A Phase 3, Multicenter, Randomized, Double-blind, Active-controlled, Parallel-group Trial with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Oral E5501 versus Eltrombopag, in Adults with Chronic Immune Thrombocytopenia (Idiopathic Thrombocytopenic Purpura)

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Core StudyPrimary objective• To compare the efficacy of E5501 (in addition to standard of care) to eltrombopag (in addition to standard of care) for the treatment of adult subjects with chronic immune thrombocytopenia (idiopathic thrombocytopenic...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Platelet disorders
Study type	Interventional

Summary

ID

NL-OMON37816

Source
ToetsingOnline

Brief title
E5501 ITP-305

Condition

- Platelet disorders
- Autoimmune disorders

Synonym
chronic immune thrombocytopenia, ITP

Research involving
Human

Sponsors and support

Primary sponsor: Eisai
Source(s) of monetary or material Support: Eisai Ltd.

Intervention

Keyword: chronic immune thrombocytopenia (cITP), E5501, Eltrombopag, phase 3

Outcome measures

Primary outcome

Primary efficacy endpoint:

Durable platelet response rate as defined by:

• Proportion of subjects who have at least 6 of 8 (i.e., >=75%) weekly platelet responses during the last 8 weeks of treatment (i.e., at Visits 15 through 22, inclusive) over the 6-month treatment period in absence of rescue therapy

• Subjects using rescue therapy at any time during the 6-month treatment period will be considered to not have a durable platelet response

• A platelet response will be defined as a platelet count of >= 50 x 109/L and nonresponse will also be defined as a platelet count of < 50 x 109/L

• Missing platelet assessments at any given time point will be considered to be a nonresponse at that time point. Subjects who discontinue the study or who are lost to follow-up before 6 months will have all subsequent unobserved scheduled platelet assessments at the scheduled time points as having *missing* platelet values.

• All analyses of platelet counts will be based on local laboratory results.

Secondary outcome

Key secondary efficacy endpoint:

• Platelet response rate at Day 8 as defined by: proportion of subjects with a platelet response >=50 x 109/L at Day 8. Subjects with missing platelet counts at Day 8 or use of a rescue therapy before or on Day 8 will be considered platelet nonresponders.

Study description

Background summary

Thrombocytopenia is the presence of relatively low numbers of platelets in the blood, and in severe cases can be associated with significant morbidity and mortality. ITP is one of the numerous disease-related thrombocytopenias and there are estimated to be approximately 50,000 individuals with chronic ITP (cITP) in Europe. People with cITP often bleed from small blood vessels, resulting in bruising, nosebleeds or, more rarely, fatal bleeds, in particular intracranial bleeds.
E5501 monomaleate is an orally administered, small molecule c-Mpl agonist that mimics the biological effects of TPO in vitro and in vivo. TPO is the principal physiologic regulator of platelet production and exerts its effect on megakaryocytopoiesis and thrombocytopoiesis via binding and activation of the c-Mpl receptor, which is expressed on hematopoietic stem cells, on cells of the megakaryocytic lineage, and on platelets. Like TPO, E5501 also binds to the human c-Mpl receptor and affects signal transduction through the induction of downstream signaling, thereby enhancing human megakaryocytic proliferation and differentiation.
E5501 is a small molecule that can be administered orally, and thus presents neither the clinical/safety risks associated with parenteral agents nor the immunogenic risks of recombinant proteins and peptide -based products. E5501 has increased platelet production in normal healthy subjects both in single- and multiple-dose oral administration, and has demonstrated superior efficacy in cITP subjects compared with placebo, as measured by platelet response on Day 28, as well as a favorable safety profile (protocol 6.1.2.2).
This is a Phase 3 multicenter, randomized, double-blind, active-controlled, parallel-group trial with an open-label extension phase that will further evaluate the efficacy of oral E5501 versus eltrombopag in raising and

maintaining platelet counts within 6 months from the start of dosing, and the safety of E5501 over a long-term 2.5-year treatment period in adult subjects with cITP. This study has been designed to provide efficacy and safety data for five doses of E5501 in cITP subjects in order to gain regulatory approval to make E5501 available for clinical use worldwide. A noninferiority (NI) study design is planned in response to feedback from the FDA at the End of Phase 2 meeting and the EMA scientific advisory meeting. Eltrombopag is selected as an active comparator because this is the only other available oral TPO-agonist therapy and would be the most appropriate for the proposed NI study.

