CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

22291Orig1s021

Trade Name:	**PROMACTA**
Generic or Proper Name:	eltrombopag
Sponsor:	NOVARTIS PHARMACEUTICALS CORPORATION
Approval Date:	November 16, 2018

Indication:

PROMACTA is a thrombopoietin receptor agonist indicated:

- for the treatment of thrombopoietin in adult and pediatric patients 1 year and older with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. PROMACTA should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.
- For the treatment of thrombocytopenia in patients with chronic hepatitis PROMACTA should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy of limits the ability to maintain interferon-based therapy.
- In combination with standard immunosuppressive therapy for the first line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.
- For the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022291/S-021

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: John Noh, PharmD
Senior Global Program Regulatory Manager
Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Noh:

Please refer to your Supplemental New Drug Application (sNDA) dated March 29, 2018, received March 29, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Promacta® (eltrombopag) tablets, 12.5 mg, 25 mg, 50 mg, 75 mg, and 100 mg.

We acknowledge receipt of your major amendment dated August 1, 2018, which extended the goal date by three months.

This Prior Approval supplemental new drug application provides for a new indication: Promacta in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled *"SPL Standard for Content of Labeling Technical Qs and As"* at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kimberly Scott, Regulatory Project Manager, at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Prescribing Information
Medication Guide
Instructions for Use

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALBERT B DEISSEROTH
11/16/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROMACTA safely and effectively. See full prescribing information for PROMACTA.

PROMACTA® (eltrombopag) tablets, for oral use
PROMACTA® (eltrombopag) for oral suspension
Initial U.S. Approval: 2008

WARNING: RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C

RISK OF HEPATOTOXICITY

See full prescribing information for complete boxed warning.

In patients with chronic hepatitis C, PROMACTA in combination with interferon and ribavirin may increase the risk of hepatic decompensation. (5.1)

PROMACTA may increase the risk of severe and potentially life-threatening hepatotoxicity. Monitor hepatic function and discontinue dosing as recommended. (5.2)

----------RECENT MAJOR CHANGES----------

Indications and Usage, Treatment of Severe Aplastic Anemia (1.3)	11/2018
Dosage and Administration, Severe Aplastic Anemia (2.3)	11/2018
Dosage and Administration, Administration (2.4)	7/2018
Warnings and Precautions, Hepatotoxicity (5.2)	11/2018

----------INDICATIONS AND USAGE----------

PROMACTA is a thrombopoietin receptor agonist indicated:

- for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. PROMACTA should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. (1.1)
- for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. PROMACTA should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy. (1.2)
- in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia. (1.3)
- for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. (1.3)

Limitations of Use:

- PROMACTA is not indicated for the treatment of patients with myelodysplastic syndrome (MDS). (1.4)
- Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection. (1.4)

----------DOSAGE AND ADMINISTRATION----------

- Take on an empty stomach (1 hour before or 2 hours after a meal). (2.4)
- **Chronic ITP:** Initiate PROMACTA at 50 mg once daily for most adult and pediatric patients 6 years and older, and at 25 mg once daily for pediatric patients aged 1 to 5 years. Dose reductions are needed for patients with hepatic impairment and some patients of Asian ancestry. Adjust to maintain platelet count greater than or equal to 50 x 10^9/L. Do not exceed 75 mg per day. (2.1, 8.6, 8.7)
- **Chronic Hepatitis C-associated Thrombocytopenia:** Initiate PROMACTA at 25 mg once daily for all patients. Adjust to achieve target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 100 mg. (2.2)
- **First-line Severe Aplastic Anemia:** Initiate PROMACTA once daily at 2.5 mg/kg (in pediatric patients aged 2 to 5 years old), 75 mg (pediatric patients aged 6 to 11 years old), or 150 mg for patients aged 12 years and older concurrently with standard immunosuppressive therapy. Reduce initial dose in patients of Asian ancestry. Modify dosage for toxicity or elevated platelet counts. (2.3, 8.7)
- **Refractory Severe Aplastic Anemia:** Initiate PROMACTA at 50 mg once daily. Reduce initial dose in patients with hepatic impairment or patients of Asian ancestry. Adjust to maintain platelet count greater than 50 x 10^9/L. Do not exceed 150 mg per day. (2.3, 8.6, 8.7)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 12.5 mg, 25 mg, 50 mg, and 75 mg (3)
- For oral suspension: 12.5 mg, 25 mg (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Monitor liver function before and during therapy. (5.2)
- Increased Risk of Death and Progression of Myelodysplastic Syndromes to Acute Myeloid Leukemia. (5.3)
- Thrombotic/Thromboembolic Complications: Portal vein thrombosis has been reported in patients with chronic liver disease receiving PROMACTA. Monitor platelet counts regularly. (5.4)

----------ADVERSE REACTIONS----------

Across all indications, the most common adverse reactions (≥ 20% in any indication) were: anemia, nausea, pyrexia, ALT increased, cough, fatigue, headache, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Take PROMACTA at least 2 hours before or 4 hours after any medications or products containing polyvalent cations such as antacids, calcium-rich foods, and mineral supplements. (2.4, 7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise women not to breastfeed during treatment. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C

RISK OF HEPATOTOXICITY

In patients with chronic hepatitis C, PROMACTA® in combination with interferon and ribavirin may increase the risk of hepatic decompensation *[see Warnings and Precautions (5.1)]*.

PROMACTA may increase the risk of severe and potentially life-threatening hepatotoxicity. Monitor hepatic function and discontinue dosing as recommended *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Treatment of Thrombocytopenia in Patients with Chronic ITP

PROMACTA is indicated for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. PROMACTA should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.

1.2 Treatment of Thrombocytopenia in Patients with Hepatitis C Infection

PROMACTA is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. PROMACTA should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy.

1.3 Treatment of Severe Aplastic Anemia

- PROMACTA is indicated in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.
- PROMACTA is indicated for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

1.4 Limitations of Use

- PROMACTA is not indicated for the treatment of patients with myelodysplastic syndromes (MDS) *[see Warnings and Precautions (5.3)]*.
- Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection.

2 DOSAGE AND ADMINISTRATION

2.1 Chronic Immune Thrombocytopenia

Use the lowest dose of PROMACTA to achieve and maintain a platelet count greater than or equal to 50 x 10^9/L as necessary to reduce the risk for bleeding. Dose adjustments are based upon the platelet count response. Do not use PROMACTA to normalize platelet counts *[see Warnings and Precautions (5.4)]*. In clinical trials, platelet counts generally increased within 1 to 2 weeks after starting PROMACTA and decreased within 1 to 2 weeks after discontinuing PROMACTA *[see Clinical Studies (14.1)]*.

Initial Dose Regimen: *Adult and Pediatric Patients 6 Years and Older with ITP:* Initiate PROMACTA at a dose of 50 mg once daily, except in patients who are of Asian ancestry (such as Chinese, Japanese, Taiwanese, or Korean) or who have mild to severe hepatic impairment (Child-Pugh Class A, B, C).

For patients of Asian ancestry with ITP, initiate PROMACTA at a reduced dose of 25 mg once daily *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

For patients with ITP and mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, C), initiate PROMACTA at a reduced dose of 25 mg once daily *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

For patients of Asian ancestry with ITP and hepatic impairment (Child-Pugh Class A, B, C), consider initiating PROMACTA at a reduced dose of 12.5 mg once daily *[see Clinical Pharmacology (12.3)]*.

Pediatric Patients with ITP Aged 1 to 5 Years: Initiate PROMACTA at a dose of 25 mg once daily *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

Monitoring and Dose Adjustment: After initiating PROMACTA, adjust the dose to achieve and maintain a platelet count greater than or equal to 50 x 10^9/L as necessary to reduce the risk for bleeding. Do not exceed a dose of 75 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with PROMACTA and modify the dosage regimen of PROMACTA based on platelet counts as outlined in Table 1. During therapy with PROMACTA, assess CBCs with differentials, including platelet counts, weekly until a stable platelet count has been achieved. Obtain CBCs with differentials, including platelet counts, monthly thereafter.

When switching between the oral suspension and tablet, assess platelet counts weekly for 2 weeks, and then follow standard monthly monitoring.

Table 1. Dose Adjustments of PROMACTA in Patients with Chronic Immune Thrombocytopenia

Platelet Count Result	Dose Adjustment or Response
< 50 x 10^9/L following at least 2 weeks of PROMACTA	Increase daily dose by 25 mg to a maximum of 75 mg/day. For patients taking 12.5 mg once daily, increase the dose to 25 mg daily before increasing the dose amount by 25 mg.
≥ 200 x 10^9/L to ≤ 400 x 10^9/L at any time	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. For patients taking 25 mg once daily, decrease the dose to 12.5 mg once daily.
> 400 x 10^9/L	Stop PROMACTA; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is < 150 x 10^9/L, reinitiate therapy at a daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinitiate therapy at a daily dose of 12.5 mg.
> 400 x 10^9/L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

In patients with ITP and hepatic impairment (Child-Pugh Class A, B, C), after initiating PROMACTA or after any subsequent dosing increase, wait 3 weeks before increasing the dose.

Modify the dosage regimen of concomitant ITP medications, as medically appropriate, to avoid excessive increases in platelet counts during therapy with PROMACTA. Do not administer more than one dose of PROMACTA within any 24-hour period.

Discontinuation: Discontinue PROMACTA if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy with PROMACTA at the maximum daily dose of 75 mg. Excessive platelet count responses, as outlined in Table 1, or important liver test abnormalities also necessitate discontinuation of PROMACTA *[see Warnings and Precautions (5.2)]*. Obtain CBCs with differentials, including platelet counts, weekly for at least 4 weeks following discontinuation of PROMACTA.

2.2 Chronic Hepatitis C-associated Thrombocytopenia

Use the lowest dose of PROMACTA to achieve and maintain a platelet count necessary to initiate and maintain antiviral therapy with pegylated interferon and ribavirin. Dose adjustments are based upon the platelet count response. Do not use PROMACTA to normalize platelet counts *[see Warnings and Precautions (5.4)]*. In clinical trials, platelet counts generally began to rise within the first week of treatment with PROMACTA *[see Clinical Studies (14.2)]*.

Initial Dose Regimen: Initiate PROMACTA at a dose of 25 mg once daily.

Monitoring and Dose Adjustment: Adjust the dose of PROMACTA in 25-mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy. Monitor platelet counts every week prior to starting antiviral therapy.

During antiviral therapy, adjust the dose of PROMACTA to avoid dose reductions of peginterferon. Monitor CBCs with differentials, including platelet counts, weekly during antiviral therapy until a stable platelet count is achieved. Monitor platelet counts monthly thereafter. Do not exceed a dose of 100 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with PROMACTA.

For specific dosage instructions for peginterferon or ribavirin, refer to their respective prescribing information.

Table 2. Dose Adjustments of PROMACTA in Adults with Thrombocytopenia due to Chronic Hepatitis C

Platelet Count Result	Dose Adjustment or Response
$< 50 \times 10^9$/L following at least 2 weeks of PROMACTA	Increase daily dose by 25 mg to a maximum of 100 mg/day.
$\geq 200 \times 10^9$/L to $\leq 400 \times 10^9$/L at any time	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
$> 400 \times 10^9$/L	Stop PROMACTA; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is $< 150 \times 10^9$/L, reinitiate therapy at a daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinitiate therapy at a daily dose of 12.5 mg.
$> 400 \times 10^9$/L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

Discontinuation: The prescribing information for pegylated interferon and ribavirin include recommendations for antiviral treatment discontinuation for treatment futility. Refer to pegylated interferon and ribavirin prescribing information for discontinuation recommendations for antiviral treatment futility.

PROMACTA should be discontinued when antiviral therapy is discontinued. Excessive platelet count responses, as outlined in Table 2, or important liver test abnormalities also necessitate discontinuation of PROMACTA *[see Warnings and Precautions (5.2)]*.

2.3 Severe Aplastic Anemia

First-line Severe Aplastic Anemia

Initiate PROMACTA concurrently with standard immunosuppressive therapy *[see Clinical Studies (14.3)]*.

Initial Dose Regimen:

The recommended initial dose regimen is listed in Table 3. Do not exceed the initial dose of PROMACTA.

Table 3. Recommended Initial PROMACTA Dose Regimen in the First-Line Treatment of Severe Aplastic Anemia

Age	Dose Regimen
Patients 12 Years and Older	150 mg once daily for 6 months
Pediatric Patients 6 to 11 Years	75 mg once daily for 6 months
Pediatric Patients 2 to 5 Years	2.5 mg/kg once daily for 6 months

For patients with severe aplastic anemia of Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean, or Thai) or those with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, C), decrease the initial PROMACTA dose by 50% as listed in Table 4 *[see Use in Specific Populations (8.6, 8.7), Clinical Pharmacology (12.3)]*.

If baseline ALT or AST levels are > 6 x ULN, do not initiate PROMACTA until transaminase levels are < 5 x ULN. Determine the initial dose for these patients based on Table 3 or Table 4.

Table 4. Recommended Initial PROMACTA Dose Regimen for Patients of Asian Ancestry or Those with Mild, Moderate, or Severe Hepatic Impairment (Child-Pugh Class A, B, C) in the First-Line Treatment of Severe Aplastic Anemia

Age	Dose Regimen
Patients 12 Years and Older	75 mg once daily for 6 months
Pediatric Patients 6 to 11 Years	37.5 mg once daily for 6 months
Pediatric Patients 2 to 5 Years	1.25 mg/kg once daily for 6 months

Monitoring and Dose Adjustment for PROMACTA: Perform clinical hematology and liver tests regularly throughout therapy with PROMACTA (see *Warnings and Precautions (5.2)]*.

Modify the dosage regimen of PROMACTA based on platelet counts as outlined in Table 5.

Table 5. Dose Adjustments of PROMACTA for Elevated Platelet Counts in the First-line Treatment of Severe Aplastic Anemia

Platelet Count Result	Dose Adjustment or Response
> 200 x 10^9/L to ≤ 400 x 10^9/L	Decrease the daily dose by 25 mg every 2 weeks to lowest dose that maintains platelet count ≥ 50 x 10^9/L. In pediatric patients under 12 years of age, decrease the dose by 12.5 mg.
> 400 x 10^9/L	Discontinue PROMACTA for one week. Once the platelet count is < 200 x 10^9/L, reinitiate PROMACTA at a daily dose reduced by 25 mg (or 12.5 mg in pediatric patients under 12 years of age).

Table 6 summarizes the recommendations for dose interruption, reduction, or discontinuation of PROMACTA in the management of elevated liver transaminase levels and thromboembolic events.

Table 6. Recommended Dose Modifications for PROMACTA for ALT or AST Elevations and Thromboembolic Events

Event	Recommendation
ALT or AST Elevations	Increase in ALT or AST > 6 x ULN Discontinue PROMACTA. Once ALT or AST is < 5 x ULN, reinitiate PROMACTA at the same dose. Increase in ALT or AST > 6 x ULN after reinitiating PROMACTA Discontinue PROMACTA and monitor ALT or AST at least every 3 to 4 days. Once ALT or AST is < 5x ULN, reinitiate PROMACTA at a daily dose reduced by 25 mg compared to the previous dose. If ALT or AST returns to > 6 x ULN on the reduced dose Reduce the daily dose of PROMACTA by 25 mg until ALT or AST is < 5 x ULN. In pediatric patients under 12 years of age, reduce the daily dose by at least 15% to the nearest dose that can be administered.
Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolus, stroke, myocardial infarction)	Discontinue PROMACTA but remain on horse antithymocyte globulin (h-ATG) and cyclosporine.

The total duration of PROMACTA treatment is 6 months.

Refractory Severe Aplastic Anemia

Use the lowest dose of PROMACTA to achieve and maintain a hematologic response. Dose adjustments are based upon the platelet count. Hematologic response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting PROMACTA *[see Clinical Studies (14.3)]*.

Initial Dose Regimen: Initiate PROMACTA at a dose of 50 mg once daily.

For patients with severe aplastic anemia of Asian ancestry or those with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, C), initiate PROMACTA at a reduced dose of 25 mg once daily *[see Use in Specific Populations (8.6, 8.7), Clinical Pharmacology (12.3)]*.

Monitoring and Dose Adjustment: Adjust the dose of PROMACTA in 50-mg increments every 2 weeks as necessary to achieve the target platelet count greater than or equal to 50 x 10^9/L as necessary. Do not exceed a dose of 150 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with PROMACTA and modify the dosage regimen of PROMACTA based on platelet counts as outlined in Table 7.

Table 7. Dose Adjustments of PROMACTA in Patients with Refractory Severe Aplastic Anemia

Platelet Count Result	Dose Adjustment or Response
< 50 x 10^9/L following at least 2 weeks of PROMACTA	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg.
≥ 200 x 10^9/L to ≤ 400 x 10^9/L at any time	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 400 x 10^9/L	Stop PROMACTA for 1 week. Once the platelet count is < 150 x 10^9/L, reinitiate therapy at a dose reduced by 50 mg.
> 400 x 10^9/L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

For patients who achieve tri-lineage response, including transfusion independence, lasting at least 8 weeks: the dose of PROMACTA may be reduced by 50% *[see Clinical Studies (14.3)]*. If counts remain stable after 8 weeks at the reduced dose, then discontinue PROMACTA and monitor blood counts. If platelet counts drop to less than 30 x 10^9/L, hemoglobin to less than 9 g/dL, or ANC to less than 0.5 x 10^9/L, PROMACTA may be reinitiated at the previous effective dose.

Discontinuation: If no hematologic response has occurred after 16 weeks of therapy with PROMACTA, discontinue therapy. If new cytogenetic abnormalities are observed, consider discontinuation of PROMACTA *[see Adverse Reactions (6.1)]*. Excessive platelet count responses (as outlined in Table 3) or important liver test abnormalities also necessitate discontinuation of PROMACTA *[see Warnings and Precautions (5.2)]*.

2.4 Administration

Administration of Tablets and Oral Suspension: Take PROMACTA on an empty stomach (1 hour before or 2 hours after a meal) *[see Clinical Pharmacology (12.3)]*. Take PROMACTA at least 2 hours before or 4 hours after other medications (e.g., antacids), calcium-rich foods (e.g., dairy products and calcium-fortified juices), or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

Do not split, chew, or crush tablets and mix with food or liquids.

Preparation of the Oral Suspension: Prior to use of the oral suspension, ensure patients or caregivers receive training on proper dosing, preparation, and administration of PROMACTA for oral suspension.

Administer the oral suspension immediately after preparation. **Discard any suspension not administered within 30 minutes after preparation.**

Prepare the suspension with water only. NOTE: Do not use hot water to prepare the suspension.

For details on preparation and administration of the suspension, including the recommended duration of use of each oral dosing syringe, see **Instructions for Use**.

3 DOSAGE FORMS AND STRENGTHS

Tablets

- 12.5-mg tablets — round, biconvex, white, film-coated tablets debossed with GS MZ1 and 12.5 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 12.5 mg of eltrombopag free acid.

- 25-mg tablets — round, biconvex, orange, film-coated tablets debossed with GS NX3 and 25 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 25 mg of eltrombopag free acid.
- 50-mg tablets — round, biconvex, blue, film-coated tablets debossed with GS UFU and 50 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 50 mg of eltrombopag free acid.
- 75-mg tablets — round, biconvex, pink, film-coated tablets debossed with GS FFS and 75 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 75 mg of eltrombopag free acid.

For Oral Suspension

- 12.5-mg packet – contains a reddish-brown to yellow powder for reconstitution.
- 25-mg packet — contains a reddish-brown to yellow powder for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Decompensation in Patients with Chronic Hepatitis C

In patients with chronic hepatitis C, PROMACTA in combination with interferon and ribavirin may increase the risk of hepatic decompensation. In two controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, ascites and encephalopathy occurred more frequently on the arm receiving treatment with PROMACTA plus antivirals (7%) than the placebo plus antivirals arm (4%). Patients with low albumin levels (less than 3.5 g/dL) or Model for End-Stage Liver Disease (MELD) score greater than or equal to 10 at baseline had a greater risk for hepatic decompensation on the arm receiving treatment with PROMACTA plus antivirals. Discontinue PROMACTA if antiviral therapy is discontinued.

5.2 Hepatotoxicity

PROMACTA may increase the risk of severe and potentially life-threatening hepatotoxicity *[see Adverse Reactions (6.1)]*. One patient (<1%) with chronic ITP treated with PROMACTA in clinical trials experienced drug-induced liver injury. Eleven patients (1%) with chronic hepatitis C treated with PROMACTA in clinical trials experienced drug-induced liver injury.

Treatment of ITP, Chronic Hepatitis C-associated Thrombocytopenia, and Refractory Severe Aplastic Anemia

Measure serum ALT, AST, and bilirubin prior to initiation of PROMACTA, every 2 weeks during the dose adjustment phase, and monthly following establishment of a stable dose. PROMACTA inhibits UDP-glucuronosyltransferase (UGT)1A1 and organic anion-transporting polypeptide (OATP)1B1, which may lead to indirect hyperbilirubinemia. If bilirubin is elevated, perform fractionation. Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until resolved or stabilized. Discontinue PROMACTA if ALT levels increase to greater than or equal to 3 x ULN in patients with normal liver function or greater than or equal to 3 x baseline (or greater than 5 x ULN, whichever is the lower) in patients with pre-treatment elevations in transaminases and are:

- progressively increasing, or
- persistent for greater than or equal to 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

If the potential benefit for reinitiating treatment with PROMACTA is considered to outweigh the risk for hepatotoxicity, then consider cautiously reintroducing PROMACTA and measure serum liver tests weekly

during the dose adjustment phase. Hepatotoxicity may reoccur if PROMACTA is reinitiated. If liver test abnormalities persist, worsen, or recur, then permanently discontinue PROMACTA.

First-Line Treatment of Severe Aplastic Anemia

Measure ALT, AST, and bilirubin prior to initiation of PROMACTA, every other day while hospitalized for h-ATG therapy, and then every 2 weeks during treatment. During treatment, manage increases in ALT or AST levels as recommended in Table 6.

5.3 Increased Risk of Death and Progression of Myelodysplastic Syndromes (MDS) to Acute Myeloid Leukemia (AML)

A randomized, double-blind, placebo-controlled, multicenter trial in patients with International Prognostic Scoring System (IPSS) intermediate-1, intermediate-2 or high risk MDS with thrombocytopenia, receiving azacitidine in combination with either PROMACTA (n = 179) or placebo (n = 177) was terminated due to lack of efficacy and safety reasons, including increased progression to AML. Patients received PROMACTA or placebo at a starting dose of 200 mg once daily, up to a maximum of 300 mg once daily, in combination with azacitidine for at least six cycles. The incidence of death (overall survival) was 32% (57/179) in the PROMACTA arm versus 29% (51/177) in the placebo arm (HR [95% CI] = 1.42 [0.97, 2.08], showing an increased relative risk of death in this trial by 42% in the PROMACTA arm). The incidence of progression to AML was 12% (21/179) in the PROMACTA arm versus 6% (10/177) in the placebo arm (HR [95% CI] = 2.66 [1.31, 5.41], showing an increased relative risk of progression to AML in this trial by 166% in the PROMACTA arm).

5.4 Thrombotic/Thromboembolic Complications

Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts.

Consider the potential for an increased risk of thromboembolism when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). To minimize the risk for thrombotic/thromboembolic complications, do not use PROMACTA in an attempt to normalize platelet counts. Follow the dose adjustment guidelines to achieve and maintain target platelet counts *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

In two controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, 3% (31/955) treated with PROMACTA experienced a thrombotic event compared with 1% (5/484) on placebo. The majority of events were of the portal venous system (1% in patients treated with PROMACTA versus less than 1% for placebo).

In a controlled trial in patients with chronic liver disease and thrombocytopenia not related to ITP undergoing elective invasive procedures (N = 292), the risk of thrombotic events was increased in patients treated with 75 mg of PROMACTA once daily. Seven thrombotic complications (six patients) were reported in the group that received PROMACTA and three thrombotic complications were reported in the placebo group (two patients). All of the thrombotic complications reported in the group that received PROMACTA were portal vein thrombosis (PVT). Symptoms of PVT included abdominal pain, nausea, vomiting, and diarrhea. Five of the six patients in the group that received PROMACTA experienced a thrombotic complication within 30 days of completing treatment with PROMACTA and at a platelet count above 200 x 10^9/L. The risk of portal venous thrombosis was increased in thrombocytopenic patients with chronic liver disease treated with 75 mg of PROMACTA once daily for 2 weeks in preparation for invasive procedures.

5.5 Cataracts

In the three controlled clinical trials in adults with chronic ITP, cataracts developed or worsened in 15 (7%) patients who received 50 mg of PROMACTA daily and 8 (7%) placebo-group patients. In the extension trial,

cataracts developed or worsened in 11% of patients who underwent ocular examination prior to therapy with PROMACTA. In the two controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, cataracts developed or worsened in 8% of patients treated with PROMACTA and 5% of patients treated with placebo.

Cataracts were observed in toxicology studies of eltrombopag in rodents *[see Nonclinical Toxicology (13.2)]*. Perform a baseline ocular examination prior to administration of PROMACTA and, during therapy with PROMACTA, regularly monitor patients for signs and symptoms of cataracts.

6 ADVERSE REACTIONS

The following serious adverse reactions associated with PROMACTA are described in other sections.

- Hepatic Decompensation in Patients with Chronic Hepatitis C *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Increased Risk of Death and Progression of Myelodysplastic Syndromes to Acute Myeloid Leukemia *[see Warnings and Precautions (5.3)]*
- Thrombotic/Thromboembolic Complications *[see Warnings and Precautions (5.4)]*
- Cataracts *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Chronic Immune Thrombocytopenia: *Adults:* In clinical trials, hemorrhage was the most common serious adverse reaction and most hemorrhagic reactions followed discontinuation of PROMACTA. Other serious adverse reactions included thrombotic/thromboembolic complications *[see Warnings and Precautions (5.4)]*. The data described below reflect exposure of PROMACTA to patients with chronic ITP aged 18 to 85 years, of whom 66% were female, in three placebo-controlled trials and one open-label extension trial *[see Clinical Studies (14.1)]*. PROMACTA was administered to 330 patients for at least 6 months and 218 patients for at least 1 year.

Table 8 presents the most common adverse drug reactions (experienced by greater than or equal to 3% of patients receiving PROMACTA) from the three placebo-controlled trials, with a higher incidence in PROMACTA versus placebo.

Table 8. Adverse Reactions (≥ 3%) from Three Placebo-controlled Trials in Adults with Chronic Immune Thrombocytopenia

Adverse Reaction	PROMACTA 50 mg n = 241 (%)	Placebo n = 128 (%)
Nausea	9	3
Diarrhea	9	7
Upper respiratory tract infection	7	6
Vomiting	6	< 1
Urinary tract infection[a]	5	4
Increased ALT	5	3
Myalgia	5	2
Oropharyngeal pain	4	3
Increased AST	4	2
Pharyngitis	4	2
Back pain	3	2
Influenza	3	2
Paresthesia	3	2
Rash	3	2

[a] Includes PTs of Urinary tract infection, Cystitis, Urinary tract infection bacterial, and Bacteruria

In the three controlled clinical chronic ITP trials, alopecia, musculoskeletal pain, blood alkaline phosphatase increased, and dry mouth were the adverse reactions reported in 2% of patients treated with PROMACTA and in no patients who received placebo.

Among 302 patients with chronic ITP who received PROMACTA in the single-arm extension trial, the adverse reactions occurred in a pattern similar to that seen in the placebo-controlled trials. Table 9 presents the most common treatment-related adverse reactions (experienced by greater than or equal to 3% of patients receiving PROMACTA) from the extension trial.

Table 9. Treatment-related Adverse Reactions (≥ 3%) from Extension Trial in Adults with Chronic Immune Thrombocytopenia

Adverse Reaction	PROMACTA 50 mg n = 302 (%)
Headache	10
ALT increased	5
AST increased	5
Cataract	5
Fatigue	5
Blood bilirubin increased	4
Nausea	4
Hyperbilirubinemia	3
Diarrhea	3

In the three controlled chronic ITP trials, serum liver test abnormalities (predominantly Grade 2 or less in severity) were reported in 11% and 7% of patients for PROMACTA and placebo, respectively. Four patients (1%) treated with PROMACTA and three patients in the placebo group (2%) discontinued treatment due to hepatobiliary laboratory abnormalities. Seventeen of the patients treated with PROMACTA in the controlled trials with hepatobiliary laboratory abnormalities were re-exposed to PROMACTA in the extension trial. Eight

of these patients again experienced liver test abnormalities (less than or equal to Grade 3) resulting in discontinuation of PROMACTA in one patient. In the extension chronic ITP trial, six additional patients had PROMACTA discontinued due to liver test abnormalities (less than or equal to Grade 3).

In the three controlled chronic ITP trials, cataracts developed or worsened in 7% of patients treated with PROMACTA and 7% of patients in the placebo group. All patients had documented, preexisting risk factors for cataractogenesis including corticosteroid use. In the extension trial, cataracts developed or worsened in 11% of patients who underwent ocular examination prior to therapy with PROMACTA. Seventy-two percent of patients had preexisting risk factors, including corticosteroid use.

The safety of PROMACTA was also assessed in all patients treated in 7 adult chronic ITP clinical trials (N=763 PROMACTA-treated patients and 179 placebo-treated patients). Thromboembolic events were reported in 6% of PROMACTA-treated patients versus 0% of placebo-treated patients and thrombotic microangiopathy with acute renal failure was reported in < 1% of PROMACTA-treated patients versus 0% of placebo-treated patients.

In a placebo-controlled trial of PROMACTA in patients with chronic liver disease and thrombocytopenia not related to ITP, six patients treated with PROMACTA and one patient in the placebo group developed portal vein thromboses *[see Warnings and Precautions (5.4)]*.

Pediatric Patients: The data described below reflect median exposure to PROMACTA of 91 days for 107 pediatric patients (aged 1 to 17 years) with chronic ITP, of whom 53% were female, across the randomized phase of two placebo-controlled trials.

Table 10 presents the most common adverse drug reactions (experienced by greater than or equal to 3% of pediatric patients 1 year and older receiving PROMACTA) across the two placebo-controlled trials, with a higher incidence for PROMACTA versus placebo.

Table 10. Adverse Reactions (≥ 3%) with a Higher Incidence for PROMACTA versus Placebo from Two Placebo-controlled Trials in Pediatric Patients 1 Year and Older with Chronic Immune Thrombocytopenia

Adverse Reaction	PROMACTA n = 107 (%)	Placebo n = 50 (%)
Upper respiratory tract infection	17	6
Nasopharyngitis	12	4
Cough	9	0
Diarrhea	9	2
Pyrexia	9	8
Abdominal pain	8	4
Oropharyngeal pain	8	2
Toothache	6	0
ALT increased[a]	6	0
Rash	5	2
AST increased	4	0
Rhinorrhea	4	0

[a] Includes adverse reactions or laboratory abnormalities > 3 x ULN

In the two controlled clinical chronic ITP trials, cataracts developed or worsened in 2 (1%) patients treated with PROMACTA. Both patients had received chronic oral corticosteroids, a risk factor for cataractogenesis.

Chronic Hepatitis C-associated Thrombocytopenia: In the two placebo-controlled trials, 955 patients with chronic hepatitis C-associated thrombocytopenia received PROMACTA. Table 11 presents the most common adverse drug reactions (experienced by greater than or equal to 10% of patients receiving PROMACTA compared with placebo).

Table 11. Adverse Reactions (≥ 10% and Greater than Placebo) from Two Placebo-controlled Trials in Adults with Chronic Hepatitis C

Adverse Reaction	PROMACTA + Peginterferon/Ribavirin n = 955 (%)	Placebo + Peginterferon/Ribavirin n = 484 (%)
Anemia	40	35
Pyrexia	30	24
Fatigue	28	23
Headache	21	20
Nausea	19	14
Diarrhea	19	11
Decreased appetite	18	14
Influenza-like illness	18	16
Insomnia[a]	16	15
Asthenia	16	13
Cough	15	12
Pruritus	15	13
Chills	14	9
Myalgia	12	10
Alopecia	10	6
Peripheral edema	10	5

[a] Includes PTs of Insomnia, Initial insomnia, and Poor quality sleep

Rash was reported in 9% and 7% of patients receiving PROMACTA and placebo, respectively.

In the two controlled clinical trials in patients with chronic hepatitis C, hyperbilirubinemia was reported in 8% of patients receiving PROMACTA compared with 3% for placebo. Total bilirubin greater than or equal to 1.5 x ULN was reported in 76% and 50% of patients receiving PROMACTA and placebo, respectively. ALT or AST greater than or equal to 3 x ULN was reported in 34% and 38% of patients for PROMACTA and placebo, respectively.

In the two controlled clinical trials in patients with chronic hepatitis C, cataracts developed or worsened in 8% of patients treated with PROMACTA and 5% of patients treated with placebo.

The safety of PROMACTA was also assessed in all patients treated with PROMACTA in the two controlled trials, including patients who initially received PROMACTA in the pre-antiviral treatment phase of the trial and were later randomized to the placebo arm (N = 1520 PROMACTA-treated patients). Hepatic failure was reported in 0.8% of PROMACTA-treated patients and 0.4% of placebo-treated patients.

Severe Aplastic Anemia:

First-Line Treatment of Severe Aplastic Anemia

The safety of PROMACTA was established based upon a single-arm trial of 153 patients with severe aplastic anemia who had not received prior definitive immunosuppressive therapy. In this trial, PROMACTA was administered in combination with horse antithymocyte globulin (h-ATG) and cyclosporine *[see Clinical Studies (14.3)]*. Among the 153 patients who were dosed in this trial, 92 patients were evaluable for safety of the concurrent use of PROMACTA, h-ATG, and cyclosporine at the recommended dose and schedule.

In this cohort, PROMACTA was administered at up to 150 mg once daily on Day 1 to Month 6 (D1-M6) in combination with h-ATG on Days 1 to 4 and cyclosporine for 6 months, followed by low dose of cyclosporine (maintenance dose) for an additional 18 months for patients who achieved a hematologic response at 6 months.

The median duration of exposure to PROMACTA in this cohort was 183 days with 70% of patients were exposed for > 24 weeks.

Table 12 presents the most common adverse reactions (experienced by greater than or equal to 5% of patients) associated with PROMACTA in the D1-M6 cohort.

Table 12. Adverse Reactions (≥ 5%) from One Open-label Trial in First-line Treatment of Patients with Severe Aplastic Anemia

Adverse Reaction	PROMACTA n = 92 (%)
ALT increased	29
AST increased	17
Blood bilirubin increased	17
Rash	8
Skin discoloration including hyperpigmentation	5

In the PROMACTA D1-M6 cohort, ALT increased (29%), AST increased (17%), and blood bilirubin increased (17%) were reported more frequently than in patients with refractory severe aplastic anemia (see Table 13).

New or worsening liver function laboratory abnormalities (CTCAE Grade 3 and Grade 4) in the Promacta D1-M6 cohort were 15% and 2% for AST, 26% and 4% for ALT, and 12% and 1% for bilirubin, respectively.

In this single-arm open-label clinical trial, ALT or AST > 3 x ULN with total bilirubin > 1.5 x ULN and ALT or AST > 3 x ULN with total bilirubin > 2 x ULN were reported in 44% and 32% of patients, respectively, in the PROMACTA D1-M6 cohort.

Pediatric Patients

A total of 34 pediatric patients (2 patients 2 to 5 years of age, 12 patients 6 to 11 years of age, and 20 patients 12 to 16 years of age) were enrolled in this single-arm trial of which 26 pediatric patients were enrolled in the PROMACTA D1-M6 cohort. In this cohort, the most frequent serious adverse reactions (experienced by ≥ 10% of patients) were upper respiratory tract infection (12% in patients age 2 to 16 years compared to 5% in patients 17 years of age and older, respectively) and rash (12% compared to 2%). The most common adverse reactions (experienced by ≥ 10% of patients) associated with PROMACTA were ALT increased (23% in patients age 2 to 16 years compared to 32% in patients 17 years of age and older, respectively), blood bilirubin increased (12% compared to 20%), AST increased (12% compared to 20%), and rash (12% compared to 6%).

Cytogenetic Abnormalities

In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Seven patients in the PROMACTA D1-M6 cohort had a new cytogenetic abnormality reported of which 4 had the loss of chromosome 7; these 4 occurred within 6.1 months. Across all cohorts, clonal cytogenetic evolution occurred in 15 out of 153 (10%) patients. Of the 15 patients who experienced a cytogenetic abnormality: 7 patients had the loss of chromosome 7, 6 of which occurred within 6.1 months; 4 patients had chromosomal aberrations which were of unclear significance; 3 patients had a deletion of chromosome 13; and 1 patient had a follow-up bone marrow assessment at 5 years with features of dysplasia with hypercellularity concerning for potential development of MDS. It is unclear whether these findings occurred due to the underlying disease, the immunosuppressive therapy, and/or treatment with PROMACTA.

Refractory Severe Aplastic Anemia

In the single-arm, open-label trial, 43 patients with refractory severe aplastic anemia received PROMACTA. Eleven patients (26%) were treated for greater than 6 months and 7 patients (16%) were treated for greater than 1 year. The most common adverse reactions (greater than or equal to 20%) were nausea, fatigue, cough, diarrhea, and headache.

Table 13. Adverse Reactions (≥ 10%) from One Open-label Trial in Adults with Refractory Severe Aplastic Anemia

Adverse Reaction	PROMACTA n = 43 (%)
Nausea	33
Fatigue	28
Cough	23
Diarrhea	21
Headache	21
Pain in extremity	19
Pyrexia	14
Dizziness	14
Oropharyngeal pain	14
Abdominal pain	12
Muscle spasms	12
Transaminases increased	12
Arthralgia	12
Rhinorrhea	12

Rash and hyperbilirubinemia were reported in 7% of patients; cataract was reported in 2% of patients.

In this trial, concurrent ALT or AST greater than 3 x ULN with total bilirubin greater than 1.5 x ULN were reported in 5% of patients. Total bilirubin greater than 1.5 x ULN occurred in 14% of patients.

In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight patients had a new cytogenetic abnormality reported on therapy, including 5 patients who had complex changes in chromosome 7.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of PROMACTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders: Skin discoloration including hyperpigmentation and skin yellowing.

7 DRUG INTERACTIONS

7.1 Polyvalent Cations (Chelation)

Eltrombopag chelates polyvalent cations (such as iron, calcium, aluminum, magnesium, selenium, and zinc) in foods, mineral supplements, and antacids.

Take PROMACTA at least 2 hours before or 4 hours after any medications or products containing polyvalent cations such as antacids, dairy products, and mineral supplements to avoid significant reduction in absorption of PROMACTA due to chelation *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

7.2 Transporters

Use caution when concomitantly administering PROMACTA and drugs that are substrates of OATP1B1 (e.g., atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, olmesartan, pitavastatin, pravastatin, rosuvastatin, repaglinide, rifampin, simvastatin acid, SN-38 [active metabolite of irinotecan], valsartan) or BCRP (e.g., imatinib, irinotecan, lapatinib, methotrexate, mitoxantrone, rosuvastatin, sulfasalazine, topotecan). Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 or

BCRP and consider reduction of the dose of these drugs, if appropriate. In clinical trials with PROMACTA, a dose reduction of rosuvastatin by 50% was recommended.

7.3 Protease Inhibitors

HIV Protease Inhibitors: No dose adjustment is recommended when PROMACTA is coadministered with lopinavir/ritonavir (LPV/RTV). Drug interactions with other HIV protease inhibitors have not been evaluated.

Hepatitis C Virus (HCV) Protease Inhibitors: No dose adjustments are recommended when PROMACTA is coadministered with boceprevir or telaprevir. Drug interactions with other HCV protease inhibitors have not been evaluated.

7.4 Peginterferon alfa-2a/b Therapy

No dose adjustments are recommended when PROMACTA is coadministered with peginterferon alfa-2a (PEGASYS®) or -2b (PEGINTRON®).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from a small number of published case reports and postmarketing experience with PROMACTA use in pregnant women are insufficient to assess any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction and developmental toxicity studies, oral administration of eltrombopag to pregnant rats during organogenesis resulted in embryolethality and reduced fetal weights at maternally toxic doses. These effects were observed at doses resulting in exposures that were 6 times the human clinical exposure based on AUC in patients with chronic ITP at 75 mg/day, and 3 times the AUC in patients with chronic hepatitis C at 100 mg/day *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

In an early embryonic development study, female rats received oral eltrombopag at doses of 10, 20, or 60 mg/kg/day (0.8, 2, and 6 times, respectively, the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.3, 1, and 3 times, respectively, the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Increased pre- and post-implantation loss and reduced fetal weight were observed at the highest dose which also caused maternal toxicity.

In an embryo-fetal development study eltrombopag was administered orally to pregnant rats during the period of organogenesis at doses of 10, 20, or 60 mg/kg/day (0.8, 2, and 6 times, respectively, the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.3, 1, and 3 times, respectively, the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Decreased fetal weights (6% to 7%) and a slight increase in the presence of cervical ribs were observed at the highest dose which also caused maternal toxicity. However, no evidence of major structural malformations was observed.

In an embryo-fetal development study eltrombopag was administered orally to pregnant rabbits during the period of organogenesis at doses of 30, 80, or 150 mg/kg/day (0.04, 0.3, and 0.5 times, respectively, the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.02, 0.1, and 0.3 times, respectively, the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). No evidence of fetotoxicity, embryolethality, or teratogenicity was observed.

In a pre- and post-natal developmental toxicity study in pregnant rats (F0), oral eltrombopag was administered from gestation day 6 through lactation day 20. No adverse effects on maternal reproductive function or on the development of the offspring (F1) were observed at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and similar to the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Eltrombopag was detected in the plasma of offspring (F1). The plasma concentrations in pups increased with dose following administration of drug to the F0 dams.

8.2 Lactation

Risk Summary

There are no data regarding the presence of eltrombopag or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. However, eltrombopag was detected in the pups of lactating rats 10 days postpartum suggesting the potential for transfer during lactation. Due to the potential for serious adverse reactions in a breastfed child from PROMACTA, breastfeeding is not recommended during treatment.

8.3 Females and Males of Reproductive Potential

Contraception

Based on animal reproduction studies, PROMACTA can cause fetal harm when administered to a pregnant woman. Sexually-active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) when using PROMACTA during treatment and for at least 7 days after stopping treatment with PROMACTA.

8.4 Pediatric Use

The safety and efficacy of PROMACTA have been established in pediatric patients 1 year and older with chronic ITP and in pediatric patients 2 years and older with definitive immunosuppressive therapy (IST)-naïve severe aplastic anemia (in combination with horse antithymocyte globulin [h-ATG] and cyclosporine). Safety and efficacy in pediatric patients below the age of 1 year with ITP have not been established. Safety and efficacy in pediatric patients with thrombocytopenia associated with chronic hepatitis C and refractory severe aplastic anemia have not been established.

The safety and efficacy of PROMACTA in pediatric patients 1 year and older with chronic ITP were evaluated in two double-blind, placebo-controlled trials *[see Adverse Reactions (6.1), Clinical Studies (14.1)]*. The pharmacokinetics of eltrombopag have been evaluated in 168 pediatric patients 1 year and older with ITP dosed once daily *[see Clinical Pharmacology (12.3)]*. See *Dosage and Administration (2.1)* for dosing recommendations for pediatric patients 1 year and older.

The safety and efficacy of PROMACTA in combination with h-ATG and cyclosporine for the first-line treatment of severe aplastic anemia in pediatric patients 2 years and older were evaluated in a single-arm, open-label trial *[see Adverse Reactions (6.1), Clinical Studies (14.3)]*. A total of 26 pediatric patients (ages 2 to <17 years) were evaluated; 12 children (aged 2 to <12 years) and 14 adolescents (aged 12 to <17). See *Dosage and Administration (2.3)* for dosing recommendations for pediatric patients 2 years and older. The safety and efficacy of PROMACTA in combination with h-ATG and cyclosporine in pediatric patients younger than 2 years for the first-line treatment of severe aplastic anemia have not yet been established. In patients 2 to 16 years of age, 69% of patients experienced serious adverse events compared to 42% in patients 17 years and older. Among the 12 patients who were 2 to 11 years of age in the PROMACTA D1 – M6 cohort and reached the 6-month assessment or withdrew earlier, the complete response rate at Month 6 was 8% versus 46% in patients age 12 to 16 years and 50% in patients 17 years of age and older.

8.5 Geriatric Use

Of the 106 patients in two randomized clinical trials of PROMACTA 50 mg in chronic ITP, 22% were 65 years of age and over, while 9% were 75 years of age and over. Of the 1439 patients in two randomized clinical trials of PROMACTA in patients with chronic hepatitis C and thrombocytopenia, 7% were 65 years of age and over,

while < 1% were 75 years of age and over. Of the 196 patients who received PROMACTAfor the treatment of severe aplastic anemia, 18% were 65 years of age and over, while 3% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients.

8.6 Hepatic Impairment

Patients with Chronic ITP and Severe Aplastic Anemia

Reduce the initial dose of PROMACTA in patients with chronic ITP (adult and pediatric patients 6 years and older only) or refractory severe aplastic anemia who also have hepatic impairment (Child-Pugh Class A, B, C) *[see Dosage and Administration (2.1, 2.3), Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.

In a clinical trial in patients with severe aplastic anemia who had not received prior definitive immunosuppressive therapy, patients with baseline ALT or AST > 5 x ULN were ineligible to participate. If a patient with hepatic impairment (Child-Pugh Class A, B, C) initiates therapy with PROMACTA for the first-line treatment of severe aplastic anemia, reduce the initial dose *[see Dosage and Administration (2.3), Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.

