A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Oral E5501 Plus Standard of Care for the Treatment of Thrombocytopenia in Adults with Chronic Immune Thrombocytopenia (Idiopathic Thrombocytopenic Purpura).

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Core Study:Primary objective: • To demonstrate that the efficacy of E5501 (in addition to standard of care) is superior to placebo (in addition to standard of care) for the treatment of adult subjects with chronic immune thrombocytopenia (idiopathic...

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

Summary

ID

NL-OMON37708

Source
ToetsingOnline

Brief title
E5501 in cITP

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), double-blind, E5501, phase 3

Outcome measures

Primary outcome

Core Study:

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., Visits 15 to 22, inclusive) over the 6-month treatment period in the 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 be defined as a platelet count < 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

• Platelet response rate at Day 8 (as defined by the 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.

• Alternative durable platelet response as defined by: proportion of subjects with at least 75% of platelet assessments between >= 50 x109/L and <= 400 x 109/L from the time of first response over a 6-month treatment period in the absence of rescue therapy (durability by flexible period)

• Proportion of subjects with a reduction in use of concomitant ITP medications from baseline

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, parallel group and placebo-controlled trial with an open-label extension phase that will further evaluate the efficacy of oral E5501 (in addition to standard of care) versus placebo 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 the best possible efficacy and safety evidence for E5501 in the treatment of cITP subjects in order to gain regulatory approval to make E5501 available for clinical use worldwide.

Study objective

Core Study:
Primary objective:
• To demonstrate that the efficacy of E5501 (in addition to standard of care) is superior to placebo (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 placebo (in addition to standard of care) as measured by platelet response rate at Day 8
• To demonstrate that the efficacy of E5501 (in addition to standard of care) is superior to the efficacy of placebo (in addition to standard of care) as measured by an alternate durable response
• To demonstrate that the efficacy of E5501 (in addition to standard of care) is superior to the efficacy of placebo (in addition to standard of care) as

measured by the proportion of subjects with reduction in concomitant ITP medication use
• To evaluate the safety of E5501 compared with placebo

Additional Objectives:
• To evaluate the efficacy of E5501 (in addition to standard of care) is superior to the efficacy of placebo (in addition to standard of care) with regard to bleeding minimization and use of rescue therapy
• To evaluate the population pharmacokinetic/pharmacodynamics (PK/PD) 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 study is a multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group study of E5501 in men and women >= 18 years who have cITP. Approximately 84 subjects who meet all the eligibility requirements will be randomized into the study. Splenectomized subjects must make up at least 35% of the study population, therefore, when enrollment of nonsplenectomized subjects reaches 65%, 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.

No single platelet count should be > 35 x 109/L. Subjects will be centrally stratified at time of randomization by splenectomy status and 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 TP medication) at baseline, and will be randomized by an Interactive Voice and Web Response System (IxRS) to receive either E5501 or placebo in a 2:1 ratio in double-blind fashion. Subjects will receive blinded therapy at a starting dose of 20 mg E5501 or placebo once daily. Subjects will be allowed to have their dose titrated up (maximum dose 40 mg for E5501 or matching placebo) or down (minimum dose 5 mg for E5501 or matching placebo) in accordance with their individual responses to study drug; a placebo titration will be used to maintain the blind. The overall goal of any dose modification will be to

maintain the
peripheral platelet count at levels >= 50 × 109/L and <= 150 × 109/L, and to decrease the need for ITP-directed concomitant medications, if possible.

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 (90 weeks), Dose-tapering (up to 4 weeks), and Follow up (30 days).

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 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): During this period, 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 down titration of
concomitant ITP medication will be permitted during this period (except for reasons of subject safety). Subjects will return on Days 5, 8, 14, 21 and 28 during this period.

Concomitant ITP Medication Reduction Period (Visits 8 to 13): During this period, downward titration of concomitant ITP medication will be permitted in accordance with the Concomitant ITP Downward Titration Guidelines. Additional

study drug dose adjustments before and after the ITP concomitant downward titration may be needed. 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 titration guidelines. No down 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 of the study 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 with placebo substitution occurring as required, 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 (Visit 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 during this period 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 5 weekly visits thereafter. The E1 Visit will be performed on the same day as the EOT Visit of the Core Study. No washout is required between the Core and the Extension