Study objective

Core Study
Primary objective
• To compare the efficacy of E5501 (in addition to standard of care) to eltrombopag (in addition to standard of care) for the treatment of adult subjects with chronic immune thrombocytopenia (idiopathic thrombocytopenic purpura [ITP]) as measured by durable platelet response

Secondary objectives
• To demonstrate that the efficacy of E5501 (in addition to standard of care) is superior to the efficacy of eltrombopag (in addition to standard of care) as measured by platelet response rate at Day 8
• To evaluate the safety of E5501 compared with eltrombopag

Additional Objectives
• To evaluate the efficacy of E5501 (in addition to standard of care) compared with the efficacy of eltrombopag (in addition to standard of care) with regard to alternate durable response, bleeding minimization, use of rescue therapy, and reduction in concomitant ITP medication use
• To evaluate the population pharmacokinetics/pharmacodynamics of plasma E5501 exposure and effect on platelet counts

Extension Phase
Primary Objective
• To evaluate the safety and tolerability of long-term therapy with E5501 in subjects with chronic ITP (cITP)

Secondary Objectives
• To demonstrate the effectiveness of long-term therapy with E5501 as measured by platelet response, bleeding, and the use of rescue therapy
• To assess the reduction in use of steroids and concomitant ITP medication in subjects receiving E5501

Study design

This is a multicenter, multinational, randomized, double-blind, active-controlled, parallel-group study of E5501 in men and women >= 18 years of age who have cITP. Approximately 286 subjects who meet all the eligibility requirements will be randomized. Splenectomized subjects must make up at least 35% of the study population. Therefore, when enrollment of nonsplenectomized subjects reaches 65%, the enrollment of those subjects will be stopped. The Screening Visit and Day 1 Baseline/Randomization Visit platelet counts will be averaged to obtain the
baseline platelet count value. The two samples must be obtained >= 48 hours and <= 2 weeks apart and the results must be available prior to randomization. Therefore, an additional screening platelet count may be required due to issues with scheduling.

No single platelet count should be > 35 x 109/L. Subjects will be centrally stratified at time of randomization by splenectomy status, baseline platelet count (<=15 x 109/L or >15 to <30 x 109/L), and use of concomitant ITP medication (i.e., yes or no for the use of concomitant ITP medication) at baseline, and will be randomized by an Interactive Voice and Web Response System (IxRS) to receive either double-blind E5501 or eltrombopag in a 1:1 ratio. Subjects will receive blinded therapy at a starting dose of 20-mg E5501 once daily or 50-mg eltrombopag once daily. Subjects will be allowed to have their dose titrated up (maximum dose 40 mg for E5501 and 75 mg for eltrombopag) or down (minimum dose 5 mg for E5501 and 25 mg for eltrombopag) in accordance with their individual response to study drug. The overall goal of any dose modification will be to maintain the platelet count at
levels >= 50 × 109/L and <= 150 × 109/L, and to decrease the need for concomitant ITP medications.

The study will consist of three phases: Prerandomization, Randomization (Core Study), and the Extension. The Prerandomization Phase will have one Screening Period (up to 4 weeks). The Randomization Phase (Core Study)
will have six periods: Baseline/Randomization (1 day), Titration (6 weeks), Concomitant ITP Medication Reduction (12 weeks), Maintenance (8 weeks including the End-of-treatment [EOT] Visit [Visit 22]), Dose-tapering (up to
4 weeks), and Follow-up (30 days). Dose-tapering and Follow-up are required only for those subjects not continuing into the Extension Phase.

The Extension Phase will consist of four periods: Conversion (6 weeks), Maintenance Period/Concomitant ITP Medication Reduction Period (98 weeks), Dose-tapering (up to 4 weeks), and Follow-up (30 days).

The end of the study will be the date of the last scheduled study visit for the last subject in the study.

Prerandomization Phase
Screening Period (Visit 1): During this period, subjects will be assessed for eligibility and have a platelet count performed.

The Screening Visit and Day 1 Baseline/Randomization Visit platelet counts will be averaged to obtain the baseline platelet count value. The two samples must be obtained >= 48 hours and <= 2 weeks apart and the results must be available prior to randomization. Therefore an additional screening platelet count may be required due to issues with scheduling. If an additional platelet count is taken, an average of the last two platelet counts of >= 48 hours apart needs to be < 30 x 109/L as a baseline value for eligibility.

Core Study
Randomization Phase
Baseline/Randomization Period (Visit 2): During this period, baseline assessments, including platelet count and randomization, will be performed. Blinded study drug administration will be started.

Titration Period (Visits 3 to 7): Titration of study drug from the initial starting dose will be performed in accordance with protocol-specified titration guidelines in order to find the minimum dose required to maintain platelet counts of >= 50 × 109/L and <= 150 × 109/L. No downward titration of concomitant ITP medication will be permitted during this period unless there is a safety concern. Subjects will return on Days 5, 8, 14, 21, and 28 during this period.

Concomitant ITP Medication Reduction Period (Visits 8 to 13): Downward titration of concomitant ITP medication will be permitted in accordance with the Concomitant ITP Downward Titration Guidelines. This may require additional study drug dose adjustments before and after the concomitant ITP downward titration. Subjects will return every 2 weeks during this period.