Patients with Chronic Hepatitis C

No dosage adjustment is recommended in patients with chronic hepatitis C and hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Ethnicity

Reduce the initial dose of PROMACTA for patients of Asian ancestry (such as Chinese, Japanese, Taiwanese, or Korean) with ITP (adult and pediatric patients 6 years and older only) or severe aplastic anemia *[see Dosage and Administration (2.1, 2.3), Clinical Pharmacology (12.3)]*. No reduction in the initial dose of PROMACTA is recommended in patients of Asian ethnicity with chronic hepatitis C *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications.

In one report, a subject who ingested 5,000 mg of PROMACTA had a platelet count increase to a maximum of 929 x 10^9/L at 13 days following the ingestion. The patient also experienced rash, bradycardia, ALT/AST elevations, and fatigue. The patient was treated with gastric lavage, oral lactulose, intravenous fluids, omeprazole, atropine, furosemide, calcium, dexamethasone, and plasmapheresis; however, the abnormal platelet count and liver test abnormalities persisted for 3 weeks. After 2 months' follow-up, all events had resolved without sequelae.

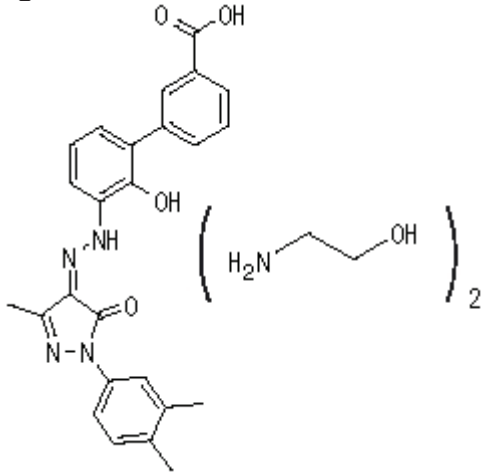
In case of an overdose, consider oral administration of a metal cation-containing preparation, such as calcium, aluminum, or magnesium preparations to chelate eltrombopag and thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with PROMACTA in accordance with dosing and administration recommendations *[see Dosage and Administration (2.1, 2.2)]*.

11 DESCRIPTION

PROMACTA (eltrombopag) tablets contain eltrombopag olamine, a small molecule thrombopoietin (TPO) receptor agonist for oral administration. Eltrombopag interacts with the transmembrane domain of the TPO receptor (also known as cMpl) leading to increased platelet production.

Eltrombopag olamine is a biphenyl hydrazone. The chemical name for eltrombopag olamine is 3'-{(2Z)-2-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]hydrazino}-2'-hydroxy-3-biphenylcarboxylic acid - 2-aminoethanol (1:2). It has the molecular formula $C_{25}H_{22}N_4O_4 \cdot 2(C_2H_7NO)$. The

molecular weight is 564.65 g/mol for eltrombopag olamine and 442.5 g/mol for eltrombopag free acid. Eltrombopag olamine has the following structural formula:



Eltrombopag olamine is practically insoluble in aqueous buffer across a pH range of 1 to 7.4, and is sparingly soluble in water.

PROMACTA (eltrombopag) tablets contain eltrombopag olamine in the amount equivalent to 12.5 mg, 25 mg, 50 mg, or 75 mg of eltrombopag free acid. The inactive ingredients of PROMACTA tablets are:

Tablet Core: magnesium stearate, mannitol, microcrystalline cellulose, povidone, and sodium starch glycolate. **Coating:** hypromellose, polyethylene glycol 400, titanium dioxide, polysorbate 80 (12.5-mg tablet), FD&C Yellow No. 6 aluminum lake (25-mg tablet), FD&C Blue No. 2 aluminum lake (50-mg tablet), or Iron Oxide Red and Iron Oxide Black (75-mg tablet).

PROMACTA (eltrombopag) for oral suspension packets contain a reddish-brown to yellow powder which produces a reddish-brown suspension when reconstituted with water. Each packet delivers eltrombopag olamine equivalent to 12.5 mg or 25 mg of eltrombopag free acid. The inactive ingredients of PROMACTA for oral suspension are mannitol, sucralose, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eltrombopag is an orally bioavailable, small-molecule TPO-receptor agonist that interacts with the transmembrane domain of the human TPO-receptor and initiates signaling cascades that induce proliferation and differentiation from bone marrow progenitor cells.

12.2 Pharmacodynamics

In clinical trials, treatment with PROMACTA resulted in dose-dependent increases in platelet counts following repeated (daily) dosing. The increase in platelet counts reached a maximum approximately two weeks after the initiation of dosing, and returned to baseline within approximately two weeks after the last dose of PROMACTA.

Cardiac Electrophysiology

At doses up to 150 mg (the maximum recommended dose) daily for 5 days, PROMACTA did not prolong the QT/QTc interval to any relevant extent.

12.3 Pharmacokinetics

Eltrombopag demonstrated a dose-proportional increase in exposure between doses of 50 to 150 mg/day in healthy adult subjects. Eltrombopag AUC was approximately 1.7 fold higher in patients with chronic ITP and approximately 2.8-fold higher in patients with HCV compared to healthy subjects. Steady-state was achieved

after approximately 1 week of once daily treatment, with geometric mean accumulation ratio of 1.56 (90% confidence interval 1.20, 1.63) at 75 mg/day. Eltrombopag AUC was approximately 3.2 fold higher in patients with definitive immunosuppressive therapy-naïve severe aplastic anemia compared to healthy subjects suggesting higher relative exposure compared to healthy subjects or patients with ITP and similar exposure compared to patients with chronic hepatitis C. Eltrombopag for oral suspension delivered 22% higher plasma $AUC_{0\text{-}INF}$ than the tablet formulation.

Absorption

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Oral absorption of drug-related material following administration of a single 75-mg solution dose was estimated to be at least 52%.

Effect of Food

A standard high-fat breakfast (876 calories, 52 g fat, 71 g carbohydrate, 34 g protein, and 427 mg calcium) significantly decreased plasma eltrombopag $AUC_{0\text{-}INF}$ by approximately 59% and C_{max} by 65% and delayed T_{max} by 1 hour. The calcium content of this meal may have also contributed to this decrease in exposure.

The effect of administration of a single 25-mg dose of eltrombopag for oral suspension with a high-calcium, moderate-fat, moderate calorie meal on $AUC_{0\text{-}INF}$ and C_{max} in healthy adult subjects is presented in Table 14.

Table 14. Effect on Plasma Eltrombopag Pharmacokinetic Parameters After Administration of a Single 25-mg Dose of Eltrombopag for Oral Suspension with a High Calcium Meal[a] in Healthy Adult Subjects

Timing of eltrombopag for oral suspension dose	Mean (90% CI) reduction in plasma eltrombopag $AUC_{0\text{-}INF}$	Mean (90% CI) reduction in plasma eltrombopag C_{max}
With a high-calcium, moderate-fat, moderate-calorie meal	75% (71%, 88%)	79% (76%, 82%)
2 hours after the high-calcium, moderate-fat, moderate-calorie meal	47% (40%, 53%)	48% (40%, 54%)
2 hours before the high-calcium, moderate-fat, moderate-calorie meal	20% (9%, 29%)	14% (2%, 25%)

[a] 372 calories, 9 g fat, and 448 mg calcium

Distribution

The concentration of eltrombopag in blood cells is approximately 50% to 79% of plasma concentrations based on a radiolabel study. *In vitro* studies suggest that eltrombopag is highly bound to human plasma proteins (greater than 99%). Eltrombopag is a substrate of BCRP, but is not a substrate for P-glycoprotein (P-gp) or OATP1B1.

Elimination

The plasma elimination half-life of eltrombopag is approximately 21 to 32 hours in healthy subjects and 26 to 35 hours in patients with ITP.

Metabolism: Absorbed eltrombopag is extensively metabolized, predominantly through pathways including cleavage, oxidation, and conjugation with glucuronic acid, glutathione, or cysteine. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for the oxidative metabolism of eltrombopag. UGT1A1 and UGT1A3 are responsible for the glucuronidation of eltrombopag.

Excretion: The predominant route of eltrombopag excretion is via feces (59%), and 31% of the dose is found in the urine. Unchanged eltrombopag in feces accounts for approximately 20% of the dose; unchanged eltrombopag is not detectable in urine.

Specific Populations

Ethnicity

Eltrombopag concentrations in Asian (i.e., Japanese, Chinese, Taiwanese, Korean) patients with ITP or chronic hepatitis C, were 50% to 55% higher compared with non-Asian subjects *[see Dosage and Administration (2.1, 2.3)]*.

Eltrombopag exposure in healthy African-American subjects was approximately 40% higher than that observed in Caucasian subjects in one clinical pharmacology trial and similar in three other clinical pharmacology trials. The effect of African-American ethnicity on exposure and related safety and efficacy of eltrombopag has not been established.

Hepatic Impairment

Following a single dose of PROMACTA (50 mg), plasma eltrombopag $AUC_{0\text{-}INF}$ was 41% higher in patients with mild hepatic impairment (Child-Pugh Class A) compared with subjects with normal hepatic function. Plasma eltrombopag $AUC_{0\text{-}INF}$ was approximately 2-fold higher in patients with moderate (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C) compared with subjects with normal hepatic function. The half-life of eltrombopag was prolonged 2-fold in these patients. This clinical trial did not evaluate protein-binding effects.

Chronic Liver Disease

Following repeat doses of eltrombopag in patients with thrombocytopenia and with chronic liver disease, mild hepatic impairment resulted in an 87% to 110% higher plasma eltrombopag $AUC_{(0\text{-}\tau)}$ and moderate hepatic impairment resulted in approximately 141% to 240% higher plasma eltrombopag $AUC_{(0\text{-}\tau)}$ values compared with patients with normal hepatic function. The half-life of eltrombopag was prolonged 3-fold in patients with mild hepatic impairment and 4-fold in patients with moderate hepatic impairment. This clinical trial did not evaluate protein-binding effects.

Chronic Hepatitis C

Patients with chronic hepatitis C treated with PROMACTA had higher plasma $AUC_{(0\text{-}\tau)}$ values as compared with healthy subjects, and $AUC_{(0\text{-}\tau)}$ increased with increasing Child-Pugh score. Patients with chronic hepatitis C and mild hepatic impairment had approximately 100% to 144% higher plasma $AUC_{(0\text{-}\tau)}$ compared with healthy subjects. This clinical trial did not evaluate protein-binding effects.

Renal Impairment

Following a single dose of PROMACTA (50 mg), the average total plasma eltrombopag $AUC_{0\text{-}INF}$ was 32% to 36% lower in subjects with mild (estimated creatinine clearance (CLCr) by Cockcroft - Gault equation: 50 to 80 mL/min), to moderate (CLCr of 30 to 49 mL/min) renal impairment and 60% lower in subjects with severe (CLCr less than 30 mL/min) renal impairment compared with healthy subjects. The effect of renal impairment on unbound (active) eltrombopag exposure has not been assessed.

Pediatric Patients

The pharmacokinetics of eltrombopag have been evaluated in 168 pediatric patients 1 year and older with ITP dosed once daily in two trials. Plasma eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. Asian pediatric patients with ITP had approximately 43% higher plasma eltrombopag $AUC_{(0\text{-}\tau)}$ values as compared with non-Asian patients.

Plasma eltrombopag $AUC_{(0\text{-}\tau)}$ and C_{max} in pediatric patients aged 12 to 17 years was similar to that observed in adults. The pharmacokinetic parameters of eltrombopag in pediatric patients with ITP are shown in Table 15.

Table 15. Geometric Mean (95% CI) Steady-state Plasma Eltrombopag Pharmacokinetic Parameters[a] in Patients with ITP (Normalized to a Once-daily 50-mg Dose)

Age	C_{max}[b] (mcg/mL)	$AUC_{(0-\tau)}$[b] (mcg·hr/mL)
Adults (n = 108)	7.03 (6.44, 7.68)	101 (91.4, 113)
12 to 17 years (n = 62)	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n = 68)	10.3 (9.42, 11.2)	153 (137, 170)
1 to 5 years (n = 38)	11.6 (10.4, 12.9)	162 (139, 187)

[a] PK parameters presented as geometric mean (95% CI)
[b] Based on population PK post-hoc estimates

Drug Interaction Studies

Clinical Studies

Effect of Drugs on Eltrombopag

Effect of Polyvalent Cation-containing Antacids on Eltrombopag:

The coadministration of a single dose of PROMACTA (75 mg) with a polyvalent cation-containing antacid (1,524 mg aluminum hydroxide, 1,425 mg magnesium carbonate, and sodium alginate) decreased plasma eltrombopag $AUC_{0\text{-}INF}$ and C_{max} by approximately 70%. The contribution of sodium alginate to this interaction is not known.

Effect of HIV Protease Inhibitors on Eltrombopag:

The coadministration of repeat-dose lopinavir 400 mg/ritonavir 100 mg (twice daily) with a single dose of PROMACTA (100 mg) decreased plasma eltrombopag $AUC_{0\text{-}INF}$ by 17%.

Effect of HCV Protease Inhibitors on Eltrombopag:

The coadministration of repeat-dose telaprevir (750 mg every 8 hours) or boceprevir (800 mg every 8 hours) with a single dose of PROMACTA (200 mg) to healthy adult subjects in a clinical trial did not alter plasma eltrombopag $AUC_{0\text{-}INF}$ or C_{max} to a significant extent.

Effect of Cyclosporine on Eltrombopag:

The coadministration of a single dose of PROMACTA (50 mg) with a single dose of an OATP and BCRP inhibitor cyclosporine (200 mg or 600 mg) decreased plasma eltrombopag $AUC_{0\text{-}INF}$ by 18% to 24% and C_{max} by 25% to 39%.

Effect of Pegylated Interferon alfa-2a + Ribavirin and Pegylated Interferon alfa-2b + Ribavirin on Eltrombopag:

The presence of pegylated interferon alfa + ribavirin therapy did not significantly affect the clearance of eltrombopag.

Effect of Eltrombopag on Other Drugs

Effect of Eltrombopag on Cytochrome P450 Enzymes Substrates:

The coadministration of multiple doses of PROMACTA (75 mg once daily for 7 days) did not result in the inhibition or induction of the metabolism of a combination of probe substrates for CYP1A2 (caffeine), CYP2C19 (omeprazole), CYP2C9 (flurbiprofen), or CYP3A4 (midazolam) in humans.

Effect of Eltrombopag on Rosuvastatin:

The coadministration of multiple doses of PROMACTA (75 mg once daily for 5 days) with a single dose of rosuvastatin (OATP1B1 and BCRP substrate; 10 mg) increased plasma rosuvastatin $AUC_{0\text{-}INF}$ by 55% and C_{max} by 103%.

Effect of Eltrombopag on HCV Protease Inhibitors:

The coadministration of repeat-dose telaprevir (750 mg every 8 hours) or boceprevir (800 mg every 8 hours) with a single dose of PROMACTA (200 mg) to healthy adult subjects in a clinical trial did not alter plasma telaprevir or boceprevir $AUC_{0\text{-}INF}$ or C_{max} to a significant extent.

In vitro Studies

Eltrombopag Effect on Metabolic Enzymes

Eltrombopag has demonstrated the potential to inhibit CYP2C8, CYP2C9, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15.

Eltrombopag Effect on Transporters

Eltrombopag has demonstrated the potential to inhibit OATP1B1 and BCRP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Eltrombopag does not stimulate platelet production in rats, mice, or dogs because of unique TPO receptor specificity. Data from these animals do not fully model effects in humans.

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 2 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day).

Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two *in vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical exposure based on C_{max} in patients with ITP at 75 mg/day and 7 times the human clinical exposure based on C_{max} in patients with chronic hepatitis C at 100 mg/day). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (less than 3-fold increase in mutation frequency).

Eltrombopag did not affect female fertility in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and similar to the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 2 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day).

13.2 Animal Pharmacology and/or Toxicology

Treatment-related cataracts were detected in rodents in a dose- and time-dependent manner. At greater than or equal to 6 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 3 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day, cataracts were observed in mice after 6 weeks and in rats after 28 weeks of dosing. At greater than or equal to 4 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 2 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing *[see Warnings and Precautions (5.5)]*.

Renal tubular toxicity was observed in studies up to 14 days in duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2-year oral

carcinogenicity study in mice at doses of 25, 75, and 150 mg/kg/day. The exposure at the lowest dose was 1.2 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.6 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day. No similar effects were observed in mice after 13 weeks at exposures greater than those associated with renal changes in the 2-year study, suggesting that this effect is both dose- and time-dependent.

14 CLINICAL STUDIES

14.1 Chronic ITP

Adults: The efficacy and safety of PROMACTA in adult patients with chronic ITP were evaluated in three randomized, double-blind, placebo-controlled trials and in an open-label extension trial.

In Study TRA100773B and Study TRA100773A (referred to as Study 773B and Study 773A, respectively [NCT00102739]), patients who had completed at least one prior ITP therapy and who had a platelet count less than 30 x 10^9/L were randomized to receive either PROMACTA or placebo daily for up to 6 weeks, followed by 6 weeks off therapy. During the trials, PROMACTA or placebo was discontinued if the platelet count exceeded 200 x 10^9/L.

The median age of the patients was 50 years and 60% were female. Approximately 70% of the patients had received at least 2 prior ITP therapies (predominantly corticosteroids, immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine) and 40% of the patients had undergone splenectomy. The median baseline platelet counts (approximately 18 x 10^9/L) were similar among all treatment groups.

Study 773B randomized 114 patients (2:1) to PROMACTA 50 mg or placebo. Study 773A randomized 117 patients (1:1:1:1) among placebo or 1 of 3 dose regimens of PROMACTA, 30 mg, 50 mg, or 75 mg each administered daily.

The efficacy of PROMACTA in this trial was evaluated by response rate, defined as a shift from a baseline platelet count of less than 30 x 10^9/L to greater than or equal to 50 x 10^9/L at any time during the treatment period (Table 16).

Table 16. Studies 773B and 773A: Platelet Count Response (≥ 50 x 10^9/L) Rates in Adults with Chronic Immune Thrombocytopenia

Study	PROMACTA 50 mg Daily	Placebo
773B	43/73 (59%)[a]	6/37 (16%)
773A	19/27 (70%)[a]	3/27 (11%)

[a] *p*-value < 0.001 for PROMACTA versus placebo

The platelet count response to PROMACTA was similar among patients who had or had not undergone splenectomy. In general, increases in platelet counts were detected 1 week following initiation of PROMACTA and the maximum response was observed after 2 weeks of therapy. In the placebo and 50-mg–dose groups of PROMACTA, the trial drug was discontinued due to an increase in platelet counts to greater than 200 x 10^9/L in 3% and 27% of the patients, respectively. The median duration of treatment with the 50-mg dose of PROMACTA was 43 days in Study 773B and 42 days in Study 773A.

Of 7 patients who underwent hemostatic challenges, additional ITP medications were required in 3 of 3 placebo group patients and 0 of 4 patients treated with PROMACTA. Surgical procedures accounted for most of the hemostatic challenges. Hemorrhage requiring transfusion occurred in one placebo group patient and no patients treated with PROMACTA.

In the RAISE study (NCT00370331), 197 patients were randomized (2:1) to receive either PROMACTA 50 mg once daily (n = 135) or placebo (n = 62) for 6 months, during which time the dose of PROMACTA could be adjusted based on individual platelet counts. Patients were allowed to taper or discontinue concomitant ITP

medications after being treated with PROMACTA for 6 weeks. Patients were permitted to receive rescue treatments at any time during the trial as clinically indicated.

The median ages of the patients treated with PROMACTA and placebo were 47 years and 52.5 years, respectively. Approximately half of the patients treated with PROMACTA and placebo (47% and 50%, respectively) were receiving concomitant ITP medication (predominantly corticosteroids) at randomization and had baseline platelet counts less than or equal to 15 x 10^9/L (50% and 48%, respectively). A similar percentage of patients treated with PROMACTA and placebo (37% and 34%, respectively) had a prior splenectomy.

The efficacy of PROMACTA in this trial was evaluated by the odds of achieving a platelet count greater than or equal to 50 x 10^9/L and less than or equal to 400 x 10^9/L for patients receiving PROMACTA relative to placebo and was based on patient response profiles throughout the 6-month treatment period. In 134 patients who completed 26 weeks of treatment, a sustained platelet response (platelet count greater than or equal to 50 x 10^9/L and less than or equal to 400 x 10^9/L for 6 out of the last 8 weeks of the 26-week treatment period in the absence of rescue medication at any time) was achieved by 60% of patients treated with PROMACTA, compared with 10% of patients treated with placebo (splenectomized patients: PROMACTA 51%, placebo 8%; non-splenectomized patients: PROMACTA 66%, placebo 11%). The proportion of responders in the group of patients treated with PROMACTA was between 37% and 56% compared with 7% and 19% in the placebo treatment group for all on-therapy visits. Patients treated with PROMACTA were significantly more likely to achieve a platelet count between 50 x 10^9/L and 400 x 10^9/L during the entire 6-month treatment period compared with those patients treated with placebo.

Outcomes of treatment are presented in Table 17 for all patients enrolled in the trial.

Table 17. RAISE: Outcomes of Treatment in Adults with Chronic Immune Thrombocytopenia

Outcome	PROMACTA N = 135	Placebo N = 62
Mean number of weeks with platelet counts ≥ 50 x 10^9/L	11.3	2.4
Requiring rescue therapy, n (%)	24 (18)	25 (40)

Among 94 patients receiving other ITP therapy at baseline, 37 (59%) of 63 patients treated with PROMACTA and 10 (32%) of 31 patients in the placebo group discontinued concomitant therapy at some time during the trial.

In the EXTEND study (NCT00351468), patients who completed any prior clinical trial with PROMACTA were enrolled in an open-label, single-arm trial in which attempts were made to decrease the dose or eliminate the need for any concomitant ITP medications. PROMACTA was administered to 302 patients in EXTEND; 218 patients completed 1 year, 180 patients completed 2 years, 107 patients completed 3 years, 75 patients completed 4 years, 34 patients completed 5 years, and 18 patients completed 6 years of therapy. The median baseline platelet count was 19 x 10^9/L prior to administration of PROMACTA. Median platelet counts at 1, 2, 3, 4, 5, 6, and 7 years on study were 85 x 10^9/L, 85 x 10^9/L, 105 x 10^9/L, 64 x 10^9/L, 75 x 10^9/L, 119 x 10^9/L, and 76 x 10^9/L, respectively.

Pediatric Patients: The efficacy and safety of PROMACTA in pediatric patients 1 year and older with chronic ITP were evaluated in two double-blind, placebo-controlled trials. The trials differed in time since ITP diagnosis: at least 6 months versus at least 12 months. During the trials, doses could be increased every 2 weeks to a maximum of 75 mg once daily. The dose of PROMACTA was reduced if the platelet count exceeded 200 x 10^9/L and interrupted and reduced if it exceeded 400 x 10^9/L.

In the PETIT2 study (NCT01520909), patients refractory or relapsed to at least one prior ITP therapy with a platelet count less than 30 x 10^9/L (n = 92) were stratified by age and randomized (2:1) to PROMACTA (n = 63) or placebo (n = 29). The starting dose for patients aged 6 to 17 years was 50 mg once daily for those at least 27 kg and 37.5 mg once daily for those less than 27 kg, administered as oral tablets. A reduced dose of 25 mg once daily was used for East Asian patients aged 6 to 17 years regardless of weight. The starting dose for

patients aged 1 to 5 years was 1.2 mg/kg once daily (0.8 mg/kg once daily for East Asian patients) administered as oral suspension.

The 13-week, randomized, double-blind period was followed by a 24-week, open-label period where patients from both arms were eligible to receive PROMACTA.

The median age of the patients was 9 years and 48% were female. Approximately 62% of patients had a baseline platelet count less than or equal to 15 x 10^9/L, a characteristic that was similar between treatment arms. The percentage of patients with at least 2 prior ITP therapies (predominantly corticosteroids and immunoglobulins) was 73% in the group treated with PROMACTA and 90% in the group treated with placebo. Four patients in the group treated with PROMACTA had undergone splenectomy.

The efficacy of PROMACTA in this trial was evaluated by the proportion of subjects on PROMACTA achieving platelet counts ≥ 50 x 10^9/L (in the absence of rescue therapy) for at least 6 out of 8 weeks between Weeks 5 to 12 of the randomized, double-blind period (Table 18).

Table 18. PETIT2: Platelet Count Response (≥ 50 x 10^9/L without Rescue) for 6 out of 8 Weeks (between Weeks 5 to 12) Overall and by Age Cohort in Pediatric Patients 1 Year and Older with Chronic Immune Thrombocytopenia

Age Cohort	PROMACTA	Placebo
Overall	26/63 (41%)[a]	1/29 (3%)
12 to 17 years	10/24 (42%)	1/10 (10%)
6 to 11 years	11/25 (44%)	0/13 (0%)
1 to 5 years	5/14 (36%)	0/6 (0%)

[a] *p*-value = < 0.001 for PROMACTA versus placebo

More pediatric patients treated with PROMACTA (75%) compared with placebo (21%) had at least one platelet count greater than or equal to 50 x 10^9/L during the first 12 weeks of randomized treatment in absence of rescue therapy. Fewer pediatric patients treated with PROMACTA required rescue treatment during the randomized, double-blind period compared with placebo-treated patients (19% [12/63] versus 24% [7/29]). In the patients who achieved a platelet response (≥ 50 x 10^9/L without rescue) for 6 out of 8 weeks (between weeks 5 to 12), 62% (16/26) had an initial response in the first 2 weeks after starting PROMACTA.

Patients were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the trial. Among 15 patients receiving other ITP therapy at baseline, 53% (8/15) reduced (n = 1) or discontinued (n = 7) concomitant therapy, mainly corticosteroids, without needing rescue therapy.

In the PETIT study (NCT00908037), patients refractory or relapsed to at least one prior ITP therapy with a platelet count less than 30 x 10^9/L (n = 67) were stratified by age and randomized (2:1) to PROMACTA (n = 45) or placebo (n = 22). The starting dose for patients aged 12 to 17 years was 37.5 mg once daily regardless of weight or race. The starting dose for patients aged 6 to 11 years was 50 mg once daily for those greater than or equal to 27 kg and 25 mg once daily for those less than 27 kg, administered as oral tablets. Reduced doses of 25 mg (for those greater than or equal to 27 kg) and 12.5 mg (for those less than 27 kg), each once daily, were used for East Asian patients in this age range. The starting dose for patients aged 1 to 5 years was 1.5 mg/kg once daily (0.8 mg/kg once daily for East Asian patients) administered as oral suspension.

The 7-week, randomized, double-blind period was followed by an open-label period of up to 24 weeks where patients from both arms were eligible to receive PROMACTA.

The median age of the patients was 10 years and 60% were female. Approximately 51% of patients had a baseline platelet count less than or equal to 15 x 10^9/L. The percentage of patients with at least 2 prior ITP therapies (predominantly corticosteroids and immunoglobulins) was 84% in the group treated with PROMACTA and 86% in the group treated with placebo. Five patients in the group treated with PROMACTA had undergone splenectomy.

The efficacy of PROMACTA in this trial was evaluated by the proportion of patients achieving platelet counts greater than or equal to 50 x 10^9/L (in absence of rescue therapy) at least once between Weeks 1 and 6 of the randomized, double-blind period (Table 19). Platelet response to PROMACTA was consistent across the age cohorts.

Table 19. PETIT: Platelet Count Response (≥ 50 x 10^9/L without Rescue) Rates in Pediatric Patients 1 Year and Older with Chronic Immune Thrombocytopenia

	PROMACTA	Placebo
Overall	28/45 (62%)[a]	7/22 (32%)
12 to 17 years	10/16 (62%)	0/8 (0%)
6 to 11 years	12/19 (63%)	3/9 (33%)
1 to 5 years	6/10 (60%)	4/5 (80%)

[a] *p*-value = 0.011 for PROMACTA versus placebo

Fewer pediatric patients treated with PROMACTA required rescue treatment during the randomized, double-blind period compared with placebo-treated patients (13% [6/45] versus 50% [11/22]).

Patients were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the trial. Among 13 patients receiving other ITP therapy at baseline, 46% (6/13) reduced (n = 3) or discontinued (n = 3) concomitant therapy, mainly corticosteroids, without needing rescue therapy.

14.2 Chronic Hepatitis C-associated Thrombocytopenia

The efficacy and safety of PROMACTA for the treatment of thrombocytopenia in adult patients with chronic hepatitis C were evaluated in two randomized, double-blind, placebo-controlled trials. The ENABLE1 study (NCT00516321) utilized peginterferon alfa-2a (PEGASYS®) plus ribavirin for antiviral treatment and the ENABLE2 study (NCT00529568) utilized peginterferon alfa-2b (PEGINTRON®) plus ribavirin. In both trials, patients with a platelet count of less than 75 x 10^9/L were enrolled and stratified by platelet count, screening HCV RNA, and HCV genotype. Patients were excluded if they had evidence of decompensated liver disease with Child-Pugh score greater than 6 (class B and C), history of ascites, or hepatic encephalopathy. The median age of the patients in both trials was 52 years, 63% were male, and 74% were Caucasian. Sixty-nine percent of patients had HCV genotypes 1, 4, 6, with the remainder genotypes 2 and 3. Approximately 30% of patients had been previously treated with interferon and ribavirin. The majority of patients (90%) had bridging fibrosis and cirrhosis, as indicated by noninvasive testing. A similar proportion (95%) of patients in both treatment groups had Child-Pugh Class A (score 5 to 6) at baseline. A similar proportion of patients (2%) in both treatment groups had baseline international normalized ratio (INR) greater than 1.7. Median baseline platelet counts (approximately 60 x 10^9/L) were similar in both treatment groups. The trials consisted of 2 phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, patients received open-label PROMACTA to increase the platelet count to a threshold of greater than or equal to 90 x 10^9/L for ENABLE1 and greater than or equal to 100 x 10^9/L for ENABLE2. PROMACTA was administered at an initial dose of 25 mg once daily for 2 weeks and increased in 25-mg increments over 2- to 3-week periods to achieve the optimal platelet count to initiate antiviral therapy. The maximal time patients could receive open-label PROMACTA was 9 weeks. If threshold platelet counts were achieved, patients were randomized (2:1) to the same dose of PROMACTA at the end of the pre-treatment phase or to placebo. PROMACTA was administered in combination with pegylated interferon and ribavirin per their respective prescribing information for up to 48 weeks.

The efficacy of PROMACTA for both trials was evaluated by sustained virologic response (SVR) defined as the percentage of patients with undetectable HCV-RNA at 24 weeks after completion of antiviral treatment. The median time to achieve the target platelet count greater than or equal to 90 x 10^9/L was approximately 2 weeks. Ninety-five percent of patients were able to initiate antiviral therapy.

In both trials, a significantly greater proportion of patients treated with PROMACTA achieved SVR (see Table 20). The improvement in the proportion of patients who achieved SVR was consistent across subgroups

based on baseline platelet count (less than 50 x 10^9/L versus greater than or equal to 50 x 10^9/L). In patients with high baseline viral loads (greater than or equal to 800,000), the SVR rate was 18% (82/452) for PROMACTA versus 8% (20/239) for placebo.

Table 20. ENABLE1 and ENABLE2: Sustained Virologic Response (SVR) in Adults with Chronic Hepatitis C

	ENABLE1[a]		ENABLE2[b]	
Pre-antiviral Treatment Phase	**N = 715**		**N = 805**	
% Patients who achieved target platelet counts and initiated antiviral therapy[c]	95%		94%	
Antiviral Treatment Phase	**PROMACTA N = 450 %**	**Placebo N = 232 %**	**PROMACTA N = 506 %**	**Placebo N = 253 %**
Overall SVR[d]	23	14	19	13
HCV Genotype 2,3	35	24	34	25
HCV Genotype 1,4,6	18	10	13	7

[a] PROMACTA given in combination with peginterferon alfa-2a (180 mcg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1,200 mg daily in 2 divided doses orally)

[b] PROMACTA given in combination with peginterferon alfa-2b (1.5 mcg/kg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1,400 mg daily in 2 divided doses orally)

[c] Target platelet count was ≥ 90 x 10^9/L for ENABLE1 and ≥ 100 x 10^9/L for ENABLE2

[d] *p*-value < 0.05 for PROMACTA versus placebo

The majority of patients treated with PROMACTA (76%) maintained a platelet count greater than or equal to 50 x 10^9/L compared with 19% for placebo. A greater proportion of patients on PROMACTA did not require any antiviral dose reduction as compared with placebo (45% versus 27%).

14.3 Severe Aplastic Anemia

First-Line Treatment of Severe Aplastic Anemia

PROMACTA in combination with horse antithymocyte globulin (h-ATG) and cyclosporine was investigated in a single-arm, single-center, open-label sequential cohort trial (Study ETB115AUS01T, referred to as Study US01T [NCT01623167]) in patients with severe aplastic anemia who had not received prior immunosuppressive therapy (IST) with any ATG, alemtuzumab, or high dose cyclophosphamide. A total of 153 patients received PROMACTA in Study US01T in three sequential cohorts and an extension of the third cohort. The multiple cohorts received the same PROMACTA starting dose but differed by treatment start day and duration. The starting dose of PROMACTA for patients 12 years and older was 150 mg once daily (a reduced dose of 75 mg was administered for East and Southeast Asians), 75 mg once daily for pediatric patients aged 6 to 11 years (a reduced dose of 37.5 mg was administered for East and Southeast Asians), and 2.5 mg/kg once daily for pediatric patients aged 2 to 5 years (a reduced dose of 1.25 mg/kg was administered for East and Southeast Asians).

- Cohort 1 (n=30): PROMACTA on Day 14 to Month 6 (D14-M6) plus h-ATG and cyclosporine
- Cohort 2 (n=31): PROMACTA on Day 14 to Month 3 (D14-M3) plus h-ATG and cyclosporine
- Cohort 3 + Extension cohort [PROMACTA D1-M6 cohort] (n=92): PROMACTA on Day 1 to Month 6 (D1-M6) plus h-ATG and cyclosporine (with all patients eligible to receive low dose of cyclosporine (maintenance dose) if they achieved a hematologic response at 6 months)

PROMACTA dose reductions were conducted for elevated platelet counts and hepatic impairment. Table 21 includes the dosages of h-ATG and cyclosporine administered in combination with PROMACTA in Study US01T.

Data from the Cohort 3 + Extension cohort support the efficacy of PROMACTA for the first-line treatment of patients with severe aplastic anemia (Table 22). The results presented in this section represent the findings from the Cohort 3 and Extension cohort (n=92).

Table 21. Dosages of Immunosuppressive Therapy Administered with PROMACTA in Study US01T

Agent	Dose Administered in the Pivotal Trial
Horse antithymocyte globulin (h-ATG)	40 mg/kg/day, based on actual body weight, administered intravenously on Days 1 to 4 of the 6-month treatment period
Cyclosporine[a] (therapeutic dose for 6 months, from Day 1 to Month 6, adjusted to obtain a target therapeutic trough level between 200 mcg/L and 400 mcg/L)	Patients 12 years and older (total daily dose of 6 mg/kg/day) 3 mg/kg, based on actual body weight, orally every 12 hours for 6 months, starting on Day 1 *Patients > 20 years of age with a body mass index > 35 or patients 12 to 20 years of age with a body mass index > 95th percentile*: 3 mg/kg, based on adjusted body weight[b], orally every 12 hours for 6 months, starting on Day 1 Patients 2 to 11 years of age (total daily dose of 12 mg/kg/day) 6 mg/kg, based on actual body weight, orally every 12 hours for 6 months, starting on Day 1 *Patients 2 to 11 years of age with a body mass index > 95th percentile*: 6 mg/kg, based on adjusted body weight[b], orally every 12 hours for 6 months, starting on Day 1
Cyclosporine (maintenance dose, from Month 6 to Month 24)	For patients who achieve a hematologic response at 6 months 2 mg/kg/day administered orally at a fixed dose for an additional 18 months

[a] Dose of cyclosporine may need was adjusted to achieve the above recommended target trough levels; refer to the appropriate cyclosporine prescribing information

[b] Calculated as the midpoint between the ideal body weight and actual body weight

In the PROMACTA D1-M6 cohort, the median age was 28 years (range 5 to 82 years) with 16% and 28% of patients ≥ 65 years of age and < 17 years of age, respectively. Forty-six percent of patients were male and the majority of patients were White (62%). Patients weighing 12 kg or less or patients with ALT or AST > 5x upper limit of normal were excluded from the trial.

The efficacy of PROMACTA in combination with h-ATG and cyclosporine was established on the basis of complete hematological response at 6 months. A complete response was defined as hematological parameters meeting all 3 of the following values on 2 consecutive serial blood count measurements at least one week apart: absolute neutrophil count (ANC) > 1,000/mcL, platelet count > 100 x 10^9/L and hemoglobin > 10 g/dL. A partial response was defined as blood counts no longer meeting the standard criteria for severe pancytopenia in severe aplastic anemia equivalent to 2 of the following values on 2 consecutive serial blood count measurements at least one week apart: ANC > 500/mcL, platelet count > 20 x 10^9/L, or reticulocyte count >60,000/mcL. Overall response rate is defined as the number of partial responses plus complete responses.

Table 22. Study US01T: Hematologic Response in First-Line Treatment of Patients with Severe Aplastic Anemia

	PROMACTA D1-M6 + h-ATG + cyclosporine N = 92
Month 6, n[a]	**87**
Overall response, n (%) [95% CI]	69 (79) [69, 87]
Complete response, n (%) [95% CI]	38 (44) [33, 55]
Median duration of overall response, n[b]	**70**
Months (95% CI)	24.3 (21.4, NE)
Median duration of complete response, n[b]	**46**
Months (95% CI)	24.3 (23.0, NE)

[a] The number of patients who reached the 6-month assessment or withdrew earlier is the denominator for percentage calculation
[b] Number of responders at any time
NE = not estimable

The overall and complete hematological response rates at Year 1 (N=78) are 56.4% and 38.5% and at Year 2 (N=62) are 38.7% and 30.6%, respectively.

Pediatric Patients

Thirty-four patients 2 to 16 years of age were enrolled in Study US01T. In the D1-M6 cohort, 7 and 17 out of 25 pediatric patients achieved a complete and overall response, respectively, at 6 months.

Refractory Severe Aplastic Anemia

PROMACTA was studied in a single-arm, single-center, open-label trial (Study ETB115AUS28T, referred to as Study US28T [NCT00922883]) in 43 patients with severe aplastic anemia who had an insufficient response to at least one prior immunosuppressive therapy and who had a platelet count less than or equal to 30 x 10^9/L. PROMACTA was administered at an initial dose of 50 mg once daily for 2 weeks and increased over 2-week periods up to a maximum dose of 150 mg once daily. The efficacy of PROMACTA in the study was evaluated by the hematologic response assessed after 12 weeks of treatment. Hematologic response was defined as meeting 1 or more of the following criteria: 1) platelet count increases to 20 x 10^9/L above baseline, or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) hemoglobin increase by greater than 1.5 g/dL, or a reduction in greater than or equal to 4 units of RBC transfusions for 8 consecutive weeks; 3) ANC increase of 100% or an ANC increase greater than 0.5 x 10^9/L. PROMACTA was discontinued after 16 weeks if no hematologic response was observed. Patients who responded continued therapy in an extension phase of the trial.

The treated population had median age of 45 years (range: 17 to 77 years) and 56% were male. At baseline, the median platelet count was 20 x 10^9/L, hemoglobin was 8.4 g/dL, ANC was 0.58 x 10^9/L, and absolute reticulocyte count was 24.3 x 10^9/L. Eighty-six percent of patients were RBC transfusion dependent and 91% were platelet transfusion dependent. The majority of patients (84%) received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

Table 23 presents the efficacy results.

Table 23. Study US28T: Hematologic Response in Patients with Refractory Severe Aplastic Anemia

Outcome	**PROMACTA N = 43**
Response rate[a], n (%) 95% CI (%)	17 (40) (25, 56)
Median of duration of response in months (95% CI)	NR[b] (3.0, NR[b])

[a] Includes single- and multi-lineage

[b] NR = Not reached due to few events (relapsed)

In the 17 responders, the platelet transfusion-free period ranged from 8 to 1,096 days with a median of 200 days, and the RBC transfusion-free period ranged from 15 to 1,082 days with a median of 208 days.

In the extension phase, 8 patients achieved a multi-lineage response; 4 of these patients subsequently tapered off treatment with PROMACTA and maintained the response (median follow up: 8.1 months, range: 7.2 to 10.6 months).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Tablets

- The 12.5-mg tablets are round, biconvex, white, film-coated tablets debossed with GS MZ1 and 12.5 on one side and are available in bottles of 30: NDC 0078-0684-15
- The 25-mg tablets are round, biconvex, orange, film-coated tablets debossed with GS NX3 and 25 on one side and are available in bottles of 30: NDC 0078-0685-15
- The 50-mg tablets are round, biconvex, blue, film-coated tablets debossed with GS UFU and 50 on one side and are available in bottles of 30: NDC 0078-0686-15
- The 75-mg tablets are round, biconvex, pink, film-coated tablets debossed with GS FFS and 75 on one side and are available in bottles of 30: NDC 0078-0687-15

Store at room temperature between 20°C and 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*. Dispense in original bottle.

16.2 For Oral Suspension

- The 12.5-mg for oral suspension is a reddish-brown to yellow powder in unit-dose packets, co-packaged in a kit with a 40-cc reconstitution vessel, a threaded closure with syringe-port capability, and 30 single-use oral dosing syringes.

  Each kit (NDC 0078-0972-61) contains 30 packets: NDC 0078-0972-19.

- The 25-mg for oral suspension is a reddish-brown to yellow powder in unit-dose packets, copackaged in a kit with a 40-cc reconstitution vessel, a threaded closure with syringe-port capability, and 30 single-use oral dosing syringes.

  Each kit (NDC 0078-0697-61) contains 30 packets: NDC 0078-0697-19

Store at room temperature between 20°C and 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Following reconstitution, the product should be administered immediately but may be stored for a maximum period of 30 minutes between 20°C and 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Throw away (discard) the mixture if not used within 30 minutes.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Prior to treatment, patients should fully understand and be informed of the following risks and considerations for PROMACTA:

Risks

Hepatotoxicity

- Therapy with PROMACTA may be associated with hepatobiliary laboratory abnormalities *[see Warnings and Precautions (5.2)]*.

- Advise patients with chronic hepatitis C and cirrhosis that they may be at risk for hepatic decompensation when receiving PROMACTA with alfa interferon therapy *[see Warnings and Precautions (5.1)]*.
- Advise patients that they should report any of the following signs and symptoms of liver problems to their healthcare provider right away *[see Warnings and Precautions (5.2)]*.
  - yellowing of the skin or the whites of the eyes (jaundice)
  - unusual darkening of the urine
  - unusual tiredness
  - right upper stomach area pain
  - confusion
  - swelling of the stomach area (abdomen)

Risk of Bleeding Upon PROMACTA Discontinuation

- Advise patients that thrombocytopenia and risk of bleeding may reoccur upon discontinuing PROMACTA, particularly if PROMACTA is discontinued while the patient is on anticoagulants or antiplatelet agents. Advise patients that during therapy with PROMACTA, they should continue to avoid situations or medications that may increase the risk for bleeding.

Thrombotic/Thromboembolic Complications

- Advise patients that too much PROMACTA may result in excessive platelet counts and a risk for thrombotic/thromboembolic complications *[see Warnings and Precautions (5.4)]*.

Cataracts

- Advise patients to have a baseline ocular examination prior to administration of PROMACTA and be monitored for signs and symptoms of cataracts during therapy *[see Warnings and Precautions (5.5)]*.

Drug Interactions

- Advise patients to take PROMACTA at least 2 hours before or 4 hours after foods, mineral supplements, and antacids which contain polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc *[see Dosage and Administration (2.4), Drug Interactions (7.1)]*.

Lactation

- Advise women not to breastfeed during treatment with PROMACTA *[see Use in Specific Populations (8.2)]*.

Administration of PROMACTA

- For patients with chronic ITP, therapy with PROMACTA is administered to achieve and maintain a platelet count greater than or equal to 50 x 10^9/L as necessary to reduce the risk for bleeding *[see Indications and Usage (1.1)]*.
- For patients with chronic hepatitis C, therapy with PROMACTA is administered to achieve and maintain a platelet count necessary to initiate and maintain antiviral therapy with pegylated interferon and ribavirin *[see Indications and Usage (1.2)]*.
- Prior to use of the oral suspension, ensure patients or caregivers receive training on proper dosing, preparation, and administration *[see Dosage and Administration (2.4)]*.
- Inform patients or caregivers how many packets to administer to get the full dose *[see Instructions for Use]*.
- Inform patients or caregivers to use a new oral dosing syringe to prepare each dose of PROMACTA for oral suspension *[see Instructions for Use]*.

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T2018-11

MEDICATION GUIDE

PROMACTA® (pro-MAC-ta)
(eltrombopag)
tablets

PROMACTA® (pro-MAC-ta)
(eltrombopag)
for oral suspension

What is the most important information I should know about PROMACTA?

PROMACTA can cause serious side effects, including:

Liver problems:

- If you have chronic hepatitis C virus and take PROMACTA with interferon and ribavirin treatment, PROMACTA may increase your risk of liver problems. If your healthcare provider tells you to stop your treatment with interferon and ribavirin, you will also need to stop taking PROMACTA.
- PROMACTA may increase your risk of liver problems that may be severe and possibly life threatening. Your healthcare provider will do blood tests to check your liver function before you start taking PROMACTA and during your treatment. Your healthcare provider may stop your treatment with PROMACTA if you have changes in your liver function blood tests.

