinically meaningful for the newly diagnosed pediatric ITP population. A platelet response of >50 x109/L, rather than >100 x109/L, was chosen since the main goal of treatment in patients with primary ITP is resolution or prevention of bleeding, rather than normalization of the platelet count. This is a primary outcome that is similar to those used in prior ITP studies as well (Kuter Lancet 2008, Grainger Lancet 2015, Bussel AJH 2018). A number of International Working Group platelet-specific endpoints are included as exploratory outcomes in this study (p.8 of manuscript). Due to space limitations we did not detail the exploratory outcomes in the manuscript, but these include response with platelet count >100x10^9/L and absence of bleeding as well as time to platelet count >100x10^9/L and absence of bleeding.
Of note, since the original submission of this manuscript, the study DSMC recommended a change to the primary endpoint due to COVID-19 pandemic-related concerns. This is detailed on p.7 of the revised manuscript.

- Apart from just measuring the percentages of Tregs, the suppressive function of Tregs could also be determined in biological assays.
Thank you for this important point. We also wished to include functional assays, but unfortunately these and several other correlative biology studies were eliminated from the final protocol due to funding constraints.

- Will anti-platelet antibodies also be determined? It could be considered to also measure these, as it has been suggested in animal models that TPO-RA may reduce these anti-platelet antibody levels (Kapur et al, Platelets 2020).
This is a great thought, but we were limited in the correlative biology studies we were able to include due to funding constraints.

Reviewer: 4
Dr. Alexandra Schifferli, University Children's Hospital Basel
Comments to the Author:
Interesting and challenging study in the field of pediatric ITP.

4 comments:
- Do you recommend (or request) special initial diagnostic to exclude secondary forms? Only coombs test and HIV serology are mentioned in the exclusion criteria.
Thank you for this question. The study is open only to patients with primary ITP. There are no specific required evaluations to evaluate for secondary ITP, but known secondary ITP is an exclusion, and patients are removed from the study if they are determined to have secondary ITP during the course of the study. Clarification of this eligibility requirement has been added to the manuscript (p. 5).

- For patients in the eltrombopag arm: it is not clear what will be the treatment recommended to overcome the 1-2 weeks delay until the drug shows an effect. If the patients needs IVIG: dropout?
A patient who requires immediate normalization of platelet counts at study entry (for instance due to grade 4 bleeding) would be excluded from enrollment. However, for both the standard therapy arm and eltrombopag arm, patients are permitted to receive rescue therapies of IVIg, steroids, or anti-D globulin at protocol-prescribed doses if needed for significant bleeding or other indication. If a patient in either arm requires rescue therapy, he or she will be categorized as a non-responder for the purpose of the primary outcome. This clarification has been added to the manuscript (p.7).

- It is not clear if the percentage of the Tregs are calculated on total lymphocyte or CD4-Tcells, or something else. Please define this outcome.
The percentage of the Tregs is calculated as a proportion of CD4-Tcells, and this clarification has been added to Table 3.

Will the FACS analysis be done only for Tregs? Or will you measure also B/T Subpopulation?
The analysis will only be performed for Tregs. While we wished to include B and T cell subpopulations as well, these and several other correlative biology studies were eliminated from the final protocol due to funding constraints.

-what is the amount of blood required at day 0 if you considere diagnostic tests+ study tests (iron, Tregs) + blood banking?
The minimum amount of blood for screening and day 0 labs is 4.2 mL for screening labs (CBC, retic, LFTs, cre, LDH, DAT), 6.8 mL for study labs (Tregs, iron studies), and 8.5mL for optional banking studies. Of note, the study manual includes the reminder to “ensure that the total volume of blood collected from each patient over any 24 hours is within permitted limits.”

VERSION 2 – REVIEW

REVIEWER	Lee , Anselm Chi-Wai Mount Elizabeth Hospital, Children's Haematology and Cancer Centre
REVIEW RETURNED	27-Jun-2021

GENERAL COMMENTS	Thank you for the clarifications. I have no further queries.

REVIEWER	Kapur, Rick Sanquin Research
REVIEW RETURNED	05-Jul-2021

GENERAL COMMENTS	Thank you for your answers. Too bad you are unable to conduct biological assays due to funding constraints, it would have provided valuable insights. No further comments.