Maintenance Period (Visits 14 to 22): Subjects will continue treatment in order to maintain platelet counts of >= 50 × 109/L and <= 150 × 109/L. Study drug dose adjustments will be made in accordance with the titration guidelines. No downward titration of concomitant ITP medication will be permitted during this period unless there is a safety concern. Subjects will return weekly for visits. At the EOT Visit, subjects will have the choice to enter the Extension Phase and receive open-label E5501 therapy. Subjects who are unable or unwilling to continue in the Extension Phase will enter the Dose-tapering and Follow-up Periods.

Subjects who require study drug dose adjustments, who undergo concomitant ITP medication reduction, or who receive rescue therapy during the periods of Concomitant Medication Reduction and Maintenance are required to return for weekly visits for 3 consecutive weeks.

Dose-tapering Period (Visits 23 to 26): Subjects who do not continue into the Extension Phase will be required to attend weekly visits at which the study drug will be down titrated one dose level per week until the study drug is discontinued. This will be done in a blinded fashion and will take up to 4 weeks to get all subjects off study drug. During the Dose-tapering Period,

subsequent up-titration or addition of concomitant ITP medication should be considered at the investigator*s discretion. Once the dose-tapering of study drug is completed, subjects will enter the Follow-up Period.

Follow-up Period (Visits 27 to 30): Subjects will be followed for 30 days after the last dose taken in the Dose-tapering Period. Subjects will return every week for visits and will have their final evaluations on the last day of the Follow-up Period.

Extension Phase
Subjects who meet all the eligibility requirements for the Extension Phase and who are willing and able will enter the Extension Phase. Subjects who discontinue the Core Study early because of lack of treatment effect (see Study Drug Discontinuation) will still be eligible to continue into the Extension Phase. Subjects entering directly into the Extension Phase will not enter the Dose-tapering and Follow-up Periods of the Core Study.

Conversion Period (Visits E1 to E8): This period will consist of E1 Visit (Day 1 Visit of the Extension Phase), E2 Visit (Day 5 Visit of the Extension Phase), E3 Visit (Day 8 Visit of the Extension Phase), and then five weekly visits thereafter. A 1-week washout period (to ensure PK washout of blinded study therapy) is required between the Core Study (i.e., the EOT Visit [Visit 22]) and the Extension Phases (i.e., Visit E1). Subject eligibility for the Extension Phase will be determined at the E1 Visit. Open-label E5501 therapy will be dispensed at the E1 Visit.

Subjects will be converted from blinded therapy to open-label E5501 therapy. All subjects and investigators will remain blinded to the treatment received in the Core Study. Subjects entering the Extension Phase will receive a starting dose of open-label E5501 that is determined by the last dose level based on the number of upward or downward titrations from the starting dose of study drug at the EOT Visit (Visit 22) of the Core Study. This will be determined via the IxRS system in a blinded manner.

Subjects who discontinue the Core Study early because of lack of treatment effect and enter the Extension Phase will receive open-label E5501 treatment at a starting dose of 20 mg once daily. No downward titration of concomitant ITP medication will be permitted during this period unless there is a safety concern.

Maintenance Period/Concomitant ITP Medication Reduction Period (Visits E9 to E31): Titration of open-label E5501 treatment will be performed in accordance with E5501 dose-adjustment guidance in order to find the minimum dose required to maintain platelet counts of >= 50 × 109/L and <= 150 × 109/L. Downward titration of concomitant ITP medication will also be permitted during this period of the Extension Phase. Concomitant ITP Downward Titration Guidelines will be specified.

Subjects will return after 2 weeks for Visit E9. Thereafter, subjects will return for monthly visits during this period unless they require E5501 dose adjustments and/or concomitant ITP medication downward titration. Affected subjects will be required to return to undergo 3 consecutive weekly visits. Unplanned visits may be scheduled at any time for subjects who require urgent correction of platelet counts, E5501 dose adjustment, or for other reasons at the investigator*s discretion.

Dose-tapering Period (Visits E32 to E35): Dose tapering of E5501 treatment will be performed in all subjects who have either completed the Extension Phase of the study (2 years total duration) or who discontinue early from any phase. Subjects will be required to attend up to 4 weekly visits for downward titration of the dose of E5501 at 10 mg per week until the 10-mg dose is reached, followed by 1 week of treatment at 5 mg, then 1 week of treatment at 0 mg. During the Dose-tapering Period, subsequent upward titration or addition of concomitant ITP medication should be considered at the investigator*s discretion. Once the dose tapering of the study drug has finished, subjects will enter the Follow-up Period.

Follow-up Period (Visits E36 to E39): Subjects will be followed for 30 days after the last dose of the Dose-tapering Period. Subjects will return every week for visits and will have their final evaluations on the last day of the Follow-up Period.

Study Drug Dose-Adjustment Guidelines
To minimize the risk of developing thrombocytosis, dose adjustment of the study drug will target maintaining the platelet count of >= 50 × 109/L and <= 150 × 109/L. Study drug dose adjustment for the Core Study must follow the dose adjustment guidelines.