Tell your healthcare provider right away if you have any of these signs and symptoms of liver problems:

- yellowing of the skin or the whites of the eyes (jaundice)
- unusual darkening of the urine
- unusual tiredness
- right upper stomach area (abdomen) pain
- confusion
- swelling of the stomach area (abdomen)

See "What are the possible side effects of PROMACTA?" for other side effects of PROMACTA.

What is PROMACTA?

PROMACTA is a prescription medicine used to treat adults and children 1 year of age and older with low blood platelet counts due to chronic immune thrombocytopenia (ITP), when other medicines to treat ITP or surgery to remove the spleen have not worked well enough.

PROMACTA is also used to treat people with:

- low blood platelet counts due to chronic hepatitis C virus (HCV) infection before and during treatment with interferon.
- severe aplastic anemia (SAA) in combination with other medicines to treat SAA, as the first treatment for adults and children 2 years of age and older.
- severe aplastic anemia (SAA) when other medicines to treat SAA have not worked well enough.

PROMACTA is used to try to raise platelet counts in order to lower your risk for bleeding.

PROMACTA is not used to make platelet counts normal.

PROMACTA is not for use in people with a pre-cancerous condition called myelodysplastic syndrome (MDS), or in people with low platelet counts caused by certain other medical conditions or diseases.

It is not known if PROMACTA is safe and effective when used with other antiviral medicines to treat chronic hepatitis C.

It is not known if PROMACTA is safe and effective in children:

- younger than 1 year with ITP
- with low blood platelet counts due to chronic hepatitis C
- whose severe aplastic anemia (SAA) has not improved after previous treatments.
- younger than 2 years when used in combination with other medicines to treat SAA as the first treatment for SAA.

Before you take PROMACTA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- have a precancerous condition called MDS or a blood cancer
- have or had a blood clot
- have a history of cataracts
- have had surgery to remove your spleen (splenectomy)
- have bleeding problems
- are of Asian ancestry (such as Chinese, Japanese, Taiwanese, or Korean). You may need a lower dose of PROMACTA.

- are pregnant or plan to become pregnant. It is not known if PROMACTA will harm an unborn baby. Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with PROMACTA.
  - Females who are able to become pregnant, should use effective birth control (contraception) during treatment with PROMACTA and for at least 7 days after stopping treatment with PROMACTA. Talk to your healthcare provider about birth control methods that may be right for you during this time.
- are breastfeeding or plan to breastfeed. You should not breastfeed during your treatment with PROMACTA. Talk to your healthcare provider about the best way to feed your baby during this time.
- **Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements. PROMACTA may affect the way certain medicines work. Certain other medicines may affect the way PROMACTA works.

Especially tell your healthcare provider if you take:

- certain medicines used to treat high cholesterol, called “statins”
- a blood thinner medicine

Certain medicines may keep PROMACTA from working correctly. Take PROMACTA at least 2 hours before or 4 hours after taking these products:

- antacid medicine used to treat stomach ulcers or heartburn
- multivitamins or products that contain iron, calcium, aluminum, magnesium, selenium, and zinc which may be found in mineral supplements

Ask your healthcare provider if you are not sure if your medicine is one that is listed above.
Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take PROMACTA?

- Take PROMACTA exactly as your healthcare provider tells you to take it. Your healthcare provider will prescribe the dose of PROMACTA tablets or PROMACTA for oral suspension that is right for you.
- If your healthcare provider prescribes PROMACTA tablets, take PROMACTA tablets whole. **Do not split, chew, or crush PROMACTA tablets and do not mix with food or liquids.**
- If your healthcare provider prescribes PROMACTA for oral suspension, see the **“Instructions for Use”** that comes with your medicine for instructions on how to correctly mix and take a dose of PROMACTA.
- Use a new single-use oral dosing syringe to prepare each dose of PROMACTA for oral suspension. **Do not re-use the oral dosing syringe**.
- **Do not** stop taking PROMACTA without talking with your healthcare provider first. Do not change your dose or schedule for taking PROMACTA unless your healthcare provider tells you to change it.
- Take PROMACTA on an empty stomach, either 1 hour before or 2 hours after eating food.
- Take PROMACTA at least 2 hours before or 4 hours after eating dairy products and calcium-fortified juices.
- If you miss a dose of PROMACTA, wait and take your next scheduled dose. Do not take more than 1 dose of PROMACTA in 1 day.
- If you take too much PROMACTA, you may have a higher risk of serious side effects. Call your healthcare provider right away.
- Your healthcare provider will check your platelet count during your treatment with PROMACTA and change your dose of PROMACTA as needed.
- Tell your healthcare provider about any bruising or bleeding that happens while you take and after you stop taking PROMACTA.
- If you have SAA, your healthcare provider may do tests to monitor your bone marrow during treatment with PROMACTA.

What should I avoid while taking PROMACTA?

Avoid situations and medicines that may increase your risk of bleeding.

What are the possible side effects of PROMACTA?

PROMACTA may cause serious side effects, including:

- See **“What is the most important information I should know about PROMACTA?”**

- **Increased risk of worsening of a precancerous blood condition called myelodysplastic syndrome (MDS) to acute myelogenous leukemia (AML).** PROMACTA is not for use in people with a precancerous condition called myelodysplastic syndromes (MDS). See "**What is PROMACTA**?" If you have MDS and receive PROMACTA, you have an increased risk that your MDS condition may worsen and become a blood cancer called AML. If your MDS worsens to become AML, you may have an increased risk of death from AML.
- **High platelet counts and higher risk for blood clots.** Your risk of getting a blood clot is increased if your platelet count is too high during treatment with PROMACTA. Your risk of getting a blood clot may also be increased during treatment with PROMACTA if you have normal or low platelet counts. You may have severe problems or die from some forms of blood clots, such as clots that travel to the lungs or that cause heart attacks or strokes. Your healthcare provider will check your blood platelet counts, and change your dose or stop PROMACTA if your platelet counts get too high. Tell your healthcare provider right away if you have signs and symptoms of a blood clot in the leg, such as swelling, pain, or tenderness in your leg.
  People with chronic liver disease may be at risk for a type of blood clot in the stomach area (abdomen). Tell your healthcare provider right away if you have stomach-area (abdomen) pain, nausea, vomiting, or diarrhea as these may be symptoms of this type of blood clot.
- **New or worsened cataracts (a clouding of the lens in the eye).** New or worsened cataracts can happen in people taking PROMACTA. Your healthcare provider will check your eyes before and during your treatment with PROMACTA. Tell your healthcare provider about any changes in your eyesight while taking PROMACTA.

The most common side effects of PROMACTA in adults and children include:

- low red blood cell count (anemia)
- nausea
- fever
- abnormal liver function tests
- cough
- tiredness
- headache
- diarrhea

Laboratory tests may show abnormal changes to the cells in your bone marrow.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of PROMACTA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PROMACTA tablets and PROMACTA for oral suspension?

Tablets:

- Store PROMACTA tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep PROMACTA in the bottle given to you.

For oral suspension:

- Store PROMACTA for oral suspension at room temperature between 68°F to 77°F (20°C to 25°C).
- After mixing, PROMACTA should be taken right away but may be stored for no more than 30 minutes between 68°F to 77°F (20°C to 25°C). Throw away (discard) the mixture if not used within 30 minutes.

Keep PROMACTA and all medicines out of the reach of children.

General information about the safe and effective use of PROMACTA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PROMACTA for a condition for which it was not prescribed. Do not give PROMACTA to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about PROMACTA that is written for health professionals.

What are the ingredients in PROMACTA?

Tablets:

Active ingredient: eltrombopag olamine

Inactive ingredients:

- **Tablet Core:** magnesium stearate, mannitol, microcrystalline cellulose, povidone, and sodium starch glycolate.
- **Coating:** hypromellose, polyethylene glycol 400, titanium dioxide, polysorbate 80 (12.5-mg tablet), and FD&C Yellow No. 6 aluminum lake (25-mg tablet), FD&C Blue No. 2 aluminum lake (50-mg tablet), or Iron Oxide Red and Iron Oxide Black (75-mg tablet).

For oral suspension:

Active ingredient: eltrombopag olamine.

Inactive ingredients: mannitol, sucralose, and xanthan gum

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For more information about PROMACTA, go to www.PROMACTA.com or call 1-888-669-6682.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised November 2018

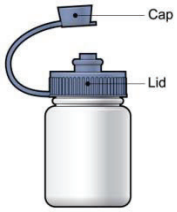
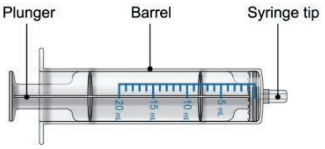
INSTRUCTIONS FOR USE
PROMACTA® (pro-MAC-ta)
(eltrombopag)
for oral suspension

Read all the Instructions for Use and follow the steps below to mix and give a dose of PROMACTA for oral suspension.

Important:

- **Do not take PROMACTA for oral suspension or give it to someone else until you have been shown how to properly mix and give a dose of PROMACTA for oral suspension.** Your healthcare provider or nurse will show you how to mix and give a dose of PROMACTA for oral suspension properly.
- **PROMACTA for oral suspension must be mixed with cool or cold water only.** Do not use hot water to prepare the oral suspension.
- Give the dose of suspension right away after mixing with water. **If the medicine is not given within 30 minutes, you will have to mix a new dose.** Throw away (discard) the unused mixture into the trash. Do not pour it down the drain.
- If PROMACTA for oral suspension comes in contact with your skin, wash the skin right away with soap and water. Call your healthcare provider if you have a skin reaction or if you have any questions. If you spill any powder or liquid, follow the clean-up instructions in **Step 12**.
- Contact your healthcare provider or pharmacist if you have any questions about how to mix or give PROMACTA to your child, or if you damage or lose any of the supplies in your kit.
- **Do not** re-use the oral dosing syringe. Use a new single-use oral dosing syringe to prepare each dose of PROMACTA for oral suspension.
- After you have used all 30 packets, throw all the remaining supplies (mixing bottle, lid with cap, and oral dosing syringe) away in the trash.

Each PROMACTA for oral suspension kit contains the following supplies:

30 packets of PROMACTA for oral suspension	
1 Reusable mixing bottle with lid and cap	
30 Single-use 20-mL oral dosing syringes (Use a new (single-use) oral dosing syringe to prepare each dose of PROMACTA for oral suspension)	

You will need the following to give a dose of PROMACTA for oral suspension.

From the kit:

- prescribed number of packets
- 1 reusable mixing bottle with lid and cap. **Note:** Due to its small size, the cap may pose a danger of choking to small children.
- 1 single-use 20-mL oral dosing syringe (Use a new (single-use) oral dosing syringe to prepare each dose of PROMACTA for oral suspension)

Not included in the kit:

- 1 clean glass or cup filled with drinking water
- scissors to cut packet
- paper towels or disposable cloth
- disposable gloves (optional)

How do I prepare a dose of PROMACTA for oral suspension?

Step 1. Make sure that the mixing bottle, cap, lid and oral dosing syringe are dry before use. Remove the lid from the mixing bottle.

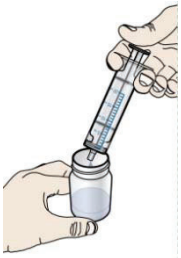
- Prepare a clean, flat work surface.
- Wash and dry your hands before preparing the medicine.

Step 2. Fill the oral dosing syringe with 20 mL of drinking water from the glass or cup.

- Start with the plunger pushed all the way into the syringe.
- Place the tip of the oral dosing syringe all the way into the water and pull back on the plunger to the 20 mL mark on the barrel of the oral dosing syringe.

Note: Use a new (single-use) oral dosing syringe to prepare each dose of PROMACTA for oral suspension.

Step 3. Place the tip of the oral dosing syringe into the open mixing bottle. Empty water into open mixing bottle by slowly pushing the plunger all the way into the oral dosing syringe.



Step 4. Take only the prescribed number of packets for one dose out of the kit. You may need to use more than one packet to prepare the entire dose.

12.5-mg packet

- 12.5-mg dose (1 packet)

25-mg packet

- 12.5-mg dose (1 packet); Note: See Step 9 for instructions on how to give a 12.5-mg dose using a 25-mg packet.
- 25-mg dose (1 packet)
- 50-mg dose (2 packets)
- 75-mg dose (3 packets)

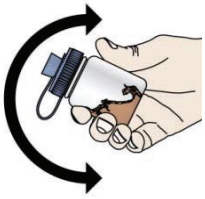
Step 5. Add the prescribed number of packets to the mixing bottle.

- Tap the top of each packet to make sure the contents fall to the bottom.
- Cut off the top of the packet with scissors and empty the entire contents of the packet into the mixing bottle.
- Make sure not to spill the powder outside the mixing bottle.

Step 6. Screw the lid tightly onto the mixing bottle. Make sure the cap is pushed onto the lid.

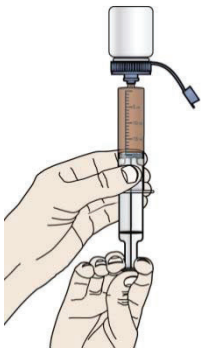
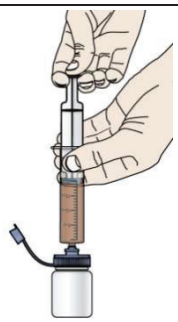
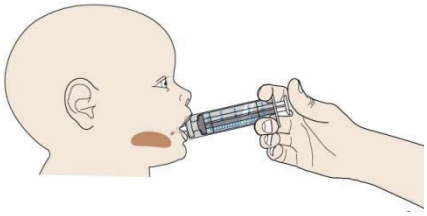
Step 7. Gently and slowly shake the mixing bottle back and forth for at least 20 seconds to mix the water with the powder.

- To prevent the mixture from foaming, do not shake the mixing bottle hard.



How should I give a dose of PROMACTA for oral suspension?

Step 8. Make sure the plunger is pushed all the way into the oral dosing syringe. Pull cap off the mixing bottle lid and insert the tip of the oral dosing syringe into the hole in the lid.

Step 9. Transfer the mixture into the oral dosing syringe. The liquid will be dark brown in color. • Turn the mixing bottle upside down along with the oral dosing syringe. • Pull back the plunger: 12.5-mg packet ○ until all the medicine is in the oral dosing syringe (12.5-mg dose) 25-mg packet ○ to the 10 mL mark on the oral dosing syringe for a **12.5-mg dose only** **OR** ○ until all the medicine is in the oral dosing syringe (25-mg, 50-mg, or 75-mg dose).	
Step 10. Return the mixing bottle to the upright position and remove the oral dosing syringe from the mixing bottle.	
Step 11. Giving a dose of PROMACTA for oral suspension to a child. • Place the tip of the oral dosing syringe into the child's mouth against the inside of the child's cheek. • Slowly push the plunger all the way down to give the entire dose. Make sure the child has time to swallow the medicine.	

How should I clean up?

Step 12. Carefully clean up any spill of the powder or suspension with a damp paper towel or disposable cloth.

- To avoid possibly staining your skin, consider using disposable gloves.
- Throw away (discard) used paper towel or disposable cloth and gloves in the trash.

Step 13. Clean the mixing supplies.

- **Do not reuse any of the mixture remaining in the mixing bottle.**
- Throw away (discard) any mixture remaining in the mixing bottle in the trash. Do not pour down the drain.
- Throw away (discard) the used oral dosing syringe. Use a new (single-use) oral dosing syringe to prepare each dose of PROMACTA for oral suspension.
- Rinse the mixing bottle and lid under running water and air dry. The mixing bottle may become stained from the medicine. This is normal.
- Wash hands with soap and water.

How should I store PROMACTA for oral suspension?

- Store PROMACTA for oral suspension at room temperature between 68°F to 77°F (20°C to 25°C).
- After mixing, PROMACTA should be taken right away but may be stored for no more than 30 minutes between 68°F to 77°F (20°C to 25°C). Throw away (discard) the mixture if not used within 30 minutes.

Keep PROMACTA and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Distributed by:
Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

T2018-11
Revised: November 2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22291Orig1s021

DIVISION DIRECTOR REVIEW

SUMMARY REVIEW OF DIVISION DIRECTOR

Application Number	**NDA 022291 S-021**
Application Type	351(a)
Document Type	Supervisory Associate Division Director Summary Review
From	Albert Deisseroth, MD, PhD
Priority or Standard	Regular
Submit Date	March 29, 2018
Received Date	March 29, 2018
PDUFA Goal Date	November 15, 2018
Division/Office	DHP/OHOP
Review Completion Date	November 14, 2018
Applicant	Novartis
Established Name	Eltrombopag olamine
Trade Name	Promacta
Pharmacologic Class	Thrombopoietin Receptor Agonist
Dosage Forms/Strength	Tablets for oral use at 12.5, 25, 50, 75 and 100 mg.
Recommended Indication	Promacta in combination with standard immunosuppressive therapy for the first line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.
Recommended Regulatory Action	Approval

Resources consulted:

Clinical	Hyon-Zu Lee, PharmD, MD/Kathy Robie Suh, PhD, MD
Biostatistics	Xin Gao, PhD/Yuan Li Shen, PhD
Clinical Pharmacology	Olanrewaju Okusanya, PhD/Ruby Leong, PharmD
CDTL Review	Kathy Robie Suh, PhD, MD
RPM	Kimberly Scott

Division Director's Summary Review of NDA 022291 S-021

(This review was based in part on the reviews of Drs. Hyon-Zu Lee, Kathy Robie Suh, Olanrewaju Okusanya, and Sharita McLamore-Hines)

Background: On March 29, 2018, Novartis submitted NDA 022291 S-021, in which approval was requested for the following new indication: eltrombopag (Promacta) in combination with standard immunosuppressive therapy for the first line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia (SAA). Eltrombopag is already approved for: 1. Thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune idiopathic thrombocytopenia ITP who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy and whose degree of thrombocytopenia and clinical condition increase the risk for bleeding; 2. Thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy; and 3. Patients with SAA who have had an insufficient response to immunosuppressive therapy (IST).

This request was based on study ETB115AUS01T (US01T) which was a single center (NHLBI, NIH) single arm non-randomized Phase I/II trial in which adult and pediatric (≥2 years) patients with SAA who had not received prior definitive IST were assigned to receive the combination of 4 days of horse anti-thymocyte globulin (h-ATG) at 40 mg/kg/day starting on Day 1, + six months of daily oral cyclosporin A (CSA) at a bid dose starting on Day 1 which was adjusted to keep trough levels between 200-400 mcg/L (responders eligible for CSA maintenance therapy from 6-24 months), with one of the three following schedules of eltrombopag (given at a starting dose of 150 mg daily for patients >12 years old, 75 mg daily for patients 6 to 11 years old, and 2.5 mg/kg daily for patients 2 to 5 years old):

Cohort 1: 5.5 months of daily oral eltrombopag starting on Day 14 (N=30 patients);

Cohort 2: 2.5 months of daily oral eltrombopag starting on Day 14 (N=31 patients);

Cohort 3: 6 months of daily oral eltrombopag starting on Day 1 (N=31 patients plus additional patients on an Extension Cohort).

The efficacy analysis focused on Cohort 3 + Extension Cohort because this is the schedule sought.The primary endpoint was investigator assessment of CR and ORR at 6 months defined as follows: ANC>1,000/µL, platelet count>100,000/µL and hemoglobin>10 g/dL

Four published studies (out of a candidate group of 71 publications) were selected as historical controls for the effect of IST without eltrombopag: Scheinberg 2011 (06-H-0034), Scheinberg 2009 (03-H-0193), Tisdale 2000 (97-H-0117) and Rosenfeld 2003 (90-H-0146).

Efficacy Results: Data from Cohort 3 and Extension Cohort from Study US01T were pooled to compare the effect of eltrombopag/h-ATG/CSA on SAA with that of h-ATG/CSA from the four historical control studies, using two different types of analyses:

1. Propensity score matching or inverse probability treatment weighting (IPTW);
2. Analysis using summary-level data from the 4 historical trials for ORR and 3 of the 4 historical control studies for CR.

The results of the statistical reviewer's (Dr. Xin Gao) analysis of the CR and ORR at 6 months in Cohort 3 + Extension Cohort from the US01T trial are presented in Table 1 below. In Table 2 are shown the results of CR and ORR at 6 months of treatment with eltrombopag and h-ATG/CSA (IST) in Cohort 3 + Extension Cohort from the US01T trial compared to IST treatment of SAA without eltrombopag using 4 historical control studies reported by three different authors.

Table 1: Results of CR and ORR at 6 months (Data Cut Off February 2018) from Study US01T

6 Months	Cohort 3 + Extension
Evaluable N	87
CR (95% CI)	43.7% (33,55)
ORR (95% CI)	79.3% (69, 87)

Table 2: Results of US01T Compared 4 Historical Control Studies

Response at 6 months	Scheinberg (06-H-0034) N=60	Scheinberg (03-H-0193) N=42	Tisdale N=16	Rosenfeld N=122	US01T* N=87
CR	20%	11.9%	25.0%	NA	43.7%
ORR	68.3%	61.9%	56.3%	61.5%	79.3%

* Results of CR and ORR at 6 months (Data Cut Off February, 2018)

The CR rate at 6 months in the US01T trial was 43.7% whereas the CR rates for the 4 historical trials for patients with SAA in the Scheinberg, Tisdale and Rosenfeld studies were below that number (20%, 11.9%, 25.0% and NA respectively). The median duration of the CR estimated by the KM method was 24.3 months (23.0, NE). The ORR rate at 6 months in the US01T trial was 79.3% whereas the ORR rates in the Scheinberg (06-H-0034), Scheinberg (03-H-0193), Tisdale and Rosenfeld studies were numerically below that rate (61.9%, 56.3% and 61.5% respectively). The duration of the ORR was also 24.3 months (23.0, NE).

The CR and ORR differences between the US01T and the historical controls at 6 months by IPTW propensity score analysis are presented in Table 3.

Table 3: IPTW Propensity Score Analysis of CR and ORR rates at 6 Months

	Treatment Effect
CR Rate Difference %(95% CI)	27.1 (12.0, 42.2)
ORR Rate difference %(95% CI)	9.9 (-2.1, 21.9)

There were limitations of the comparison of the results of US01T with the historical control studies. The US01T was not contemporaneous with the historical control trials. Only two of the historical trials had patient level data. Small numbers of patients were involved. The Tisdale contained only adults whereas the rest of the trials including US01T contained both pediatric and adult patients. There was heterogeneity with respect to patient ages among the 5 trials.

Despite these limitations, the statistical reviewer (Dr. Xin Gao) concluded in her analysis that: "Even though there are statistical concerns of the adequacy of using historical control data for comparative purposes, the results appear to be supportive. The difference of CR rate at 6 months (see Table 3) appears consistent, suggesting the benefit of adding eltrombopag to h-ATG and CSA."

Safety Results: The safety review was conducted on 153 patients with SAA who were entered on US01T. All of the patients met the criteria for severe aplastic anemia: bone marrow cellularity <30% and at least two of the following: ANC<500/µL, platelet count <20,000/µL and reticulocytes <20,000/µL. The median age of the patients was 30 years of age (3 minimum to 82 maximum).

Three deaths occurred in Cohort 3 + Extension Cohort in the USO1T trial, none of them related to study treatment. In Cohort 3, SAEs occurred in 42% of the patients. The most frequently reported SAEs occurring in ≥5% of patients in Cohort 3 and Extension Study respectively were: serum sickness, febrile neutropenia, rash, infusion related reaction, and lung infection.

In Cohort 3 + Extension Cohort, the most common ≥Grade 3 adverse reactions ≥5% were: ALT increased, febrile neutropenia, serum sickness, lung infection, upper respiratory tract infection and hypertension.

Overall, the safety profile of eltrombopag plus h-ATG/CSA was consistent with the known safety profile of each agent. No new safety signals were observed.

Benefit Risk Discussion: These results indicate that the addition of eltrombopag to h-ATG/CSA IST is associated with an increase in the rates of CRs of patients with SAA to IST (h-ATG with CSA). The statistical reviewer concluded that "The difference of CR rate with historical control at 6 months (see Table 3) appear

consistent, suggesting the benefit of adding eltrombopag to h-ATG and CSA." There are no safety signals seen associated with the addition of eltrombopag to h-ATG/CSA to IST. The benefit risk profile is favorable**.**

Recommended Regulatory Action: This Supervisory Associate Division Director reviewer agrees with the recommendation of the review teams that approval be given to eltrombopag in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALBERT B DEISSEROTH
11/15/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22291Orig1s021

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 13, 2018
From	Kathy M. Robie Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	22-291 S-021
Applicant	Novartis Pharmaceuticals, Inc.
Date of Submission	March 29, 2018
PDUFA Goal Date	December 29, 2018
Proprietary Name / **Established (USAN) names**	Promacta/ Eltrombopag olamine
Dosage forms / Strength	Oral tablets, (25 mg, 50 mg, 75 mg); proposed new 100 mg tablet
Proposed Indication(s)	"PROMACTA is indicated in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia."
Recommended:	Approval for indication: Promacta is indicated in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia."

1. Introduction

Severe aplastic anemia (SAA) is a life-threatening, acquired bone marrow failure disease characterized by tri-lineage marrow hypoplasia and a lack of hematopoietic stem and progenitor cells (HSPC) due to an immune-mediated attack on the bone marrow. Current first-line treatment for SAA includes intensive immunosuppressive therapy (IST) with horse anti-thymocyte globulin and cyclosporine (ATG/CsA), or hematopoietic stem cell transplantation (HSCT), where appropriate and possible. Eltrombopag (Promacta) is an orally available small molecule thrombopoietin receptor (TPO-R) agonist that interacts with the transmembrane domain of the human TPO-receptor and initiates signaling cascades that induce proliferation and differentiation from bone marrow progenitor cells and is currently approved for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy and for other indications as shown below.

In the current supplemental application the sponsor seeks to expand approval of Promacta to first-line treatment of patients SAA who have not received prior immunosuppressive therapy. The proposed indication is: "PROMACTA is indicated in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia."

Eltrombopag has been granted Orphan Product Designation (November 8, 2013) for treatment of aplastic anemia. The sponsor requested and was granted priority review for the current supplemental application; however, the PDUFA action due date was extended due to a major amendment submitted on July 25, 2018.

2. Background

Eltrombopag (Promacta) is an orally available small molecule thrombopoietin receptor (TPO-R) agonist approved for:

- the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy (accelerated approval, 11/20/2008; converted to full approval 2/25/2011), The approved dose is 50 mg once daily (25 mg in patients of East Asian ancestry or with hepatic impairment) and dose is adjusted to maintain platelet count $\geq 50 \times 10^{9}$/L but is not to exceed 75 mg daily.
- the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. The approved dose is 25 mg once daily for all patients and dose is adjusted to achieve platelet count required to initiate antiviral therapy, not to exceed 100mg daily. (11/16/2012).
- the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. (8/26/2014)

Severe aplastic anemia (SAA) is a life-threatening, acquired bone marrow failure disease, often fatal, due to infection or hemorrhage. Currently used treatments include intensive immunosuppressive therapy (IST) with horse anti-thymocyte globulin and cyclosporine (ATG + CsA), or hematopoietic stem cell transplantation (HSCT), where appropriate and possible. Promacta is currently approved (August 2014) for treatment for those patients (approximately half of treated) who either fail initial therapy or relapse after treatment. In the current supplemental application the sponsor seeks to expand approval of Promacta to first-line treatment in combination with standard IST for patients with severe aplastic anemia who have not received prior immunosuppressive therapy. In the primary SAA clinical trial submitted for the first-line indication patients meeting the criteria for SAA who had not received prior immunosuppressive therapy with ATG, alemtuzumab, or high dose cyclophosphamide were studied.

To support this supplemental application the sponsor has submitted a report for an ongoing, single-arm pivotal Study ETB115AUS01T ("Study AUS01T"), a single center, single arm, non-randomized, Phase I/II trial investigating the efficacy and safety of horse antithymocyte globulin (h-ATG) + cyclosporine in combination with eltrombopag as experimental therapy in patients with severe aplastic anemia who have not received prior definitive immunosuppressive therapy. Study AUS01T was sponsored by the National Heart, Lung, and Blood Institute (NHLBI; trial conducted by the National Institutes of Health). The submission also includes data from Study CETB115E1202, an ongoing single-arm study evaluate the efficacy and safety of eltrombopag in combination with rabbit ATG/CsA in Japanese subjects with moderate or more severe aplastic anemia (AA) who had not received prior ATG/ALG-based immunosuppressive therapy and a literature report of single-institution experience for clinical outcomes in adult patients with aplastic anemia treated with various combinatorial ATG-based immunosuppressive therapy regimens.

3. CMC/Device

This supplement did not include any new Chemistry, Manufacturing and Controls (CMC) and there were no proposed changes to the CMC information in the product label. There is no CMC Review for this supplement application.

4. Nonclinical Pharmacology/Toxicology

This supplement did not include any new Pharmacology/Toxicology information and there were no changes proposed in the Nonclinical Toxicology section of the labeling. There is no Nonclinical Pharmacology/Toxicology review for this supplement.

5. Clinical Pharmacology/Biopharmaceutics

Office of Clinical Pharmacology Review (O. Okusanya, 11/2/2018) found the application to be approvable from a clinical pharmacology perspective. The Review summarizes the following for proposed dosing:

(b) (4)

There were no recommendations for post-marketing commitments.

6. Clinical Microbiology

No clinical microbiology information was submitted for this application.

7. Clinical/Statistical- Efficacy

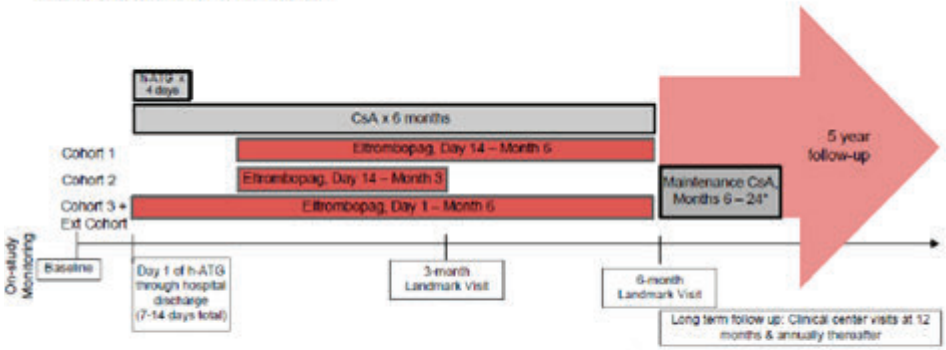
The detailed primary Clinical Review of efficacy for this supplemental application was conducted by Hyon-Zu Lee, PharmD. (Clinical Review, final signature 11/2/2018). The primary Statistical Review and Evaluation was conducted by C. Gao, Ph.D. (final signature 11/1/2018). The primary evidence for efficacy is from Study AUS01T, a single-arm, open-label, single-center, non-randomized, study investigating the standard IST regimen of h-ATG+CsA, in combination with eltrombopag as experimental therapy in patients age ≥ 2 years with SAA who have not received prior definitive IST.

The design of Study AUS01T as described in Dr. Lee's Clinical Review is as follows:

Study AUS01T is a single-arm, single-center, pilot phase 1/2 trial to investigate the combination of eltrombopag and standard regimen of h-ATG/CsA as experimental therapy in patients with SAA who have not received prior definitive immunosuppressive therapy. The protocol was initially designed for enrollment of 95 patients in 3 cohorts, and was amended to add an Extension Cohort to obtain more experience with the recommended regimen (which was determined to be Cohort 3). Patients were to be enrolled sequentially in consecutive cohorts with each cohort informing the design of the subsequent cohort (duration of eltrombopag, addition of maintenance CsA, and concurrent start of administration of all 3 drugs in the study treatment): Cohort 1 (n=31), Cohort 2 (n=33), Cohort 3 (n=31) and Extension Cohort (n=55). The differences between the cohorts are the starting day and duration of eltrombopag and the addition of a low dose of CsA (maintenance dose) for responders. In Cohorts 1 and 2, eltrombopag was to be initiated on day 14 to avoid overlap with the known transient hepatotoxicities associated with ATG and cyclosporine. Cohort 3 was to be initiated with h-ATG, CsA, and eltrombopag on Day 1 if no significant hepatotoxicities were seen in Cohorts 1 and 2.

- Cohort 1: h-ATG on Days 1-4 + CsA from Day 1 to month 6 + eltrombopag from Day 14 to month 6.
- Cohort 2: h-ATG on Days 1-4 + CsA from Day 1 to month 6 + eltrombopag from Day 14 to month 3. For responding patients who do not relapse at month 6, low dose of CsA (maintenance dose) from month 6 to 24.
- Cohort 3 and Extension Cohort: All 3 drugs start concurrently on Day 1: h-ATG on Days 1-4, + CsA and eltrombopag from Day 1 to month 6. For responding patients, low dose of CsA (maintenance dose) from month 6 to 24.

Figure 1 AUS01T: Study Design



*Following an amendment to the protocol (starting with patient 46 in Cohort 2) responders received maintenance CsA up to month 24. In all cohorts, therapeutic doses of CsA could be re-started in patients who had evidence of relapse after month 6. Eltrombopag could be restarted in patients who had evidence of relapse after month 3 in Cohort 2 and after month 6 in all other cohorts.
[Source: AUS01T CSR]

The findings of Study AUS01T supporting efficacy of eltrombopag come primarily from Cohort 3 and Extension Cohort. Study drug dosing in Cohort 3 was: h-ATG 40 mg/kg/day (based on actual body weight) for 4 consecutive days administered intravenously; cyclosporine (CsA) 3 mg/kg/dose orally every 12 hours (total daily dose of 6 mg/kg/day) for subjects ≥ 12 years of age and for subjects < 12 years of age, CsA 6 mg/kg/dose orally every 12 hours (total daily dose of 12 mg/kg/day) for the first 6 months then CsA dose was reduced to maintenance of 2 mg/kg/day for remainder of 24 months study treatment; eltrombopag starting dose 150 mg daily for patients >12 years old, 75 mg daily for patients 6 to 11 years old, and 2.5 mg/kg daily for patients 2 to 5 years old. Eltrombopag dose was reduced by half in patients of Asian ancestry. CsA dose was reduced in obese patients. Eltrombopag was to be discontinued at end of 6-months treatment, but patients who relapsed while in the 5-year followup period could restart eltrombopag and also CsA dose could be increased. All patients had premedication (diphenhydramine, acetaminophen) to minimize infusion reaction prior to h-ATG. See the Clinical Review for details of study drug dosing and management during the study.

The major criteria for enrollment were male or female age ≥ 2 years, weight > 12 kg and having SAA characterized by: (a)Bone marrow cellularity < 30% (excluding lymphocytes) AND, (b)at least 2 of the following laboratory parameters, within 60 days prior to treatment initiation: Absolute neutrophil count (ANC) < 500 /μL, Platelet count < $20x10^3$/μL, and/or Absolute reticulocyte count <$60x10^3$ /μL ("Camitta" criteria). Patients having prior IST with any ATG, alemtuzumab, or high dose cyclophosphamide were excluded. In the study report

for Study AUS01T the sponsor described the enrolled patients as "subjects with SAA who have not received prior definitive immunosuppressive therapy (IST)". Patients with diagnosis of Fanconi's anemia or evidence of a clonal disorder on cytogentics performed within 12 weeks of study entry were excluded. (See the primary Clinical Review of the application for detailed inclusion/exclusion criteria).

The primary objective of the study was to evaluate the safety and activity profile of eltrombopag in combination with h-ATG and CsA in treatment naïve SAA. For assessment of efficacy, response was defined as blood counts no longer meeting the standard ("Camitta") criteria for severe pancytopenia in SAA, equivalent to 2 of the following values obtained on 2 serial blood count measurements at least one week apart at landmark time points (3, and 6 months): Absolute neutrophil count > 500/µL, Platelet count > 20,000/µL, and Reticulocyte count > 60,000/µL. A complete response (CR) was defined as achieving all three of: Absolute neutrophil count >1,000/µL, Platelet count >100,000/µL, and Hgb>10 g/dL. A partial response was defined as blood counts not meeting criteria for severe pancytopenia but not sufficient for a CR. Primary efficacy was assessed as CR at 6-Months. Important secondary objectives included evaluation of relapse over time, evaluation of clonal evolution to PNH, clonal chromosomal population in bone marrow, myelodysplasia by morphology, or acute leukemia; evaluation of overall survival, and evaluation of health-related quality of life (HRQL).

Enrollment in the study as presented in the initial supplement submission is shown in the following table from the Clinical Review:

Table 10 AUS01T: Analysis Population

	Cohort 1 N=31	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62	All Patients N=124
Patients enrolled	31 (100%)	31 (100%)	31 (100%)	62 (100%)	124 (100%)
Full analysis set (FAS)	30 (97%)	31 (100%)	31 (100%)	62 (100%)	123 (99%)
Per-protocol set (PPS)	30 (97%)	30 (97%)	31 (100%)	58 (94%)	118 (95%)
Safety set	30 (97%)	31 (100%)	31 (100%)	62 (100%)	123 (99%)

[Source: ADSL and ADEX.xpt]

The 120-Day Safety Update included significantly more patients in the Cohort 3 + Extension population and provided the basis for the primary efficacy and safety review of the supplemental application. The findings for Cohort 3+Extension are summarized below. See the Clinical Review for detailed analysis and results for Cohorts 1 and 2. The following table from the Clinical Review shows the baseline demographics for Cohort 3+Extension at initial submission cutoff (original) and at 120-Day Safety Update cutoff (updated) for the application.

Table 29 AUS01T: Updated Patient Baseline Demographics (Cohort 3+Extension Cohort, FAS)

Cutoff date	Sept 30, 2016	Feb 28, 2018
	Cohort 3+Ext. N=62	Cohort 3+Ext. N=92
Gender		
Female	31 (50%)	50 (54%)
Male	31 (50%)	42 (46%)
Age		
Median	26.5	28.0
Range	5-82	5-82
<18	18 (29%)	26 (28%)
2-5	1 (2%)	1 (1%)
6-11	7 (11%)	11 (12%)
12-17	10 (16%)	14 (15%)
< 65	52 (84%)	77 (84%)
≥ 65	10 (16%)	15 (16%)
≥ 75	2 (3%)	4 (4%)
Race		
White	39 (63%)	57 (62%)
Black or African American	9 (15%)	16 (17%)
East or South-East Asian	4 (6%)	6 (7%)
Non-East or South-East Asian	1 (2%)	2 (2%)
Other/Unknown	9 (15%)	11 (12%)

[Source: ADSL.xpt]

The pre-study baseline disease characteristics for these populations are summarized in the following table from the Clinical Review.

Table 30 AUS01T: Updated Pre-Study Hematological Parameters and Baseline Disease Information (Cohort 3+Extension Cohort, FAS)

Cutoff date	Sept 30, 2016	Feb 28, 2018
	Cohort 3+Ext. N=62	Cohort 3+Ext. N=92
Pre-study hematological parameters (within 60 days prior to treatment)		
Platelet count (10^3/mcL)		
Median	9.0	8.0
Range	1-40	0-40
Absolute neutrophil count (10^3/mcL)		
Median	0.25	0.27
Range	0-1.93	0-1.93
Absolute reticulocyte count (10^3/mcL)		
Median	23.0	21.0
Range	2-86	2-97.1
Severity of aplastic anemia		
Severe	42 (68%)	51 (55%)
Very severe	20 (32%)	41 (45%)
Cytogenic analysis[a]		
Normal	25 (40%)	41 (45%)
Abnormal[b]	3 (5%)	4 (4%)
Missing/not evaluable	34 (55%)	47 (51%)

a. Normal = either 46XX or 46XY with 20 metaphases; Not evaluable = 46XX or 46XY with less than 20 metaphases or unambiguously stated as not evaluable; Abnormal = anything else; Missing = no result provided.
b. Per applicant: no patients had cytogenetics analysis indicating an acquired disorder. However, abnormal cytogenetics such as constitutional translocation (in all cells) without clinical relevance and, unrelated to disease, germline variations or loss of Y chromosome (common in normal aging men), both which can be observed in healthy normal individuals, and one alteration was in a subject with previously undiagnosed Klinefelter's syndrome, also unrelated to the aplastic anemia were observed in these patients.
[Source: ADSL.xpt]

Median age of patients in the updated Cohort 3+ Extension was 28 years, 56% were females. In the Clinical Review Dr. Lee states, "The pre-study hematological parameters and baseline disease characteristics were similar to the original cutoff date except that at the February 28, 2018 cutoff date, a higher proportion of patients had very severe aplastic anemia (45%) compared at the original cutoff date (32%). All patients including the additional 30 patients who were enrolled by the updated cutoff in the FAS met the prestudy hematological parameters criteria for SAA."

Efficacy results for the primary efficacy endpoint for the original and updated Cohort3+Extension are shown in the following table from the Clinical Review:

Table 31 AUS01T: Updated Primary Endpoint Result: Complete Hematological Response Rate at Month 6 (Cohort 3+Extension Cohort, FAS)

Cutoff date	Sept 30, 2016	Feb 28, 2018
	Cohort 3+Ext. N=62	Cohort 3+Ext. N=92
Patients who reached the 6-month visit or withdrew earlier	46	87
Complete response	24 (52.2%)	38 (43.7%)
95% CI	36.9, 67.1	33.1, 54.7

-CR is calculated as the number of patients who achieved a CR at month 6 landmark, divided by the total number of patients enrolled into that cohort who had reached the 6-month landmark or had withdrew earlier for any reason and including non-evaluable subjects. The 2-sided 95% confidence interval (CI) of the CR rate was computed based on the exact method of Clopper and Pearson.
[Source: ADRS.xpt]

The Clinical Review commented that, "The CR rates by subgroup in Cohort 3+Extention *(sic)* Cohort were also generally lower in the update when compared with the original submission. At the updated February 28, 2018 cutoff, the CR rate in patients with very severe disease was lower (33%) compared to patients with severe disease (52%) as expected and males had a higher CR (49%) than in females (40%). Patients who were 18 to 64 years of age had a higher CR (55%) compared to patients <18 years (28%) and ≥65 years (33%). However, the severity of disease was not balanced by age; among patients who were <18 years, 18-64 years and ≥ 65 years of age, 56%, 34% and 60% of patients, respectively, had very severe aplastic anemia which was reflected in the CR rates. Also, the results of some subgroups should be interpreted with caution due to the small number of patients."

The FDA Statistical Review (C. Gao, 11/1/2018) agreed with the sponsor's analysis that the CR rate at 6 month in Cohort 3+Extension (updated) is 43.7% (95% CI, 33.1%, 54.7%). The Statistical Review performed additional exploratory analyses examining the results of Study AUS01T as compared to historical controls for SAA treatment based on published studies from the literature. Major aspects of the published studies used in the historical control are summarized in the following table from the Statistical Review.

Table 4 Summary of Historical Studies

	Scheinberg 2011 (06-H-0034) N = 60 [1]	Scheinberg 2009 (03-H-0193) N = 42 [1]	Tisdale et al 2000 (97-H-0117) N = 16 [1]	Rosenfeld et al. 2003 (90-H-0146) N = 122 [1]	Study AUS01T Cohort 3 + Extension N = 92
Design	RCT, parallel arms, 60 patients in each treatment arm of h-ATG+CsA and r-ATG+CsA. Median follow up = 28 months	RCT, parallel arms, 42 patients in the h-ATG+CsA arm and 35 patients in the h-ATG+CsA + sirolimus arm.	RCT, parallel arms, 15 patients in cyclophosphamide +CsA arm vs. 16 patients in h-ATG+CsA arm. Median follow up = 21.9 months	Single arm, median follow up – 7.2 years	Non-randomized, 31 patients in each of 3 cohorts and an extension cohort, median follow up = 12 months in cohort 3 + extension
Pediatric or adult population	Pediatric and adult	Pediatric and adult	Adult	Pediatric and adult	Pediatric and adult

Treatment regime	h-ATG (day 1-4) + CsA (day 1 – month 6) vs. r-ATG (day 1-5) + CsA (day 1-month 6)	h-ATG (day 1-4) + CsA (day 1 – month 6) vs. h-ATG (day 1-4) +CsA (day 1 – month 6) + sirolimus (day 1 – month 6)	Cyclophosphamide (day 1-4) + CsA (day 1 – month 6) vs. h-ATG (day 1-4) + CsA (day 1 – month 6)	h-ATG (day 1-4) +CsA (day 1 – month 6)	Cohort 1: h-ATG (day 1-4) + CsA (day 1-m 6) + eltrombopag (day 14-m 6); cohort 2: h-ATG (day 1-4) + CsA (day 1-m 6) + eltrombopag (day 14-m 3); cohort 3 + Extension: h-ATG (day 1-4) + CsA (day 1-m 6) + eltrombopag (day 1-m 6); maintenance CsA for responders from m 6 – m 24
Dose in arm of interest	h-ATG (day 1-4): 40 mg/kg/day; CsA (day1 -month 6) starting dose: age ≥12 years with 6 mg/kg/day, age < 12 years with 12 mg/kg/day	h-ATG (day 1-4): 40 mg/kg/day; CsA (day 1-month 6) starting dose: age ≥12 years with 10 mg/kg/day, age < 12 years with 15 mg/kg/day	h-ATG (day 1-4): 40 mg/kg/day; CsA (day 1-month 6) starting dose: 12 mg/kg/day	h-ATG (day 1-4): 40 mg/kg/day; CsA (day 1-month 6) starting dose: adults with 10 mg/kg/day, children with 15 mg/kg/day	h-ATG (day 1-4): 40 mg/kg/day; CsA (day 1-month 6) starting dose: age ≥12 years with 6 mg/kg/day, age < 12 years with 12 mg/kg/day; eltrombopag (day 1 – month 6) depends on age and ethnicity, maximum 150 mg/day
CR at month 3, n (%) [2]	7 (11.7)	3 (7.1)	2 (12.5)	NA	19 (35.2)
CR at month 6, n (%) [2]	12 (20.0)	5 (11.9)	4 (25.0)	NA	24 (52.2)
OR at month 3, n (%) [2]	37 (61.7)	24 (57.1)	11 (68.8)	73 (59.8)	43 (79.6)
OR at month 6, n (%) [2]	41 (68.3)	26 (61.9)	9 (56.3)	75 (61.5)	39 (84.8)

[1] number of patients in the h-ATG+CsA arm, which were included in the analysis of the review
[2] from the paper
Source: adapted from Table 1-1 in Summary of Clinical Efficacy in first line severe aplastic anemia.