Phases. Subject eligibility for the Extension Phase will be determined at the E1 visit. The results of the EOT assessments will be used for the E1 Visit and serve as a baseline for the Extension Phase. Open-label E5501 therapy will be dispensed at the E1 Visit and should be started on the next day as the subject would have received the last dose of blinded therapy at EOT Visit of the Core Study for PK assessment.
During the Conversion Period of the Extension Phase, 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 20 mg of open-label E5501. Titration of E5501 will be performed in accordance with the protocol-specified titration guidelines. No down 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 by the protocol. Subjects will return after 2 weeks for the Visit E9. Thereafter, the 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 down 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, before reaching 0 mg. 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 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 defined below.
Investigators must consider dose titration in accordance with a subject*s platelet count every 2 weeks (as most subjects take approximately 10 to 14 days to demonstrate the full effect of study drug on platelet count). However, dose titration 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 or;
• 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 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/L and the investigator would like to down-titrate the subject*s concomitant ITP medication, the subject*s study drug can be up titrated.

A maximum dose of 40 mg E5501 will be permitted for upward titration and a minimum dose level titration of 5 mg E5501 will be permitted for downward titration. 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.

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 guidance for the Extension Phase

Study Drug Discontinuation
In both the Core Study and the Extension Phase, study drug may be permanently discontinued at 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 (subjects can be discontinued after 7 days of therapy at the maximum dose if they have dangerously low platelet counts in the opinion of the investigator) or
o Subjects who require rescue therapy more than three times or continuous rescue therapy for more than 3 weeks (Core Study only)

• Treatment with some ITP therapies/procedures, such as vinca alkaloids, cyclophosphamide, rituximab, splenectomy, and other TPO-receptor agonists (eltrombopag, romiplostim)
• 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
• Subjects with elevated fasting gastrin-17 greater than 5 times upper limit of normal (ULN) will be requested to undergo an endoscopy and will be discontinued.
• Subjects with two consecutive elevated fasting gastrin-17 greater than 2.5 times ULN who, in the opinion of the gastric biomarker expert review committee, require discontinuation due to gastric safety concerns
• Subjects with significant gastric atrophy (OLGA staging >=II)

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 down 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 prior to the down 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 (PgP) inhibitor should be avoided unless deemed medically necessary. If deemed medically necessary, then 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, at the discretion of the investigator.

Subjects treated with proton pump inhibitors (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 PgP. Co-administration with strong inhibitors of PgP should be avoided unless deemed medically necessary. If a strong P-gP inhibitor is to be added to E5501 therapy or if the dose of a concomitantly-administered strong P-gP inhibitor
is altered, platelet counts should be monitored weekly for the next 3 weeks as a dose adjustment of E5501 may be required. If E5501 is
administered with any concomitant medications which are substrates of PgP, clinical signs of toxicity or blood levels (if available) of these concomitant medications need to be assessed.

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 CsA is a PgP inhibitor, it 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 a 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, factor Xa inhibitors, direct thrombin inhibitors, fresh frozen plasma and cryoprecipitate, chronic antiplatelet therapy (>4 weeks) with aspirin, clopidogrel, prasugrel, ticlopidine, or glycoprotein IIb/IIIa antagonists (e.g., tirofiban) are prohibited during the treatment phase of the study. However, a 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 subjects are at risk for thromboembolism. The use of nonsteroidal anti-inflammatory drugs other than aspirin for more 7 days per month is prohibited.
Some ITP therapies/procedures, such as vinca alkaloids, cyclophosphamide, rituximab, splenectomy, and other TPO receptor agonists (eltrombopag, romiplostim) are prohibited during the treatment phase due to the long-term effects of these treatments, 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 result will be sent directly to the investigators and will be used for: qualifying 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 into the CRF for analysis. All other hematological parameters will be collected and loaded into the database for analysis according to results derived from the designated central laboratory.

Bone marrow evaluation
Bone marrow evaluations 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 evaluations 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 (biopsy or aspirate) consistent with ITP within the last 3 years before randomization.
2. Bone marrow biopsies will be required during the study in the following situation:
Subjects who have a 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 biopsies:
Optional bone marrow biopsies will be requested from all subjects. These evaluations should be strongly encouraged to allow 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 Visi
• 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 thestudy (whichever occurs first)

If a subject has had a bone marrow biopsy within 6 months prior to randomization (including during screening) and has not received any subsequent TPO agonists, this bone marrow biopsy 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 required. 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 optional bone marrow biopsies will still be eligible for enrollment.