Investigators must consider dose adjustment in accordance with a subject*s platelet counts every 2 weeks (as most subjects take approximately 10 to 14 days to demonstrate the full effect of E5501/eltrombopag on platelet count). However, dose adjustment may be performed weekly for subjects with platelet counts < 50 × 109/L or > 250 × 109/L.

The proposed dose-adjustment guidelines should be adhered to with the exception of the following clinical scenarios:
• If a subject has recently received rescue therapy and the subject*s platelet count is expected to rise, making upward dose titration of the study drug inappropriate
• If a subject*s platelet count has risen as a result of receiving rescue therapy and this rise in platelet count is transient and expected to fall, making downward dose titration of the study drug inappropriate
• If a subject*s study drug is stopped due to elevated platelet counts (i.e., platelet count > 250 × 109/L) the investigator can choose not to place the subject onto the same dose of study drug that originally caused this high rise

in platelet count. This is to avoid large fluctuations in platelet counts.
• If a subject*s platelet count is >= 50 × 109/L and <= 150 × 109/Land the investigator would like to down titrate the subject*s concomitant ITP medication, the subject*s study drug can be up titrated.

A maximum of two dose level titration steps from the starting dose (i.e., 20-mg E5501/50-mg eltrombopag) will be permitted for both upward titration and downward titration in the Core Study. After two downward titrations from the starting dose, if the platelet count remains > 250 × 109/L after 3 consecutive weeks, the subject*s concomitant ITP medication should, if possible, be down titrated provided a) the subject is in the concomitant ITP medication reduction period of the Core Study (i.e., Visits 8 to 13) or b) maintenance period/concomitant ITP medication reduction period of the Extension Phase (i.e., Visits E9 to E31). Otherwise, the subject should be discontinued.

In order to maintain the blind, a placebo titration step will be implemented in the Core Study in those subjects who have reached the highest (75 mg) and lowest (25 mg) dose levels of eltrombopag.

E5501 dose adjustment in the Extension Phase of the study are identical to those of the Core Study but will be performed with open-label E5501 as defined by E5501 dose adjustment guideline for the Extension Phase.

Study Drug Discontinuation
In both the Core Study and the Extension Phases, study drug may be discontinued at the discretion of the investigator due to safety reasons or as follows:
• Due to lack of treatment effect defined as:
o Platelet count remains < 30 × 109/L more than 3 weeks at the maximum dose or
o Subjects who require rescue treatment more than three times or continuous rescue treatment for more than 3 weeks (Core Study only)
• Excessive platelet count responses (>250 × 109/L) after more than 3 weeks at the minimum dose and the subject is unable to down titrate concomitant ITP medication
• Treatment with some ITP therapies/procedures, such as vinca alkaloids, cyclophosphamide, rituximab, splenectomy, and other thrombopoietin (TPO) receptor agonists (eltrombopag, romiplostim) other than eltrombopag provided in the study
• Subjects with elevated fasting gastrin-17 greater than 5 times the upper limit of normal (ULN)
• Subjects with two consecutive elevated fasting gastrin-17 greater than 2.5 times ULN in the absence of other obvious clinical causes who refuse referral to an appropriate specialist for consideration of endoscopy
• Subjects with gastric atrophy as determined by endoscopy and biopsy assessment

Concomitant ITP Medication Downward Titration Guidelines
Those subjects receiving concomitant ITP medication when entering the study may have this medication down titrated and ultimately eliminated. This can only

occur during the Concomitant ITP Medication Reduction Period (Visits 8 to 13) of the Core Study and Maintenance Period/Concomitant ITP Medication Reduction Period of the Extension Phase (Visits E9 to E31).

Concomitant ITP medication downward titration can be implemented at the discretion of the investigator. Downward titration of concomitant ITP medication can only be considered if the subject*s platelet count remains > 150 × 109/L. The downward titration of concomitant ITP medication will be made as an alternative to downward titration of E5501 (i.e., instead of titrating down E5501, the concomitant ITP medication will be down titrated). Any downward titration of ITP medication should occur in a controlled manner in order to prevent an excessive and unsafe drop in the subject*s platelet count.
Concomitant ITP Medication Downward Titration
Guidelines are detailed below:
• Concomitant ITP medication downward titration should not take place at a rate faster than once (one time) every 14 days.
• If a subject has two or more concomitant ITP medications, only one medication can be down titrated at a time.
• It is preferable that a concomitant ITP medication is eliminated before the downward titration of a second concomitant ITP medication, unless the investigator considers it beneficial for the subject to continue to receive low-dose steroids.
• Each titration step cannot be larger than 25% to 50% of the original concomitant ITP medication dose unless the subject is receiving a low dose of the concomitant ITP medication being down titrated.