Results of the exploratory analyses are summarized in the following table from the Statistical Review:

Table 2 Reviewer's Analysis Results of CR at 6 Months (Data cut off Feb 2018)

	Study AUS01T	Historical Control
Unadjusted Analysis		
# of patients included the analysis	87	102
CR, n (%)	38 (43.7)	17 (16.7)
CR rate difference (95% CI)	27.0 (14.3, 39.7)	
Propensity Score Matching Analysis		
# of patients included the analysis	68	68
CR rate difference (95% CI)	28.4 (12.99, 43.73)	
IPTW Analysis		
# of patients included the analysis	87	102
CR rate difference (95% CI)	27.1 (12.0, 42.2)	
Fixed Effect Analysis		
# of patients included the analysis	87	102
CR rate difference (95% CI)	27.0 (14.57, 39.33)	

The Statistical Review concluded the following:

Taken in total, the analysis showed that the combination of all three therapies has benefits of the treatment. The exploratory analyses provide some evidence, although possibly biased and weaker than evidence from a randomized controlled trial, that the addition of eltrombopag to the (h-ATG) + cyclosporine provides added benefit compared to (h-ATG) + cyclosporine without eltrombopag.

Duration of response for response at any time and for response at Month 6 was as shown in the following tables from the Clinical Review:

Table 35 AUS01T: Updated Duration of Response in Patients who Responded at Anytime (Cohort 3+Extension Cohort, FAS)

Cutoff date	Sept 30, 2016	Feb 28, 2018
	Cohort 3+Ext. N=62	Cohort 3+Ext. N=92
Complete responders at any time	27 (43.5%)	46 (50.0%)
Relapsed	3 (11.1%)	9 (19.6%)
Median duration of CR in months (95% CI)	9.3 (9.0, 9.3)	24.3 (23.0, NE)
Overall responders at any time	45 (72.6%)	70 (76.1%)
Died	0	0
Relapsed	7 (15.6%)	19 (27.1%)
Median duration of ORR in months (95% CI)	9.3 (9.3, NE)	24.3 (21.4, NE)

[Source: ADRS.xpt and ADTTE.xpt]

Table 36 AUS01T: Updated Duration of Response in Patients who Responded at Month 6 (Cohort 3+Extension Cohort, FAS)

Cutoff date	Sept 30, 2016	Feb 28, 2018
	Cohort 3+Ext. N=46	Cohort 3+Ext. N=87
Complete responders at Month 6	24 (52.2%)	38 (43.7%)
Median duration of CR in months (95% CI)	9.3 (9.0, 9.3)	24.3 (23.0, NE)
Overall responders at Month 6	39 (84.8%)	69 (79.3%)
Median duration of ORR in months (95% CI)	9.3 (9.3, NE)	24.3 (21.4, NE)

"N" is the number of subjects in the treatment group who reached this timepoint or withdrew earlier. It is denominator for percentage (%) calculation.
Overall Response = Complete or Partial Response
[Source: ADRS.xpt and ADTTE.xpt]

Regarding efficacy Dr. Lee concluded in the Clinical Review:

The supplemental new drug application (sNDA) contained primary efficacy data from one phase 1/2, single-arm, sequential cohort trial (AUS01T) that studied eltrombopag in combination with standard IST (horse anti-thymocyte globulin [h-ATG] and cyclosporine [CsA]) in adult and pediatric patients (≥2 years) with SAA as first-line therapy. The efficacy conclusions were based on results from a total of 87 of the 92 patients enrolled in Cohort 3+Extension Cohort in the study who received the recommended dosing regimen of the combination therapy and had undergone Month 6 efficacy evaluation at the time of the clinical cut-off date. Among the 87 patients with a Month 6 efficacy evaluation, a total of 25 patients were pediatric patients (2 to 17 years of age).

The investigator-assessed complete and overall hematologic responses at Month 6 based on the 87 patients were 44% (95% CI: 33%, 55%) and 79% (95% CI: 69%, 87%), respectively, in Cohort 3+Extension Cohort. The responses were durable with estimated median duration of CR of 24.3 months (95% CI: 23.0, NE) and ORR of 24.3 months (95% CI: 21.4, NE) based on the 46 patients who achieved a CR and 70 patients who achieved an ORR at any time in Cohort 3+Extension Cohort.

Although evaluation of results across trials should be conducted with caution, when comparing the AUS01T trial efficacy results with historical control trials that studied h-ATG+CsA therapy in patients with SAA, it appears that the addition of eltrombopag to h-ATG+CsA provides improved efficacy compared to h-ATG+CsA therapy alone.

Therefore, although the primary efficacy evaluation was based on a small number of patients studied in a single-arm trial, considering that SAA is a rare and life-threatening disease with limited treatment options, the AUS01T trial results provides substantial evidence of efficacy of eltrombopag administered in combination with standard IST in adult and pediatric patients (≥2 years) with SAA as first-line therapy.

8. Safety

The detailed primary clinical review of safety for this supplemental application was conducted by Hyon-Zu Lee, PharmD. (Clinical Review, final signature 11/2/2018).

The safety evaluation for the application for first-line treatment of patients with severe aplastic anemia with eltrombopag in combination with standard immunosuppressive therapy (h-ATG and cyclosporine) was based mainly on the 153 patient who received eltrombopag in the AUS01T trial, with particular focus on the Cohort3+Extension Cohort who received the dosing regimen being proposed for labeling, namely, eltrombopag on Day 1 to Month 6 plus h-ATG+ cyclosporine followed by low cyclosporine maintenance dose for 18 additional months in patients who achieved a hematologic response at Month 6.

The Clinical Review summarized the major safety findings from the review as follows:

- A total of 7 patients (Cohort 1: 3 patients, Cohort 2: 1 patient, Cohort 3+Extension Cohort: 3 patients) died in the AUS01T trial. All 7 deaths were assessed as unrelated to study treatment. One patient in Cohort 1 died on-treatment with eltrombopag and CsA, due to toxic metabolic encephalopathy and central respiratory failure attributed to thymoma that existed before the study entry. The other two patients in Cohort 1 died due to HSCT-related cause during follow-up approximately 1 and 2 years after the end of therapy, respectively. The remaining 4 deaths also occurred during follow-up (109-881 days after the last dose of eltrombopag).
- In Cohort 3+Extension Cohort, 50% of patients experienced SAEs which was higher than the incidences in Cohorts 1 (43%), 2 (39%) and 3 (42%). The most frequently reported SAEs (≥5%) in Cohort 3+Extension Cohort were serum sickness, febrile neutropenia, upper respiratory infection and lung infection.
- A higher proportion of patients in Cohort 3+Extension Cohort (64%) experienced ≥ grade 3 AEs compared to Cohort 1 (53%) or Cohort 2 (58%). The most frequently reported ≥ grade 3 AEs (≥5%) in Cohort 3+Extension Cohort were ALT increased, AST increased, blood bilirubin increased, febrile neutropenia, serum sickness, lung infection, upper respiratory tract infection and hypertension.
- The incidence of AEs in Cohort 3+Extension Cohort was 78% and was higher than in Cohort 1 (63%) or Cohort 2 (68%). The differences were mostly due the higher incidences of ALT increased and AST increased. The most frequently reported AEs (≥10%) in Cohort 3+Extension Cohort were ALT increased, AST increased, blood bilirubin increased and febrile neutropenia.
- A total of 15 patients (10%) (Cohort 1: 6 patients, Cohort 2: 2 patients, Cohort 3+Extension Cohort: 7 patients) had clonal evolution. Of the 15 patients with clonal evolution, 9 patients had progressed to MDS or AML. The median time to clonal evolution in Cohort 1 was 60.5 months (95% CI: 48.3, NE) and not evaluable in other cohorts. The incidence of clonal evolution in the historical experience with standard IST (h-ATG + CsA) without eltrombopag as first-line therapy in SAA range from 9.5% to 21%. Therefore, it does not appear that eltrombopag is associated with higher frequency.

- The AUS01T trial enrolled a total of 37 pediatric patients (24%) <18 years of age (Cohort 1: 5 patients, Cohort 2: 6 patients, Cohort 3: 8 patients, Cohort 3+Extension Cohort: 26 patients). In general, the safety profile of pediatric patients was largely consistent with the adult patients except the incidence of febrile neutropenia was higher in pediatrics <18 years (39%) compared with patients ≥18 of age (8%). In addition, SAEs occurred at a higher rate in pediatric patients (69%) compared with adult patients (42%).
- The following toxicities are listed in the current Warnings and Precautions section of the eltrombopag prescribing information: hepatotoxicity, increased risk of death and progression of MDS to AML, thrombotic/thromboembolic complications, and cataracts. No new safety signals were observed in the AUS01T trial.

Reviewer's comment: The primary Clinical Review found and I agree that the safety profile of the eltrombopag plus h-ATG+CsA combination therapy was consistent with the known safety profile of each agent. No new safety signals were observed.

9. Advisory Committee Meeting

There was no Advisory Committee meeting held for this supplemental application.

10. Pediatrics

Eltrombopag has been granted Orphan Drug Designation for treatment of aplastic anemia and therefore, the sponsor is exempt from requirement for pediatric studies of Promacta under Pediatric Research Equity Act (PREA).

Patients age 2 years and older were included in Study AUS01T and the proposed indication proposes to include this pediatric population. As described in the Clinical Review, a total of 37 pediatric patients (24%) 2 to 17 years of age including 26 patients in Cohort 3+Extension Cohort were enrolled and treated in the study. Regarding efficacy, the Clinical Review summarizes that, "For the 25 pediatric patients (2 to 17 years of age) who had a Month 6 efficacy assessment in Cohort 3+Extension Cohort, the complete and overall hematologic response rates were 28% and 68%, respectively." Regarding safety, the Clinical Review summarizes that, "In general, the safety profile of the pediatric patients was largely consistent with that of adult patients except the incidence of febrile neutropenia was higher in pediatric patients <18 years (39%) compared with patients ≥18 of age (8%). In addition, SAEs occurred at a higher rate in pediatric patients (69%) compared with adult patients (42%)."

11. Other Relevant Regulatory Issues

The Division of Clinical Compliance Evaluation, Office of Scientific Investigations (OSI) (A. Orencia, M.D., final signature 7/31/2018) conducted an inspection of the one clinical site for

Study ETB115AUS01T (Study AUS01T) with audit of source documents for 12 enrolled subjects and review of a total of 60 subject records. The inspection found that in general the clinical site appeared to be in compliance with Good Clinical Practice. The final inspectional classification was No Action Indicated and the report stated the study data from the clinical site is considered to be reliable in support of the requested indication.

12. Labeling

Recommendations from the Clinical Review (Hyon-Zu Lee, final signature 11/2/2018) included that the dosing for h-ATG and cyclosporine used in the pivotal study should be included in section 14 Clinical Trials (b) (4) as the sponsor had proposed and that presentation of efficacy results in section 14 Clinical Trials should show the analysis for the primary efficacy endpoint (Complete Response at 6 months) and not (b) (4). The review also recommended revisions for presentation of the pediatric data from the study. gives the following key recommendations for the labeling:

Labeling recommendations for the application were provided by the Office of Prescription Drug Promotion (OPDP)(Memorandum by Robert Nguyen, signed in DARRTS 11/6/2018).

The package insert and Medication Guide changes were discussed and final wording developed at labeling meetings and discussions involving the entire review team.

13. Recommendations/Risk Benefit Assessment

Promacta (eltrombopag) is currently approved for the treatment of patients with severe aplastic anemia (SAA) who have had an insufficient response to immunosuppressive therapy. The sponsor is seeking approval of eltrombopag for use in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with SAA. The data for clinical trial AUS01T from a cohort of 93 patients with SAA who had not previously received definitive immunosuppressive therapy who received treatment in the trial with the proposed regimen of horse anti-thymocyte globulin (ATG) and cyclosporine A (CsA) plus eltrombopag support that the regimen provides benefit for these patients with severe aplastic anemia who have not received standard immunosuppressive therapy. The safety of eltrombopag in the proposed combination treatment for the indication appears acceptable. Overall, the application supports a favorable benefit/risk assessment of the proposed treatment regimen for the indication.

A randomized trial of standard immunosuppressive therapy versus eltrombopag plus standard immunosuppressive therapy may help to better define and quantitate the contribution of eltrombopag to the management of patients with SAA, particularly in terms of long-term outcomes. Nevertheless, the data available at present support approval of eltrombopag as

proposed to provide an additional treatment strategy for management of patients with this severe but uncommon disease.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATHY M ROBIE SUH
11/13/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22291Orig1s021

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number	22291
Priority or Standard	Priority
Submit Date	March 29, 2018
Received Date	March 29, 2018
PDUFA Goal Date	December 28, 2018
Division/Office	DHP/OHOP
Reviewer Name	Hyon-Zu Lee, PharmD
Review Completion Date	October 23, 2018
Established/Proper Name	Eltrombopag
Trade Name	Promacta
Applicant	Novartis Pharmaceuticals Corporation
Dosage Forms	Tablet and oral suspension
Applicant Proposed Dosing Regimens	Eltrombopag to be administered concurrently with standard immunosuppressive therapy for 6 months as follows: For adult & adolescent patients 12 to 17 years: 150 mg orally once daily For pediatric patients 6 to 11 years: 75 mg orally once daily For pediatric patients 2 to 5 years: 2.5 mg/kg orally once daily
Applicant Proposed Indication/Population	Eltrombopag in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	Eltrombopag in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.

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Glossary

AC	advisory committee
ADaM	Analysis Data Model
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COA	clinical outcome assessment
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CsA	cyclosporine A
DILI	drug-induced liver injury
DSMB	data safety monitoring board
ECG	electrocardiogram
eCTD	electronic common technical document
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
GCSF	granulocyte colony stimulating factor
GRMP	good review management practice
GSK	GlaxoSmithKline
h-ATG	horse anti-thymocyte globulin
HCV	Hepatitis C Virus
HSCT	hematopoietic stem cell transplantation
IND	Investigational New Drug Application

ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITP	immune thrombocytopenia
IST	immunosuppressive therapy
ITT	intent to treat
MAH	Marketing Authorization Holder
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NTE	not to exceed
OCS	Office of Computational Science
ORR	overall response rate
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
r-ATG	rabbit anti-thymocyte globulin
REMS	risk evaluation and mitigation strategy
SAA	severe aplastic anemia
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
STDM	Study Data Tabulation Model
TEAE	treatment emergent adverse event
TPO	thrombopoietin
ULN	upper limit normal
WHO	World Health Organization

1. Executive Summary

1.1. Product Introduction

Established name:	Eltrombopag
Trade name:	Promacta®
Applicant:	Novartis
Drug Class:	Thrombopoietin (TPO) receptor agonist
Approved Indications:	Treatment of: -Thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. -Thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. -Patients with severe aplastic anemia (SAA) who have had an insufficient response to immunosuppressive therapy (IST).
Proposed Indication:	Eltrombopag in combination with standard IST for the first-line treatment of adult and pediatric patients 2 years and older with SAA.
Proposed Dosage and Administration:	The initial dose of eltrombopag is as follows and should be initiated concurrently with standard IST. -Adults/adolescents 12-17 years: 150 mg once daily x 6 months -Pediatric patients 6-11 years: 75 mg once daily for 6 months -Pediatric patients 2-5 years: 2.5 mg/kg once daily for 6 months
Drug Product:	Eltrombopag is available in tablets (12.5 mg, 50 mg. 75 mg and 100 mg); and oral suspension (25 mg packet containing powder for reconstitution).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The supplemental new drug application (sNDA) contained primary efficacy data from one phase 1/2, single-arm, sequential cohort trial (AUS01T) that studied eltrombopag in combination with standard IST (horse anti-thymocyte globulin [h-ATG] and cyclosporine [CsA]) in adult and pediatric patients (≥2 years) with SAA as first-line therapy. The efficacy conclusions were based on results from a total of 87 of the 92 patients enrolled in Cohort 3+Extension Cohort in the study who received the recommended dosing regimen of the combination therapy and had undergone Month 6 efficacy evaluation at the time of the clinical cut-off date. Among the 87 patients with a Month 6 efficacy evaluation, a total of 25 patients were pediatric patients (2 to 17 years of age).

The investigator-assessed complete and overall hematologic responses at Month 6 based on the 87 patients were 44% (95% CI: 33%, 55%) and 79% (95% CI: 69%, 87%), respectively, in Cohort 3+Extension Cohort. The responses were durable with estimated median duration of CR of 24.3 months (95% CI: 23.0, NE) and ORR of 24.3 months (95% CI: 21.4, NE) based on the 46 patients who achieved a CR and 70 patients who achieved an ORR at any time in Cohort 3+Extension Cohort.

Although evaluation of results across trials should be conducted with caution, when comparing the AUS01T trial efficacy results with historical control trials that studied h-ATG+CsA therapy in patients with SAA, it appears that the addition of eltrombopag to h-ATG+CsA provides improved efficacy compared to h-ATG+CsA therapy alone.

Therefore, although the primary efficacy evaluation was based on a small number of patients studied in a single-arm trial, considering that SAA is a rare and life-threatening disease with limited treatment options, the AUS01T trial results provides substantial evidence of efficacy of eltrombopag administered in combination with standard IST in adult and pediatric patients (≥2 years) with SAA as first-line therapy.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The benefit-risk assessment supports regular approval of eltrombopag in combination with standard immunosuppressive therapy (IST) for the treatment of adult and pediatric patients 2 years and older with severe aplastic anemia (SAA) as first-line therapy.

The efficacy evaluation of eltrombopag in combination with IST (h-ATG+CsA) for the proposed indication was based on the results of one phase 1/2, single-arm, sequential cohort trial (AUS01T) as described in Section **1.2. Conclusions on the Substantial Evidence of Effectiveness** above.

The safety review was primarily based on a total of 153 patients who participated in the AUS01T trial and more specifically on the 92 patients enrolled in the Cohort 3+Extension Cohort who received the recommended dosing regimen of the combination therapy (eltrombopag from Day 1 to Month 6 plus h-ATG on Days 1-4 plus cyclosporine from Day 1 to Month 6 followed by low cyclosporine maintenance dose for 18 additional months for patients who achieved a hematologic response at Month 6). The median duration of eltrombopag therapy in Cohort 3+Extension Cohort was 183 days (range: 12-204 days) with 70% of patients receiving eltrombopag longer than 24 weeks. In Cohort 3+Extension Cohort, the most frequently reported serious adverse reactions (≥5%) were serum sickness, febrile neutropenia, upper respiratory infection and lung infection and most common ≥ grade 3 adverse reactions (≥5%) were ALT increased, AST increased, blood bilirubin increased, febrile neutropenia serum sickness, lung infection, upper respiratory tract infection and hypertension. Also, the most frequently reported adverse reactions (≥10%) in Cohort 3+Extension Cohort were ALT increased, AST increased, blood bilirubin increased and febrile neutropenia.

A total of 15 patients (10%) had clonal evolution including 7 patients in Cohort 3+Extension Cohort. Of the 15 patients with clonal evolution, 9 patients had progressed to MDS or AML. The median time to clonal evolution in Cohort 1 was 60.5 months (95% CI: 48.3, NE) and not evaluable in other cohorts. The incidence of clonal evolution in the historical experience with standard IST (h-ATG + CsA) without eltrombopag as first-line therapy in SAA ranges from 9.5% to 21%. Therefore, it does not appear that eltrombopag is associated with higher frequency.

The trial enrolled a total of 37 pediatric patients (24%) 2 to 17 years of age including 26 patients in Cohort 3+Extension Cohort. In general, the safety profile of the pediatric patients was largely consistent with that of adult patients except the incidence of febrile neutropenia was higher in pediatric patients <18 years (39%) compared with patients ≥18 of age (8%). In addition, SAEs occurred at a higher rate in pediatric patients (69%) compared with adult patients (42%).

Overall, the safety profile of eltrombopag plus h-ATG+CsA combination therapy was consistent with the known safety profile of each agent. No

new safety signals were observed. The benefit-risk assessment of eltrombopag in combination with standard IST for the treatment of adult and pediatric patients 2 years and older with SAA as first-line therapy is favorable.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Severe aplastic anemia (SAA) is a rare, life-threatening, bone marrow failure disorder characterized by pancytopenia and hypocellular bone marrow. • In the US, approximately 600-900 people are diagnosed with aplastic anemia each year. • With bone marrow transplant and immunosuppressive therapies, the maximum 10-year survival is 80%.	SAA can have a fatal outcome secondary to infection, bleeding or complications.
Current Treatment Options	• Combination therapy with anti-thymocyte globulin and cyclosporine: Up to 33% of patients do not respond and 30%-40% of responders relapse. • Hematopoietic stem cell transplantation (HSCT): More than 70% of patients are not candidates for HSCT. • The addition of other immunosuppressive agents including alemtuzumab do not improve the efficacy. • Supportive therapy	There is a need for more effective treatment for patients with SAA.
Benefit	• Study AUS01T was a phase 1/2, single-arm trial of eltrombopag in combination with standard IST (h-ATG + CsA) in patients with SAA who have not received prior definitive IST. • The eltrombopag plus h-ATG+CsA combination therapy at the recommended dosing regimen had complete and hematologic	Although the comparisons are based on different studies, the addition of eltrombopag to the standard IST (h-ATG+CsA) provides improved complete and hematologic response rates compared to h-ATG+CsA therapy alone in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	response rates of 44% (95% CI: 33%, 55%) and 79% (95% CI: 69%, 87%), respectively, at Month 6. • The estimated median duration of CR and ORR were 24.3 months (95% CI: 23.0, NE) and 24.3 month (95% CI: 21.4, NE), respectively. • When comparing the above response rates with the historical control studies that evaluated h-ATG+CsA, it appears there is improved efficacy.	previously untreated patients with SAA.
Risk and Risk Management	• Promacta (eltrombopag) was initially approved in 2008. The toxicities of eltrombopag listed in the current Warnings and Precautions section of the prescribing information are hepatotoxicity, increased risk of death and progression of myelodysplastic syndromes (MDS) to acute myeloid leukemia (AML), thrombotic/thromboembolic complications, and cataracts. Overall, the safety profile of the eltrombopag plus h-ATG+CsA combination therapy was consistent the known safety profile of each agent. No new safety signals were observed. • Based on the safety profile, there is no need for Risk Evaluation and Mitigation Strategy (REMS).	Overall, the toxicity of eltrombopag administered in combination with h-ATG+CsA is manageable with adequate recommendations for monitoring and treatment modifications in the label.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		Sections 6.1.2 and 6.1.3
		x	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
x	Patient experience data was not submitted as part of this application.			

Also see section 6.1.2 of this review.

2. Therapeutic Context

2.1. Analysis of Condition

Severe aplastic anemia (SAA) is a rare and life-threatening, bone marrow failure disease characterized by tri-lineage marrow hypoplasia and a lack of hematopoietic stem and

progenitor cells. Per the modified Camitta criteria, SAA is defined as hypocellular bone marrow <25% (or 25–50% with <30% residual hematopoietic cells), plus at least 2 of the following: (i) neutrophils <0.5x10^9/L, (ii) platelets <20 x10^9/L (iii) reticulocyte count <20x10^9/L [<60 x10^9/L via automated counter]). With bone marrow transplant and immunosuppressive therapies, aplastic anemia is now considered a chronic disease with 10-year survival rates of up to 80%. In the Western countries, the incidence of aplastic anemia is approximately 2 out of every 1 million people and approximately 600-900 people in the US are diagnosed with aplastic anemia each year. Patients with SAA are treated with either intensive immunosuppressive therapy (IST) or hematopoietic stem cell transplantation (HSCT). Transplantation is potentially curative; however, most patients are not suitable candidates due to advanced age, lack of a histocompatible sibling (or suitable unrelated donor), presence of comorbidities, inaccessibility to transplantation and patients are exposed to graft versus host disease. Patients treated with IST, may have incomplete or no recovery, are exposed to late clonal disorders and may have relapse of the original disease. Patients treated with IST may subsequently receive transplantation. Patients with SAA present with fatigue, weakness and headache attributed to anemia, bleeding or hemorrhage due to thrombocytopenia and infection due to neutropenia. Death can occur secondary to infection, bleeding or complications of severe anemia.

2.2. Analysis of Current Treatment Options

Approved drugs for aplastic anemia include Atgam (lymphocyte immune globulin, anti-thymocyte globulin [equine] sterile solution) and eltrombopag. Atgam is indicated for the treatment of moderate to severe aplastic anemia in patients who are unsuitable for bone marrow transplantation. Eltrombopag was approved in 2014 for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. Currently, the recommended first-line IST for severe aplastic anemia is horse AGT (Atgam) in combination with cyclosporine.

The approval of Atgam was based on three controlled studies. The effectiveness of Atgam therapy in these studies was evaluated by hematological response and survival rates.

In Study 1, patients who were not candidates for bone marrow transplantation were enrolled in a randomized controlled study. The objective was to determine the efficacy of Atgam as a single agent, in restoring hematopoiesis in patients with moderate to severe aplastic anemia. Patients in the Atgam arm were treated for 8 days while patients in the control arm were observed for 3 months. Efficacy was evaluated as sustained improvement in peripheral blood counts within 3 months of study entry. Based on investigator's evaluation, there was a statistically significant ($p<0.01$) improvement in hematologic response rate (Atgam: 52%, control: 0%). Estimated 1-year survival rate was 62% for all 32 patients treated with Atgam.

Study 2 was a randomized, double-blind, placebo-controlled, prospective study to compare the safety and efficacy of Atgam and androgen (oxymetholone; OXY) immunosuppressive therapy

with the combination of Atgam, androgen (OXY) and an infusion of HLA mismatched bone marrow in patients with severe aplastic anemia who were not candidates for bone marrow transplantation. Allocation to treatment group was based on the availability of mismatched bone marrow donors. Eighteen patients received Atgam with concomitant androgens (OXY) for a minimum of 3 months, and 24 patients received an infusion of bone marrow from an HLA-mismatched donor 48 hours after the completion of Atgam treatment. Hematological response rate at 3 months was 44% for the Atgam and androgen group and 43% for the group receiving Atgam, androgen and bone marrow infusion. The group of patients who received mismatched bone marrow infusion had better estimated 1-year survival rate, although the difference between these estimates was not statistically significant (p=0.14); 83% at 12 months for the group receiving bone marrow infusion versus 59% for the Atgam and androgen alone group.

Study 3 was a randomized, placebo-controlled, double-blind study to determine if androgens add to the efficacy of Atgam in providing favorable hematologic response rates in patients with moderate to severe aplastic anemia. All patients were treated with Atgam and were randomized to receive the oral androgen or a matched placebo. A group of historical controls from previous studies who received Atgam without androgens were included for treatment results comparison. The proportions of subjects who presented complete or partial response at 6 months were 42% in the Atgam plus androgen group, 44% in the Atgam plus placebo group, and 51% in the historical controls. The difference in response rates was not significant (p>0.9). Survival at 2 years was also comparable in the two groups for patients with severe aplastic anemia.

The table below summarizes the efficacy results of these studies.

Table 1 Atgam: Efficacy Results in the Aplastic Anemia Studies

Study	ATGAM + comparator or other therapy	No. of Subjects	Response rate % (endpoint)*	P Value	Survival rate % (time point)	P Value (or 95% CI)
10 to 20 mg/kg/day for 8 to 14 days						
Study 1	ATGAM	21	47††/ 52§§ (3 mo)	<0.01††/< 0.01§§	62§ (12 mo)	NA
	Control	20	6††/ 0§§ (3 mo)			
Study 2	ATGAM + Bone marrow infusion	24	43 (3 mo)	Not reported	83 (12 mo)	=0.14
	ATGAM	18	44 (3 mo)		59 (12 mo)	
Study 3	ATGAM + Androgen	26	42 (6 mo)	>0.9	55** (24 mo)	=0.65
	ATGAM + Placebo	27	44 (6 mo)		50** (24 mo)	
	ATGAM historical controls	68	51 (6 mo)	NA	56 (24 mo)	

*Hematologic response was defined differently in different studies.
†† Sponsor's evaluation of response
§§ Investigator's evaluation of response
§ This survival estimate includes the 21 subjects who were randomized to receive ATGAM, plus another 11 subjects who were crossed over from the control group.
**Patients with severe aplastic anemia only.

[Source: Atgam package insert]

Other therapies for SAA include hematopoietic stem cell transplant, rabbit ATG, alemtuzumab, and supportive therapy. Mycophenolate mofetil, sirolimus, corticosteroids and cyclophosphamide are not recommended in the treatment of AA. Corticosteroids are ineffective; it can cause bacterial and fungal colonization and precipitate serious gastrointestinal hemorrhage in the presence of severe thrombocytopenia.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Promacta (eltrombopag) was approved initially under the provisions of the accelerated approval regulations on November 20, 2008 and in 2011 was granted regular approval for the treatment of thrombocytopenia in adult patients with immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. In 2015, the ITP indication was expanded to include pediatric patients ≥1 years of age and an oral suspension dosage form was approved in 2015 (under NDA 207027).

In addition, eltrombopag received the following indications:

- Regular approval (in 2012) for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.
- Regular approval (in 2014) for the treatment of patients with severe aplastic anemia (SAA) who have had an insufficient response to immunosuppressive therapy.

The approval of refractory SAA was based on study ETB115AUS28T (ELT112523) which was a single-arm, open-label trial in 43 patients with SAA who had an insufficient response to at least one prior immunosuppressive therapy.

3.2. Summary of Presubmission/Submission Regulatory Activity

The table below summarizes the relevant regulatory history pertaining to this sNDA.

Table 2 Regulatory History

November 8, 2013	Eltrombopag was granted orphan-drug designation for treatment of aplastic anemia.
August 2, 2016	Pre-sNDA meeting was held. Key clinical and statistical discussions were as follows: -The FDA did not agree that the proposed Study US01T provides adequate data demonstrating a positive risk/benefit and support expansion of the prescribing information to include combination use with standard immunosuppressive therapy for the treatment of patients with SAA as a first-line therapy. The effect of eltrombopag has

	not been isolated. The study does not provide a comparison of the effect of adding eltrombopag to ATG plus Cyclosporine A (CsA). -The FDA stated that Novartis has not addressed the requirement for independent substantiation of the results of this single center trial. -The FDA stated that in addition to the proposed primary efficacy response analysis, of importance will be assessment of the durability of response. In addition, the applicant will need to provide evidence that the addition of eltrombopag contributes to the effect of ATG and CSA. - The proposed safety data may be adequate for submission to support the review of eltrombopag. Safety analyses in the sNDA should distinguish between adverse reactions due to standard therapy and those due to eltrombopag. - The applicant stated that low grade 1 and 2 AE's, and labeled events or reactions were not consistently captured (per NIH protocol) during the study and therefore will not be presented.
April 21, 2017	Type C meeting was held to discuss plans to utilize historical data in the planned sNDA; the adequacy of the total data package to support filing; and proposal for handling data analysis for patients who choose to enroll in another NIH trial once they complete their cyclosporine dosing through 24 months. Key communications were as follows: - The FDA stated that whether it is appropriate to combine the efficacy results from Cohort 3 and Extended Cohort and compare to the historical control data will be a review issue. The applicant clarified that Cohort 3 and Extended Cohort represented the same population. -Regarding to the historical control information, the FDA had the following comments: i) There is inconsistency of the choice of historical control studies between the analysis using summary level data and the analysis using the patient level data. The applicant clarified that for CR, they will generate summary level data for study 06 and the analysis will include data from NIH Study 03-H-0193, NIH Study 97-H-0117, and NIH Study 06-H-0034. For OR, studies NIH Study 03-H-0193, NIH Study 97-H-0117, NIH Study 06-H-0034, and NIH Study 90-H-0146 will be used. The applicant clarified they only have individual level data for studies NIH 03-H-0193 and NIH 06-H-0034. ii) The proposed historical control data for the analyses of CR rates at 6 months are limited (4 studies for analyses using summary level data and 2 studies for analyses using patient level data). iii) The data quality of the historical control data is unclear. Whether the historical control data and the analysis results can be used to support the approval will be a review issue. -Regarding the analysis, the FDA had the following comments:

	i) The analysis plan involving historical control patients should be finalized during the design stage of the studies without the knowledge of efficacy of the treatment group. FDA acknowledged that the proposed analyses would be considered for exploratory purpose including both analyses using summary level data and patient level data. ii) The applicant proposed to determine the propensity score using a logistic model with the binary variable of the treatment versus control as dependent variable and baseline covariates as independent variables. Since the important prognostic variables are not pre-specified and the small sample size in the treatment and the historical control, whether the analysis results from the proposed propensity score analysis are reliable is questionable. -Regarding the durability of response analysis, the applicant explained that they do not have the data (from historical studies) to support comparison of durability of response between Study US01T and the historical controls. The applicant proposed that CR in Study US01T would be a sufficiently strong endpoint for supporting durability of response and they would present durability in that context. The FDA acknowledged this approach but commented that depending on the findings at review, additional data on durability may be needed. - The applicant stated that the sNDA will discuss the safety of h-ATG+CsA +eltrombopag in the context of historical safety data for h-ATG+CsA. The FDA stated that the proposed analysis of safety data from study US01T compared to historical controls is acceptable. -The FDA stated that it appears that the totality of data that will be submitted from study US01T and the historical controls is adequate to support filing of a sNDA. However, the acceptability of the data to support the proposed indication will be a review issue. - The applicant stated that the NIH has recently amended the protocol for Study US01T to include a provision for patients who have completed their maintenance CsA dosing the option to enroll in another ongoing NIH trial (Study 17-H-0019, NCT02979873) where they may receive sirolimus and asked if the FDA agree with Novartis' proposal for handling the analyses for these patients' long-term assessments. The FDA commented that the addition of other IST to the treatment regimen of patients previously enrolled in study US01T may confound the assessment of the long term treatment effect of eltrombopag in these patients. Data obtained prior to the addition of other IST, i.e., sirolimus will be analyzed to evaluate the long term treatment effect of eltrombopag. It is expected that the addition of other IST, i.e., sirolimus, for the long term therapy of SAA will affect

	only cohort 3 (patients previously enrolled in study US01T who subsequently enroll in study 17H-0019 and are then randomized to the sirolimus treatment arm).
January 2, 2018	Eltrombopag received Breakthrough Therapy Designation for the treatment of patients with severe aplastic anemia in combination with standard immunosuppressive therapy.

[Source: FDA compilation]

3.3. Foreign Regulatory Actions and Marketing History

GlaxoSmithKline (GSK) was the original Marketing Authorization Holder (MAH) for eltrombopag until 2015 when Novartis acquired GSK Oncology portfolio in the US. The transfer of MAH from GSK to Novartis is still ongoing or has been completed in the countries where the product is approved (dates and status vary per country). Novartis is currently the MAH in more than 70 countries. Eltrombopag is authorized for marketing in over 90 countries for the treatment of adult chronic idiopathic thrombocytopenia (ITP), over 30 countries for the treatment of pediatric chronic ITP, over 40 countries for the treatment of Hepatitis C Virus (HCV) associated thrombocytopenia, and over 30 countries for the treatment of SAA. Eltrombopag is registered in the following indications:

- Chronic ITP (since March 11, 2010 in EU and November 20, 2008 in US).
- Pediatric chronic ITP (since April 4, 2016 in EU and June 11, 2015 in US).
- Hepatitis C virus associated thrombocytopenia (since September 19, 2013 in EU and November 16, 2012 in US).
- SAA in patients who are refractory to prior immunosuppressive therapy (since August 28, 2015 in EU and August 26, 2014 in the US).

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Study AUS01T is the pivotal trial to support safety and efficacy of eltrombopag for the proposed indication. Study AUS01T was conducted at a single-center (National Heart, Lung, and Blood Institute [NHLBI]); OSI inspection was requested for all patients enrolled at NHLBI.

Table 3 Requested OSI Clinical Site Audit for AUS01T

Protocol ID	Site ID	Number of enrolled patients	Name of the Principal Investigator	Location
AUS01T	1	124	Dr. Neal Young	Warren Grant Magnuson Clinical Center, Building 10 Center Drive, MSC 1202, NIH, Bethesda, Maryland 20892-1202

Source documents for 12 enrolled subjects were reviewed comprehensively. Review included documentation of informed consent, eligibility criteria, electronic medical records, and safety reporting. A total of 60 subject records were reviewed and verified against the case report forms and NDA subject data line listings for the primary efficacy endpoint. Source data for the following laboratory endpoints were verified: ANC, absolute reticulocyte counts, platelet counts, hemoglobin, transfusion dates, and sample dates. Random records were reviewed and verified for reported SAEs and protocol deviations, under-reporting of AEs or protocol deviations There were no limitations during conduct of the clinical site inspection.
In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

OSI's overall assessment of findings and general recommendations were as follows:

"The final inspectional classification of Dr. Young is No Action Indicated."

Therefore, the overall compliance with GCP is acceptable.

For specifics regarding the OSI inspection, refer to the OSI review dated July 31, 2018.

4.2. Product Quality

No new information was provided.

4.3. Clinical Microbiology

This section is not applicable.

4.4. Nonclinical Pharmacology/Toxicology

No new information was provided.

4.5. Clinical Pharmacology

Refer to Clinical Pharmacology review.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The clinical trials that are pertinent to the efficacy and safety review included in this sNDA are summarized in the table below.

Published studies [Tisdale et al (2000)], [Rosenfeld et al (2003)], [Scheinberg et al (2009)], [Scheinberg et al (2011)] were used to determine the historical response rates in patients with SAA treated with h-ATG+CsA.

Table 4 Listing of Clinical Trials Relevant to this sNDA

Trial ID	Trial Design	Regimen/duration	Primary Endpoints	Patients enrolled	No. of Centers and Countries/ Status
Pivotal study to support efficacy and safety					
AUS01T (also known as ETB115AUS01T, 12-H-150, ELT116643	A single-arm, phase 1/2 study investigating the standard IST regimen of h-ATG+CsA, in combination with eltrombopag as experimental therapy in patients of age ≥ 2 years with SAA who have not received prior definitive IST.	Duration of treatment: All cohorts: CsA: twice daily from day 1 to month 6 h-ATG: once daily from day 1 for 4 days Cohort 1: Eltrombopag once daily from day 14 up to month 6 Cohort 2: Eltrombopag once daily from day 14 up to month 3 Cohort 3: Eltrombopag once daily from day 1 up to month 6 Cohort 3+Ext: Eltrombopag once daily from day 1 to month 6 Doses: All patients were treated with eltrombopag with CsA + h-ATG. Starting eltrombopag doses differed by age and ethnicity: -East or South-East Asian 12 to 85 years: 75mg/day 6 to 11 years: 37.5mg/day 2 to 5 years: 1.25mg/kg/day -All other patients 12 to 85 years: 150mg/day 6 to 11 years: 75mg/day 2 to 5 years: 2.5mg/kg/day	CR rate at 6 months	124 patients (123 treated, age: 3-82 years) -Cohort 1: 30 -Cohort 2: 31 -Cohort 3: 31 -Cohort 3+Ext: 62	1 site in US/ ongoing

		h-ATG: 40 mg/kg/day CsA: ≥ 12 years: 3 mg/kg/dose every 12 hours or < 12 years: 6 mg/kg/dose every 12 hours. Adjusted to obtain a goal therapeutic trough level between 200 and 400 mcg/L.			
Other study reports to support efficacy or safety					
ETB115E1201 (200926)	A single-arm, open-label, phase 2 study to assess the efficacy and safety of eltrombopag in moderate or more SAA patients with a platelet count<30,000/mcL who are refractory to anti-thymocyte globulin based immunosuppressive therapy (ATG-based IST), who have relapsed after ATG-based IST, or who are ineligible for ATG-based IST.	Eltrombopag for 26 weeks at 25 mg daily initial dose and adjusted every 2 weeks thereafter (25-100 mg daily) according to the platelet count.	Hematological response	21 patients (age: 19-79 years)	12 sites in Japan/ ongoing
ETB115E1202 (201793)	A single-arm, phase 2 study to evaluate the efficacy and safety of eltrombopag in combination with rabbit ATG/CsA in Japanese patients with moderate or more severe AA who had not received prior ATG-based immunosuppressive therapy.	r-ATG 2.5 to 3.75 mg/kg daily x 5 days. CsA 3 mg/kg twice daily x 26 weeks. Eltrombopag for 24 weeks at 75 mg daily initial dose and adjusted every 2 weeks thereafter (25-75 mg/daily) according to the platelet count or hematologic response criteria.	ORR (safety and efficacy analyses conducted at Weeks 26 and 52)	10 patients (age: 39-67 years)	11 sites in Japan/ ongoing
ETB115AUS28T (ELT112523, 09-H-0154)	A single-arm, phase 2, dose modification study of eltrombopag in patients with	-East or South-East Asian Eltrombopag: Starting dose 25 mg once daily, dose escalation every 2 weeks	Hematological response	43 patients (age: 17-77 years)	1 site in US/ ongoing

	SAA and thrombocytopenia with a baseline platelet count ≤30,000/mcL, following insufficient response to immunosuppressive therapy.	to 75 mg once daily). -All other patients Eltrombopag: Starting dose 50 mg once daily, dose escalation every 2 weeks to 150 mg once daily).			
ETB1115AUS18T (ELT116826, 13-H-0133): no datasets were provided	A single-arm, phase 2, dose modification study of eltrombopag in subjects aged 2 and above with refractory SAA.	Duration: 24 weeks + Responding patients are eligible to enter an extended treatment portion of the trial. Doses: Starting eltrombopag doses differed by age and ethnicity: -East or South-East Asian ≥ 12 years: 75mg/day 6 to 11 years: 37.5mg/day 2 to 5 years: 1.25mg/kg/day -All other patients ≥ 12 years: 150mg/day 6 to 11 years: 75mg/day 2 to 5 years: 2.5mg/kg/day Then decreased depending on platelet count. Extended access: dose of eltrombopag is to be at the lowest dosage that maintains stable platelet counts.	Hematological response	15 patients (age: 12-70 years)	1 site in US/ ongoing
06-H-0034 (Scheinberg et al., 2011): publication and limited efficacy data provided	A randomized trial comparing h-ATG + CsA with r-ATG + CsA in patients with severe aplastic anemia who have not previously received treatment.	Duration: 6 months -h-ATG: 40 mg/kg of body weight daily X 4 days. -Cyclosporine 10 mg/kg/day (15 mg/kg/day for children <12 years of age), given in divided doses every 12 hours for 6 months. -r-ATG: 3.5 mg/kg daily for 5 days	hematologic response	120 patients (age: 2-77 years)	1 site in US/ completed

		-Cyclosporine 10 mg/kg/day (15 mg/kg/day for children < 12 years of age), given in divided doses every 12 hours for 6 months.			
03-H-0193 (Scheinberg et al., 2009): publication and limited efficacy data provided	A prospective single center, 2-arms randomized study comparing h-ATG/CsA/sirolimus to standard h-ATG/CsA to test if addition of sirolimus to standard horse antithymocyte globulin (h-ATG) and cyclosporine (CsA) would improve response rates in treatment naïve SAA patients of age > 2 years, due to its complementary and synergistic properties to cyclosporine A.	Duration: up to 24 months -h-ATG: 40mg/kg/day for 4 days. -Prednisone 1mg/kg daily x 10 days followed by tapering dose x 7 days. -CsA: divided doses every 12 hours for 6 months (for 18 additional months for responders) at 10 mg/kg/day (15 mg/kg/day for children under 12 years old) with dose adjustments to maintain CsA levels between 200-400 ng/mL. -h-ATG: 40 g/kg/day for 4 days. -Prednisone 1mg/kg daily x 10 days followed by tapering dose x7 days. -CsA: divided doses every 12 hours for 6 months at 10 mg/kg/day (15 mg/kg/day for children < 12 years old) with dose adjustments to maintain CsA levels between 200-400 ng/mL. -Sirolimus: for 6 months at 2 mg/day in adults and 1 mg/m^2/day in children (< 40 kg) adjusted to maintain sirolimus levels between 5–15 ng/mL.	Overall response rate	77 patients (age: 4-78 years) 35 patients received h-ATG +CsA+ sirolimus; and 42 received h-ATG + CsA.	1 site in US/ completed
90-H-0146 (Rosenfeld et al., 2003): only publication	A single site, single arm interventional research protocol analyzing long-term outcomes of the use of combined h-ATG and	Duration: 6 months -Equine ATG 40 mg/kg per day x 4 days. -Methylprednisolone 1 mg/d x 2 wks. -Cyclosporine for 6 months: 12 mg/kg	Overall response rate	122 patients 31 patients ≤18 91 patients >18 median age: 35	1 site in US/ completed

provided	CsA in SAA to determine the association between relapse and survival and the rate and significance of evolutionary events.	per day in adults (15 mg/kg/day in children aged 3 to 18 years) and adjusted to maintain serum levels of 200 to 400 ng/mL or for renal toxicity.			
97-H-0117 (Tisdale et al., 2000): only publication provided	A prospective, randomized trial to compare response rates to immunosuppression with either high-dose cyclophosphamide plus cyclosporine or conventional immunosuppression with ATG plus cyclosporine in previously untreated patients.	Duration: 6 months -Cyclophosphamide+cyclosporine: Cyclophosphamide: 1 hour IV of 50 mg/kg once daily for 4 days. Cyclosporine: 12 mg/kg daily with adjustment to maintain concentrations at 200–400 mcg/L for 6 months. -ATG+cyclosporine: ATG: 40 mg/kg daily for 4 days. Prednisone 1mg/kg daily x 10 days followed by tapering dose x 7 days. Cyclosporine: 12 mg/kg daily with adjustment to maintain concentrations at 200–400 mcg/L for 6 months.	Overall response rate	31 patients (age: 18-67 years)	1 site in US/ completed
PA17–0265 (Boddu et al., 2017): only publication provided	Compare outcomes of adult patients with aplastic anemia treated sequentially over the years with various combinatorial antithymoglobulin-based standard IST regimens in the frontline and relapsed setting. Compare to other studies and explored the predictive utility of baseline hematological indices and bone marrow cellularity	Duration: 12 months -A: h-ATG 40 mg/kg/day for 4 days. Cyclosporine 5 mg/kg/day x 12 months. Prednisone for 1 month. B: h-ATG 40 mg/kg/day x 4 days. Cyclosporine 5 mg/kg/day x 12 months. Prednisone for 1 month. GCSF 5 mcg/kg/day for 3 months. C: h-ATG 40 mg/kg/day for 4 days. Cyclosporine 5 mg/kg/day x 12 months. Prednisone for 1 month.	Overall response rate	126 patients (19-88 years)	1 site in US/ completed

	changes on IST response and the dynamics of response	GCSF 5 mcg/kg/day for 3 months. Eltrombopag 50 mg to 150mg PO daily. D: r-ATG 3-5 mg/kg/day x 5 days Cyclosporine 5 mg/kg/day x 12 months. Prednisone for 1 month. E: r-ATG 3-5 mg/kg/day x 5 days. Cyclosporine 5 mg/kg/day x 12 months. Prednisone for 1 month. GCSF 5 mcg/kg/day for 3 months.			