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
All endoscopy assessments will only be considered if clinically appropriate, 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 5 & 6):
> oral intake of study medication (once daily, with food): tablets with 5mg, 10mg, 20mg or 40mg of either E5501 or placebo in a flexidose design. E5501 will be started at a dose of 20mg, with dose titration down to 5mg or up to 40mg as

per specified guidelines (protocol 8.4.5 and table2).
> 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, or is aged 60 years and older, 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.
> possibly an endoscopy, if the results from the fasting blood samples suggest that further testing is necessary.
> patients will be asked to attend all scheduled study visits, to take the study medication as instructed (once daily, with food), 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 104 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
-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
-joint pains
-collection of fluid in feet and legs
-Back pain
-increased gas in stomach or intestines
-stomach pain

Because of the way E5501 works there is a potential risk for developing blood clots or blockage of blood vessels in the body. The patient will be closely monitored for any signs of clotting or high levels of platelets in the blood. If platelet counts increase, the study doctor will stop study drug, and may prescribe aspirin if he/she believes the patient may be at risk for clotting. If the patient is unable to take aspirin, an alternative anti-platelet drug such as clopidogrel, may be prescribed. By giving aspirin or alternative anti-platelet drugs, this should reduce the patient's risk of developing blood clots or blocked blood vessels.

E5501, like other medications that increase platelet count, may cause changes in the bone marrow. These changes may cause the bone marrow to make fewer than normal cells or to make abnormal cells. These blood cell problems may be life threatening. These changes were seen with other medications after long-term use (> 6 months) although rare cases were reported after 1 months use. These bone marrow changes were generally reversible when the medication stopped. The patient's blood counts will be monitored throughout the study.

E5501 is not for use in people with blood cancer or a precancerous condition called myelodysplastic syndrome (MDS). E5501 may worsen this cancer or condition.

In laboratory studies, an increase in the cells of the stomach lining (hyperplasia), as well as tumours (known as carcinoids) was seen in rats, mice and monkeys. These findings were observed at higher doses 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 changes in the stomach lining.

Discomforts that may be casued 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). Thus, treatment with E5501 in this study is expected to increase the durable platelet response in adult subjects with cITP with superior efficacy compared to placebo (in addition to standard care) and thereby improve the patients' medical condition. 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 prior ITP therapies (including, but are 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 and activated partial thromboplastin time 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 white blood count [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 is clearly attributable to ITP (excessive blood loss).
• Absolute neutrophil count (ANC) >= 1500/µL (1.5 x 109/L) was required for inclusion (elevated WBC/ANC due to corticosteroid treatment is acceptable).
• Elevated WBC or ANC (e.g., due to corticosteroid treatment) provided this is discussed with the medical monitor;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., with known Helicobacter pylori-induced ITP, subjects infected with known human immunodeficiency virus [HIV] or hepatitis C virus [HCV] or subjects with known systemic lupus erythematosus).
2. Subjects with significant medical conditions that may impact on the safety of the subject or interpretation of the study results (e.g., acute hepatitis, active chronic hepatitis;

lymphoproliferative disease; myeloproliferative disorders, leukemia).
3. History of MDS.
4. History of gastric atrophy
5. History of pernicious anemia or subjects with vitamin B12 deficiency
(defined as 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: hormone replacement therapy, 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 corrected for heart rate of > 450 msec, angina, coronary artery stent placement, angioplasty, 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 proton pump inhibitors (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 the upper limit of normal
(ULN) at Screening for subjects not on PPIs or H2 antagonists
18. Fasting gastrin-17 blood levels exceeding 1.5 times the ULN at Screening for subjects on PPIs or H2 antagonists.
19. Blood creatinine exceeding ULN by more than 20% OR total albumin exceeding the lower limit (LLN) of normal by 10%.
20. Alanine aminotransferase (ALT) OR aspartate aminotransferase (AST) levels exceeding 3 times the ULN OR total bilirubin exceeding 2 times the ULN.
21. 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.
22. Females who are pregnant (positive beta-human chorionic gonadotropin positive [β-hCG] test) or breastfeeding
23. Subjects with a known allergy to E5501 or its excipients ;Extension Phase:
1. Subjects for whom participation in the Extension Phase is considered unsafe, based on the

investigator*s judgment.
2. Subjects considered unable, or unwilling to comply with the study protocol requirements or give informed consent, as determined by the investigator.
3. Subjects requiring the following drugs or treatments at the time of enrollment in the Extension Phase:
a) Rituximab
b) Splenectomy
c) 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:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	27-08-2012
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-

Ethics review

Approved WMO Date:	22-08-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-08-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-10-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-11-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2011-000830-12-NL
CCMO	NL37761.078.11