Permitted Concomitant Therapy
Permitted ITP concomitant background therapies are as follows:
• Corticosteroids and/or azathioprine must be taken at a stable dose for 4 weeks before randomization.
• Mycophenolate mofetil (MMF) or danazol must be taken at a stable dose for at least 12 weeks before randomization.
• Cyclosporine A (CsA) (due to the fact that it is a P-glycoprotein-mediated transport [P-gp] inhibitor) should be avoided unless deemed medically necessary; CsA must be taken at a stable dose for at least 12 weeks before randomization.

At the discretion of the investigator, subjects will be allowed to use aspirin, other salicylates, or approved adenosine diphosphate (ADP) receptor antagonists, (e.g., clopidogrel, prasugrel) during the study once their platelet count has risen.

Subjects treated with PPIs and H2 antagonist therapy must be receiving a stable dose for at least 6 weeks prior to randomization or treatment with these therapies must have been completed at least 2 weeks prior to randomization.

E5501 is a substrate and an inhibitor of P-gp. Co-administration with

moderate/strong inhibitors of P-gp should be avoided unless deemed medically necessary. If E5501 is administered with any concomitant medications which are substrates of P-gp, clinical signs of toxicity or blood levels (if available) of these concomitant medications need to be assessed.

Eltrombopag is an inhibitor of organic anion transporter polypeptide 1B1 (OATP1B1) transporter. Subjects must be closely monitored for signs and symptoms of excessive exposure to drugs that are substrates of OATP1B1 (e.g., rosuvastatin) and reduction of the dose of these drugs should be considered.

Polyvalent cations (e.g., iron, calcium, aluminum, magnesium, selenium, and zinc) significantly reduce the absorption of eltrombopag: Eltrombopag must not be taken within 4 hours of any medications or products containing polyvalent cations such as antacids, dairy products, and mineral supplements.

Rescue therapy
Subjects will be allowed to receive rescue therapy at the discretion of the investigator or subinvestigator based on their clinical assessment. Rescue therapy should be considered if there is an urgent need to increase platelet count, for example:
• Life-threatening thrombocytopenia, such as a platelet count < 10 x 109/L
• Clinical signs or symptoms suggesting potential bleed (i.e., wet purpura)
• Major bleed

Rescue therapy will be defined as:
• The addition of any new ITP medication or medication to treat thrombocytopenia (for example):
o Corticosteroids
o Intravenous immunoglobulin (IVIg) therapy
o Anti-D therapy
o MMF
o Azathioprine
o Danazol
o Dapsone
o CsA (Due to the fact that it is a P-gp inhibitor, CsA should be avoided unless deemed medically necessary and/or no other suitable alternative treatment options are available.)
o Platelet transfusion
• Any increase in baseline dose of concomitant ITP medication

TPO agonists are not allowed as rescue therapy.

Prohibited Concomitant Therapy
Platelet transfusion is prohibited within 7 days before the first dose of study drug. Antifibrinolytic agents (aprotinin, tranexamic acid, and aminocaproic acid) and recombinant activated factor VII are prohibited during the treatment

phase of the study. Heparin, warfarin, fresh frozen plasma and cryoprecipitate, antiplatelet therapy with aspirin, clopidogrel, prasugrel, ticlopidine, or glycoprotein IIb/IIIa antagonists (e.g., tirofiban) are prohibited during the treatment phase of the study. However, short-term use of aspirin, other salicylates, or ADP receptor antagonists are only permitted if the platelet count has risen and the investigator judges that the subject is at risk for thromboembolism. The use of nonsteroidal anti-inflammatory drugs other than aspirin for more than 7 days per month is prohibited.

Some ITP therapies/procedures, such as vinca alkaloids, cyclophosphamide, rituximab, splenectomy, and other TPO receptor agonists (eltrombopag, romiplostim) other than the eltrombopag provided in the study are prohibited during the treatment phase due to the long-term effects of these treatments, their safety profile, and potential to confound efficacy results. Subjects requiring these therapies will be discontinued from the study.

Hematology Tests
When a hematology test is required, two blood samples will be collected; one for central laboratory analysis and one for local laboratory analysis. The local laboratory hematology test results will be sent directly to the investigators and
will be used to qualify a subject*s entry into the study, study drug and concomitant ITP medication dose titration, and clinical assessment.

Only platelet count data from local laboratories will be collected and entered in the case report form (CRF) for analysis. All other study-specific hematological parameters (except the platelet count) derived from the central laboratories will be collected and databased for analysis.