[Source: FDA compilation from Applicant's submission]

5.2. **Review Strategy**

As AUS01T is the pivotal trial to support the efficacy and safety for the proposed indication, the clinical review was primarily based on the AUS01T trial data and included the following:

- Electronic submission of the clinical study reports of other relevant trials and other relevant portions of the sNDA
- Efficacy and safety data were audited or reproduced using ADaM and STDM;
- Regulatory history;
- Applicant's responses to FDA information requests;
- Existing labels;
- Relevant published literature; and
- The 120-day safety update.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. **Study AUS01T**

6.1.1. **Study Design**

Overview and Objective

Trial ID and Title:
AUS01T (also known as ETB115AUS01T, ELT116643, 12-H-0150 or T-H-0242): Eltrombopag added to standard immunosuppression in treatment-naïve severe aplastic anemia.

Study AUS01T is an ongoing investigator initiated trial, sponsored by the Intramural Research Program of the National Heart, Lung, and Blood Institute (NHLBI) and is to evaluate the safety and efficacy of eltrombopag in combination with standard regimen of horse antithymocyte globulin (h-ATG) and cyclosporine (CsA) as first-line therapy in subjects with severe aplastic anemia (SAA).

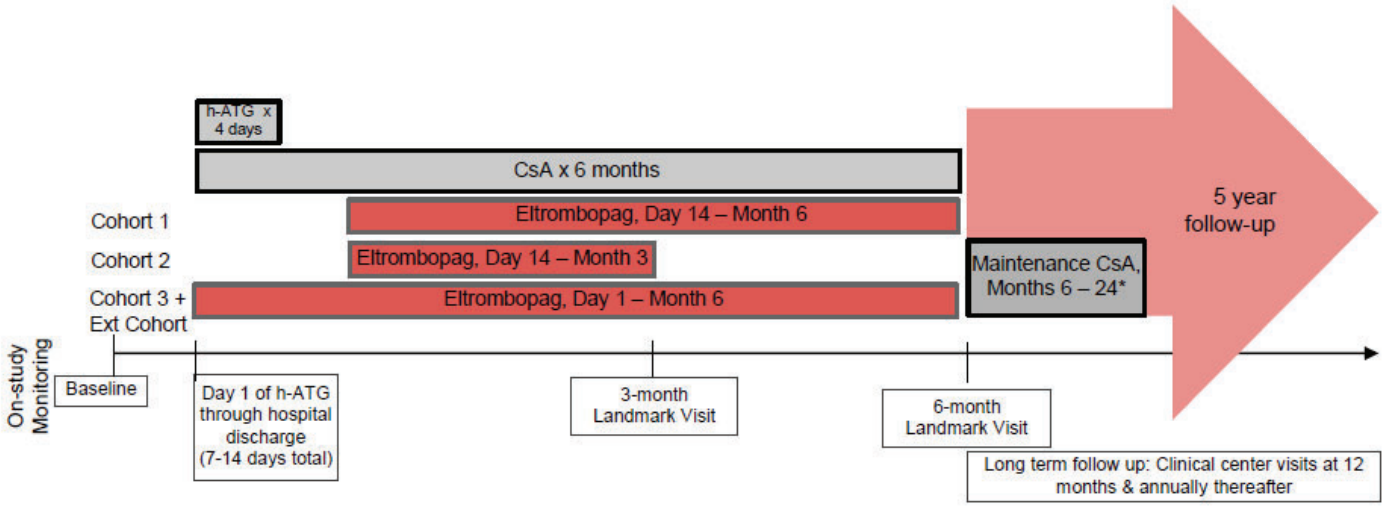
Trial Design

Study AUS01T is a single-arm, single-center, pilot phase 1/2 trial to investigate the combination of eltrombopag and standard regimen of h-ATG/CsA as experimental therapy in patients with SAA who have not received prior definitive immunosuppressive therapy. The protocol was initially designed for enrollment of 95 patients in 3 cohorts, and was amended to add an Extension Cohort to obtain more experience with the recommended regimen (which was determined to be Cohort 3). Patients were to be enrolled sequentially in consecutive cohorts

with each cohort informing the design of the subsequent cohort (duration of eltrombopag, addition of maintenance CsA, and concurrent start of administration of all 3 drugs in the study treatment): Cohort 1 (n=31), Cohort 2 (n=33), Cohort 3 (n=31) and Extension Cohort (n=55). The differences between the cohorts are the starting day and duration of eltrombopag and the addition of a low dose of CsA (maintenance dose) for responders. In Cohorts 1 and 2, eltrombopag was to be initiated on day 14 to avoid overlap with the known transient hepatotoxicities associated with ATG and cyclosporine. Cohort 3 was to be initiated with h-ATG, CsA, and eltrombopag on Day 1 if no significant hepatotoxicities were seen in Cohorts 1 and 2.

- Cohort 1: h-ATG on Days 1-4 + CsA from Day 1 to month 6 + eltrombopag from Day 14 to month 6.
- Cohort 2: h-ATG on Days 1-4 + CsA from Day 1 to month 6 + eltrombopag from Day 14 to month 3. For responding patients who do not relapse at month 6, low dose of CsA (maintenance dose) from month 6 to 24.
- Cohort 3 and Extension Cohort: All 3 drugs start concurrently on Day 1: h-ATG on Days 1-4, + CsA and eltrombopag from Day 1 to month 6. For responding patients, low dose of CsA (maintenance dose) from month 6 to 24.

Figure 1 AUS01T: Study Design



*Following an amendment to the protocol (starting with patient 46 in Cohort 2) responders received maintenance CsA up to month 24. In all cohorts, therapeutic doses of CsA could be re-started in patients who had evidence of relapse after month 6. Eltrombopag could be restarted in patients who had evidence of relapse after month 3 in Cohort 2 and after month 6 in all other cohorts.
[Source: AUS01T CSR]

Eltrombopag:
The eltrombopag starting dose in patients of East Asian and South East Asian ancestry was 50% of that for non-Asian patients to adjust for the higher expected exposure. Eltrombopag was to be administered orally as tablets or oral suspension from sachet of eltrombopag powder and

consistent with the current prescribing information with regard to medication or products containing polyvalent cations such as antacid and calcium-rich foods. The starting dose of eltrombopag by age and ethnicity is shown in the table below.

Table 5 Eltrombopag Dosing by Age and Ethnicity

Age Groups	Daily Dose
Non-Asian	
12-85	150 mg
6-11	75 mg
2-5	2.5 mg/kg
East Asian, South East Asian	
12-85	75 mg
6-11	37.5 mg
2-5	1.25 mg/kg

[Source: Protocol AUS01T]

Horse Anti-thymocyte Globulin (h-ATG):
One course of h-ATG at a dose of 40 mg/kg/day (based on actual body weight) for 4 consecutive days were to be administered intravenously for approximately 4 hours. Infusion times could be extended up to 24 hours to improve tolerance of infusional side effects, if necessary. Serum sickness prophylaxis with oral prednisone at 1 mg/kg/day was to begin prior to the first dose of h-ATG and be continued for 10 days total and then tapered over the subsequent 7-14 days. Patients who develop serum sickness could require a longer tapering schedule and as clinically indicated.

Patients were to receive pre-medication 30 minutes prior to infusion of ATG as follows:

- oral diphenhydramine 1-1.5 mg/kg/dose (NTE 50 mg) orally or intravenously and
- oral acetaminophen 10-15 mg/kg/dose (NTE 650 mg)

Infusion reaction was to be treated symptomatically (e.g., antiemetics, IV fluid hydration, acetaminophen, antihistamines, inhaled bronchodilators, meperidine). In case of moderate or severe reactions hydrocortisone was to be given and the infusion discontinued and restarted at a slower rate once the symptoms have subsided. If a patient had a persistent severe infusion reaction that did not respond to measures to ameliorate the signs/symptoms associated with the infusion, the h-ATG infusion was to be discontinued and patient would go off study.

Cyclosporine (Gengraf, Sandimmune, Neoral):
Day 1 to Month 6 dosing: For subjects ≥ 12 years of age, cyclosporine 3 mg/kg/dose orally every 12 hours (total daily dose of 6 mg/kg/day); and for subjects < 12 years of age, cyclosporine 6 mg/kg/dose orally every 12 hours (total daily dose of 12 mg/kg/day). Dosing was to be based on actual body weight except in obese subjects. For obese subjects (defined as a body mass index > 35 in adult subjects > 20 years of age and > 95th percentile in subjects 12 to 20 years of age),

cyclosporine dosage was to be based on an adjusted body weight that is calculated as the midpoint between the ideal body weight and actual body weight.

In patients who had a therapeutic CsA level established prior to protocol enrollment, the same CsA dose was to be initiated with h-ATG and adjusted accordingly. Cyclosporine dose could be interrupted when clinically indicated. Cyclosporine dosing was to be adjusted to obtain a goal therapeutic trough level between 200 and 400 mcg/L.

Month 6 to Month 24 cyclosporine dosing for patients in Cohorts 2, 3 and Extension: At the 6-month landmark visit, responders were to have CsA maintenance therapy with the dose reduced to 2.0 mg/kg/day administered orally through the 24 month timepoint to improve relapse.

Extended Access to Study Drug:
Responders in Cohorts 1 and 2:
- Eltrombopag administration was to be discontinued at Month 6 for patients in Cohort 1 and at Month 3 for patients in Cohort 2;
- Cyclosporine was to be discontinued at Month 6 for both cohorts.

Patients who relapse in Cohorts 1 and 2:
In Cohort 2, if a patient who received eltrombopag for 3 months had evidence of relapse, eltrombopag and/or cyclosporine could be restarted. Such Cohort 2 patients, who required treatment prior to Month 6, were to be denoted as non-responders at 6 months for statistical purposes. Patients in Cohort 1 or 2 who relapse after the end of 6-month treatment period while in follow-up could have eltrombopag and/or cyclosporine restarted. Patients in Cohort 2 who received the reduced CsA dose (2mg/kg/day) starting after the 6-month landmark visit who relapsed despite the prolonged reduced dose of CsA could have the CsA dose increased to achieve therapeutic levels (trough levels 200-400 mcg/L). Patients could remain on the drugs until the end of the 5-year follow-up period.

Patients who relapse in Cohort 3 and Extension Cohort:
Patients who relapsed after the end of 6-month treatment period while in follow-up could have eltrombopag restarted. In addition, the cyclosporine dose could be increased to achieve a therapeutic level. Patients could remain on the drugs until the end of the 5-year follow-up period.

Supportive care including transfusion support (blood and platelets), hematopoietic growth factors (e.g., G-CSF, GM-CSF, or erythropoietin) and estrogens or combination OCP's were permitted as clinically indicated. Patients were permitted to continue on any of the medications that they were prescribed prior to study enrollment for co-morbid conditions. The administration of romiplostim (N-Plate) or IL-11 (Neumega) was not allowed.

Trial Objectives:

Primary objective was to evaluate the safety and activity of h-ATG/CsA + eltrombopag in treatment naïve SAA.

Secondary objectives were to evaluate the following:

- Hematological response at 3, 6 and 12 months and yearly thereafter.
- Relapse.
- Clonal evolution to paroxysmal nocturnal hemoglobinuria (PNH), clonal chromosomal population in bone marrow, myelodysplasia by morphology, or acute leukemia.
- Overall survival
- Health-related quality of life
- Hematological response of relapsed subjects that re-start treatment
- The effect of a 2 mg/kg/day CsA dose starting Month 6 for 18 months until Month 24 on the rate of relapse of subjects deemed responders at Month 6

Eligibility Criteria:

Key Inclusion Criteria:

1. Severe aplastic anemia characterized by bone marrow cellularity <30% (excluding lymphocytes). If a range is provided instead of the overall bone marrow cellularity the median value of that range was to be used for this inclusion criterion and at least two of the following within 60 days prior to treatment initiation:
    - Absolute neutrophil count (ANC) < 500/ mcL
    - Platelet count < 20,000/ mcL
    - Absolute reticulocyte count <60,000/ mcL
2. Age ≥2 years old
3. Weight > 12 kg

Key Exclusion Criteria:

1. Known diagnosis of Fanconi anemia
2. Evidence of a clonal disorder on cytogenetics performed within 12 weeks of study entry. Patients with severe neutropenia (ANC < 200 /mcL) will not be excluded initially if cytogenetics are not available or pending. If evidence of a clonal disorder consistent with myelodysplasia is later identified, the patient will go off study.
3. Prior immunosuppressive therapy with any ATG, alemtuzumab, or high dose cyclophosphamide
4. SGOT or SGPT > 5 times the upper limit of normal
5. Subjects with known liver cirrhosis in severity that would preclude tolerability of cyclosporine and eltrombopag as evidenced by albumin < 35 g/L
6. Hypersensitivity to eltrombopag or its components
7. Infection not adequately responding to appropriate therapy

8. Moribund status or concurrent hepatic, renal, cardiac, neurologic, pulmonary, infectious, or metabolic disease of such severity that it would preclude the patient's ability to tolerate protocol therapy, or that death within 7-10 days is likely
9. Potential subjects with cancer who are on active chemotherapeutic treatment or who take drugs with hematological effects will not be eligible
10. Current pregnancy, or unwillingness to take oral contraceptives or use a barrier method of birth control or practice abstinence to refrain from pregnancy if of childbearing potential during the course of this study.

Schedule of Events:

Table 6 AUS01T: Schedule of Events

Assessment	Pre-study (Baseline) evaluation	On study monitoring (Day 1 of h-ATG through hospital discharge)	On study monitoring (hospital discharge through 6 months)	Landmark 3-and 6-month monitoring	Long term follow-up (12 months to 5 years)	Extended access for relapse (up to year 5)
Medical history and physical examination	X			X		X
Concurrent medication review	X	X	X	X	X	X
HRQL survey administration[1]	X			X	X	
CBC with differential	X	X (daily)	X (every 1-2 weeks ±3 days)	X	X	X
Reticulocyte count	X	X (weekly ±3 days)		X	X	X
Chemistry panel						
Acute care[2]	X	X	X	X	X	X
Mineral care[3]	X	X	X	X	X	X
Hepatic care[4]	X	X	X	X	X	X
Other[5]	X	X	X	X	X	X
Home lab chemistry panel[6]			X			X
Coagulation and thrombosis screens (PT, PTT, D-dimer)	X					
Thyroid function test	X					
Viral serologies[7]	X					
EBV and CMV PCR	X					
PPD (at risk subjects only based on history)	X					
Folate level	X					
B12 level	X					

Iron panel (ferritin, transferrin, %saturation)	X					
HLA typing (if not available)	X					
Pregnancy test (urine or blood HCG)	X	X[11]		X		X
Bone marrow aspiration and core biopsy[8]	X			X	X	X
Bone marrow chromosomal analysis via standard cytogenetic techniques	X			X	X	X
Telomere length of leukocytes	X					
Flow cytometry of peripheral blood to quantitate GPI-negative cells	X			X	X	
Lymphocyte peripheral blood phenotyping[9]	X			X	X	X
Chest X-ray[10]	X					
ECG	X			X (at month 3 only)		
Vital signs	X	X (daily)				
CsA blood level monitoring		X[12]	X[12]			X
PK sampling				X[13]		

HRQL: Health related Quality of Life; CBC: Complete blood count; DAT: direct antiglobulin test; PT: prothrombin time; PTT: partial thromboplastin time

1. HRQL survey administration (pre-eltrombopag; within 2 days of Day 14 post ATG on Cohorts 1 and 2). Surveys were not required for the Extension Cohort.
2. Acute care included: Na, K, Cl, CO2, creatinine, glucose, and urea nitrogen
3. Mineral care included: phosphorous, magnesium, albumin, and calcium
4. Hepatic care included: alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, and direct bilirubin and was conducted at baseline, every other day from Day 1 through hospital discharge, then every 1-2 weeks (from hospital discharge through Month 6). Subjects will remain hospitalized after completing h-ATG administration until clinically stable (7-14 days total).
5. Other panel included: total protein, creatine kinase, uric acid, and LDH panel
6. Home laboratory chemistry panel including electrolytes, hepatic transaminases, urea nitrogen (BUN), serum creatinine, and total bilirubin
7. Viral serologies for hepatitis A, B, C, HIV, HSV, EBV and CMV
8. Bone marrow aspiration and core biopsy, to be stained for standard morphologic analysis and quantitation of cellularity with hematoxylin and eosin, and special stains to assess reticulin and collagen, primitive stem and progenitor cells via CD34 immunohistochemistry, and other lineage-specific or special stains as indicated to classify any abnormalities
9. Analysis of T, B, and MK subset via flow cytometry
10. Chest X-ray not needed to be performed if a clinically indicated chest CT was performed.
11. Pregnancy test (urine or blood HCG in women of child bearing potential) does not need to be repeated if done within two weeks (Day 0 to Day -14)
12. CsA blood levels were monitored every week (+/- 3 days) for the first month and then every other week (+/- 3 days) for the remainder of the treatment period once levels are stabilized in the therapeutic range of 200-400 ng/ml. CsA dosage was to be adjusted to target this range. More frequent drug serum levels may be obtained as needed to achieve target therapeutic levels and avoid toxicity. CsA monitoring was discontinued at 6 months for

all cohorts
13. Peripheral blood for PK sampling (3-month only in Cohort 1)
[Source: AUS01T CSR]

All patients were followed at the NHLBI at Month 3 and Month 6 visits (the landmark visits). Subsequent follow-up visits at the NHLBI were scheduled at Month 12 and then annually for up to 5 years. The patients were also followed between landmark visits as needed.

Treatment Modification Plan:
The eltrombopag dose could be interrupted when clinically indicated. For subjects in Cohort 2, if eltrombopag dosing is delayed or interrupted for more than 1 week and the interruption is not the result of an SAE related to eltrombopag, then the subject was to receive additional eltrombopag in order to receive a total of 10 weeks as originally planned for Cohort 2. The daily dose of eltrombopag was to be decreased according to the following rules:

Table 7 Eltrombopag Dose Adjustment Plan

Platelet Count	Dose Adjustment or Response
>200,000/mcL (untransfused) at any time on study	Decrease dosage by 25mg every 2 weeks to lowest dosage that maintains platelet count ≥ 50,000/mcL. In children under 12, the dose will be decreased by 12.5 mg.
>400,000/mcL (untransfused) at any time on study	Discontinue eltrombopag for one week, if platelets fall to <200,000/mcL; restart at dosage decreased by 25 mg/day (or 12.5 mg in children under 12).

[Source: Protocol AUS01T]

Review comment: The recommendation to discontinue eltrombopag for one week when the platelet count rises >400,000/mcL (untransfused) at any time on study and to restart eltrombopag if platelets fall to <200,000/mcL is not consistent with the current eltrombopag prescribing information. The current prescribing information recommends reinitiating therapy once the platelet count is <150,000/mcL.

Infection:
For patients who experience an infection requiring intravenous antibiotics, treatment with eltrombopag was not to be discontinued. If the patient experiences infection severe enough to require vasopressors or intubation, the drug was to be withheld until the patient is stable.

Liver function abnormalities:
- Cohorts 1 and 2: In the event of an increase in the ALT level to > 6 x ULN, patients were to have blood tests drawn every 3-4 days. If the ALT remains > 6 x ULN on a second blood test, eltrombopag was to be discontinued until ALT is < 5 x ULN. Eltrombopag was to be restarted at

a dose level 25 mg/day lower than the prior dose. If liver test abnormalities return to an ALT of > 6 x ULN on this reduced dose, the eltrombopag dose was to be reduced by 25 mg/day until there is reduction of ULN to < 5 ULN.

-Cohort 3 and Extension Cohort: Transient hepatotoxicity is an expected and common side effect of h-ATG that occurs during the first 14 days following the start of h-ATG administration. In the event of an increase in the ALT level to > 6 x ULN during Days 1 - 14, eltrombopag was to be held until ALT is < 5 x ULN and then resumed at the same dose. If the ALT rises to > 6 x ULN after resuming eltrombopag (and is not attributable to other factors such as serum sickness, sepsis, or azole antifungal agents) then the ALT was to be monitored at least every 3-4 days. If the ALT remains > 6 x ULN on repeat blood tests, eltrombopag was to be stopped until the ALT is < 5 x ULN. Then eltrombopag was to be restarted at a dose level that is 25 mg/day lower than the prior dose. If liver test abnormalities returned to an ALT of > 6 x ULN on this reduced dose, the eltrombopag dose was to be reduced by 25 mg/day until there is reduction of ULN to < 5 ULN.

Review comment: The recommendation to continue treatment with eltrombopag if the ALT rises to > 6 x ULN after resuming eltrombopag (and is not attributable to other factors such as serum sickness, sepsis, or azole antifungal agents) is not adequate. Treatment with eltrombopag should be held if the ALT rises to > 6 x ULN regardless whether it is due to other factors such as serum sickness, sepsis, or azole antifungal agents.

Thrombosis/Embolism:
Patients who experience a deep venous thrombosis (other than a line-related upper extremity thrombosis) or a pulmonary embolus, a TIA or stroke, or a myocardial infarction at any time while on eltrombopag were to discontinue eltrombopag but remain on CsA and hATG. Patients with platelet counts of > 50,000/mcL at the time of thrombosis were to be treated with enoxaparin or another appropriate anticoagulant as clinically indicated until the platelet count drops below 20,000/mcL or complete a standard 3-6 month course of anticoagulation.

Review comment: According to the enoxaparin prescribing information, enoxaparin should be discontinued if the platelet count falls below 100,000/mcL. Currently, there is no adequate guideline for treating patients with SAA who experience a thromboembolic event. It is not clear whether the above recommendation "to treat patients with platelet counts of > 50,000/mcL at the time of thrombosis with enoxaparin (or another anticoagulant) until the platelet count drops below 20,000/mcL" is optimal for patients with SAA.

Off-Study Criteria:
Study drug administration was to be discontinued with any of the following events:

- Intolerance of eltrombopag not resolved by dose reduction
- Thrombosis/embolism (DVT, PE, stroke or TIA, myocardial infarction) other than central line thrombosis.

- Persistent hepatotoxicity
- Infusion-related h-ATG reactions refractory to all appropriate supportive measures
- Life threatening acute hypersensitivity reactions
- Pregnancy or unwillingness to refrain from pregnancy
- Initiation of additional immunosuppressive therapy other than steroids or cyclosporine (if beyond 6 months then mycophenolate mofetil could be administered in patients who could not tolerate cyclosporine and who required immunosuppression)
- Evidence of a clonal disorder identified in patients with severe baseline neutropenia (ANC < 200 /mcL) who were not initially excluded because cytogenetics was not available or pending.

Study Endpoints

The primary efficacy endpoint was investigator-assessed complete response (CR) rate at 6 months. CR was defined as meeting all the following 3 criteria on 2 consecutive serial blood count measurements at least one week apart at landmark time points (3 and 6 months):

- Absolute neutrophil count >1,000/mcL
- Platelet count >100,000/mcL
- Hgb >10 g/dL

Secondary endpoints included the following:

a. Hematological response based on investigator assessment:
   - CR rates at 3 months, 12 months and yearly thereafter up to 5 years
   - Overall response rate (ORR, CR or PR) at 3, 6 and 12 months and yearly thereafter
b. Relapse defined as the observation of a decline in blood counts not explained by another clinical process (e.g., acute infection) that is either (i) a substantial decline in one or more blood counts, or (ii) a progressive decline in one or more blood counts on at least two consecutive blood draws.
c. Time to clonal evolution to PNH, clonal chromosomal population in bone marrow, myelodysplasia by morphology, or acute leukemia;
d. Overall survival;
e. Health-related quality of life;
f. Hematological response of relapse subjects that re-start treatment; and
g. Affects of a 2.0 mg/kg/day CsA dose starting Month 6 for 18 months until Month 24 on the rate of relapse of subjects deemed responders at month 6.

For the Month 3 and Month 6 assessments, the criteria for CR and PR were to be met on two consecutive serial blood count measurements at least one week apart. For yearly assessments thereafter only one blood count measurement was required.

Response was defined as blood counts no longer meeting the standard ("Camitta") criteria for

severe pancytopenia in SAA, equivalent to at least 2 of the 3 criteria obtained on 2 consecutive serial blood measurements at least one week apart at landmark time points (3 and 6 months):

- Absolute neutrophil count > 500/mcL
- Platelet count > $20x10^3$/mcL
- Reticulocyte count > $60x10^3$/mcL

A partial response was defined as blood counts that do not meet criteria for severe pancytopenia but are not sufficient for a CR.

The presence of evolution to PNH was to be defined by flow cytometric detection of > 1% glucose phosphate isomerase (GPI)-deficient neutrophils at baseline and landmark time points through 5 years. Evolution to myelodysplasia and/or acute leukemia was assessed at landmark time points, or as clinically indicated between landmarks by peripheral blood and bone marrow and diagnosis and classification according to the WHO criteria. Evolution to clonal hematopoiesis was to be defined by detection of new bone marrow cytogenetic abnormalities at landmark time points.

Improvement in blood counts following administration of therapies such as growth factors or transfusions (including re-introduction of eltrombopag after Month 3 for subjects in Cohort 2) were not considered as fulfilling the criteria for response. The exclusion period of these therapies was follows:

- Platelet transfusions: 7 days preceding the assessment of platelet count
- Packed RBC transfusions: 14 days preceding the assessment of hemoglobin
- Growth factors: 21 days preceding the assessment of response

The response was also derived programmatically using laboratory results.

Patients who drop out, who have failed to respond and opt for alternative therapy (e.g. bone marrow transplant), or who require eltrombopag to be restarted (Cohort 2 only) before the 6-month evaluation were to be counted as non-responders.

Statistical Analysis Plan

Based on experience with h-ATG/CsA, the CR probability at 6 months for previously untreated patients was set at 10%-12%. The sample size was determined by testing the null hypothesis using the Simon two-stage design: H_0: p≤10%, versus the alternative, H_1: p ≥30%, at 0.05 significance level and 0.865 for power. The p was set as the CR probability at 6 months.

Table 8 AUS01T: Statistical Design

	Sample size (n)	Eltrombopag	Primary efficacy endpoint	Statistical design
Cohort 1	31	Day 14 - 6 months	CR rate at 6 months	Simon Two-Stage
Cohort 2	33	Day 14 – 3 months	CR rate at 6 months	Simon Two-Stage
Cohort 3	31	Day 1 – 6 months	CR rate at 6 months	Simon Two-Stage

[Source: Protocol AUS01T]

The protocol added an Extension Cohort of 55 subjects to allow subjects to be enrolled and treated while a new SAA treatment naïve protocol is developed and approved. Data from subjects enrolled into the Extension Cohort were not to be used for the primary analysis of Cohort 3.

For each of Cohort 1, Cohort 2 and Cohort 3, an interim analysis was conducted at the end of the first stage once 24 subjects had reached the month 6 landmark visit and, if 3 or more CRs were observed, 7 additional subjects were to be enrolled.

Hematological responses at Month 3, Month 6, Month 12 and yearly thereafter:
For the analysis of ORR and CR, subjects who were still ongoing but had not reached the considered timepoint yet were not included in the analysis of response at that timepoint. However, subjects with a missing or 'Non-evaluable' response for other reasons were treated as non-responders at that timepoint in the calculation of the OR and CR rate. Therefore, for each cohort, the rate of CR was calculated as the number of subjects who achieved a CR at Month 6 landmark, divided by the total number of subjects enrolled into that cohort who had reached the 6-month landmark or had withdrawn earlier for any reason and including non-evaluable subjects.

Effect of CsA maintenance dose on the rate of relapse of patients deemed responders at Month 6: Patients who were not complete or partial responders at the Month 6 evaluation were not included in this analysis. Complete and partial responders at the Month 6 evaluation who did not relapse at the data cut-off date were censored at the date of the last assessment of response with a known outcome.

Results for each cohort were to be compared separately to the historical data from patients treated at the NIH with immunosuppression from prior NHLBI studies:

- h-ATG/CsA protocol (90-H-0146);
- h-ATG/CsA vs. Cytoxan/CsA protocol (97-H-0117);
- h-ATG/CsA/MMF protocol (00-H-0032);
- h-ATG/CsA/Rapamune protocol (03-H-0193);
- r-ATG vs. alemtuzumab protocol (03-H-0249); and
- h-ATG/CsA vs. r-ATG/CsA protocol (06-H-0034).

However, trial results for studies 00-H-0032 and 03-H-0249 were not provided in this sNDA.

The primary analysis was conducted when all patients in the considered cohort reached the 6-month landmark. The null hypothesis H_0: p(CR) ≤ 10% was to be rejected if at least 7 CRs were observed within 6-month. The NHLBI DSMB reviewed the protocol at 6 to 12 month intervals and recommended early termination of the study for considerations of safety and efficacy. The study was not controlled. However, hematological responses and clonal evolution were to be checked against historical data available in patients with SAA.

Analysis Populations:

1. Full analysis set (FAS): All subjects who received at least one dose of study drug eltrombopag.
2. Per Protocol set (PPS): Subset of subjects in the FAS without any major protocol deviation and who have completed a minimum exposure requirement. Reasons for excluding a subject from the PPS were:
   -Any of the criteria defining SAA not met at study entry:
   - Bone marrow cellularity < 30% (excluding lymphocytes)
   - At least two of the following:
     - Absolute neutrophil count < 500/mcL
     - Platelet count < $20x10^3$/mcL
     - Absolute reticulocyte count < $60x10^3$/mcL

   -Use of prior IST with any ATG, alemtuzumab, or high dose cyclophosphamide
   -Minimum exposure requirement, as defined below, not met:
   - 4 days exposure to h-ATG
   - Half of the required exposure to CsA and eltrombopag between Day 1 and Day 91 inclusive (i.e. until the first efficacy assessment) as defined below:
     - for CsA: exposure of 45 days or more
     - for eltrombopag: exposure of 39 days or more for patients enrolled in Cohorts 1 and 2 (i.e. half of the 78 days between Days 14 and 91); exposure of 45 days or more for subjects enrolled in Cohort 3 and Extension Cohort.

   However, if a subject discontinued any drug for safety reason (death, AE) or physician decision, or discontinued eltrombopag for clonal evolution or high platelet count (platelet count > $200x10^3$/mcL or platelet count > $400x10^3$/mcL) before the minimum exposure requirement could be met, that subject was still included in the PPS.
3. Safety set: All subjects who received at least one dose of study drug eltrombopag.

Protocol Amendments

The clinical trial landmarks and protocol amendments are summarized below.

Table 9 AUS01T: Key Landmarks and Key Protocol Amendments

Date	Landmarks
May 1, 2012	Original protocol
November 20, 2012	Amendment B (2): - Increased the accrual to 31 subjects from 25 subjects for Cohort 1 to increase the likelihood to have at least 25 evaluable subjects at the 6-month time point for analysis of secondary endpoints while maintaining the statistical power for the primary endpoint of the study. - Allowed determination of eligibility testing on any another active Hematology branch protocol. - Clarified dosing for children whose dose is based on body weight. - Added that standard of care tests will be done as needed and may include the tests required for on study monitoring.
January 4, 2013	Amendment C (3): -Removed the exclusion criteria for subjects with a PNH clone size in granulocytes of > 50% by flow cytometric analysis.
February 5, 2013	Amendment D (4): - Allowed for deviation from a goal therapeutic cyclosporine (CsA) trough level between 200-400 mcg/L for subjects when medically indicated.
April 29, 2013	Amendment E (5): -Allowed subjects to remain on study if they initiate cyclosporine therapy in order to keep subjects on study longer to assess late events.
October 29, 2013	Amendment H (8): -Added a second cohort of 31 subjects (Cohort 2), receiving same treatment as Cohort 1 except that they would receive a reduction in exposure to eltrombopag from 6 to 3 months. The primary and secondary endpoints, objectives, eligibility, statistics, including sample size and stopping rules, monitoring and ancillary studies remained unchanged. Cohort 2 was to have the same statistical design as Cohort 1 and, like Cohort 1, response data were to be compared against that of the historical controls. In Cohort 2, if a subject who received eltrombopag for 3 months has evidence of relapse, eltrombopag was to be restarted until the end of the 6-month treatment period. Such subjects, who required treatment, were to be denoted as non-responders at 6 months for statistical purposes.
February 18, 2014	Amendment J (10): -Clarified that subjects with a known diagnosis of Fanconi anemia will be ineligible. -Clarified that h-ATG and prednisone doses will be calculated based on actual weight. -Amended the protocol to allow subjects that relapse after end of the

	treatment period may have eltrombopag and/or cyclosporine re-started. -Revised the stopping rules to remove evolution to clonal hematopoiesis. -Added secondary endpoint for relapse subjects who re-start treatment.
June 24, 2014	Amendment L (12): -An EKG evaluation was added at month 3.
September 19, 2014	Amendment O (15): -Revised that Cohort 2 will continue CsA administration month 6 to month 24 at 2.0 mg/kg. Based on the data as of September 17, 2014 where a trend towards a higher than expected number of relapses after the 6-month landmark visit were observed and salvaged by resuming cyclosporine, the protocol was amended to prolong administration of cyclosporine beyond 6 months. -Cohort 2 subjects who relapse can have CsA dose increased to achieve therapeutic levels after month 6.
October 24, 2014	Amendment P (16): -Increased Cohort 2 sample size to 33 subjects.
November 4, 2014	Amendment Q (17): -Added a third cohort of 31 subjects with a modified administration schedule to further evaluate the addition of eltrombopag to h-ATG and CsA for treatment naïve SAA. -Modified "Dose Delays, Modifications or Discontinuation of Eltrombopag" for liver function abnormalities. -Subjects will be excluded for liver cirrhosis if albumin is <35g/L. -Clarified that if the bone marrow cellularity reported by pathology is a range, then median value will be used for eligibility determination. -Revised SGOT or SGPT exclusion criteria to great than 5 x ULN.
November 3, 2015	Amendment V (22): -Added an Extension Cohort.
March 1, 2016	Amendment W (23): -The off-study criterion for the initiation of additional immunosuppressive therapy was revised to allow subjects to remain on study during the follow-up period (after 6 months) in the event that during a relapse, they are unable to tolerate cyclosporine and require additional standard of care oral immunosuppression, specifically mycophenolate mofetil.
August 2, 2016	Amendment X (24): -Increased subject accrual from 121 to 150 subjects.
September 30, 2016	Clinical data cutoff

[Source: FDA compilation from sNDA submission]

Applicant's rationale for additional cohorts:

- Addition of Cohort 2: Rapid hematologic improvements were observed in Cohort 1 that were better than the historical data. In Cohort 1, patients were receiving eltrombopag for 6 months, however as their blood counts had improved by month 3, it was proposed to include Cohort 2 with a reduction in eltrombopag duration of administration from month 6 to month 3. Later, a low daily dose of CsA (maintenance dose) was also added after month 6 to prevent relapses.
- Addition of Cohort 3: In Cohort 1 and 2, eltrombopag was administered from Day 14 only to prevent potential overlapping hepatotoxicity from the combination of all 3 drugs (i.e., eltrombopag with CsA and h-ATG). However, available data from Cohorts 1 and 2 indicated that the combination of CsA and eltrombopag was safe and well-tolerated. Therefore, to potentially accelerate the hematologic recovery, it was proposed to add Cohort 3 where eltrombopag was also started on Day 1. Additionally, in Cohort 2 eltrombopag was initially discontinued at the month 3, however early relapses were noted in this cohort. Therefore, for Cohort 3 it was decided to prolong eltrombopag up to the month 6. The maintenance dose of CsA after month 6 that was introduced for responders in Cohort 2 was also used for responders in Cohort 3.
- Addition of Extension Cohort: it was proposed to add this cohort to recruit more patients with the same dosing regimen as Cohort 3, and collect more data for the analysis of the secondary endpoints within the target regimen.

At the 6-month landmark visit, responders were to have the CsA dose reduced to 2 mg/kg/day administered orally at a fixed dose through the 24 month timepoint. Previous anecdotal experience suggested that a gradual taper of CsA may avoid relapse, but when the applicant adopted this strategy prospectively in the clinical trials (03-H-0193 and 06-H-0034) the rate of relapse was unchanged (Scheinberg, Rios, et al. AJH 2014). However, time to relapse was delayed by 1 year with the longer course of CsA and could be dose-dependent. The CsA dose at the time of relapse during the taper phase was at a median of 1.32 (range: 0.52-4.18) mg/kg/day and a mean of 1.8 mg/kg/day. This suggested that a CsA dose level above these levels might preclude relapse and improve tolerability of chronic maintenance. For remaining patients due for the 6 month timepoint on Cohort 2 the applicant prolonged the administration of cyclosporine beyond 6 months. CsA administration was to be continued from Day 1 to 6 months, but from 6 months to 2 years CsA at a lower fixed daily dose (2 mg/kg/day) to improve relapse, a secondary endpoint, among responders in the study.

6.1.2. **Study Results**

Compliance with Good Clinical Practices

The AUS01T trial was conducted in compliance with Good Clinical Practice (GCP) and according to the ethical principles of the Declaration of Helsinki. The study protocol and all amendments were reviewed by the NHLBI Institutional Review Board (IRB) and NHLBI Data Safety and

Monitoring Board (DSMB). Informed consent was obtained from each subject prior to commencement of the treatment.

Financial Disclosure

The applicant provided FDA financial certification form 3454 signed by Jo Ann Horowitz, MD, the Global Program Clinical Head of Novartis Pharmaceuticals Corporation and dated March 12, 2018. The applicant certified to the following statement:

"As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

The pivotal trial (AUS01T) is an investigator initiated trial initiated on July 2, 2012 in the US at a single study center under NHLBI sponsorship, through a Cooperative Research and Development Agreement (CRADA) with GlaxoSmithKline (GSK). Novartis states that the acquisition of the GSK Oncology portfolio was completed in March 2015. Financial arrangements between Novartis and investigators are reported from March 2, 2015 until the data cutoff date of September 30, 2016. GSK did not independently document financial interests as the study was considered out of scope per GSK SOP. Financial arrangements of all investigators participating in the study were documented by NIH ethics office clearance approvals, both from the start of the trial and annually thereafter, and are available on file at the NIH.

A total of one principal and 16 sub-investigators were reported as having participated in the AUS01T trial.

In the pivotal and supportive studies, the applicant reports that no clinical investigators are full or part-time employees of GlaxoSmithKline or Novartis Pharmaceuticals Corporation. No investigators participating in any study supporting this sNDA disclosed financial arrangements that met the criteria defined in CFR 21 Part 54.2(a).

Patient Disposition

AUS01T:
At the time of the clinical cutoff, a total of 124 patients (31 patients each in Cohorts 1, 2, 3, and Extension Cohort) were enrolled in the AUS01T trial. One patient (ID: (b) (6) enrolled in Cohort 1 did not received treatment with eltrombopag after enrollment due to disease misdiagnosis.

This patient was discontinued and was excluded from all analysis.

The full analysis set (FAS) and safety set included all patients (n=123) who received at least one dose of eltrombopag. The per-protocol set (PPS) was comprised of patients from FAS who did not have major protocol violation and completed the minimum exposure requirement.

A total of 5 patients (Cohort 2: 1 patient [ID (b) (6)], Extension Cohort: 4 patients [IDs: (b) (6) (b) (6)) did not have sufficient exposure to study treatment and were excluded from PPS:

- Subject (b) (6) (Cohort 2): Received only 2 days of h-ATG (insufficient exposure to h-ATG)
- Subject (b) (6) (Extension Cohort): Received only 32 days of CsA and eltrombopag
- Subject (Extension Cohort): Received only 23 days of CsA and eltrombopag
- Subject (Extension Cohort): Received only 15 days of CsA and eltrombopag
- Subject (Extension Cohort): Received only 3 days of CsA, eltrombopag and h-ATG

The table below summarizes the analysis population of the AUS01T trial. Cohort 3 and the Extension Cohort have the same study treatment regimen and therefore, the results of Extension Cohort and Cohort 3 are pooled throughout the review.

Table 10 AUS01T: Analysis Population

	Cohort 1 N=31	**Cohort 2 N=31**	**Cohort 3 N=31**	**Cohort 3+Ext. N=62**	**All Patients N=124**
Patients enrolled	31 (100%)	31 (100%)	31 (100%)	62 (100%)	124 (100%)
Full analysis set (FAS)	30 (97%)	31 (100%)	31 (100%)	62 (100%)	123 (99%)
Per-protocol set (PPS)	30 (97%)	30 (97%)	31 (100%)	58 (94%)	118 (95%)
Safety set	30 (97%)	31 (100%)	31 (100%)	62 (100%)	123 (99%)

[Source: ADSL and ADEX.xpt]

The median follow-up duration for all enrolled patients was 22.2 months (range. 0.1-51.0) in the AUS01T trial. The median follow-up was the longest in Cohort 1 (44.0 months) and shortest in Cohort 3+Extension Cohort (10.5 months). The table below summarizes the study follow-up duration for all cohorts.

Table 11 AUS01T: Follow-up Duration (From the Date of First Treatment to Cutoff Date)

Study follow-up (months)	**Cohort 1 N=31**	**Cohort 2 N=31**	**Cohort 3 N=31**	**Cohort 3+Ext. N=62**	**All Patients N=124**
Median	44.0	30.3	16.4	10.5	22.2
Range	35.2-51.0	22.4-33.9	10.6-22.0	0.1-22.0	0.1-51.0

[Source: AUS01T CSR]

At the time of data cutoff on September 30, 2016, patients in all cohorts had completed

treatment except 15 patients in the Extension Cohort whose treatment with eltrombopag was still ongoing (these 15 patients had not reached the month 6 visit yet).

In the UAS01T trial, the main reason for ending eltrombopag treatment was "completed per protocol" (63%). Twenty-six percent of patients withdrew from the study after the end of eltrombopag treatment. The most common reasons for study withdrawal were initiation of additional IST other than steroids or CsA (10%), insufficient response (6%) and clonal evolution or progression to MDS/AML (3%). Post-eltrombopag treatment follow-up was ongoing in 61% of patients at the September 30, 2016 data cutoff.

Table 12 AUS01T: Patient Disposition (All Patients)

	Cohort 1 N=31	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62	All Patients N=124
# of enrolled patients					
Treated with eltrombopag	30 (97%)	31 (100%)	31 (100%)	62 (100%)	123 (99%)
Not treated with eltrombopag	1 (3%)[a]	0	0	0	1 (<1%)
Patients treated with eltrombopag					
Treatment ongoing	0	0	0	15 (24%)[b]	15 (12%)
End of treatment	30 (97%)	31 (100%)	31 (100%)	47 (76%)	108 (87%)
Primary reason to end eltrombopag					
Completed per protocol	19 (61%)	27 (87%)	23 (74%)	32 (52%)	78 (63%)
Platelet count>400x10^3/mcL	3 (10%)	1 (3%)	4 (13%)	5 (8%)	9 (7%)
Platelet count>200x10^3/mcL	3 (10%)	0	2 (7%)	4 (7%)	7 (6%)
Adverse event	0	1 (3%)	1 (3%)	4 (7%)	5 (4%)
Clonal evolution	2 (7%)	0	1 (3%)	1 (2%)	3 (2%)
Patient decision	1 (3%)	1 (3%)	0	1 (2%)	3 (2%)
Death	1 (3%)	0	0	0	1 (<1%)
Investigator decision	1 (3%)	0	0	0	1 (<1%)
Protocol deviation	0	1 (3%)	0	0	1 (<1%)
Status after end of eltrombopag treatment					
Follow-up ongoing[c]	16 (52%)	23 (74%)	26 (84%)	37 (60%)	76 (61%)
Completion/withdrawal from study	14 (45%)	8 (26%)	5 (16%)	10 (16%)	32 (26%)
Primary reason for study withdrawal					

Initiation of additional IST other than steroids or CsA	9 (29%)	0	2 (7%)	3 (5%)	12 (10%)
Insufficient response	1 (3%)	3 (10%)	1 (3%)	3 (5%)	7 (6%)
Clonal evolution or progression to MDS/AML	1 (3%)	1 (3%)	2 (7%)	2 (3%)	4 (3%)
Persistent hepatotoxicity	0	0	0	1 (2%)[e]	1 (<1%)
Patient decision	0	1 (3%)	0	1 (2%)	2 (2%)
Death	1 (3%)	0	0	0	1 (<1%)
Relapse	1 (3%)	1 (3%)	0	0	2 (2%)
Toxicity	0	1 (3%)[d]	0	0	1 (<1%)
Transplant	1 (3%)	1 (3%)	0	0	2 (2%)

a. Patient (b) (6) was misdiagnosed at baseline, and had AML and not SAA. The subject received h-ATG (4 days) and CsA (2 weeks) but did not start eltrombopag.
b. 15 patients in the Extension Cohort had not yet reached month 6 treatment with eltrombopag at data cut-off (9/30/16).
c. Patients still followed-up for yearly assessments at data cut-off.
d. Patient (b) (6) completed the course of h-ATG and of eltrombopag (3 months) as per protocol, however discontinued CsA and withdrew from the study because of nephrotoxicity 2 weeks after the last dose of eltrombopag. Nephrotoxicity is listed in the Warnings and Precautions section of cyclosporine prescribing information.
e. Patient (b) (6) discontinued eltrombopag on Day 12 due to typhlitis (SAE) and CsA on Day 22 due to elevated liver function tests. On Day 71, the patient withdrew from the study due to persistent hepatotoxicity. See the narrative for this patient under section 8.6.
[Source: AUST01 CSR and ADSL.xpt]

Protocol Violations/Deviations

Overall, a total of 69 patients (56%) had protocol violations in the AUS01T trial at the September 30, 2016 data cutoff. Most of the violations were related to laboratory tests/procedures (19%), incompletion of Quality of life questionnaire (15%), prophylaxis not administered as per protocol (9%) or related to eltrombopag dosing error (9%). A total of 2 patients had eligibility criteria violations: one patient in Cohort 2 had baseline ALT > 5 x ULN and one patient in Cohort 1 was misdiagnosed for SAA.

As most of the protocol violations are not considered major violations, it is not likely that these protocol violations affected the analysis of the primary endpoint. The table below summarizes the protocol violations that occurred in the AUS01T trial.

Table 13 AUS01T: Protocol Violations (FAS)

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62	All Patients N=123
All patients	19 (63%)	18 (58%)	12 (39%)	20 (32%)	69 (56%)
Lab test/procedure not done	4 (13%)	10 (32%)	6 (19%)	9 (15%)	23 (19%)

or delayed					
Quality of life questionnaire not completed	2 (7%)	4 (13%)	0	12 (19%)	18 (15%)
Prophylaxis not administered as per protocol	8 (27%)	0	1 (3%)	2 (3%)	11 (9%)
Eltrombopag missed/dosing error	2 (7%)	2 (7%)	3 (10%)	7 (11%)	11 (9%)
Cyclosporine missed/dosing error	2 (7%)	0	3 (10%)	4 (7%)	6 (5%)
Baseline ALT > 3xULN (prior to protocol amendment approval) or > 5xULN (after protocol amendment approval) (Exclusion criteria)	0	1 (3%)	0	0	1 (<1%)
Did not perform baseline test/procedure as required	3 (10%)	0	0	0	3 (2%)
Cyclosporine maintenance continued for >18 months	0	1 (3%)	0	0	1 (<1%)
Cyclosporine level below the therapeutic range and dose not adjusted	1 (3%)	0	0	0	1 (<1%)
Eltrombopag not discontinued at Month 3 (Cohort 2)	0	1 (2%)	0	0	1 (<1%)
Eltrombopag not initiated on Day 14 (Cohorts 1 &2)	2 (7%)	1 (3%)	0	0	3 (2%)
Eltrombopag overdose	1 (3%)	0	0	0	1 (<1%)
Informed consent obtained not appropriately	1 (3%)	0	1 (3%)	1 (2%)	2 (2%)
Landmark visit (Month 3, Month 6, or yearly FU visits) not done or delayed	2 (7%)	1 (3%)	0	1 (2%)	4 (3%)
PK sample not performed	3 (10%)	0	0	0	3 (2%)
Physical exam not recorded	0	1 (3%)	0	0	1 (<1%)

Based on number of patients. A patient can appear in more than one category.
[Source: ADDV.xpt]

Table of Demographic Characteristics

In the AUS01T trial, patients were not randomized between the cohorts and therefore, there were variations in some of the demographic characteristics between the cohorts. At the September 30, 2016 data cutoff, the median age was 30 years (range 3-82), 29 patients (24%) were pediatric (<18 years), 17 patients (14%) were 65 years or older and 52% of patients were males. Most of the patients were White (60%) or African American (18%) and 10% of patients were Asian.

Review comment: According to "Guidance for Industry: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling", although the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research generally define the pediatric population from birth to younger than 17 years of age, the ICH guidance for industry E11 Clinical Investigation of Medicinal Products in the Pediatric Population includes 16-18 years (dependent on region). The use of age categories depends on the indication and drug being studied.

In the AUS01T trial, a total of 3 patients who were 17 years of age were enrolled, all in Cohort 1. Therefore, when defining the pediatric population to younger than 17 years of age, the analyses conducted in this review in pediatric patients remain the same in the recommended dosing cohort (Cohort 3+Extension Cohort).

Table 14 AUS01T: Patient Baseline Demographics (FAS)

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62	All Patients N=123
Gender					
Female	14 (47%)	14 (45%)	14 (45%)	31 (50%)	59 (48%)
Male	16 (53%)	17 (55%)	17 (55%)	31 (50%)	64 (52%)
Age					
Median	39.0	28.0	29.0	26.5	30.0
Range	12-72	3-68	11-82	5-82	3-82
<18	5 (17%)	6 (19%)	8 (26%)	18 (29%)	29 (24%)
2-5	0	1 (3%)	0	1 (2%)	2 (2%)
6-11	0	1 (3%)	1 (3%)	7 (11%)	8 (7%)
12-17	5 (17%)	4 (13%)	7 (23%)	10 (16%)	19 (15%)
< 65	25 (83%)	29 (94%)	26 (84%)	52 (84%)	106 (86%)
≥ 65	5 (17%)	2 (7%)	5 (16%)	10 (16%)	17 (14%)
Race					
White	16 (53%)	19 (61%)	23 (74%)	39 (63%)	74 (60%)
Black or African American	6 (20%)	7 (23%)	4 (13%)	9 (15%)	22 (18%)
East or South-East Asian	2 (7%)	1 (3%)	0	4 (6%)	7 (6%)
Non-East or South-East Asian	1 (3%)	3 (10%)	1 (3%)	1 (2%)	5 (4%)
Other/Unknown	5 (17%)	1 (3%)	3 (10%)	9 (15%)	15 (12%)
Weight (kg)					
Median	69	77	67	67	70
Range	47-116	14-127	37-105	17-143	14-143
Height (cm)					
Median	169	168	170	167	168
Range	141-194	98-190	140-187	115-198	98-198

[Source: ADSL.xpt]

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

AUS01T:
The applicant states that the eligibility criteria with regard to hematological laboratory results were obtained within 60 days prior to treatment initiation and was referred to as pre-study hematological parameters. Hematological results at baseline defined as the last assessment before or on the day of treatment start, could have been different from the hematological counts used for the eligibility. To be eligible for the trial, at least two of the following had to be met:

- Absolute neutrophil count < 500/ mcL
- Platelet count < 20,000/ mcL
- Absolute reticulocyte count <60,000/ mcL

All patients included in the FAS met the prestudy hematological parameters criteria for SAA.

By pre-study laboratory results, the median platelet count was 9 x 10^3/mcL (range: 1 x 10^3/mcL to 40 x 10^3/mcL), the median ANC was 0.27 x 10^3/mcL (range: 0-1.93 x10^3/mcL), and the median absolute reticulocyte 20 x 10^3/mcL (range: 2 x 10^3/mcL to 86 x 10^3/mcL) which were generally lower than the baseline values.

Table 15 AUS01T: Hematological Parameters (FAS)

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62	All Patients N=123
Pre-study hematological parameters (within 60 days prior to treatment)					
Platelet count (10^3/mcL)					
Median	10.0	8.0	9.0	9.0	9.0
Range	2-37	1-14	1-27	1-40	1-40
Absolute neutrophil count (10^3/mcL)					
Median	0.28	0.33	0.31	0.25	0.27
Range	0.00-1.38	0.00-0.90	0.00-1.81	0.00-1.93	0.00-1.93
Absolute reticulocyte count (10^3/mcL)					
Median	22.5	15.0	24.0	23.0	20.0
Range	2-52	2-53	2-60	2-86	2-86
By baseline hematological parameters					
Platelet count (10^3/mcL)					

Median	30.5	39.0	32.0	31.0	32.0
Range	12-83	8-78	8-68	7-79	7-83
Absolute neutrophil count (10^3/mcL)					
Median	0.41	0.27	0.37	0.36	0.33
Range	0-1.51	0.01-0.89	0.01-1.66	0-2.88	0-2.88
Hemoglobin (g/L)					
Median	92.5	91.0	89.0	88.0	90.0
Range	68-109	72-112	74-122	72-122	68-122
Absolute reticulocyte count (10^3/mcL)					
Median	23.5	18.0	25.0	23.0	22.0
Range	2-58	2-53	5-60	4-98	2-98

[Source: AUS01T CSR and ADSL.xpt]

The datasets/information regarding time to treatment from disease diagnosis were not provided.

With regard to severity of aplastic anemia, very severe aplastic anemia was defined as absolute neutrophil count < 200/mcL and either platelet count < 20 x 10^3/mcL, absolute reticulocyte count < 60 x 10^3/mcL or both. Regarding the PNH definition, it was advised that a glucose phosphate isomerase (GPI) threshold of 50% was considered more clinically relevant than the 1% threshold. Therefore, the threshold of 50% was used as a signal for diagnosis for PNH.

At baseline, approximately one third of patients (35%) had very severe aplastic anemia, a total of 3 patients (2%) had GPI negative neutrophil > 50% and 60 patients (49%) had a pancytopenia (deficiency of all 3 cellular components of the blood: red cells, white cells, and platelets).

Table 16 AUS01T: Patient Baseline Disease Information (FAS)

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62	All Patients N=123
Severity of aplastic anemia					
Severe	19 (63%)	19 (61%)	22 (71%)	42 (68%)	80 (65%)
Very severe	11 (37%)	12 (39%)	9 (29%)	20 (32%)	43 (35%)
Pancytopenia	21 (70%)	21 (68%)	13 (42%)	18 (29%)	60 (49%)
GPI negative neutrophil					
Median	1.00	1.00	1.00	1.00	1.00
≤ 50%	27 (90%)	29 (94%)	25 (81%)	54 (87%)	110 (89%)
> 50%	1 (3%)	1 (3%)	1 (3%)	1 (2%)	3 (2%)
Missing	2 (7%)	1 (3%)	5 (16%)	7 (11%)	10 (8%)
Cytogenic analysis[a]					
Normal	20 (67%)	22 (71%)	16 (52%)	25 (40%)	67 (55%)

Abnormal[b]	1 (3%)	2 (7%)	0	3 (5%)	6 (5%)
Missing/not evaluable	9 (30%)	7 (23%)	15 (48%)	34 (55%)	50 (41%)

a. Normal = either 46XX or 46XY with 20 metaphases; Not evaluable = 46XX or 46XY with less than 20 metaphases or unambiguously stated as not evaluable; Abnormal = anything else; Missing = no result provided.
b. No patients had cytogenetics analysis indicating an acquired disorder. However abnormal cytogenetics such as germline variations or loss of Y chromosome, both which can be observed in healthy normal individuals, were observed in these subjects.
[Source: ADSL.xpt]

Concomitant Medications

Concomitant medications:
In the AUS01T trial, all patients (100%) received concomitant medications and non-drug therapies after the start of study treatment and up to 6 month.

Concomitant medications administered during the 6-month treatment period that could affect the primary efficacy results were observed in a total of 7 patients. All 7 patients received filgrastim (a colony stimulating factor):

- Patient (b) (6) (Cohort 1) for infection prophylaxis, the subject was off-treatment prior to any respon assessment due to physician decision (bone marrow transplant) and was non-responder.
- Patient (b) (6) (Cohort 1) for neutropenia, the subject was partial responder at month 3 and at month 6.
- Patient (b) (6) (Cohort 1) for neutropenia, the subject was complete responder at month 3 and at m nth 6
- Patient (b) (6) (Cohort 1) for stimulating neutropoesis, the subject was complete responder at month 3 and at month 6.
- Patient (b) (6) (Cohort 2) received colony stimulating factor, the subject was partial responder at month 3 and at month 6.
- Patient (b) (6) (Cohort 3) for infection prophylaxis, the subject was non-responder at month 3 and was off-treatment before month 6 due to clonal evolution.
- Patient (b) (6) (Extension Cohort) for infection prophylaxis, the subject was partial responder at month 3 and month 6.

In addition, patient (b) (6) (Cohort 1) received filgrastim for neutropenia approximately 3 months after completion of the 6-months treatment, and this patient was therefore not included in this analysis of concomitant medications with the potential to impact efficacy results. This patient was complete responder at month 3 and month 6, and relapsed 2.5 month after completing study treatment. The patient was taken off study due to initiation of another IST.

All patients assessed for response at month 3 and at month 6 landmark visits had stopped filgrastim more than 3 weeks prior to their assessment as required by protocol to be evaluated

as responder. Patients (b) (6) ended filgrastim at baseline (according to the applicant, this was not correctly captured in the database).

Efficacy Results – Primary Endpoint

AUS01T:
The primary efficacy endpoint was complete hematologic response rate at 6 months following h-ATG/CsA/eltrombopag as assessed by the investigator. CR was defined as hematological parameters meeting all the following 3 criteria on two consecutive serial blood count measurements at least one week apart:

- Absolute neutrophil count > 1000/mcL
- Platelet count > 100 x 10^3/mcL
- Hemoglobin > 10 g/dL

Improvement in blood counts following administration of other therapies such as growth factors or transfusions (including re-introduction of eltrombopag after month 3 and prior to month 6 for Cohort 2) were not considered as fulfilling the response criteria. Patients were considered non-responders if they received the following therapies:

- Platelets transfusions: 7 days before the assessment of platelet count
- Packed red blood cell transfusions: 14 days before the assessment of hemoglobin
- Growth factors: 21 days before the assessment of response

In each cohort, there were more than 7 CRs at the month 6 assessment; therefore, the null hypothesis of CR ≤ 10% was rejected and the study met the primary objective for each cohort.

A total of 107 patients had reached month 6 in the AUS01T trial (Cohort 1: 30, Cohort 2: 31, Cohort 3: 31, Extension Cohort: 15) at the September 30, 2016 data cutoff.

Review comment: According to the datasets, patient (ID: (b) (6)) in the Extension Cohort discontinued treatment with eltrombopag due to platelet count>200x10^3/mcL, however, the month 6 evaluation was not conducted for this patient and was not included in the denominator for CR analysis. The following request for information was sent to the applicant on May 7, 2017:

According to CSR table 10-1, 16 out of 31 patients in the Extension Cohort reached the month 6 treatment with eltrombopag at data cut-off. However, in your analysis for the CR endpoint for the Cohort 3+Extension Cohort at month 6 is based on a total of 46 patients (including 15 patients in the Extension cohort). Provide the subject (ID) who reached the 6-month treatment with eltrombopag but not included in the primary endpoint analysis and the reason for exclusion.

On May 9, 2018, the applicant responded as follows:
Table 10-1 of the Study ETB115AUS01T (hereafter referred to as "Study AUS01T") clinical

study report shows that 16 out of the 31 patients in the Extension Cohort reached the end of treatment with eltrombopag: either completed the 6-month treatment duration or discontinued eltrombopag. One of the patients out of these 16, Patient (b) (6) *discontinued eltrombopag on* (b) (6) *(study day 154) due to platelet count >200 x 10^9/L.*

The analysis for the complete response endpoint included all patients who reached the Month 6 assessment or withdrew from the trial earlier than the 6-month timepoint. Patient (b) (6) *who discontinued eltrombopag but still remained enrolled in Study AUS01T, achieved a complete response at Month 3 and was still being followed up for efficacy at the data cutoff date, i.e., had not reached the Month 6 assessment as of 30-Sep-2016, thus was not included in the primary endpoint analysis.*

Complete hematologic response rates at month 6 in Cohorts 1, 2, 3 and Cohort 3+Extension Cohort were 33% (95% CI: 17%, 53%), 26% (95% CI: 12%, 45%), 58% (95% CI: 39%, 76%) and 52% (95% CI: 37%, 67%), respectively, at the September 30, 2016 data cutoff.

Table 17 AUS01T: Primary Endpoint Result (Complete Hematological Response Rate at Month 6, FAS)

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
Patients who reached the 6-month visit or withdrew earlier	30	31	31	46
Complete response	10 (33.3%)	8 (25.8%)	18 (58.1%)	24 (52.2%)
95% CI	17.3, 52.8	11.9, 44.6	39.1, 75,5	36.9, 67.1

-CR is calculated as the number of patients who achieved a CR at month 6 landmark, divided by the total number of patients enrolled into that cohort who had reached the 6-month landmark or had withdrawn earlier for any reason and including non-evaluable subjects. The 2-sided 95% confidence interval (CI) of the CR rate was computed based on the exact method of Clopper and Pearson.
[Source: ADRS.xpt]

Sensitivity analysis of the primary endpoint:
Using the per protocol set (PPS), the complete hematologic response rates at month 6 in the Cohort 3+Extension Cohort was 52% (95% CI: 37%, 67%) and was consistent with the results of the primary analysis.

Table 18 AUS01T: Complete Hematological Response Rate at Month 6 (PPS)

	Cohort 1 N=30	Cohort 2 N=30	Cohort 3 N=31	Cohort 3+Ext. N=58
Patients who reached the 6-month visit or withdrew earlier	30	30	31	46
Complete response	10 (33.3%)	8 (26.7%)	18 (58.1%)	24 (52.2%)

95% CI	17.3, 52.8	12.3, 45.9	39.1, 75,5	36.9, 67.1

-CR is calculated as the number of patients who achieved a CR at month 6 landmark, divided by the total number of patients enrolled into that cohort who had reached the 6-month landmark or had withdrawn earlier.
The 95% CI were computed based on the exact method of Clopper-Pearson.
[Source: ADRS.xpt]

In addition to using the PPS, sensitivity analysis was also conducted using a more stringent definition for complete response defined as complete normalization of hematological parameters, on 2 consecutive serial blood count measurements at least one week apart:

- ANC ≥ 1500/mcL
- Platelet count ≥ 150 x 10^3/mcL
- Hemoglobin ≥ 12 g/dL (female) or ≥ 13 g/dL (male)

Using this definition for CR, a total of 5 patients achieved complete normalization of hematological parameters at month 6. The complete hematologic response rate at month 6 in the Cohort 3+Extension Cohort using this definition was 4% (95% CI: 0.5%, 15%).

The applicant's explanation of the discrepancy between the results of the primary endpoint analysis and this sensitivity analysis is that most complete responders normalized 2 of the 3 hematological parameters (platelet counts and the ANC) but not all 3 parameters (the hemoglobin level were ≥ 10 g/L but still < 12 g/L).

Table 19 AUS01T: Complete Hematological Response Defined as Normalization of Parameters at Month 6 (FAS)

	Cohort 1 N=30	**Cohort 2 N=31**	**Cohort 3 N=31**	**Cohort 3+Ext. N=62**
Patients who reached the 6-month visit or withdrew earlier	30	31	31	46
Complete response	2 (6.7%)	1 (3.2%)	2 (6.5%)	2 (4.3%)
95% CI	0.8, 22.1	0.1. 16.7	0.8, 21.4	0.5, 14.8

-CR is calculated as the number of patients who achieved a CR at month 6 landmark, divided by the total number of patients enrolled into that cohort who had reached the 6-month landmark or had withdrawn earlier.
The 95% CI were computed based on the exact method of Clopper-Pearson.
[Source: ADRS.xpt]

Data Quality and Integrity

The monitoring of the study and the verification of source documents was conducted by CRO (b) (4) working under an agreement with Novartis. Data entry and cleaning were conducted by NIH and transferred to Novartis. Novartis analyzed and authored the report. In accordance with local and federal regulations, the Investigator allowed Novartis personnel access to all pertinent medical records to verify the data gathered and to audit the data

collection process.

Efficacy Results – Secondary and other relevant endpoints

AUS01T:
The secondary efficacy endpoints were as follows:

- Overall hematologic response rates (ORR, CR or PR) at 3, 6, 12 months and yearly thereafter
- Relapse
- Time to first occurrence of clonal evolution to PNH, clonal chromosomal population in bone marrow, myelodysplasia by morphology, or acute leukemia
- Overall survival
- Health-related quality of life: Change from Baseline to post-Baseline assessments in -Patient-Reported Outcomes Measurement Information System (PROMIS): Global Health, Sleep Disturbance, Applied Cognition-Abilities, Anxiety and Depression scores -Functional Assessment of Cancer Therapy (FACT) Anemia, Thrombocytopenia and Neutropenia scores
- Hematological response of relapsed subjects that re-start treatment
- The effect of a 2 mg/kg/day CsA dose starting Month 6 for 18 months until Month 24 on the rate of relapse of subjects deemed responders at Month 6

As stated above, response was defined as blood counts no longer meeting the standard ("Camitta") criteria for severe pancytopenia in SAA, equivalent to at least 2 of the 3 criteria obtained on 2 consecutive serial blood measurements at least one week apart at landmark time points (3 and 6 months):

- Absolute neutrophil count > 500/mcL
- Platelet count > $20x10^3$/mcL
- Reticulocyte count > $60x10^3$/mcL

Changes in planned analysis:
The applicant states that as certain endpoints were not clearly identified in the protocol, considering the assessments performed and the data collected, the following endpoints were proposed:

- The original secondary endpoint included "relapse". However, per the applicant, "due to the clinical component and lack of clear thresholds, this definition did not permit to derive unambiguously relapses from laboratory results. Therefore, relapse was based solely on the investigator assessment. Furthermore, in the absence of clearly identified endpoint in the protocol, duration of response was used to assess this objective."
- Analysis of clonal evolution was modified to exclude PNH because it is a different clinical entity than the other chromosomal abnormalities.
- The definition of PNH is not made solely on GPI ≥ 1%. It was advised that a threshold of 50% was considered more clinically relevant. Therefore the threshold of 50% was

used for the summary instead of 1% as planned in the SAP. The subgroup analysis of the primary endpoint by GPI negative neutrophils level (< 1% vs. ≥ 1%) was changed to (≤ 50% vs. > 50%). The shift from Baseline to worst post-Baseline status with regards to GPI negative neutrophils level using 50% threshold was reported to assess PNH that would require treatment.

- The analysis of the hematologic response in subjects who re-started eltrombopag after relapse could not be performed because the investigator confirmed that such response was not defined and not collected.

The applicant did not perform the analysis of the time to CR for the following reasons:

- Per protocol, there was no objective associated with this endpoint
- This response was only assessed at landmark 3-month and 6-month visits, which was not granular enough for the analysis of time to CR.

Duration of response was derived as the time from first documented response (either complete or partial) until the time of relapse, as defined by the investigator, or death whichever occurs first. If a subject did not have an event, the duration of response was censored at the date of the last assessment of response with a known outcome.

OS was derived as the time from date of first administration of study treatment until the date of death, regardless of the cause of death. If a subject was not known to have died, OS was censored at the date of last contact.

Review comment: In a single-arm trial, time to event endpoints, such as overall survival cannot be adequately evaluated. Because of variability in the natural history of the disease, a randomized study is necessary to evaluate time-to-event endpoints. In settings where there is no available therapy and where major improvement of the disease can be presumed to be attributed to the tested drug, the FDA has sometimes supported ORR and response duration observed in single-arm studies as substantial evidence supporting approval.

At the September 30, 2016 data cutoff, the applicant states that none of the patients in Cohort 3 had reached the 2-year assessment and none of the patients in the Extension Cohort had reached the 1-year assessment. Therefore, hematological response by assessment time, duration of response and clonal evolution should be interpreted with caution beyond month 6 in Cohort 3 and in the Extension Cohort.

<u>Hematologic response:</u>
As was the case for complete hematologic response, the overall response rate also peaked at Month 6 reaching 80%, 87%, 94% and 85% in Cohorts 1, 2 3, and Cohort 3+Extension Cohort, respectively. No patients in Cohort 1 and approximately half of responding patients in Cohort 2 received maintenance dose of CsA beyond Month 6. While relapse was not observed in any cohort at Month 6. At Month 12, the incidence of relapse was the highest in Cohort 1 (occurring

in 50%, 23%, 15% and 18% of patients in Cohorts 1, 2, 3 and Cohort 3+Extension Cohort, respectively).

Among all cohorts, the CR and ORR were generally the highest in Cohort 3 at Month 3, 6 and 12.

Review comment: Although the dosing regimen in patients treated in Cohort 3 and Extension Cohort was the same, as stated above a total of 15 patients in the Extension Cohort had not yet reached Month 6 at the data cut-off (9/30/16) which could account for the lower response rates in the combined Cohort 3+Extension Cohort.

Table 20 AUS01T: Secondary Endpoints- Hematologic Response by Assessment Time (FAS)

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
At Month 3, total n[a]	30	31	31	54
Overall response rate	23 (76.7%)	24 (77.4%)	27 (87.1%)	43 (79.6%)
95% CI	57.7, 90.1	58.9, 90.4	70.2, 96.4	66.5, 89.4
Complete response	5 (16.7%)	7 (22.6%)	15 (48.4%)	19 (35.2%)
95% CI	5.6, 34.7	9.6, 41.1	30.2, 66.9	22.7, 49.4
Partial response	18 (60.0%)	17 (54.8%)	12 (38.7%)	24 (44.4%)
No response	5 (16.7%)	7 (22.6%)	4 (12.9%)	8 (14.8%)
Withdrawal	2 (6.7%)	0	0	3 (5.6%)
At Month 6, total n[a]	30	31	31	46
Overall response rate	24 (80.0%)	27 (87.1%)	29 (93.5%)	39 (84.8%)
95% CI	61.4, 92.3	70.2, 96.4	78.6, 99.2	71.1, 93.7
Complete response	10 (33.3%)	8 (25.8%)	18 (58.1%)	24 (52.2%)
95% CI	17.3, 52.8	11.9, 44.6	39.1, 75.5	36.9, 67.1
Partial response	14 (46.7%)	19 (61.3%)	11 (35.5%)	15 (32.6%)
No response	3 (10.0%)	2 (6.5%)	1 (3.2%)	3 (6.5%)
Withdrawal	3 (10.0%)	2 (6.5%)	1 (3.2%)	4 (8.7%)
At Month 12, total n[a]	30	31	27	34
Overall response rate	9 (30.0%)	18 (58.1%)	19 (70.4%)	19 (55.9%)
95% CI	14.7, 49.4	39.1, 75.5	49.8, 86.2	37.9, 72.8
Complete response	5 (16.7%)	10 (32.3%)	12 (44.4%)	12 (35.3%)
95% CI	5.6, 34.7	16.7, 51.4	25.5, 64.7	19.7, 53.5
Partial response	4 (13.3%)	8 (25.8%)	7 (25.9%)	7 (20.6%)
Relapse	15 (50.0%)	7 (22.6%)	4 (14.8%)	6 (17.6%)
Withdrawal	6 (20.0%)	5 (16.1%)	4 (14.8%)	9 (26.5%)
Missing[b]	0	1 (3.2%)	0	0

a. "Total n" is the number of subjects in the treatment group who reached this timepoint or withdrew earlier. It is denominator for percentage (%) calculation.
b. "Missing in Cohort 2": Subject (b) (6) in Cohort 2 completed the 3 drugs treatment as per protocol. The subject was assessed as having no response a month 3 and a partial response at month 6. The subject withdrew from study

approximately one year later, however, the year 1 assessment was not done and was therefore assigned as "missing". Subsequent assessments for this subject were assigned as "withdrawal".
Response rate is calculated as the number of patients who achieved a response at each timepoint, divided by the total number of patients enrolled into that cohort who have reached that timepoint or have withdrawn earlier for any reason, including non-evaluable subjects.
Overall Response = Complete or Partial Response
The 95% CI were computed based on the exact method of Clopper-Pearson.
[Source: ADRS.xpt]

Duration of response:
At the September 30, 2016 data cutoff, among the 27 patients who achieved complete response at any time in Cohort 3+Extension Cohort, a total of 3 patients (11%) relapsed. The median duration of CR in Cohort 3+Extension Cohort was 9.3 months (95% CI: 9.0, 9.3).

Among the 45 patients who had achieved a response at any time in Cohort 3+Extension Cohort, a total of 7 patients (16%) relapsed. The median duration of ORR in Cohort 3+Extension Cohort was 9.3 month (95% CI: 9.3, NE).

Table 21 AUS01T: Secondary Endpoints (Duration of CR and ORR, FAS)

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
Complete responders at any time	13	15	20	27
Relapsed	6 (46.2%)	2 (13.3%)	3 (15.0%)	3 (11.1%)
Median duration of CR in months (95% CI)	NE (5.1, NE)	NE	9.3 (9.0, 9.3)	9.3 (9.0, 9.3)
Overall responders at any time	25	27	29	45
Died	1 (4.0%)	0	0	0
Relapsed	15 (60.0%)	8 (29.6%)	5 (17.2%)	7 (15.6%)
Median duration of ORR in months (95% CI)	6.2 (5.1, NE)	NE (9.5, NE)	NE (9.3, NE)	9.3 (9.3, NE)

[Source: ADRS.xpt and ADTTE.xpt]

Overall survival:
The overall survival data were not yet mature for each cohort in the AUS01T trial at September 30, 2016 clinical cutoff.

Effect of CsA maintenance on the rate of relapse in responders at Month 6:
At the time of September 30, 2016 data cutoff, the rate of relapse for patients who responded at Month 6 was similar across cohorts (Cohort 2: 20%, Cohort 3: 18%, Cohort 3+Extension Cohort: 18%). However, longer follow-up is needed as none of the responders in Cohort 3 or in Extension Cohort had yet completed 18 months of maintenance CsA.

Table 22 AUS01T: Duration of Overall Response by Use of Maintenance Dose of CsA – Overall Responders at Month 6 (FAS)

	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
Use of maintenance CsA* (N)	15	28	38
Relapsed	3 (20.0%)	5 (17.9%)	7 (18.4%)
Median duration of ORR in months (95% CI)	NE (6.1, NE)	NE (9.3, NE)	NE (9.0, NE)

*Maintenance CSA: maintenance dose (2 mg/kg/day) of CsA from month 6 to month 24 in subjects who were responders at month 6 assessment.
[Source: ADRS.xpt and ADTTE.xpt]

Health-related quality of life:
Health-related quality of life was assessed using the PROMIS and FACT instruments.

PROMIS:
With the PROMIS instrument, Global Physical (GPH) and Mental (GMH) Health, sleep disturbance, anxiety, depression and applied cognitive abilities were assessed. For analysis, scores were converted into T-scores where a score of 50 represented the mean for the US population with a standard deviation of 10. For the GPH or GMH, a higher score represented better quality-of-life outcome (i.e., a person who has a score of 60 is one standard deviation better than the general population). For the symptom scales, however, a higher score represented a worse outcome (i.e., more sleep disturbance, more anxiety and/or more depression).

A change of 10 points on each PROMIS subscale is equal to one standard deviation difference from the population mean; this value may be useful for interpretation of clinical relevance where minimally important differences (MID) have not been established. However, the 3 subscales from published MIDs are: Sleep disturbance MID=7.4 (Purvis 2017); anxiety MID=4.5 (Yost 2011); and depression MID=4.5 (Yost 2011).

At baseline, the mean T-scores on GPH for adult patients in Cohort 1, 2, and 3 were 43.5, 43.8 and 44.6, respectively, which were slightly lower than the US general population mean indicating a sicker population than the overall US population. The mean T-scores on GMH were closer to the US general population mean (Cohort 1: 47.6, Cohort 2: 50.0, and Cohort 3: 50.3). On the symptom scales, the mean T-scores for sleep disturbance (range: 50.2-52.8) and depression (range: 48.4-51.4) were close the US general population; while for anxiety (range: 53.1-54.4) the T-scores were slightly worse; and for applied cognition abilities (range: 47.1-47.9) the T-scores were slightly better.

Table 23 AUS01T: Baseline PROMIS T-scores by Hematological Response at Month 6 (Adults from FAS)

Baseline	Cohort 1 N=30		Cohort 2 N=31		Cohort 3 N=31	
	All	Responders	All	Responders	All	Responders
Global Physical Health Score						
No. of patients	22	18	23	19	23	22
Mean	43.50	42.85	43.82	43.25	44.61	44.83
Global Mental Health Score						
No. of patients	22	18	23	19	23	22
Mean	47.64	47.36	50.03	49.81	50.33	50.07
Sleep disturbance Score						
No. of patients	21	17	23	19	23	22
Mean	51.09	50.12	52.76	52.84	50.16	50.34
Anxiety Score						
No. of patients	22	18	22	18	23	22
Mean	53.08	53.11	54.42	55.24	53.60	54.21
Depression Score						
No. of patients	22	18	23	19	23	22
Mean	51.43	51.71	49.89	50.66	48.41	48.75
Applied Cognition-Abilities Score						
No. of patients	22	18	23	19	23	22
Mean	47.90	48.46	47.51	46.94	47.10	47.09

HRQL questionnaires were not required for the Extension Cohort at any time.
Responders: Overall responders at month 6
[Source: AUS01T CSR]

At Month 6 in Cohort 3, there was a mean improvement on GPH, sleep disturbance and anxiety for responders and all assessed patients while on GMH, depression and applied cognition abilities the scores worsened or were similar to baseline. The table below summarizes score changes by hematologic response at Month 6 from baseline in adult patients.

Table 24 AUS01T: Change from Baseline to Month 6 of PROMIS T-scores by Hematological Response (Adults from FAS)

	Cohort 1 N=30		Cohort 2 N=31		Cohort 3 N=31	
	All	Responders	All	Responders	All	Responders
Global Physical Health Score						
Number of patients	20	18	20	18	23	22
Mean	5.09	5.97	2.03	2.43	5.15	4.88
Global Mental Health Score						
Number of patients	20	18	20	18	23	22
Mean	0.61	1.47	-1.54	-1.38	-0.51	-0.41
Sleep disturbance Score						

Number of patients	19	17	20	18	23	22
Mean	-1.64	-1.29	1.98	2.11	-3.62	-3.39
Anxiety Score						
Number of patients	20	18	19	17	23	22
Mean	-1.12	-1.63	-2.52	-4.53	-4.87	-5.80
Depression Score						
Number of patients	20	18	20	18	23	22
Mean	-0.74	-1.42	0.72	-0.74	0.70	0.15
Applied Cognition-Abilities Score						
Number of patients	20	18	20	18	23	22
Mean	2.15	2.28	-0.28	0.09	4.21	3.95

HRQL questionnaires were not required for the Extension Cohort at any time.
Responders: Overall responders at month 6
[Source: AUS01T CSR]

In addition to the PROMIS assessment at Month 6, the applicant also conducted the assessments at Day 14 and Month 3. Overall, there was a mean improvement in anxiety for responders in Cohort 2 and Cohort 3. Other subscales were essentially stable and similar between responders and non-responders.

FACT:
HRQL for anemia, thrombocytopenia and neutropenia were evaluated. Higher FACT scores indicate better functioning and better quality of life.

At month 6, overall there were improvements on the 3 symptom-specific FACT scales in each cohort compared to the baseline and greater improvements among patients who responded to eltrombopag treatment. The improvements in each of the 3 symptom-specific FACT scales were the highest among patients enrolled in Cohort 3.

The table below summarizes changes from baseline to Month 6 for FACT scores by hematological response in adult subjects (≥ 18 years).

Table 25 AUS01T: Change from Baseline to Month 6 of FACT scores by Hematological Response (Adults from FAS)

	Cohort 1 N=30		**Cohort 2 N=31**		**Cohort 3 N=31**	
	All	**Response**	**All**	**Response**	**All**	**Response**
Global Total Score						
Number of patients	19	17	19	17	22	21
Mean	5.5	7.4	3.6	5.2	11.0	10.9
Anemia Trial Outcome Index						
Number of patients	19	17	18	16	22	21
Mean	13.4	15.8	13.3	15.7	20.5	20.7
Anemia Total Score						

Number of patients	19	17	18	16	22	21
Mean	14.4	17.5	13.2	16.5	22.4	22.4
Thrombocytopenia Trial Outcome Index						
Number of patients	19	17	19	17	22	21
Mean	13.1	15.2	11.2	13.2	21.3	21.6
Thrombocytopenia Total Score						
Number of patients	19	17	19	17	22	21
Mean	14.1	17.0	10.9	13.8	23.1	23.3
Neutropenia Trial Outcome Index						
Number of patients	19	17	18	16	22	21
Mean	12.8	15.4	14.7	17.6	21.0	21.3
Neutropenia Total Score						
Number of patients	19	17	18	16	22	21
Mean	13.8	17.2	14.4	18.1	22.9	23.0

HRQL questionnaires were not required the Extension Cohort at any time
Response: Overall responders at month 6
[Source: AUS01T CSR]

Review comment: PRO results from single-arm clinical trials are difficult to interpret and are not adequate to support labeling claims.

For the remaining secondary endpoint for clonal evolution, see section 8.8.1 below.

Dose/Dose Response

The PK data from study AUS01T was available from only a subset of 21 subjects enrolled in Cohort 1 collected at Month 3 visit. Therefore, a thorough dose-response evaluation could not be performed and only descriptive PK parameters were reported. The exposure in definitive IST-naïve subjects with SAA from study AUS01T was similar to the exposure in subjects with chronic liver disease while 2-3 times higher than in healthy subjects and in subjects with ITP.

Dose of eltrombopag 150 mg once daily was selected as the starting dose as this regimen was demonstrated to be safe and effective in increasing platelet counts in a pilot phase 2 study (ELT112523) of eltrombopag as a single agent in patients with refractory SAA.

The dose for pediatric patients was based on the Study TRA108062 (PETIT), a phase 2 pediatric chronic ITP trial, in which patients between 1 to 5 years received 1.2 to 2.5 mg/kg eltrombopag once daily, and patients between 6 to 17 years of age received average daily dose of 58.5 mg daily. The preliminary PK data collected for 3 subjects (ages ranging from 2 to 5 years) receiving eltrombopag 1.1 to 1.2 mg/kg once daily at Week 6 suggested that this dose delivered plasma eltrombopag exposure similar to a 37.5 to 50 mg once daily regimen in adults. The platelet count, safety, and PK data available for the subjects enrolled in the PETIT trial supported starting dose of 2.5 mg/kg once daily for non-Asian patients aged between 2 to 5 years. A

starting dose of 75 mg once daily was selected for children of 12 years up to adults of East and South-East Asian ethnicity due to ethno-pharmacologic differences in exposure summarized as follow:

- In healthy Japanese patients, plasma eltrombopag AUC was approximately 80% higher when compared to non-Japanese healthy subjects who were predominantly Caucasian.
- Similarly, in patients with ITP, plasma eltrombopag exposure was 70% higher in East and South-East Asian subjects when compared with other ethnicities, who were predominantly Caucasian.

See Clinical Pharmacology review for details.

Durability of Response

See tables 21 and 22 above (under the secondary endpoints section).

Persistence of Effect

As shown in table 21 above, among the 27 patients in Cohort 3+Extension Cohort who had a CR at any time, 24 patients (89%) had not relapsed at the September 30, 2016 clinical cutoff with 60% of patients still on follow-up. Per the applicant, none of the complete responders in the Extension Cohort had reached the 6-months of post-treatment assessment. The median duration of CR was 9.3 (95% CI: 9.0, 9.3).

Among the 45 patients in Cohort 3+Extension Cohort who had a response at any time, the response in 38 patients (84%) was still ongoing with the median duration of ORR of 9.3 (9.3, NE). None of the responders in Cohort 3 or in Extension Cohort had yet completed 18 months of maintenance CsA. Per the applicant, the actual duration of response assessment for study AUS01T will be conducted at a later time.

Additional Analyses Conducted on the Individual Trial

<u>Subgroup analysis of the primary endpoint:</u>
In the AUS01T trial, in general complete hematologic responses at 6 months by subgroups were broadly consistent with the primary analysis. Of the 23 pediatric patients (2 to 17 years of age) who reached the 6-month assessment or withdrew earlier throughout the cohorts, the overall complete hematologic response rate was 39% (9 patients). The overall complete hematologic response rate in geriatric patients 65 years or older (n=14) was 36% (5 patients) (all cohorts combined).

However, the results of this subgroup analysis should be interpreted with caution due to small number of patients in most of the subgroups.

Table 26 AUS01T: Complete Hematologic Response by Subgroup at Month 6 (FAS)

Category	Cohort 1 N=30		Cohort 2 N=31		Cohort 3 N=31		Cohort 3+Ext. N=62	
Patients who reached the 6-month visit or withdrew earlier	30		31		31		46	
	N	CR	N	CR	N	CR	N	CR
All	30	10 (33.3%)	31	8 (25.8%)	31	18 (58.1%)	46	24 (52.2%)
Gender								
Female	14	5 (35.7%)	14	4 (28.6%)	14	8 (57.1%)	22	11 (50.0%)
Male	16	5 (31.3%)	17	4 (23.5%)	17	10 (58.8%)	24	13 (54.2%)
Age								
<18	5	1 (20.0%)	6	3 (50.0%)	8	5 (62.5%)	12	5 (41.7%)
2-5	0	0	1	0	0	0	0	0
6-11	0	0	1	0	1	0	4	0
12-17	5	1 (20.0%)	4	3 (75.0%)	7	5 (71.4%)	8	5 (62.5%)
18-64	20	7 (35.0%)	23	5 (21.7%)	18	10 (55.6%)	27	16 (59.3%)
≥ 65	5	2 (40.0%)	2	0	5	3 (60.0%)	7	3 (42.9%)
Race								
White	16	8 (50.0%)	19	5 (26.3%)	23	15 (65.2%)	30	18 (60.0%)
African American	6	0	7	2 (28.6%)	4	1 (25.0%)	7	3 (42.9%)
Asian	3	1 (33.3%)	4	1 (25.0%)	1	0	3	1 (33.3%)
Other	5	1 (20.0%)	1	0	3	2 (66.7%)	6	2 (33.3%)
Severity of aplastic anemia								
Severe	19	4 (21.1%)	19	5 (26.3%)	22	13 (59.1%)	31	17 (54.8%)
Very severe	11	6 (54.5%)	12	3 (25.0%)	9	5 (55.6%)	15	7 (46.7%)
GPI negative neutrophil								
≤ 50%	27	10 (37.0%)	29	8 (27.6%)	25	15 (60.0%)	38	21 (55.3%)
>50%	1	0	1	0	1	0	1	0
Missing	2	0	1	0	5	3 (60.0%)	7	3 (42.9%)

-CR is calculated as the number of patients who achieved a CR at month 6 landmark, divided by the total number of patients enrolled into that cohort who had reached the 6-month landmark or had withdrew earlier.
[Source: ADRS.xpt and ADSL.xpt]

Overall response rate by age group:

The overall response rate at 6 month by age was also consistent with the overall trial population. In pediatric patients 2 to 17 years of age (n=23), the ORR was 83% (19 patients) and 86% (12 patients) in geriatric patients 65 years and older (n=14) (all cohorts combined).

Table 27 AUS01T: ORR by Age at Month 6 (FAS)

Category	Cohort 1 N=30		Cohort 2 N=31		Cohort 3 N=31		Cohort 3+Ext. N=62	
Patients who reached the 6-month visit or withdrew earlier	30		31		31		46	
	N	ORR	N	ORR	N	ORR	N	ORR
All	30	24 (80.0%)	31	27 (87.1%)	31	29 (93.5%)	46	39 (84.8%)
Age								
<18	5	3 (60.0%)	6	6 (100.0%)	8	7 (87.5%)	12	10 (83.3%)
2-5	0	0	1	1 (100.0%)	0	0	0	0
6-11	0	0	1	1 (100.0%)	1	1 (100.0%)	4	3 (75.0%)
12-17	5	3 (60.0%)	4	4 (100.0%)	7	6 (85.7%)	8	7 (87.5%)
18-64	20	17 (85.0%)	23	19 (82.6%)	18	17 (94.4%)	27	23 (85.2%)
≥ 65	5	4 (80.0%)	2	2 (100.0%)	5	5 (100.0%)	7	6 (85.7%)

ORR is calculated as the number of patients who achieved a ORR at month 6 landmark, divided by the total number of patients enrolled into that cohort who had reached the 6-month landmark or had withdrew earlier.
[Source: ADRS.xpt and ADSL.xpt]

Hematologic response in subjects who re-started eltrombopag after relapse:

On June 20, 2018, a request for information was sent to the applicant to provide a summary and analysis of outcomes for patients who relapsed after initial response to eltrombopag and subsequently received additional treatment with eltrombopag. On July 11, 2018, the applicant provided a listing of patients who resumed eltrombopag after relapse and the hematologic response information in these patients. Datasets were not provided.