Bone Marrow Evaluation
Bone marrow biopsies will be divided into three categories: those required for eligibility, those required during the study, and those required due to the subject agreeing to enroll into the optional bone marrow evaluations:
1. Bone marrow biopsies will be required for eligibility in the following situation:
Subjects who have never initially responded (platelet count >50 × 109/L) to a previous ITP therapy and who don*t have a bone marrow examination consistent with ITP within the last 3 years before randomization. These subjects will be required to undergo a bone marrow biopsy during screening before entering the study.
2. Subjects who are known nonresponders (defined as platelet counts that never exceed 50 x 109/L) to all previous TPO-agonist therapy (including previous E5501 therapy) who do not have a bone marrow examination consistent with ITP taken at any point after failure of TPO therapy will be required to undergo a bone marrow biopsy before entering the study. Bone marrow biopsies will be required during the study in the following situation:
Subjects who have a white blood cell (WBC) differential and the subsequent

peripheral blood smear confirming the presence of immature or dysplastic cells at either the Baseline Visit or during the study
3. Optional bone marrow evaluations:
Optional bone marrow evaluations will be requested from all subjects. These evaluations should be strongly encouraged to allow for the assessment of bone marrow safety of E5501. For those subjects who consent to undergo these optional bone marrow evaluations, bone marrow biopsies will be performed as follows:
For subjects who do enter the Extension Phase:
• At Visit 2 (Baseline/Randomization Visit)
• At Visit E13 (6 month Visit of the Extension Phase) or on exit from the study (whichever occurs first)
For subjects who do not enter the Extension Phase:
• At Visit 2 (Baseline/Randomization Visit)
• At Visit 22 (EOT Visit of the Core study) or on exit from the study (whichever occurs first)

If a subject has had a bone marrow evaluation within 6 months prior to randomization (including during screening) and has not received anysubsequent TPO agonists, this bone marrow evaluation may be considered as a valid baseline (i.e., the Visit 2 (Baseline/Randomization Visit), providing the bone marrow specimen is available for re-examination. If no previous bone marrow evaluation is available, a bone marrow biopsy should be performed at
Visit 2 (Baseline/Randomization Visit) as detailed above.

Subjects unwilling to consent to the routine bone marrow biopsies will still be eligible for enrolment.

A central laboratory will be used for all bone marrow evaluations. Collagen and reticulin will be measured. The modified Bauermeister scale will be used to grade the severity of marrow fibrosis.

Endoscopy
Endoscopy assessments will be performed at the Week 4 Visit (Visit 7) as an optional assessment and at Week 26 (Visit 22/End of Treatment) of the Core study as a requirement to enter the open-label extension phase. In the openlabel extension phase, two additional endoscopy assessments will be performed; one assessment each year (i.e., at the 12-month Visit [Visit E19] and the 24-month Visit [Visit E31]).

All endoscopy assessments will only be considered if clinically possible, as assessed by the treating physician and endoscopist (i.e., there is no excessive risk of the subject bleeding, in particular, subjects will only be requested to undergo endoscopies if their platelet counts are > 50 x 109/L).

Intervention

Patients will be subjected to the following interventions/procedures and defined behavioural rules (for a schedule of procedures at each site visit: please see protocol tables 8 & 9):
> oral intake of study medication tablets: initially either 20mg E5501 plus eltombopag placebo or 50mg eltrombopag plus E5501 placebo. See Protocol section 8.4.5 for dose adjustment instructions.
> physical examinations
> measurement of vital signs
> blood sample collection (including an optional pharmacogenomic (PG) sample, for which there is a seperate patient information leaflet and consent form): for certain visits, patients will be asked to be fasting and to not smoke in the 12 hours prior to collection.
> pregnancy tests (blood and urine)
> collection of urine samples
> electrocardiogram (ECG)
> questionaires (EQ-5D, SF-36, TSQM)
> bone marrow biopsy (if patient has never responded to previous treatment for ITP and has not had a bone marrow biopsy within past 3 years to confirm they have ITP AND/OR if the blood samples taken at any point during the study show that levels of blood cells are abnormal)
> optional bone marrow biopsy, for which there is a separate patient information leaflet and consent form.
> endoscopy; if patient enters the extension phase and only if deemed safe
> patients will be asked to attend all scheduled study visits, to take the study medication as instructed, to inform their study doctor if they missed any doses or took more tablets than supposed to, to return all study medication boxes (even if empty) given at each visit and to bring their study drug to every study visit.
> patients will be asked to report all side effects, symptoms and medical problems.
> patients will be asked not to take certain drugs, to inform the study team of any changes in their medication and to consult their study team before taking any over the counter medicines/vitamins/supplements/herbals and prescription drugs or alternative procedures.
> female patients must agree to use an effective method of contraception 30 days before, during the entire study period and for 30 days after their participation in the study. If they become pregnant during the course of the study, the patient must tell her study doctor immediately and she and her unborn baby will be followed to term.

Study burden and risks

Burden:
The study procedures that will be performed are listed in K2 "Interventions", The duration of treatment for each subject is 26 weeks for the randomized treatment period and 112 weeks (~2 years) for the extension period.

Side effects and risks:
The side effects most commonly reported in previous research studies of E5501 were:

• Headache
• Fatigue
• Diarrhoea
• Excessive Platelet Count Increase
• Nausea
• Vomiting
• Dizziness
• Drowsiness/Sleepiness
• Reoccurrence of a low level of platelets in the blood upon stopping E5501
• Minor bleeding events (e.g. nose bleeds, bleeding gums, bruising)
• Common cold
• Back pain
• Collection of fluid in feet and legs
• Joint pains
• Increased gas in stomach or intestines
• Stomach pain

The following potentially serious but infrequent side effects were reported in prior studies of E5501:

• One subject had a heart attack, mini stroke (or Transient Ischemic Attack, TIA, i.e. a stroke that resolves after 24 hours) and reduced blood flow in one eye.
• A high white blood cell count (leukocytosis) occurred in one subject which was diagnosed as acute myeloid leukaemia (abnormal production of cancerous blood cells).

Because of the way E5501 works there is a potential risk for developing blood clots or blockage of blood vessels in the body. Patients will be closely monitored for any signs of clotting or abnormal levels of cells in the blood. The study doctor may prescribe aspirin if the patients platelet count increases and he/she believes the patient may be at risk for clotting. If the patient is unable to take aspirin, an alternative anti-platelet drug may be prescribed. By giving the patient aspirin or the alternative anti-platelet drug, this should reduce his/her risk of developing blood clots or blocked blood vessels.

In laboratory studies, gastric atrophy (decrease in thickness of stomach lining) as well as increase in the certain cells of the stomach lining (hyperplasia), as well as tumors (known as carcinoids) was seen in rats and mice. These findings were observed at much higher doses (23-34 x higher) than the doses used in this study; however, because the risk in humans is unknown, a blood test will be performed at different time points during the study, to monitor for potential stomach changes know as gastric atrophy (thinning of the

stomach lining).

In addition because of the way E5501 works and as noted with all medications in this class, there is a potential risk for developing or progression of bone marrow scarring and blood cancers. The patients blood counts will be monitored throughout the study.

The following are some of the most common side effects related to eltrombopag therapy

• Nausea
• Vomiting
• Heavy or longer than normal menstrual periods
• Muscle aches
• Abnormal skin sensations such as tingling, itching, or burning
• Cataract (clouding of lens in the eye)
• Indigestion
• Bruising
• Thrombocytopenia- low platelet counts
• Increased ALT/AST- increase in laboratory tests of serum alanine aminotransferase and aspartate aminotransferase
• Bleeding into the tissue that covers the eye and under side of the eyelid (conjunctival hemorrhage).

Some serious side effects of eltrombopag include
• Liver problems which may lead to death
• Bone marrow changes
• Worsening low blood count and risk of bleeding after stopping treatment
• High platelet counts
• Higher chance for blood clots
• Worsening of blood cancers

Risks for pregnancy and discomforts that may be caused by the study procedures while the patient is on this study are also listed in the patient information form.

Benefits: E5501 has increased platelet production in normal healthy subjects both in single- and multiple-dose oral administration, and has demonstrated superior efficacy in cITP subjects compared with placebo, as measured by platelet response on Day 28, as well as a favorable safety profile (protocol 6.1.2.2). Treatment with E5501 is anticipated to have an improved safety profile (potentially no severe liver toxicity) and a faster onset of action as compared to eltrombopag and may thereby improve the patients' medical condition. Patients have 50% chance of receiving E5501. However, it cannot be guaranteed that the patient will benefit from this study. The information gathered from this study may also help treat future patients with

thrombocytopenia.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Core Study
1. Men and women >= 18 years of age
2. Subjects diagnosed with cITP (>=12 months duration) according to the American Society for Hematology/British Committee for Standards in Hematology (ASH/BCSH) guidelines, and an average of two platelet counts < 30 × 109/L (no single count may be >35 × 109/L). In addition, a peripheral blood smear should support the diagnosis of ITP with no evidence of other causes of thrombocytopenia (e.g., pseudothrombocytopenia, myelofibrosis). The physical examination should not suggest any disease which may cause thrombocytopenia other than ITP.

3. Subjects who previously received one or more ITP therapies (including, but not limited to, corticosteroids, immunoglobulins, azathioprine, danazol, cyclophosphamide and/or rituximab)
4. Subjects must have had either initially responded (platelet count >50 × 109/L) to a previous ITP therapy or have had a bone marrow examination consistent with ITP within 3 years to rule out myelodysplastic syndrome (MDS) or other causes of thrombocytopenia.
5. Prothrombin time/International Normalized Ratio (PT/INR) and activated partial thromboplastin time (aPTT) must have been within 80% to 120% of the normal range with no history of hypercoagulable state.
6. A complete blood count within the reference range (including WBC differential not indicative of a disorder other than ITP), with the following exceptions:
• Hemoglobin: Subjects with hemoglobin levels between 10 g/dL (100 g/L) and the lower limit of normal (LLN) are eligible for inclusion, if anemia was clearly attributable to ITP (excessive blood loss).
• Absolute neutrophil count (ANC) >= 1500/µL (1.5 x 109/L) (elevated WBC/ANC due to corticosteroid treatment is
acceptable).;Extension Phase
1. Subjects who have completed 6 months of study treatment in the Randomization Phase or
2. Subjects who discontinue the Core Study early due to lack of treatment effects (see Study Drug Discontinuation)
3. No significant safety or tolerability concerns with the subject*s participation of Randomization Phase as determined by the investigator