After relapse, in Cohorts 1, 2 and Cohort 3+Extension Cohort, a total of 4, 6 and 12 patients, respectively, resumed treatment with eltrombopag and CsA (except patients (b) (6) who received eltrombopag only). In Cohort 3+Extension Cohort, among patients who relapsed and resumed eltrombopag treatment, the complete and overall hematologic response rates were 8.3% and 25%, respectively, at the time of the clinical cutoff date of February 28, 2018. Four of the 12 patients (33%) in Cohort 3+Extension Cohort who resumed treatment were still on eltrombopag and have not had enough follow-up to assess the response.

Review comment: The applicant noted that for patients who relapsed beyond the 6-month response assessment, transfusion support (blood and platelets) and hematopoietic growth factors (e.g., G-CSF, GM-CSF, or erythropoietin) were not recorded. For response assessment, improvements in blood counts following administration of therapies such as growth factors or transfusions were not to be considered as fulfilling the criteria for response. Thus, the hematologic response in patients who resumed eltrombopag after relapse could have been affected by supportive care including transfusion and growth factors.

The table below summarizes the hematologic response rates in patients who received eltrombopag after relapse.

Table 28 AUS01T: Hematologic Response Among Patients who Resumed Eltrombopag After Relapse

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
Number of patients who resumed eltrombopag	4	6	6	12
Overall response rate	50%	67%	17%	25%
Complete response	0	50%	17%	8%
Partial response	50%	17%	0	16%
Too early to assess	0	17%	0	33%

[Source: Response to information request on July 11, 2018]

6.1.3. **Updated Study Results**

On July 25, 2018, the applicant submitted the 120-day safety update which contained updated safety and efficacy data from the pivotal study AUS01T with a clinical data cutoff date of February 28, 2018. The submission contained data from 30 additional patients (pediatric patients: 8, adult patients: 22), all enrolled in the Extension Cohort and 17 months of longer follow-up for those patients who were included in the original submission in the AUS01T trial. With the update, a total of 154 patients were enrolled and 153 patients (Cohort 1: 30, Cohort 2: 31, Cohort 3: 31, Cohort 3+Extension Cohort: 92) received eltrombopag at the time of February 28, 2018 cut-off. Among the 92 patients enrolled in the combined Cohort 3+Extension Cohort, 5 patients (IDs: (b) (6)) were still on eltrombopag treatment (had not reached the Month 6 visit). At the original clinical cutoff date of September 30, 2018, all patients in Cohorts 1, 2 and 3 had reached the Month 6 assessment. Therefore, the hematological responses for the 3 cohorts remained the same. At the updated clinical cutoff date of February 28, 2018, a total of 87 patients (an additional 41 patients in the Extension Cohort) were evaluable for the primary efficacy endpoint. The median follow-up was 61, 47, 33 and 22 months in Cohort 1, 2, 3 and combined Cohort 3 + Extension Cohort, respectively.

For the updated study results, the efficacy analyses were primarily conducted on the combined Cohort 3+Extension Cohort, the recommended dosing regimen.

Updated patient disposition and demographic characteristics:
Of the 92 patients enrolled in the combined Cohort 3+Extension Cohort, 64 patients (70%) completed treatment with eltrombopag per protocol. The most common reasons for early discontinuation with eltrombopag treatment were due to high platelet count (> $200x10^3$/mcL or > $400x10^3$/mcL) (12%) and AEs (4%), consistent with the original submission. In the combined

Cohort 3+Extension Cohort, the median age was 28.0 years (range: 5-82 years), 54% of patients were females and 62% of patients were White.

As described above under section 6.1.2, CDER and CBER generally define the pediatric population from birth to younger than 17 years of age. In the AUS01T trial, a total of 3 patients who were 17 years of age were enrolled, all in Cohort 1. Therefore, when defining the pediatric population to younger than 17 years of age, the analyses conducted in this review in pediatric patients remain the same in the recommended dosing cohort (Cohort 3+Extension Cohort).

In the AUS01T study, patients who received prior immunosuppressive therapy with any ATG, alemtuzumab, or high dose cyclophosphamide were to be excluded.

Review comment: In the AUS01T study, definitive immunosuppressive therapy was defined as treatment with any ATG, alemtuzumab, or high dose cyclophosphamide. With the additional 30 patients enrollment, a total of 2 patients (IDs (b) (6) *both enrolled in the Extension Cohort) received prior immunosuppressive therapy. However, neither of these patients were responders:*

-Patient (b) (6) *a 15-year old female, received the following:*

- *Prednisone: 12.5 mg orally once daily from Day -487 to Day -7;*
- *Methylprednisolone 10 mg iv once daily from Day -6 to Day 1 and;*
- *Cyclosporine: 100 mg orally once daily from Day -427 to Day -5 followed by 80 mg iv twice daily from Day -4 to Day -1*

-Patient (b) (6) *a 24-year old male, received prednisone 10 mg orally once daily from Day -12 to Day 1.*

Table 29 AUS01T: Updated Patient Baseline Demographics (Cohort 3+Extension Cohort, FAS)

Cutoff date	Sept 30, 2016	Feb 28, 2018
	Cohort 3+Ext. N=62	Cohort 3+Ext. N=92
Gender		
Female	31 (50%)	50 (54%)
Male	31 (50%)	42 (46%)
Age		
Median	26.5	28.0
Range	5-82	5-82
<18	18 (29%)	26 (28%)
2-5	1 (2%)	1 (1%)
6-11	7 (11%)	11 (12%)
12-17	10 (16%)	14 (15%)
< 65	52 (84%)	77 (84%)

≥ 65	10 (16%)	15 (16%)
≥ 75	2 (3%)	4 (4%)
Race		
White	39 (63%)	57 (62%)
Black or African American	9 (15%)	16 (17%)
East or South-East Asian	4 (6%)	6 (7%)
Non-East or South-East Asian	1 (2%)	2 (2%)
Other/Unknown	9 (15%)	11 (12%)

[Source: ADSL.xpt]

The pre-study hematological parameters and baseline disease characteristics were similar to the original cutoff date except that at the February 28, 2018 cutoff date, a higher proportion of patients had very severe aplastic anemia (45%) compared at the original cutoff date (32%). All patients including the additional 30 patients who were enrolled by the updated cutoff in the FAS met the prestudy hematological parameters criteria for SAA.

Table 30 AUS01T: Updated Pre-Study Hematological Parameters and Baseline Disease Information (Cohort 3+Extension Cohort, FAS)

Cutoff date	**Sept 30, 2016**	**Feb 28, 2018**
	Cohort 3+Ext. N=62	**Cohort 3+Ext. N=92**
Pre-study hematological parameters (within 60 days prior to treatment)		
Platelet count (10^3/mcL)		
Median	9.0	8.0
Range	1-40	0-40
Absolute neutrophil count (10^3/mcL)		
Median	0.25	0.27
Range	0-1.93	0-1.93
Absolute reticulocyte count (10^3/mcL)		
Median	23.0	21.0
Range	2-86	2-97.1
Severity of aplastic anemia		
Severe	42 (68%)	51 (55%)
Very severe	20 (32%)	41 (45%)
Cytogenic analysis[a]		
Normal	25 (40%)	41 (45%)
Abnormal[b]	3 (5%)	4 (4%)
Missing/not evaluable	34 (55%)	47 (51%)

a. Normal = either 46XX or 46XY with 20 metaphases; Not evaluable = 46XX or 46XY with less than 20 metaphases

or unambiguously stated as not evaluable; Abnormal = anything else; Missing = no result provided.
b. Per applicant: no patients had cytogenetics analysis indicating an acquired disorder.
However, abnormal cytogenetics such as constitutional translocation (in all cells) without clinical relevance and, unrelated to disease, germline variations or loss of Y chromosome (common in normal aging men), both which can be observed in healthy normal individuals, and one alteration was in a subject with previously undiagnosed Klinefelter's syndrome, also unrelated to the aplastic anemia were observed in these patients.
[Source: ADSL.xpt]

Protocol violations:
With the update, a total of 58 patients (63%) in Cohort 3+Extension Cohort had protocol violations. According to the "protocol deviations" dataset, all violations were non-serious and mostly were related to laboratory tests/procedures (25%), incompletion of Quality of life questionnaire (23%) or related to eltrombopag /cyclosporine dosing error (7%). However, according to the "concomitant medications" dataset, there was one patient (ID: (b) (6)) who received prior immunosuppressive therapy with cyclosporine (see under concomitant medications section below).

Concomitant medications:
At the original cutoff date, a total of 7 patients received filgrastim during the 6-month treatment period with eltrombopag throughout the cohorts. At the updated cutoff, no additional patients received filgrastim during the 6-month treatment period.

With regard to other treatment for SAA before the study entry, there was one patient who received immunosuppressive therapy (patient (b) (6) in Extension Cohort received prednisone from Day -487 to Day -7 and cyclosporine from Day -427 to Day -1). Patient (b) (6) was a non-responder and withdrew within 6 months of study.

Updated Efficacy Results:

Primary Endpoint
At the February 28, 2018 cutoff, complete hematological response in the combined Cohort 3+Extension Cohort at Month 6 was 43.7% (95% CI: 33%, 55%) which was lower than the original 52.2% (95% CI: 37%, 67%). However, as stated above at the updated data cutoff a higher proportion of patients had very severe disease.

Table 31 AUS01T: Updated Primary Endpoint Result: Complete Hematological Response Rate at Month 6 (Cohort 3+Extension Cohort, FAS)

Cutoff date	Sept 30, 2016	Feb 28, 2018
	Cohort 3+Ext. N=62	Cohort 3+Ext. N=92
Patients who reached the 6-month visit or withdrew earlier	46	87
Complete response	24 (52.2%)	38 (43.7%)
95% CI	36.9, 67.1	33.1, 54.7

-CR is calculated as the number of patients who achieved a CR at month 6 landmark, divided by the total number of patients enrolled into that cohort who had reached the 6-month landmark or had withdrew earlier for any reason and including non-evaluable subjects. The 2-sided 95% confidence interval (CI) of the CR rate was computed based on the exact method of Clopper and Pearson.
[Source: ADRS.xpt]

The CR rates by subgroup in Cohort 3+Extention Cohort were also generally lower in the update when compared with the original submission. At the updated February 28, 2018 cutoff, the CR rate in patients with very severe disease was lower (33%) compared to patients with severe disease (52%) as expected and males had a higher CR (49%) than in females (40%). Patients who were 18 to 64 years of age had a higher CR (55%) compared to patients <18 years (28%) and ≥ 65 years (33%). However, the severity of disease was not balanced by age; among patients who were <18 years, 18-64 years and ≥ 65 years of age, 56%, 34% and 60% of patients, respectively, had very severe aplastic anemia which was reflected in the CR rates. Also, the results of some subgroups should be interpreted with caution due to the small number of patients.

Table 32 AUS01T: Updated Complete Response at Month 6 by Subgroup (Cohort 3+Extension Cohort, FAS)

Cutoff date	Sept 30, 2016		Feb 28, 2018	
	Cohort 3+Ext. N=62		Cohort 3+Ext. N=92	
Patients who reached the 6-month visit or withdrew earlier	46		87	
	N	CR	N	CR
All	46	24 (52.2%)	87	38 (43.7%)
Gender				
Female	22	11 (50.0%)	48	19 (39.6%)
Male	24	13 (54.2%)	39	19 (48.7%)
Age				
<18	12	5 (41.7%)	25	7 (28.0%)
2-5	0	0	1	0
6-11	4	0	11	1 (9.1%)

12-17	8	5 (62.5%)	13	6 (46.2%)
18-64	27	16 (59.3%)	47	26 (55.3%)
≥ 65	7	3 (42.9%)	15	5 (33.3%)
Severity of aplastic anemia				
Severe	31	17 (54.8%)	48	25 (52.1%)
Very severe	15	7 (46.7%)	39	13 (33.3%)

-CR is calculated as the number of patients who achieved a CR at month 6 landmark, divided by the total number of patients enrolled into that cohort who had reached the 6-month landmark or had withdrew earlier.
[Source: ADRS.xpt and ADSL.xpt]

Updated hematologic response:

The applicant conducted additional landmark analyses on response rates beyond Month 6. At the update, a total of 5, 14 and 30 patients had not yet reached the Month 6, Year 1 and Year 2 assessment, respectively, in the combined Cohort 3+Extension Cohort. Based on the number of evaluable patients, both the ORR and CR peaked at Month 6. The CR declined relatively slowly up to Year 2, and at Year 3 both ORR and CR were 4.5% based on 44 evaluable patients.

Among the responders at Month 6, none received platelets or packed RBC transfusion or growth factors within the assessment period at the updated analysis cutoff. For the Month 3 analysis, however, there was one patient with a PR (ID: (b) (6)) who received platelet transfusion on Day 99 which was the assessment date for the Month 3 evaluation. It is not clear whether platelet transfusion was given before or after the assessment on Day 99.

Table 33 AUS01T: Updated Hematologic Response by Assessment Time (Cohort 3+Extension Cohort, FAS)

	Cohort 3+Ext. N=92	
	N (%)	95% CI
At Month 3, total n[a]	88	
Overall response	66 (75.0%)	64.6, 83.6
Complete response	24 (27.3%)	18.3, 37.8
At Month 6, total n[a]	87	
Overall response	69 (79.3%)	69.3, 87.3
Complete response	38 (43.7%)	33.1, 54.7
At Year 1, total n[a]	78	
Overall response	44 (56.4%)	44.7, 67.6
Complete response	30 (38.5%)	27.7, 50.2
At Year 2, total n[a]	62	
Overall response	24 (38.7%)	26.6, 51.9
Complete response	19 (30.6%)	27.7, 50.2
At Year 3, total n[a]	44	
Overall response	2 (4.5%)	0.6, 15.5
Complete response	2 (4.5%)	0.6, 15.5

At Year 4, total n[a]	41	
Overall response	0	0, 8.6
Complete response	0	0, 8.6

a. "Total n" is the number of subjects in the treatment group who reached this timepoint or withdrew earlier. It is denominator for percentage (%) calculation.
Overall Response = Complete or Partial Response
The 95% CI were computed based on the exact method of Clopper-Pearson.
[Source: ADRS.xpt]

Generally, the ORR age by age was also lower at the update compared with the original cutoff. In the combined Cohort 3+Extension Cohort, the ORR was 68% in pediatric patients 2 to 17 years of age and 67% in geriatric patients 65 years and older.

Table 34 AUS01T: Updated ORR by Age at Month 6 (Cohort 3+Extension Cohort, FAS)

Cutoff date	**Sept 30, 2016**		**Feb 28, 2018**	
Category	**Cohort 3+Ext. N=62**		**Cohort 3+Ext. N=92**	
Patients who reached the 6-month visit or withdrew earlier	46		87	
	N	ORR	N	ORR
All	46	39 (84.8%)	87	69 (79.3%)
Age				
<18	12	10 (83.3%)	25	17 (68.0%)
2-5	0	0	1	1 (100%)
6-11	4	3 (75.0%)	11	6 (54.5%)
12-17	8	7 (87.5%)	13	10 (76.9%)
18-64	27	23 (85.2%)	47	42 (89.4%)
≥ 65	7	6 (85.7%)	15	10 (66.7%)

ORR is calculated as the number of patients who achieved a ORR at month 6 landmark, divided by the total number of patients enrolled into that cohort who had reached the 6-month landmark or had withdrew earlier.
[Source: ADRS.xpt and ADSL.xpt]

Updated duration of response:

With longer follow-up time at the updated clinical cutoff date on February 28, 2018, the median duration of response for both CR and ORR were extended compared with the original cutoff. At the update, among the 46 patients who had a CR at any time in Cohort 3+Extension Cohort, a total of 9 patients (20%) relapsed. The median duration of CR was 24.3 months (95% CI: 23.0, NE).

Among the 70 patients who had a response at any time in Cohort 3+Extension Cohort, a total of 19 patients (27%) relapsed. The median duration of ORR in Cohort 3+Extension Cohort was 24.3 month (95% CI: 21.4, NE).

Table 35 AUS01T: Updated Duration of Response in Patients who Responded at Anytime (Cohort 3+Extension Cohort, FAS)

Cutoff date	Sept 30, 2016	Feb 28, 2018
	Cohort 3+Ext. N=62	Cohort 3+Ext. N=92
Complete responders at any time	27 (43.5%)	46 (50.0%)
Relapsed	3 (11.1%)	9 (19.6%)
Median duration of CR in months (95% CI)	9.3 (9.0, 9.3)	24.3 (23.0, NE)
Overall responders at any time	45 (72.6%)	70 (76.1%)
Died	0	0
Relapsed	7 (15.6%)	19 (27.1%)
Median duration of ORR in months (95% CI)	9.3 (9.3, NE)	24.3 (21.4, NE)

[Source: ADRS.xpt and ADTTE.xpt]

The estimated median duration of CR and ORR based on the patients who had a CR and ORR, respectively, at Month 6 was consistent with the above results (shown in the table below) both at the original and updated cutoff dates.

Table 36 AUS01T: Updated Duration of Response in Patients who Responded at Month 6 (Cohort 3+Extension Cohort, FAS)

Cutoff date	Sept 30, 2016	Feb 28, 2018
	Cohort 3+Ext. N=46	Cohort 3+Ext. N=87
Complete responders at Month 6	24 (52.2%)	38 (43.7%)
Median duration of CR in months (95% CI)	9.3 (9.0, 9.3)	24.3 (23.0, NE)
Overall responders at Month 6	39 (84.8%)	69 (79.3%)
Median duration of ORR in months (95% CI)	9.3 (9.3, NE)	24.3 (21.4, NE)

"N" is the number of subjects in the treatment group who reached this timepoint or withdrew earlier. It is denominator for percentage (%) calculation.
Overall Response = Complete or Partial Response
[Source: ADRS.xpt and ADTTE.xpt]

Effect of maintenance dose of CsA on duration of overall response:
Approximately half of patients in Cohort 2 and all patients in Cohort 3 and Extension Cohort who were responders at Month 6 were to receive maintenance dose of CsA from Month 6 to 24. Responders in Cohort 2 who received the CsA maintenance had a longer median duration of response (35.5 months) compared with responders in Cohort 2 (26.0 months) and Cohort 1 (6.0 months) who did not receive the CsA maintenance.

Table 37 AUS01T: Updated Duration of Overall Response by Use of Maintenance Dose of CsA – Overall Responders at Month 6 (FAS, Feb 28, Data Cutoff)

	Cohort 1 N=30	**Cohort 2 N=31**		**Cohort 3+Ext. N=92**
Number of responders	24	27		69
Maintenance CsA* N**	No N=24	No N=12	Yes N=15	Yes N=67
Relapsed	15 (63%)	6 (50%)	6 (40%)	19 (28%)
Still responding	9 (38%)	5 (42%)	9 (60%)	48 (72%)
Follow-up ongoing	3 (13%)	4 (33%)	8 (53%)	45 (67%)
Median duration of ORR in months (95% CI)	6.0 (5.0, NE)	26.0 (4.4, NE)	35.5 (6.1, NE)	24.3 (21.4, NE)

*Maintenance CsA: maintenance dose (2 mg/kg/day) of CsA from month 6 to month 24 in patients who were responders at month 6 assessment.
**Number of responders who were or not given the CsA maintenance dose.
[Source: 120-day safety update]

Overall survival:
The OS data was still not yet mature for each cohort at the update. A total of 7 patients died across all cohorts (Cohort 1: 3 patients, Cohort 2: 1 patient, Cohort 3+Extension Cohort: 3 patients).

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The submission contained publications and limited efficacy data from five historical trials that treated patients with h-ATG and CsA without eltrombopag [Tisdale et al (2000)], [Rosenfeld et al (2003)], [Scheinberg et al (2009)], [Scheinberg et al (2011)] and [Boddu et al (2017)] to provide context for efficacy evaluation of eltrombopag plus h-ATG+CsA therapy.

The comparison of each cohort to historical data (from studies conducted by the NIH) was planned to be conducted with data from Cohort 3 and Extension Cohort only, and include only a subset of studies that used h-ATG/CsA in subjects with similar characteristics and with similar

study endpoints and for which the description and results were publicly available.

However, the doses of cyclosporine in these historical trials were mostly not consistent as proposed in the AUS01T pivotal trial (see table 4). For majority of the trials, the key efficacy analysis was based on complete response and overall response rates at Months 3 and 6. The duration of response results were not available in the historical control trials.

Although cross-trial results should be evaluated with caution, as shown in the table below based on literature it appears that the addition of eltrombopag to h-ATG+CsA provides improved efficacy results compared to h-ATG+CsA therapy.

Table 38 Summary of Efficacy Results from Historical Control Trials and Study AUS01T (Feb 28, 2018 Data Cutoff)

Endpoint	Scheinberg et al, 2011 (06-H-0034) N=60 h-ATG+CsA	Scheinberg et al, 2009 (03-H-0193) N=42 h-ATG+CsA	Tisdale et al, 2000 (97-H-0117) N=16 h-ATG+CsA	Rosenfeld et al, 2003 (90-H-0146) N=122 h-ATG+CsA	AUS01T Cohort 3+ Extension[1] N[4]
CR at Month 3	7 (11.7%)[2]	3 (7.1%)	2 (12.5%)[3]	NA	24 (27.3%)
CR at Month 6	12 (20.0%)[2]	5 (11.9%)	4 (25.0%)[3]	NA	38 (43.7%)
ORR at Month 3	37 (61.7%)	24 (57.1%)	11 (68.8%)[3]	73 (59.8%)	66 (75.0%)
ORR at Month 6	41 (68.3%)	26 (61.9%)	9 (56.3%)[3]	75 (61.5%)	69 (79.3%)

1. Eltrombopag + h-ATG+CsA
2. Results provided by NIH for the comparison to historical control using subject-level data
3. The original publication reported higher percentages based on evaluable subjects only
4. For month 3, N=88 and for month 6, N=87: the number of subjects who reached this time point or withdrew earlier. It is the denominator for percentage (%) calculation.
NA=Not available in the publication
[Source: Summary of Clinical Efficacy]

The applicant also conducted different methods of analysis (propensity score matching, inverse probability of treatment weighting, fixed effects and Bayesian MAP) to compare the efficacy results of AUS01T trial with historical efficacy data. The statistical reviewer conducted the fixed effect analysis, propensity score matching and inverse probability of treatment weighting analyses shown in the table below. Using these analyses, it was also shown that the CR and ORR at Month 6 results from study AUS01T were improved compared to the historical efficacy data.

Table 39 AUS01T: Efficacy Results Comparison with Historical Control (Feb 28, 2018 Data Cutoff)

Endpoint	Historical studies	Method	Treatment effect at Month 6 (95% CI)[1]
CR at Month 6	Scheinberg et al, 2009 (03-H-0193) Scheinberg et al, 2011 (06-H-0034)	Fixed effect analysis	27.0 (14.57, 39.33)
		Propensity score matching	28.4 (12.99, 43.73)
		IPTW[2]	27.1 (12.6, 41.7)
ORR at Month 6	Scheinberg et al, 2009 (03-H-0193) Scheinberg et al, 2011 (06-H-0034)	Fixed effect analysis	16.3 (5.79, 26.72)
		Propensity score matching	10.4 (-0.03, 24.25)
		IPTW[2]	9.9 (-3.1, 22.8)

1. Treatment effect [(eltrombopag + IST) – IST alone] obtained from fixed effects model using study level data when available, propensity score matching and IPTW propensity score were based on individual patient data from study Scheinberg 2009 (03-H-0193) and study Scheinberg 2011 (06-H-0034)
2. IPTW = inverse probability of treatment weighting
Note: Results may be biased due to potential inconsistent definition of response across studies, potential unobserved confounders, potential model misspecification, etc.
[Source: Statistical review]

Also refer to Statistical review for these additional analyses.

7.2. Integrated Assessment of Effectiveness

The efficacy of eltrombopag administered in combination with standard immunosuppressive therapy (h-ATG + cyclosporine) was evaluated in a phase 1/2, single-arm trial (AUS01T) that enrolled a total of 154 adult and pediatric patients (≥2 years) with SAA (Cohort 1:31 patients, Cohort 2: 31 patients, Cohort 3: 31 patients, Extension Cohort: 61 patients) as first-line therapy. The primary efficacy endpoint was investigator-assessed complete hematologic response rate at Month 6. Key secondary efficacy endpoints were investigator-assessed ORR (CR or PR) at Month 3, 6 and 12 and yearly thereafter, and duration of response.

At the time of the clinical cutoff date of February 28, 2018, the median follow-up duration was 61, 47, 33 and 22 months in Cohort 1, 2, 3 and combined Cohort 3 + Extension Cohort, respectively. Treatment with eltrombopag was ongoing for a total of 5 patients in the Extension Cohort who had not reached the Month 6 visit. Therefore, a total of 87 patients were evaluable for efficacy in Cohort 3+Extension Cohort at Month 6. The efficacy results of Cohort 3+Extension Cohort were as follows:

- Complete and overall hematologic responses at Month 6 were 44% (95% CI: 33%, 55%) and 79% (95% CI: 69%, 87%), respectively.
- The median duration of CR for the 46 patients who achieved a complete response at any time was 24.3 months (95% CI: 23.0 months, NE). The median duration of ORR for the 70 patients who had achieved a response at any time was 24.3 months (21.4 months, NE).

Table 40 AUS01T: CR and ORR as Assessed by the Investigator

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=92
At Month 3, total n[a]	30	31	31	88
Overall response rate	23 (76.7%)	24 (77.4%)	27 (87.1%)	66 (75.0%)
95% CI	57.7, 90.1	58.9, 90.4	70.2, 96.4	64.6, 83.6
Complete response	5 (16.7%)	7 (22.6%)	15 (48.4%)	24 (27.3%)
95% CI	5.6, 34.7	9.6, 41.1	30.2, 66.9	18.3, 37.8
At Month 6, total n[a]	30	31	31	87
Overall response rate	24 (80.0%)	27 (87.1%)	29 (93.5%)	69 (79.3%)
95% CI	61.4, 92.3	70.2, 96.4	78.6, 99.2	69.3, 87.3
Complete response	10 (33.3%)	8 (25.8%)	18 (58.1%)	38 (43.7%)
95% CI	17.3, 52.8	11.9, 44.6	39.1, 75.5	33.1, 54.7
At Month 12, total n[a]	30	31	31	78
Overall response rate	9 (30.0%)	18 (58.1%)	23 (74.2%)	44 (56.4%)
95% CI	14.7, 49.4	39.1, 75.5	55.4, 88.1	44.7, 67.6
Complete response	5 (16.7%)	10 (32.3%)	16 (51.6%)	30 (38.5%)
95% CI	5.6, 34.7	16.7, 51.4	33.1, 69.8	27.7, 50.2

a. "Total n" is the number of subjects in the treatment group who reached this timepoint or withdrew earlier. It is denominator for percentage (%) calculation.

For the 25 pediatric patients (2 to 17 years of age) who had a Month 6 efficacy assessment in Cohort 3+Extension Cohort, the complete and overall hematologic response rates were 28% and 68%, respectively.

8. Review of Safety

8.1. Safety Review Approach

The sNDA contained safety information from the pivotal study AUS01T and supportive trials conducted in Japanese patients with moderate aplastic anemia (MAA) and SAA (ETB115E1201, ETB115E1202) and previously submitted studies (US28T and US18T) in the refractory SAA population. However, the above supportive trials treated patients with different regimen compared to the one proposed in the AUS01T pivotal trial (see table 4). The US28T and US18T trials served as the pivotal and supportive trials, respectively, for the refractory SAA indication and were included only to provide the historic rates of cytogenic abnormalities.

In addition, four publications that contained information of patients treated with h-ATG and CsA without eltrombopag [Tisdale et al (2000)], [Rosenfeld et al (2003)], [Scheinberg et al

(2009)], and [Scheinberg et al (2011) were included to provide context for safety evaluation of eltrombopag plus h-ATG+CsA therapy (see table 4). However, limited safety information was available from the publications.

The review of safety was primarily based on the pooled analysis of Cohort 3+Extension Cohort (i.e., the recommended dosing regimen of eltrombopag and h-ATG+CsA combination therapy) and also on the other cohorts (Cohorts 1 and 2) of the pivotal study AUS01T and included the following:

- Electronic submissions of the clinical study report and other relevant portions of the NDA were reviewed;
- Safety data were audited or reproduced;
- As the treatment regimens are similar in Cohort 1 and Cohort 2 for the first 3 months, pooled results from these 2 cohorts were conducted for early safety (at 13 days);
- When applicable, safety data from the supportive studies and publications were also reviewed;
- Applicant's responses to FDA information requests;
- Relevant published literature; and
- The 120-day safety update.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

According to the applicant, since the initial approval of eltrombopag in November 28, 2008, the cumulative post-marketing exposure worldwide until June 2017 is (b) (4) subject-years.

In 2014, eltrombopag received regular approval in the US for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. Per the applicant, eltrombopag is currently approved in over 45 countries for the refractory SAA indication.

The table below summarizes the studies to support the safety for this sNDA.

Table 41 Clinical Studies Supporting Safety in Patients with SAA

Trial ID	Subjects and Treatment	Cut-off date
Pivotal study		
AUS01T: h-ATG +CsA in combination with eltrombopag in definitive immunosuppressive therapy-naïve subjects with SAA	N = 123[a]: h-ATG + CsA +eltrombopag up to 150 mg/day[b]	September 30, 2016
Supportive studies		

E1202: r-ATG +CsA in combination with eltrombopag in treatment-naïve subjects with MAA or SAA	N=10 (7 SAA and 3 MAA) r-ATG + CsA + eltrombopag 75 mg/day[b]	January 2017
E1201: Eltrombopag alone in treatment-refractory subjects with MAA or SAA	N=21 (15 MAA and 6 SAA) Eltrombopag 100 mg/day[b]	March 2016
US28T: Eltrombopag alone in treatment-refractory subjects with SAA	N=43 Eltrombopag 150 mg/day	May 2014
US18T: Eltrombopag alone in treatment-refractory subjects with SAA	N=15 Eltrombopag 150 mg/day[b]	January 2015
Literature reports of relevant historical studies: h-ATG + CsA alone in subjects with SAA		
Scheinberg et al (2011)	N=60[c]: h-ATG + CsA	July 2010
Scheinberg et al (2009)	N=42[c]: h-ATG + CsA	November 2005
Tisdale et al (2000)	N=16: h-ATG + CsA	March 2000
Rosenfeld et al (2003)	N=122: h-ATG + CsA	January 1998

a. 124 patients were enrolled as of the cut-off date but one patient did not receive eltrombopag.
b. 150 mg is the approved refractory dose and dose given in Study AUS01T. Asian subjects received 50% of maximum dose of eltrombopag due to known ethnic difference in PK (2-fold higher exposure in Asians observed across indications).
c. Number of subjects enrolled in h-ATG+CsA treatment arm.
h-ATG: horse anti-thymocyte globulin, r-ATG: rabbit anti-thymocyte globulin, CsA: cyclosporine A, MAA: moderate aplastic anemia, SAA: severe aplastic anemia.
[Source: Summary of Clinical Safety]

AUS01T:
In the pivotal trial, patients in Cohorts 1, 2, Cohort 3+Extension Cohort were to receive eltrombopag from Day 14 to month 6 (168 days), from Day 14 to month 3 (77 days), from Day 1 to month 6 (182 days), respectively. Patients in all cohorts were to receive h-ATG Days 1-4 and the therapeutic dose of CsA from Day 1 to month 6 (182 days) followed by the maintenance CsA dose Month 6 to 24 (540 days) for patients enrolled in Cohort 2 (starting with patient 46), Cohort 3 and Extension Cohort.

In the combined Cohort 3+Extension cohort, the median exposure to eltrombopag was 180 days (range: 3-195 days). The median exposure to h-ATG was 4 days (range: 3-5 days). The median exposures to the therapeutic and maintenance dose of CsA in the combined Cohort 3+Extension Cohort were 183 days (range: 3-224 days) and 167 days (range: 12-488 days), respectively.

At the time of the cutoff date of September 30, 2016, a total of 15 of the 31 patients in the Extension Cohort were receiving eltrombopag and had not yet reached the Month 6 visit. The tables below summarize exposure to eltrombopag, h-ATG and CsA.

Table 42 AUS01T: Exposure to Eltrombopag (Safety Set)

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
Duration of treatment (days)				
Median	170	83	183	180
Range	38-183	32-94	28-195	3-195
≤ 6 weeks	2 (7%)	1 (3%)	1 (3%)	7 (11%)
>6 to ≤12 weeks	4 (13%)	28 (90%)	2 (7%)	8 (13%)
>12 to ≤24 weeks	5 (17%)	2 (7%)	5 (16%)	14 (23%)
>24 weeks	19 (63%)	0	23 (74%)	33 (53%)
Relative dose intensity (%)				
Median	100	100	97.8	99.2
Range	72.9-118.3	81.9-100.7	61.4-100	60.5-100

Relative dose intensity = 100 x [(Cumulative dose/Duration of exposure)/(Planned dose intensity)].
[Source: ADSL.xpt and ADEX.xpt]

Table 43 AUS01T: Exposure to h-ATG and CsA (Safety Set)

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
Exposure to h-ATG				
Duration of treatment (days)				
Median	4	4	4	4
Range	4-8	4-5	4-4	3-5
Relative dose intensity (%)				
Median	100	100	100.1	100.1
Range	50.4-103.4	40-101.6	98.4-103.4	85.8-103.9
Exposure to CsA therapeutic dose				
Duration of treatment (days)				
Median	187	185	186	183
Range	44-196	111-197	40-195	3-224
Relative dose intensity (%)				
Median	98.3	94.5	104.2	98.7
Range	45.3-155.7	32.8-200.4	20.5-190.6	20.5-190.6
Exposure to CsA maintenance dose				
Patients who received	0	15	28	38

maintenance dose				
Duration of treatment (days)	-			
Median	-	547	203	167
Range	-	13-739	29-488	12-488
Relative dose intensity (%)	-			
Median	-	100.9	108	109.6
Range	-	42.2-179.9	31.3-125.6	31.3-151.5

Relative dose intensity = 100 x [(Cumulative dose/Duration of exposure)/(Planned dose intensity)].
[Source: ADEX.xpt]

In the combined Cohort 3 and Extension Cohort, 50% of patients required dose adjustment of eltrombopag mostly due to platelet count > 200x 10^3/mcL.

Table 44 AUS01T: Eltrombopag Dose Adjustment in Cohort 3+Extension Cohort (Safety Set)

	Cohort 3+Extension N=62
Patients with dose adjustments	31 (50%)
Total number of dose adjustments	91
Reasons	
Platelet count > 200x 10^3/mcL	51 (56%)
Toxicity	20 (22%)
Adverse event	12 (13%)
Patient compliance	8 (9%)
Other reason	0
Platelet count > 400x 10^3/mcL	0

[Source: CSR AUS01T]

8.2.2. **Relevant characteristics of the safety population:**

In the AUS01T trial, the safety set in each cohort was identical to the full analysis set (efficacy population). Refer to tables 14, 15 and 16 under section 6.1.2 of this review.

8.2.3. **Adequacy of the safety database**

As stated in sections 3.1 and 8.2.1, eltrombopag received initial approval in 2008 for the treatment of thrombocytopenia in adult patients with chronic ITP. In 2015 and 2016, the ITP indication was expanded to include pediatric patients ≥6 and ≥1 years, respectively.

In 2014, eltrombopag received regular approval for the treatment of patients with SAA who have had an insufficient response to immunosuppressive therapy based on a single-arm open-

label trial in 43 patients (study ETB115AUS28T [or ELT112523]). Eltrombopag is currently approved in over 45 countries for the refractory SAA indication.

With regard to the proposed first-line SAA indication and the proposed dosing regimen of eltrombopag in combination with h-ATG+CsA in this sNDA, the safety data is primarily based on Cohort 3 + the Extension Cohort (n=62) of the pivotal single-arm trial (AUS01T). Together with the safety data from other cohorts (Cohorts 1 and 2) of the AUS01 trial and supportive studies and literature reports (see table 41 under section 8.2.1), the total safety database is acceptable.

However, per the applicant statement during the August 2016 meeting, grade 1 and 2 AEs, and labeled events or reactions were not consistently captured (per NIH protocol) during the study and not presented. When comparing the overall incidences of reported adverse events from study AUS01T (that treated patients with eltrombopag in combination with standard IST as first-line treatment) with the safety results from the pivotal study (ETB115AUS28T) that treated patient with refractory SAA with single-agent eltrombopag, it appeared that safety events were underreported for the AUS1T trial.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The submission contains appropriate safety analyses and reports. No major concerns regarding data integrity were identified during the safety review. The overall quality of data appears to be adequate for safety evaluation.

8.3.2. Categorization of Adverse Events

In the AUS01T trial, MedDRA terminology version 20.1 was used to categorize adverse events. AEs were graded according to the National Cancer Institute Common Technology Criteria for Adverse Events (NCI-CTCAE) version 4.03 coding system. Grade Mapping of the verbatim AE terms to MedDRA Preferred Term and System Organ Class (SOC) was acceptable.

8.3.3. Routine Clinical Tests

Routine clinical assessments in the AUS01T trial included CBC with differential, reticulocyte count, chemistry panel, and CsA blood level monitoring. Refer to Table 6 for detailed schedule of safety assessments.

8.4. Safety Results

The table below summarizes the overall safety results of the AUS01T trial.

Table 45 AUS01T: Overall Summary of Safety (Safety Set, September 30, 2016 Data Cutoff)

	Cohort 1 N=30		Cohort 2 N=31		Cohort 3 N=31		Cohort 3+Ext. N=62	
	All Grades	≥Grade 3	All Grades	≥Grade 3	All Grades	≥Grade 3	All Grades	≥Grade 3
All AEs	19 (63%)	16 (53%)	21 (68%)	18 (58%)	25 (81%)	21 (68%)	47 (76%)	39 (63%)
Related to eltrombopag	13 (43%)	9 (30%)	13 (42%)	11 (36%)	22 (71%)	18 (58%)	38 (61%)	32 (52%)
All deaths	3 (10%)	-	0	-	0	-	0	-
Deaths within 30 days of last dose of eltrombopag	1 (3%)	-	0	-	0	-	0	-
SAEs	13 (43%)	12 (40%)	12 (39%)	12 (39%)	13 (42%)	11 (36%)	26 (42%)	22 (36%)
Related to eltrombopag	6 (20%)	6 (20%)	8 (26%)	8 (26%)	7 (23%)	5 (16%)	13 (21%)	10 (16%)
AEs leading to treatment discontinuation	1 (3%)	1 (3%)	1 (3%)	1 (3%)	1 (3%)	0	4 (7%)	3 (5%)
AEs requiring dose interruption/ adjustment	1 (3%)	1 (3%)	1 (3%)	1 (3%)	9 (29%)	9 (29%)	15 (24%)	15 (24%)

[Source: ADAE.xpt]

8.4.1. **Deaths**

In the AUS01T trial, a total of 3 patients (all in cohort 1) had died at the September 30, 216 clinical data cutoff. Of the 3 patients, one patient (ID: (b) (6)) died on-treatment (on Day 85) with eltrombopag and CsA, due to toxic metabolic encephalopathy and central respiratory failure that was attributed to thymoma that existed before study entry. The other 2 patients died due to HSCT-related cause during follow-up, approximately 1 and 2 years after the end of therapy, respectively. None of the deaths were assessed as related to study treatment. The narrative for patient (ID: (b) (6)) is presented below.

Patient (ID: (b) (6)) was a 55-year old male diagnosed with severe aplastic anemia. Relevant medical history included hepatic steatosis, cholecystectomy, pancytopenia, febrile neutropenia, bone marrow biopsy, and neutropenia. Active medical conditions included fatigue, mediastinal mass, pulmonary mass (all grade 3), petechiae, contusion, decreased appetite (all grade 1), pain, stomatitis, and multiple sclerosis (all grade 2). The patient was enrolled in Cohort 1 on (b) (6) and received the first dose of the study treatment (h-ATG, cyclosporine A) on Day 1 (b) (6), and eltrombopag on Day 14 (b) (6). Prior to study enrollment, the patient had severe neutropenia (ANC: 0/mcL; reference range and baseline value not reported). Baseline CT scans identified a mediastinal mass and multiple lung infiltrates. The biopsy of the

mediastinal mass was abnormal and was diagnostic for thymoma. On Day 7 (b) (6), the patient was hospitalized with grade 3 febrile neutropenia. On an unspecified day, a CT scan of the lungs showed lung lesions, which were temporally associated with the bacteremia and consistent with Pseudomonas pneumonia that spread to the blood and skin. The event febrile neutropenia (grade 3) resolved on Day 8 (b) (6). On Day 38 (b) (6), the patient had total bilirubin 60 micromol/L (grade 2), direct bilirubin 27 micromol/L, ALP 145 U/L (grade 1), ALT 12 U/L, and AST 14 U/L. From Day 39 (b) (6) to Day 83 (b) (6), ALT ranged from 12 U/L to 459 U/L (grade 3), AST ranged from 8 U/L to 676 U/L (grade 3), ALP ranged from 82 U/L to 188 U/L (grade 1), total bilirubin ranged from 70 micromol/L (grade 3) to 29 micromol/L (grade 1), and direct bilirubin ranged from 36 micromol/L to 7 micromol/L. No action was taken with the study treatment (cyclosporine, eltrombopag) due to the event (blood bilirubin increased). On Day 67 (b) (6), the patient developed pericardial tamponade (grade 4) and was also noted with hypotension (grade 4; blood pressure: 93/45 mmHg), which led to prolongation of hospitalization. The events (cardiac tamponade, hypotension) completely resolved on the same day (b) (6). The study drug (eltrombopag) was temporarily interrupted on Day 68 (b) (6) due to toxicity. The study drug (eltrombopag) was restarted at a reduced dose (125 mg once daily) on Day 72 (b) (6) (b) (6). On the same day (b) (6), the patient was intubated due to progressive deterioration of mental status and inability to maintain airway. On Day 84 (b) (6), a plasmapheresis was attempted, which was unsuccessful. The event blood bilirubin increased (grade 3) resolved the same day (b) (6) with total bilirubin at 51 micromol/L (grade 2), direct bilirubin 22 micromol/L, ALP 97 U/L (grade 1), ALT 10 U/L, and AST 14 U/L. On an unspecified day, thymoma was resected without complications; however, the patient developed progressive delirium suspicious for encephalopathy, the neurology made a presumptive diagnosis of autoimmune encephalopathy associated with thymoma and antibodies were positive, and consistent with a paraneoplastic encephalopathy associated with an extremely poor prognosis. On Day 85 (b) (6), the patient developed autoimmune encephalopathy, central respiratory failure, and was terminally extubated. On the same day (b) (6), the hemogram showed a white blood cell count 0.95 × 10^9/L, hemoglobin 79 g/L (grade 3), platelet count 26 × 10^9/L (grade 3), ANC 0 × 10^9/L (grade 4), total bilirubin 48 micromol/L (grade 2), direct bilirubin 21 micromol/L, creatinine 117 mciromol/L (grade 1), and urea nitrogen 24.3 mmol/L. The study treatment (eltrombopag, cyclosporine A) permanently discontinued due to the event (encephalopathy) and the subject received the last dose on the same day (b) (6). On the same day, the patient did not regain consciousness and was unable to maintain airway and died due to nonhematologic cause, toxic metabolic encephalopathy (grade 5) associated with thymoma and central respiratory failure. The subject's autopsy details were not reported. It was reported that the presumptive cause of death was autoimmune encephalopathy causing central respiratory failure.

No deaths were reported in studies E2102 and E2101.

8.4.2. **Serious Adverse Events**

In the AUS01T trial, 42% of patients in Cohort 3+Extension Cohort experienced an SAE which is similar to the incidences reported in Cohorts 1, 2 and 3. SAEs reported in ≥5% of patients in Cohort 3+Extension Cohort were serum sickness, febrile neutropenia, and rash maculopapular. Other SAEs that occurred in ≥ 2 patients in Cohort 3+Extension Cohort were infusion related reaction, lung infection, pharyngitis and sinusitis (all 3%).

Review comment: All cases of serum sickness was observed during the first 13 days, close to the time when the patients were receiving h-ATG (Day 1 to Day 4). Serious immune-mediated reactions such as anaphylaxis, other infusion associated reactions, and including serum sickness have been reported with the use of h-ATG. Serum sickness usually occurs 5-10 days after exposure. In the AUS01T trial, h-ATG was administered on Days 1-4 in all cohorts. All incidences of serum sickness in all cohorts began on Days 10-13 of treatment and resolved within one week.

Review comment: Rash is a known AE of eltrombopag and h-ATG.

According Scheinberg et al (2009), Scheinberg et al (2011), Tisdale et al (2000), and Rosenfeld et al (2003), the most frequently reported SAEs in patients treated with h-ATG + CsA without eltrombopag were infections (21%) and febrile neutropenia (12%). Although cross-study comparisons should be conducted with caution, it does not appear that the addition of eltrombopag causes unacceptable incidence of SAEs.