Exclusion criteria

Core Study
1. Subjects with known secondary immune thrombocytopenia (e.g., subjects with known Helicobacter pylori-induced ITP, infected with known human immunodeficiency virus [HIV] or hepatitis C virus [HCV] or with known
systemic lupus erythematosus [SLE])
2. Subjects considered unable, or unwilling to comply with the study protocol requirements or give informed consent, as determined by the investigator
3. Subjects with significant medical conditions that may impact the safety of the subject or interpretation of the study results (e.g., acute hepatitis, active chronic hepatitis; lymphoproliferative disease; myeloproliferative disorders, leukemia)
4. History of MDS
5. History of pernicious anemia or subjects with vitamin B12 deficiency who have not had pernicious anemia excluded as a cause
6. Any prior history of arterial or venous thrombosis (stroke, transient ischemic attack, myocardial infarction, deep vein thrombosis, or pulmonary embolism), and more than two of the following risk factors: estrogen-containing hormone replacement or contraceptive therapies, smoking, diabetes, hypercholesterolemia, medication for hypertension, cancer, hereditary thrombophilic disorders (e.g., Factor V Leiden antithrombin III deficiency, etc.), or any other family history of arterial or venous thrombosis
7. Subjects with a history of significant cardiovascular disease (e.g., congestive heart failure [CHF] New York Heart Association Grade III/IV), arrhythmia known to increase the risk of

thromboembolic events [e.g., atrial fibrillation], subjects with a QT interval corrected for heart rate of > 450 msec, angina, unstable angina, coronary artery stent
placement, angioplasty, or coronary artery bypass grafting)
8. Subjects with a history of cirrhosis, portal hypertension, and chronic active hepatitis
9. Subjects with concurrent malignant disease
10. Use of immunoglobulins (IVIg and anti-D) within 1 week of randomization
11. Splenectomy or use of rituximab within 12 weeks of randomization
12. Use of romiplostim or eltrombopag within 4 weeks of randomization
13. Subjects who are currently treated with corticosteroids or azathioprine but have not been receiving a stable dose for at least 4 weeks prior to randomization or have not completed these therapies more than 4 weeks prior to randomization
14. Subjects who are currently treated with MMF, CsA, or danazol but have not been receiving a stable dose for at least 12 weeks prior to randomization or have not completed these therapies more than 4 weeks prior to randomization
15. Use of cyclophosphamide or vinca alkaloid regimens within 4 weeks of randomization.
16. Subjects who are currently treated with PPIs or H2 antagonist therapy but have not been receiving a stable dose for at least 6 weeks prior to randomization or have not completed these therapies more than 2 weeks prior to randomization
17. Fasting gastrin-17 blood levels exceeding ULN (including subjects on PPIs and H2 antagonists) at Screening
18. Blood creatinine exceeding ULN by more than 20% OR total albumin below the LLN by 10%
19. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels exceeding 2 times the ULN; total bilirubin exceeding 1.5 times the ULN
20. Subjects with a history of cancer treatment with cytotoxic chemotherapy and/or radiotherapy. Subjects with a history of ITP treatment with cytotoxic chemotherapy are still eligible for enrollment.
21. Females who are pregnant (positive beta-human chorionic gonadotropin [β-hCG] test) or breastfeeding
22. Subjects with a known allergy to E5501 or eltrombopag and any of their excipients
23. Subjects with a history of significant aminotransferase elevations while receiving eltrombopag (defined as ALT and/or AST elevation >3 x ULN)
24. Subjects who are known nonresponders (defined as platelet counts that never exceed 50 x 109/L) to all previous TPO agonist therapy (including previous E5501 therapy) who do not have a bone marrow examination consistent with ITP taken at any point after failure of TPO therapy to rule out MDS or other causes of thrombocytopenia;Extension Phase
1. Subjects for whom participation in the Extension Phase is considered unsafe, based on the investigator*s judgment
2. Subjects unwilling to undergo an endoscopy at the time of enrollment into the Extension Phase
3. Subjects considered unable or unwilling to comply with the study protocol requirements or give informed consent, as determined by the investigator
4. Subjects requiring the following drugs or treatments at the time of enrollment in the Extension Phase:
• Rituximab
• Splenectomy
• Other TPO agonists

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	n/a
Generic name:	1-(3-chloro-5-{[4-(4-chloro-2-thienyl)-5-(4-cyclohexylpiperazin-1-yl)-1,3-thiazol-2-yl]carbamoyl}-2-
Product type:	Medicine
Brand name:	Revolade
Generic name:	Eltrombopag
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	23-05-2012
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	24-05-2012
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-10-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-02-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-000831-10-NL
ClinicalTrials.gov	NCT01433978
CCMO	NL39416.028.12