Table 46 AUS01T: Serious Adverse Events that Occurred in ≥ 2 Patients in Any Cohort (Safety Set)

Preferred Term	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
All SAEs	13 (43%)	12 (39%)	13 (42%)	26 (42%)
Serum sickness[a]	0	2 (7%)	4 (13%)	6 (10%)
Febrile neutropenia	2 (7%)	5 (16%)	1 (3%)	5 (8%)
Rash maculopapular	0	1 (3%)	1 (3%)	3 (5%)
Infusion related reaction	0	0	1 (3%)	2 (3%)
Lung infection	1 (3%)	1 (3%)	1 (3%)	2 (3%)
Pharyngitis	0	0	0	2 (3%)
Sinusitis	1 (3%)	0	1 (3%)	2 (3%)
Device related infection	0	2 (7%)	0	0

a. All cases of serum sickness were assessed as "unlikely" related to eltrombopag.
[Source: ADAE.xpt]

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

At the September 30, 2016 data cutoff, a total of 6 patients discontinued study treatment (eltrombopag) due to AEs (rash maculopapular: 4 patients, colitis: 1 patient, encephalopathy: 1

patient). The one patient (ID: (b) (6)) who had encephalopathy resulted in a fatal outcome (see section 8.4.1).

Table 47 Adverse Events Leading to Treatment Discontinuation (Safety Set)

Preferred Term	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
All AEs	1 (3%)	1 (3%)	1 (3%)	4 (7%)
Rash maculopapular	0	1 (3%)	1 (3%)	3 (5%)
Colitis	0	0	0	1 (2%)
Encephalopathy	1 (3%)	0	0	0

[Source: ADAE.xpt]

Treatment interruption/adjustments:
The only adverse events that required dose interruption/adjustments of study treatment (eltrombopag) in more than 1 patient in study AST01T were due to ALT increased and AST increased which occurred at higher incidences in Cohort 3 (ALT increased: 23%, AST increased: 16%) and Cohort 3+Extension Cohort (ALT increased: 18%, AST increased: 15%) compared to Cohort 1 (ALT increased: 3%, AST increased: 0%) or Cohort 2 (ALT increased: 0%, AST increased: 0%).

Review comment: In Cohorts 1 and 2, eltrombopag was administered from Day 14 to prevent potential overlapping hepatotoxicity of the combination therapy (i.e., eltrombopag with CsA and h-ATG). Cohort 3 was added to potentially accelerate the hematologic recovery after available data from Cohort 1 and 2 (which indicated that the combination of CsA+h-ATG and eltrombopag was safe and well tolerated). However, the incidences of ALT/AST increased are higher in Cohort 3 and Cohort 3+Extension Cohort in which the administration of eltrombopag started on Day 1 in combination with CsA and h-ATG.

Table 48 AUS01T: Adverse Events requiring Dose Interruption/Adjustments of Study Treatment in ≥ 2 Patients in Cohort 3+Extension Cohort (Safety Set)

Preferred Term	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
All AEs	1 (3%)	1 (3%)	9 (29%)	15 (24%)
ALT increased	1 (3%)	0	7 (23%)	11 (18%)
AST increased	0	0	5 (16%)	9 (15%)

[Source: ADAE.xpt]

8.4.4. Significant Adverse Events

In the AUS01T trial, grade 3 or higher AEs occurred in 53%, 58%, 68% and 63% of patients in Cohorts 1, 2, 3 and Cohort 3+Extension Cohort, respectively (see table 50) at the September 30, 2016 cutoff. The most frequently reported ≥ grade 3 AEs (≥5%) in Cohort 3+Extension Cohort

were ALT increased, AST increased, febrile neutropenia, blood bilirubin increased, serum sickness and lung infection.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In the AUS01T trial, adverse events by System Organ Class (SOC) that occurred ≥10% in Cohort 3+Extension Cohort were investigations (37%), infections and infestations (29%), skin and subcutaneous tissue disorders (18%), blood and lymphatic system disorders (16%), gastrointestinal disorders (15%) and immune system disorders (10%).

Table 49 AUS01T: Adverse Events that Occurred in ≥ 5% of Patients in Any Cohort by System Organ Class (Safety Set)

System Organ Class	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
All AEs	19 (63%)	21 (68%)	25 (81%)	47 (76%)
Investigations	6 (20%)	8 (26%)	13 (42%)	23 (37%)
Infections and infestations	9 (30%)	10 (32%)	7 (23%)	18 (29%)
Skin and subcutaneous tissue disorders	1 (3%)	1 (3%)	7 (23%)	11 (18%)
Blood and lymphatic system disorders	3 (10%)	5 (16%)	6 (19%)	10 (16%)
Gastrointestinal disorders	6 (20%)	2 (7%)	7 (23%)	9 (15%)
Immune system disorders	1 (3%)	2 (7%)	4 (13%)	6 (10%)
Eye disorders	3 (10%)	2 (7%)	2 (7%)	4 (7%)
Hepatobiliary disorders	0	0	2 (7%)	4 (7%)
Metabolism and nutrition disorders	1 (3%)	1 (3%)	3 (10%)	4 (7%)
Respiratory, thoracic and mediastinal disorders	1 (3%)	1 (3%)	3 (10%)	4 (7%)
Injury, poisoning and procedural complications	0	0	2 (7%)	3 (5%)
Vascular disorders	2 (7%)	0	2 (7%)	3 (5%)
Ear and labyrinth disorders	2 (7%)	0	2 (7%)	2 (3%)
Nervous system disorders	3 (10%)	2 (7%)	1 (3%)	2 (3%)
Psychiatric disorders	2 (7%)	1 (3%)	0	1 (2%)
Cardiac disorders	2 (7%)	1 (3%)	0	0
General disorders and administration site conditions	3 (10%)	1 (3%)	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (7%)	1 (3%)	0	0

[Source: ADAE.xpt]

The overall incidences of AEs in Cohort 3 and Cohort 3+Extension Cohort were 81% and 76%, respectively, and were higher than in Cohort 1 (63%) or Cohort 2 (68%). The most frequently reported AEs (≥10%) in Cohort 3+Extension Cohort were ALT increased, AST increased, febrile neutropenia, blood bilirubin increased, and serum sickness.

Table 50 AUS01T: Adverse Events that Occurred in ≥ 5% of Patients in Any Cohort (Safety Set)

Preferred Term	Cohort 1 N=30		Cohort 2 N=31		Cohort 3 N=31		Cohort 3+Ext. N=62	
	All Grades	≥Grade 3	All Grades	≥Grade 3	All Grades	≥Grade 3	All Grades	≥Grade 3
All AEs	19 (63%)	16 (53%)	21 (68%)	18 (58%)	25 (81%)	21 (68%)	47 (76%)	39 (63%)
ALT increased	1 (3%)	1 (3%)	4 (13%)	4 (13%)	11 (36%)	11 (36%)	17 (27%)	17 (27%)
AST increased	0	0	1 (3%)	1 (3%)	7 (23%)	7 (23%)	12 (19%)	12 (19%)
Febrile neutropenia	2 (7%)	2 (7%)	5 (16%)	5 (16%)	6 (19%)	6 (19%)	10 (16%)	10 (16%)
Blood bilirubin increased	5 (17%)	5 (17%)	5 (16%)	5 (16%)	4 (13%)	4 (13%)	9 (15%)	9 (15%)
Serum sickness	0	0	2 (7%)	2 (7%)	4 (13%)	3 (10%)	6 (10%)	5 (8%)
Rash[a]	1 (3%)	0	1 (3%)	1 (3%)	1 (3%)	0	4 (6%)	2 (3%)
Infusion related reaction	0	0	0	0	2 (7%)	0	3 (5%)	1 (2%)
Lung infection	2 (7%)	2 (7%)	1 (3%)	1 (3%)	1 (3%)	1 (3%)	3 (5%)	3 (5%)
Skin hyperpigmentation	0	0	0	0	2 (7%)	0	3 (5%)	0
Abdominal pain	2 (7%)	1 (3%)	1 (3%)	1 (3%)	2 (7%)	2 (7%)	2 (3%)	2 (3%)
Device related infection	0	0	2 (7%)	2 (7%)	1 (3%)	1 (3%)	2 (3%)	2 (3%)
Hypokalemia	0	0	0	0	2 (7%)	2 (7%)	2 (3%)	2 (3%)
Upper respiratory tract infection[b]	1 (3%)	0	2 (7%)	0	0	0	1 (2%)	1 (2%)
Stomatitis	2 (7%)	0	0	0	1 (3%)	0	1 (2%)	0
Depression	2 (7%)	1 (3%)	0	0	0	0	0	0
Gastro-esophageal reflux disease	2 (7%)	0	1 (3%)	0	0	0	0	0
Edema peripheral	2 (7%)	0	1 (3%)	1 (3%)	0	0	0	0
Urinary tract infection	1 (3%)	0	2 (7%)	1 (3%)	0	0	0	0

a. Includes rash maculo-papular and rash pustular.
b. Includes upper respiratory infection bacterial.
[Source: ADAE.xpt]

The most frequently reported AEs assessed as related to eltrombopag (≥10%) in Cohort

3+Extension Cohort were ALT increased, AST increased and blood bilirubin increased.

Table 51 AUS01T: Adverse Events Assessed as Related to Eltrombopag that Occurred in ≥ 5% in Any Cohort (Safety Set)

Preferred Term	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
All AEs	13 (43%)	13 (42%)	22 (71%)	38 (61%)
ALT increased	0	1 (3%)	11 (36%)	16 (26%)
AST increased	0	0	7 (23%)	12 (19%)
Blood bilirubin increased	4 (13%)	2 (7%)	4 (13%)	8 (13%)
Serum sickness[a]	0	1 (3%)	3 (10%)	4 (7%)
Febrile neutropenia	0	5 (16%)	2 (7%)	3 (5%)
Skin hyperpigmentation	0	0	2 (7%)	3 (5%)
Hypokalemia	0	0	2 (7%)	2 (3%)
Stomatitis	2 (7%)	0	1 (3%)	1 (2%)
Gastrooesophageal reflux disease	2 (7%)	1 (3%)	0	0
Edema peripheral	2 (7%)	0	0	0

a. All 5 cases of serum sickness were assessed as "unlikely" related to eltrombopag. However, it has been included in this table for completeness.
[Source: ADAE.xpt]

In the AUS01T trial, patients in Cohorts 1 and 2 eltrombopag treatment started on Day 14 while in Cohort 3+Extension Cohort eltrombopag treatment started on Day 1. The table below summarizes the AEs that occurred during the first 13 days in these cohort groups. During the first 13 days, higher proportion of patients in Cohort 3+Extension Cohort (53%) experienced AEs compared to Cohorts 1+2 (31%) mostly due to differences in ALT/AST increased and serum sickness.

Table 52 AUS01T: Adverse Events that Occurred in ≥ 2 Patients in Cohorts 1+2 or in Cohort 3+Extension Cohort During the First 13 Days (Safety Set)

Preferred Term	Cohorts 1+2 N=61	Cohort 3+Ext N=62
All AEs	19 (31%)	33 (53%)
ALT increased	3 (5%)	16 (26%)
AST increased	1 (2%)	10 (16%)
Serum sickness	2 (3%)	6 (10%)
Blood bilirubin increased	2 (3%)	3 (5%)
Febrile neutropenia	2 (3%)	3 (5%)
Abdominal pain	2 (3%)	1 (2%)
Gastroesophageal reflux disease	2 (3%)	0

[Source: ADAE.xpt]

8.4.6. **Laboratory Findings**

Hematology:
In the AUS01T trial, supportive care including transfusion support (blood and platelets) and administration of hematopoietic growth factors (e.g., G-CSF, GM-CSF, or erythropoietin) were permitted as clinically indicated at baseline and during the treatment period. The applicant notes that although transfusion could be given during the treatment period, the reporting of the worst grade post-baseline is likely to be recorded when the patient was not transfused.

The table below summarizes the shifts in hematology laboratory tests from baseline to worst grades that occurred at any time during treatment. The laboratory values could initially drop before improving. There were no clinically meaningful differences between the cohorts.

Table 53 AUS01T: Shifts in Hematology Laboratory Tests (Safety Set, On-Treatment)*

	Worsening from baseline to	**Cohort 1 N=30**	**Cohort 2 N=31**	**Cohort 3 N=31**	**Cohort 3+Ext. N=62**
Hemoglobin	Grade 1	0	0	0	0
	Grade 2	1/6 (17%)	1/6 (17%)	1/5 (20%)	2/11 (18%)
	Grade 3	25/27 (93%)	22/25 (88%)	23/29 (79%)	49/55 (86%)
Neutrophils	Grade 1	0	0	0	1/1 (100%)
	Grade 2	1/1 (100%)	0	0	0
	Grade 3	2/3 (67%)	0	1/3 (33%)	2/5 (40%)
	Grade 4	8/15 (53%)	10/11 (91%)	8/12 (67%)	10/21 (48%)
Platelets	Grade 1	0	0	0	0
	Grade 2	0	0	0	0
	Grade 3	0	0	0	0
	Grade 4	24/24 (100%)	22/22 (100%)	24/24 (100%)	41/41 (100%)

Hemoglobin and platelet assessment at Baseline could have been done after the subject has been transfused.
*The percentages= number of patients whose grade worsened/total number of patients (who had missing or less than grade x at Baseline and) with at least one post-Baseline value for the considered parameter.
All on-treatment laboratory data at any time are included.
[Source: CSR AUS01T and ADLB.xpt]

Biochemistry:
In the AUS01T trial, patients received combination therapy with eltrombopag, CsA and h-ATG. All three drugs are known to cause liver function abnormalities and; eltrombopag and CsA can also cause hyperbilirubinemia. Tables 54 and 55 summarize shifts in biochemistry and liver function tests by worsening grade from baseline, respectively.

In Cohort 3+Extension Cohort, most of the ALP, creatinine, hyper- and hypoglycemia by worst-

case values were grades 1 or 2. Worst-grade shifts to ≥grade 3 AST, ALT and bilirubin occurred in 19%, 34% and 17% of patients, respectively, in Cohort 3+Extension Cohort and generally, the incidences were not higher when compared to Cohort 1 or 2.

Table 54 AUS01T: Shifts in Chemistry Laboratory Tests (Safety Set)

		Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
	Worsening from baseline to				
AST	Grade 1	15/25 (60%)	11/29 (38%)	9/27 (33%)	17/56 (30%)
	Grade 2	3/30 (10%)	7/31 (23%)	5/31 (16%)	9/62 (15%)
	Grade 3	4/30 (13%)	7/31 (23%)	6/31 (19%)	10/62 (16%)
	Grade 4	2/30 (7%)	2/31 (7%)	1/31 (3%)	2/62 (3%)
ALT	Grade 1	7/20 (35%)	7/22 (32%)	6/24 (25%)	12/47 (26%)
	Grade 2	7/29 (24%)	3/31 (10%)	9/28 (32%)	16/58 (28%)
	Grade 3	8/30 (27%)	15/31 (48%)	11/30 (37%)	19/61 (31%)
	Grade 4	3/30 (10%)	2/31 (7%)	1/31 (3%)	2/62 (3%)
Bilirubin	Grade 1	4/19 (21%)	4/22 (18%)	4/20 (20%)	13/46 (28%)
	Grade 2	12/26 (46%)	13/27 (48%)	13/26 (50%)	25/54 (46%)
	Grade 3	12/30 (40%)	10/31 (32%)	5/31 (16%)	9/62 (15%)
	Grade 4	0	1/31 (3%)	0	1/62 (2%)
ALP	Grade 1	17/24 (71%)	14/21 (67%)	12/20 (60%)	17/39 (44%)
	Grade 2	4/30 (13%)	7/30 (23%)	3/31 (10%)	11/62 (18%)
	Grade 3	0	0	0	1/62 (2%)
	Grade 4	0	0	0	0
Creatinine	Grade 1	12/30 (40%)	13/31 (42%)	9/30 (30%)	16/61 (26%)
	Grade 2	1/30 (3%)	2/31 (7%)	2/31 (7%)	2/62 (5%)
	Grade 3	1/30 (3%)	2/31 (7%)	0	0
	Grade 4	0	0	0	0
Hyperglycemia	Grade 1	17/28 (61%)	13/23 (57%)	10/24 (42%)	27/48 (56%)
	Grade 2	11/30 (37%)	13/29 (45%)	16/29 (55%)	23/59 (39%)
	Grade 3	2/30 (7%)	2/31 (7%)	2/31 (7%)	3/61 (5%)
	Grade 4	0	0	0	0
Hypoglycemia	Grade 1	5/30 (17%)	4/31 (13%)	4/31 (13%)	11/62 (18%)
	Grade 2	0	1/31 (3%)	0	0
	Grade 3	1/30 (3%)	0	0	0
	Grade 4	0	0	0	0

*The percentages= number of patients whose grade worsened / total number of patients (who had missing or less than grade x at Baseline and) with at least one post-Baseline value for the considered parameter.
[Source: CSR AUS01T and ADLB.xpt]

In the AUS01T trial, a total of 40 patients met the criteria of ALT or AST > 3xULN and TBIL > 2xULN and (ALP < 2xULN or missing) at the September 30, 2016 data cutoff. Of the 40 patients, 26 patients were reported to have met the criteria prior to the eltrombopag treatment

initiation (Cohort 1: 8 patients, Cohort 2: 14 patients, Cohort 3: 3 patients, Extension Cohort: 1 patient). The remaining 14 cases occurred after initiation of the eltrombopag treatment, however**,** none of the cases were confirmed as drug induced liver injury (DILI) related to eltrombopag. Generally, the elevations in liver function tests were transient. Some patients had transaminases (ALT/AST) elevations that were sequential and not concomitant to the increases in bilirubin. Some patients also received concomitant medications known to cause elevations of liver function tests or confounding medical history. None of the patients discontinued eltrombopag due to elevations in liver function tests (see section 8.4.3).

Table 55 AUS01T: Elevations in Liver Function Tests (Safety Set)

	Cohort 1 N=30	**Cohort 2 N=31**	**Cohort 3 N=31**	**Cohort 3+Ext. N=62**
ALT or AST > 3xULN	18 (60%)	20 (65%)	23 (74%)	40 (65%)
ALT or AST > 5xULN	11 (37%)	17 (55%)	13 (42%)	22 (36%)
ALT or AST > 8xULN	8 (27%)	12 (39%)	6 (19%)	12 (19%)
ALT or AST > 20xULN	3 (10%)	2 (7%)	1 (3%)	2 (3%)
TBIL > 2xULN	17 (57%)	17 (55%)	15 (48%)	25 (40%)
ALT or AST > 3xULN and TBIL > 1.5xULN	13 (43%)	19 (61%)	17 (55%)	29 (47%)
ALT or AST > 3xULN and TBIL > 2xULN	9 (30%)	14 (45%)	11 (36%)	17 (27%)
ALT or AST > 3xULN and TBIL > 2xULN and (ALP < 2xULN or missing)	9 (30%)	14 (45%)	11 (36%)	17 (27%)

Based on worst post-Baseline value for each parameter, obtained from samples collected within maximum 30 days of each other.
[Source: CSR AUS01T and ADLB.xpt]

The table below summarizes the cases of the 14 patients who met the criteria of ALT or AST > 3xULN and TBIL > 2xULN and (ALP < 2xULN or missing) while receiving treatment with eltrombopag. Except for patient (b) (6) who was enrolled in Cohort 1, these patients were enrolled in Cohort 3 or the Extension Cohort indicating that the Cohort 3/Extension Cohort dose regimen is more hepatotoxic compared with the Cohort 1 or Cohort 2 dose regimen. Among the patients listed in the table below, the Hy's law can be applied to patients (b) (6). However, after eltrombopag treatment interruption, the event resolved in all three cases.

Patients (b) (6) were also taking other concomitant drugs known to cause increase in liver transaminases: therefore, Hy's law cannot be applied to these patients.

Table 56 AUS01T: Patients with ALT or AST > 3xULN and TBIL > 2xULN and (ALP < 2xULN or missing) During Treatment with Eltrombopag (Safety Set)

	Elevated LFTs or TBIL occurred at			LFTs or TBIL elevation led to eltrombopag interruption	Recovered while on eltrombopag
Patient/ Age/ Cohort	Base-line	Day on eltrombopag	Relevant medical history or concomitant med while on eltrombopag		
(b) (6)/55 yo Cohort 1	No	Transaminases and bilirubin elevation started on Day 54 and Day 52, respectively, concomitant to hospitalization due to grade 4 pericardial tamponade and pseudomonas aeruginosa infection events.	Cardiac tamponade and pseudomonas aeruginosa.	No	No (grade 5 Encephalopathy)
(b) (6)/56 yo Cohort 3	Grade 3 ALT	Transaminases and bilirubin elevation started together on Day 105 and recovered on Day 112 and Day 168, respectively.	No	No	Yes
(b) (6)/32 yo Cohort 3	No	Transaminases and bilirubin elevation started on Day 2 and Day 5, respectively. Transaminases recovered on Day 12. Bilirubin recovered on Day 7, elevated again on Day 14, persisted elevated till Day 52 and recovered.	-Gastritis -Lorazepam (as needed) on Days 1-218	Interrupted on Day 2 due to transaminitis for 3 days	Yes
(b) (6)/16 yo Cohort 3	No	Transaminases and bilirubin elevation started on Day 11. Transaminases recovered on Day 12. Bilirubin persisted elevated till Day 67 and recovered.	Sertraline	Therapy was discontinued on Day 28 due to SAE of rash	Yes

(b) (6)/26 yo Cohort 3	No	Transaminases and bilirubin elevated on Day 9. Transaminases recovered on Day 10. Bilirubin persisted elevated till Day 174 and recovered (on same day completion of eltrombopag treatment)	No	No	Yes
(b) (6)/32 yo Cohort 3	Grade 2 Total Bilirubin	Transaminases reported elevated only on Day 8. Bilirubin was elevated since baseline and recovered on Day 9.	No	No	Yes
(b) (6)/72 yo Cohort 3	No	Transaminases and bilirubin elevation started on Day 2 and Day 6, respectively. Transaminases recovered on Day 19 and bilirubin on Day 15	No	Interrupted on Day 2 due to transaminitis for 2 days.	Yes
(b) (6)/15 yo Cohort 3	No	Transaminases and bilirubin elevation started on Day 6 and Day 12, respectively. Transaminases recovered on Day 19 and bilirubin persisted elevated until Day 187 when recovered (3 days after completion of eltrombopag treatment)	No	Interrupted on Day 9 due to transaminitis for 6 days.	Yes for transaminases
(b) (6)/56 yo Cohort 3	No	Transaminases and bilirubin elevations started on Day 2 and Day 7, respectively, and recovered on Day 23 and Day 13, respectively.	No	Interrupted on Day 8 for 13 days due to transaminases increase.	Yes
(b) (6)/33 yo Cohort 3	No	Transaminases and bilirubin elevations started Day 62	Past CT scan findings of multiple gallstones and	Eltrombopag was already discontinued	Yes

		concomitant to hepatic infection event and recovered on Day 107	ALT increase - current hepatic infection	on Day 29 due to rash maculo-papular SAE.	
(b) (6)/71 yo Extension Cohort	Grade 2 TBIL	Transaminases and bilirubin elevations started on Day 3 and Day 16, respectively, and recovered on Day 8 and Day 22, respectively.	Elevated LFTs, Breast cancer, cervical cancer	Interrupted on Day 3 due to transaminitis for 5 days.	Yes
(b) (6)/ 65 yo/ Extension Cohort	No	Transaminases and bilirubin elevations stared on Day 40 and Day 41, respectively, and recovered on Day 110 and Day 117, respectively.	Hypertriglycerides simvastatin	No	Yes
(b) (6)/ 21 yo/ Extension Cohort	No	Transaminases reported elevation on Day 36 only. Isolated bilirubin elevation started on Day 54 and recovered on Day 78	Cecal infection	No	Yes
(b) (6)/ 65 yo/ Extension Cohort	No	Transaminases elevation started on Day 2 and became persistent elevated on Day 26. Bilirubin elevation started on Day 15 and persisted elevated until Day 71. On Day 51 subject was hospitalized due to SAE of septic cholestasis and withdrew from study on Day 71	hypercholesterolemia, atorvastatin	Discontinued eltrombopag on Day 12 due to serious typhilitis.	No

[Source: AUS01T CSR]

8.4.7. **Vital Signs**

No clinically relevant changes from baseline were reported for vital signs (systolic and diastolic blood pressure, pulse or temperature) in this sNDA.

8.4.8. **Electrocardiograms (ECGs)**

Overall, no clinically significant safety findings in ECG results were reported due to study treatment.

In the AUS01T trial, a total of 11 patients with normal ECGs at the baseline had ECG findings at Month 3. However, none of these ECG findings were considered clinically relevant except for patient (b) (6) (Cohort 2) who had an ECG finding (sinus bradycardia and QTcF prolongation; V-rate <60 bpm left bundle branch block; QRSd >120 msec, broad/notched R prolonged QT interval QTc >460 msec) that was associated to an SAE of grade 4 myocardial infarction which occurred prior to starting the study drug.

In the E1202 trial, one patient had clinically significant change from baseline in QTcF (>60 msec) which led to discontinuation of eltrombopag. The QTcF in the patient was 381 msec at baseline, 447 msec at the onset of the AE (Day 136), and 421 msec at the withdrawal visit (Day 154). The outcome of the electrocardiogram QT prolonged was reported as recovered/resolved and the event was considered unrelated to study treatment.

8.4.9. **QT**

See section 8.4.8.

8.4.10. **Immunogenicity**

No information regarding immunogenicity was included in this application.

8.5. **Analysis of Submission-Specific Safety Issues**

Adverse events of special interest included the following: bleeding, hepatobiliary events, thromboembolic events, renal events, hematological malignancies (incidence of new malignancy or worsening of current malignancy with suspected causality to study treatment particularly myelodysplasia), bone marrow fibrosis (development or progression of bone marrow fibrosis), recurrence of thrombocytopenia after eltrombopag withdrawal and cytogenetic abnormalities.

8.5.1. **Bleeding Events**

Bleeding is a complication of SAA. In the AUS01T trial, a total of 10 bleeding AEs were experienced in 7 patients. Of the 10 bleeding AEs, 5 events (immune thrombocytopenic purpura, small intestinal hemorrhage, hematoma, lower gastrointestinal hemorrhage and menorrhagia) were considered serious. However, none of the bleeding events led to therapy discontinuation or dose interruption/adjustment. In Cohort 1, 2 patients had several types of bleeding:

Patient (b) (6) had an active medical condition at baseline of epistaxis, gingival bleeding and abdominal pain. During the study, this patient experienced bleeding events of ileal hemorrhage, hematoma and lower gastrointestinal hemorrhage that resolved without study drug adjustment or interruption.

Patient (b) (6) had a medical history of subarachnoid hemorrhage and epistaxis, and an active medical condition at baseline of bruising and gum bleeding. During the study, this patient had bleeding events of epistaxis and conjunctival hemorrhage that resolved without study drug adjustment or interruption.

Table 57 AUS01T: The Incidences of Bleeding Events (Safety Set)

Preferred Term	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
All	4 (13%)	1 (3%)	1 (3%)	2 (3%)
Menorrhagia	0	0	0	1 (2%)
Mouth hemorrhage	0	0	1 (3%)	1 (2%)
Conjunctival hemorrhage	1 (3%)	0	0	0
Epistaxis	1 (3%)	0	0	0
Hematoma	1 (3%)	0	0	0
Immune thrombocytopenic purpura	1 (3%)	0	0	0
Lower gastrointestinal hemorrhage	1 (3%)	0	0	0
Ovarian hemorrhage	0	1 (3%)	0	0
Small intestinal hemorrhage	1 (3%)	0	0	0
Vitreous hemorrhage	1 (3%)	0	0	0

[Source: ADAE.xpt]

8.5.2. **Hepatobiliary Events**

Higher incidences of liver events were reported in Cohort 3 and Extension Cohort compared to Cohorts 1 and 2. According to the applicant the AUS01T protocol specified grade 3/4 LFTs laboratory values under certain circumstances to be captured as AEs. On retrospective review of the data, it appeared to be inconsistently applied. Therefore, the laboratory results were considered to be the primary source of hepatotoxicity, as all LFT lab values were source document verified. When considering liver related laboratory parameters (i.e., AST and ALT), there was no relevant difference between the cohorts (see section 8.4.6).

Most of the increase in transaminases and one event each of increased blood bilirubin and liver injury required dose interruption/adjustment (see section 8.4.3). None of the hepatobiliary

events led to treatment discontinuation due to study treatment. The narratives for patients who had liver injury and ocular icterus are presented below.

Patient (b) (6) was a 21 year-old African American male enrolled in the Extension Cohort who had acute grade 4 liver injury, suspected to be related to the treatment with eltrombopag, h-ATG, CsA and olanzapine. Treatment with eltrombopag and CsA were interrupted for approximately 3 weeks for increased LFTs and the treatment with CsA and eltrombopag was resumed without further increased LFTs. The event liver injury (grade 4) resolved on Day 55. The patient had some of the diagnostic imaging tests performed, which was consistent with medication induced severe acute liver injury without hepatic failure and resolution. The Investigator suspected a relationship between the event (liver injury) and the study treatment (h-ATG, cyclosporine A, eltrombopag) and olanzapine. Hepatology assessment concluded that the addition of olanzapine to the medication was the most likely cause for acute liver injury. This case did not meet the laboratory criteria for Hy's law.

Patient (b) (6) was a 60 year-old African American female enrolled in Cohort 3. On Day 1, ANC was 1.81×10^9/L (grade 1), hemoglobin was 88 g/L (grade 2, reference range: 120 to 160 g/L), platelet count was 25×10^9/L (grade 3; reference range: 150 to 350 $\times 10^9$/L), total bilirubin was 9 µmol/L (reference range: 5.1 to 20.5 µmol/L), direct bilirubin was < 3 µmol/L, AST was 11 U/L (reference range: 0 to 35 U/L), ALT was 12 U/L (reference range: 0 to 35 U/L), and ALP was 72 U/L (reference range: 36 to 92 U/L). On day 43, the patient developed ocular icterus (grade 1) with total bilirubin 17 µmol/L, AST 19 U/L, ALT 26 U/L, and ALP at 113 U/L (grade 1). No action was taken with the study treatment (eltrombopag, cyclosporine) due to the event (ocular icterus). The subject completed the scheduled study treatment as per protocol and initiated treatment with cyclosporine at a maintenance dose. The subject was discontinued from the study due to clonal evolution or progression to myelodysplastic syndrome 28 days after the last dose of eltrombopag. The Investigator suspected a relationship between the event (ocular icterus) and the study drug (eltrombopag).

Table 58 AUS01T: The Incidences of Hepatobiliary Events (Safety Set)

Preferred Term	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
All	5 (17%)	7 (23%)	14 (45%)	25 (40%)
ALT increased	1 (3%)	4 (13%)	11 (36%)	17 (27%)
AST increased	0	1 (3%)	7 (23%)	12 (19%)
Blood bilirubin increased	5 (17%)	5 (16%)	4 (13%)	9 (15%)
Blood ALP increased	0	0	0	1 (2%)
Cholestasis	0	0	0	1 (2%)
Liver injury	0	0	0	1 (2%)
Ocular icterus	0	0	1 (3%)	1 (2%)

[Source: ADAE.xpt]

8.5.3. **Thromboembolic Events**

In the AUS01T trial, a total of 4 patients had a thromboembolic event. None of the events led to treatment discontinuation or to dose interruption/adjustment. In Cohort 3+Extension Cohort, a total of 2 patients had a thromboembolic event (one patient had a catheter-related thrombosis in the basilica vein and the other patient had a non-occlusive clot in the subclavian vein).

Table 59 AUS01T: The Incidences of Thromboembolic Events (Safety Set)

Preferred Term	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
All	0	2 (7%)	1 (3%)	2 (3%)
Embolism	0	0	1 (3%)	2 (3%)
Blindness transient	0	1 (3%)	0	0
Myocardial infarction	0	1 (3%)	0	0

[Source: ADAE.xpt]

8.5.4. **Renal Events**

In the AUS01T trial a total of 2 patients (in Cohort 2 and Extension Cohort) had renal events (both were acute kidney injuries and non-serious). These events did not lead to treatment discontinuation or to dose interruption/adjustment.

8.5.5. **Others**

At baseline, most of the patients had GPI negative neutrophil level of ≤50% and 3 patients >50% which would likely to require treatment for PNH (see table 16 above). The worst post-baseline level to >50% (from ≤50% at baseline) had shifted in 1 patients each in Cohort 1 and Cohort 2 during the trial.

No hematologic malignancies, bone marrow fibrosis or recurrence of thrombocytopenia (after discontinuation of eltrombopag) adverse events were reported in the AUS01T trial (for the median follow up duration information at initial clinical cutoff see table 11; and under section 8.8.5 for the updated cutoff).

8.6. **Safety Analyses by Demographic Subgroups**

Geriatric patients:
In the AUS01T trial, a total of 17 patients (14%) were 65 years or older. There were no clinically meaningful differences when comparing the safety profile of patients ≥ 65 years with <65 years (see table 59 below).

Among patients ≥65 years, AEs that were reported in at least 2 patients were ALT increased (4 patients), AST increased (4 patients), blood bilirubin increased (3 patients) and acute kidney

injury (2 patients). Both cases of acute kidney injury were assessed as not related to eltrombopag therapy: one case was reported in a patient with diabetes that recovered and the other case occurred in a patient with diarrhea and dehydration.

There was one patient (b) (6) who experienced colitis that resulted in discontinuation of study treatment. The colitis AE occurred concomitantly with sepsis, hemorrhagic typhlitis and a cecal infection; the event typhlitis was reported as unrelated to eltrombopag. Patient (b) (6) was a 65-year old white male. The patient was enrolled in the Extension Cohort on (b) (6) and received the first dose of the study treatment (h-ATG, cyclosporine A, eltrombopag) on (b) (6) (b) (6). On Day 10 (b) (6), the patient developed maculopapular rash due to serum sickness and prednisone dose was increased. On (b) (6), the patient presented with typhlitis (colitis; grade 4) with a WBC count at 1.81×10^9/L, hemoglobin was 105 g/L (grade 1), platelet count was 14×10^9/L (grade 4), and ANC at 0.05×10^9/L (grade 4). On the same day, his condition rapidly deteriorated and emergency exploratory enterectomy with partial colectomy and creation of end-ileostomy and mucus fistula was scheduled. The study treatment (cyclosporine) was temporarily interrupted on (b) (6) due to gastrointestinal complications. On an unspecified day, blood culture results were negative, and stool culture was positive for Clostridium difficile toxin. The pathology of the resected bowel was consistent with hemorrhagic typhilitis. The study drug (eltrombopag) was permanently discontinued due to colitis, with the last dose reported of (eltrombopag) on Day 12 (b) (6). The study treatment (cyclosporine) was permanently discontinued due to the elevated liver function test. The event of colitis resolved on (b) (6). On (b) (6), 39 days after the last dose of eltrombopag and 29 days after the last dose of cyclosporine, the patient was diagnosed with septic cholestasis (grade 4); liver biopsy showed hepatic canalicular and cholangiolar cholestasis, which was consistent with septic cholestasis. The Investigator suspected a relationship between the events (colitis, cholestasis) and the study treatment (h-ATG); however, did not suspect a relationship with (eltrombopag). The Investigator did not provide any causal relationship between the events (colitis, cholestasis) and cyclosporine. The Investigator reported that the infections in the setting of neutropenia was a common occurrence of neutropenia in this patient population, also it was reported that it was possible that the event was exacerbated by the immunosuppressive treatment with h-ATG, since the event occurred during serum sickness. The Investigator further commented that infectious complications were known to occur in association with the disease, and reported as a side effect of h-ATG and cyclosporine.

None of the AEs experienced in patients ≥ 65 years had a fatal outcome.

Table 60 AUS01T: Adverse Events by Age (<65 Years vs. ≥65 Years)

Preferred Term	Cohort 1 N=30		Cohort 2 N=31		Cohort 3 N=31		Cohort 3+Ext. N=62	
	<65 yrs (n=25)	≥65 yrs (n=5)	<65 yrs (n=29)	≥65 yrs (n=2)	<65 yrs (n=26)	≥65 yrs (n=5)	<65 yrs (n=52)	≥ 65yrs (n=10)
All AEs	16 (64%)	3 (60%)	19 (66%)	2 (100%)	22 (85%)	4 (80%)	42 (81%)	8 (80%)
Serious AEs	12 (48%)	1 (20%)	10 (34%)	2 (100%)	12 (46%)	1 (20%)	23 (44%)	3 (30%)
AEs leading to withdrawal	1 (4%)	0	1 (3%)	0	1 (4%)	0	3 (6%)	1 (10%)
AEs leading to death	1 (4%)	0	0	0	0	0	0	0

[Source: ADAE.xpt]

Pediatric patients:
Among the 29 patients (24%) pediatric patients who received the study treatment in the AUS01T trial, AEs that were observed in ≥2 patients were febrile neutropenia (8 patients) ALT increased (4 patients), AST increased (2 patients), and blood bilirubin increased, serum sickness, and lung infection (3 patients each); and device related infection, infusion related reaction, sinusitis, rash (2 patients each). The 2 events of rash maculopapular led to discontinuation of treatment (1 patient 6 years of age and another patient 16 years of age). No other AE led to treatment discontinuation and none of the AEs had a fatal outcome. AEs that occurred in pediatric patients were consistent with those in the adult patients.

Table 61 AUS01T: Adverse Events by Pediatric Subgroup that Occurred in ≥ 2 Patients (Safety Set)

Preferred Term	Cohort 1	Cohort 2			Cohort 3+Ext.		
	12-17 yrs N=5	2-5 yrs N=1	6-11 yrs N=1	12-17 yrs N=4	2-5 yrs N=1	6-11 yrs N=7	12-17 yrs N=10
All AEs	4 (80%)	1 (100%)	1 (100%)	1 (25%)	0	5 (71%)	9 (90%)
ALT increased	0	0	0	0	0	1 (14%)	3 (30%)
Blood bilirubin increased	1 (20%)	0	0	0	0	0	2 (20%)
Febrile neutropenia	1 (20%)	1 (100%)	1 (100%)	0	0	3 (43%)	2 (20%)
AST increased	0	0	0	0	0	1 (43%)	1 (10%)
Device related infection	0	0	1 (100%)	0	0	0	1 (10%)
Infusion related reaction	0	0	0	0	0	1 (14%)	1 (10%)
Serum sickness	0	1 (100%)	0	1 (25%)	0	0	1 (10%)
Sinusitis	0	0	0	0	0	1 (14%)	1 (10%)
Rash maculopapular	0	0	0	0	0	1 (14%)	1 (10%)
Lung infection	1 (20%)	0	0	0	0	2 (29%)	0

[Source: ADAE.xpt]

The incidences of AEs that occurred in the pediatric patients were similar to the adult patients. However, SAEs occurred at a higher rate in the pediatric patients compared to adult patients across cohorts.

Table 62 AUS01T: Adverse Events by Age (<18 Years vs. ≥18 Years)

Preferred Term	Cohort 1 N=30		Cohort 2 N=31		Cohort 3 N=31		Cohort 3+Ext. N=62	
	<18 yrs (n=5)	≥18 yrs (n=25)	<18yrs (n=6)	≥18 yrs (n=25)	<18 yrs (n=8)	≥18 yrs (n=23)	<18 yrs (n=18)	≥ 18yrs (n=44)
All AEs	4 (80%)	15 (60%)	3 (50%)	18 (72%)	7 (88%)	19 (83%)	14 (78%)	36 (82%)
Serious AEs	4 (80%)	9 (36%)	3 (50%)	9 (36%)	5 (63%)	8 (35%)	10 (56%)	16 (36%)
AEs leading to withdrawal	0	1 (4%)	0	1 (4%)	1 (13%)	0	2 (11%)	2 (5%)
AEs leading to death	0	1 (4%)	0	0	0	0	0	0

[Source: ADAE.xpt]

With regard to the biochemistry laboratory assessments in pediatric patients, one patient (b) (6), a 17-year-old African American male experienced grade 4 hypokalemia and grade 4 hypomagnesemia that resolved. No other grade 4 biochemistry laboratory results were reported. Grade 3 incidences that occurred in pediatric patients were ALT (21%, 6 patients), bilirubin (14%, 4 patients), AST (7%, 2 patients), and hyperglycemia (3%, 1 patient). No clinically meaningful differences in biochemistry results were observed in pediatric patients when compared to those of the adult patient population.

8.7. Other Clinical Trials

In the E1202 trial (n=10) that evaluated the efficacy and safety of eltrombopag in combination with rabbit ATG/CsA, the most frequently reported AEs on treatment (≥ 4 patients) were nausea, headache, constipation, edema, pyrexia, renal impairment and vomiting. A total of 2 patients (20%) had SAEs of febrile neutropenia and nephrolithiasis on treatment, both assessed as unrelated to study treatment. No subject died as of the data cut-off date.

In the E1201 trial (n=21) of single-agent eltrombopag, the most frequently reported AEs (>10%) were nasopharyngitis, hepatic function abnormal and urticaria. A total of 4 patients (19%) experienced at least 1 on-treatment SAE of retinal detachment, enterocolitis, pain and decreased appetite, all assessed as unrelated to study treatment. No subject died as of the data cut-off date.

For the four historical trials, [Tisdale et al (2000)], [Rosenfeld et al (2003)], [Scheinberg et al (2009)], and [Scheinberg et al (2011)], limited safety data was reported in the publications. In Scheinberg et al. (2009), the most commonly reported AEs in the h-ATG/CsA arm (>10%)

were infections (in ears, nose and throat), hypertriglyceridemia, febrile neutropenia and mouth sores (presumed Herpes simplex). Overall, the most frequently reported SAEs in the h-ATG/CsA arm across the four historical trials were infections.

On October 15, 2018, Novartis notified DHP that they halted enrollment in their ongoing study CETB115E2403 (SOAR), entitled "Interventional Phase II Single-arm Trial to Assess Efficacy and Safety of Eltrombopag Combined with Cyclosporine as First-line Therapy in Patients with Severe Aplastic Anemia". This study is to assess the efficacy and safety of eltrombopag and CsA alone for the first-line treatment of SAA patients in countries where h-ATG is not available or for patients who are not eligible for h-ATG treatment. This study is being conducted entirely at foreign sites and is not being conducted under an US IND. According to Novartis, inconsistencies in eltrombopag and CsA dose management, missing or inconsistent data in the clinical database, as well as a higher number of deaths (6 deaths total [5 on-treatment and 1 in screening]) than expected were observed in the study.

On October 16, 2018, DHP had a teleconference with Novartis to obtain additional information regarding the 6 deaths. During the teleconference, DHP also mentioned that there appears to be an additional ongoing study (NCT02099747 [RACE]) of eltrombopag for the first-line treatment of SAA. The RACE trial is a randomized (1:1), controlled study comparing eltrombopag in combination with h-ATG+CsA versus h-ATG+CsA for the first-line treatment of adult and pediatric patients 15 years and older with SAA. The Agency requested that Novartis should provide safety information of the RACE trial, in addition to the assessment of the 6 fatal cases from Study ETB115E2403 and other trials conducted with eltrombopag in SAA.

On October 26, 2018, Novartis responded to the information request and provided a list of trials conducted with eltrombopag in the SAA indication.

Table 63 Novartis-sponsored and Investigator-initiated Trials of Eltrombopag in SAA

Protocol Number *NCT number*	Description	Treatment	Indication	N	Status	Data previously submitted to NDA 022291
Novartis Sponsored Interventional Trials						
ETB115E1202 / 201793 *NCT02404025*	A non-randomized, phase II study of epag in combination with rATG/CsA in subjects with moderate or more SAA who have not received prior ATG/ALG-based immunosuppressive therapy	Epag + r-ATG + CsA	IST treatment-naive moderate or more SAA	11 (Epag = 10)	Complete with final CSR - 11-Apr-2017	52-week CSR (data cutoff date of 06-Jan-2017) submitted with 1L SAA sNDA in Mar 2018; data discussed in SCS and CO
ETB115E1201 / 200926 *NCT02148133*	A non-randomized, open-label, phase II study to assess the safety and efficacy of epag in Japanese subjects with refractory, moderate or more severe aplastic anemia	Epag	Refractory moderate or more SAA	21	Complete with final CSR - 11-Jul-2016	52-week CSR (data cutoff date of 07-Mar-2016) submitted with 1L SAA sNDA in Mar 2018; data discussed in SCS and CO

ETB115E2201 *NCT03025698*	A phase II, open-label, non-controlled, intra-patient dose escalation study to characterize the pharmacokinetics after oral administration of epag in pediatric patients with refractory, relapsed or treatment naïve SAA or recurrent aplastic anemia	Epag	IST treatment-naive; refractory and relapsed SAA	15/58	Ongoing/ enrolling	N/A
ETB115E2403 *NCT02998645*	SOAR Trial, A two-part study: Interventional phase II single-arm trial to assess efficacy and safety of epag combined with CsA as first line therapy in patients with severe acquired aplastic anemia, and an extension with up to 60-months follow-up	Epag + CsA	IST treatment-naive SAA	31/50	Partial clinical hold	N/A
Novartis Sponsored Non-interventional Trials						
ETB115E2402	Medical chart review to assess burden of illness among patients with SAA with insufficient response to immunosuppressive therapy (WHOVA HEOR)	N/A	Refractory SAA	100	Complete	N/A
ETB115AFR03	Observational study on aplastic anemia patients in France: Prospective follow-up of epag treated patients	N/A	Aplastic anemia	150	Planned	N/A
ETB115EFR02	Observational study on aplastic anemia patients in France: Prospective follow-up of epag treated patients	N/A	Aplastic anemia	150	Planned	N/A
Investigator-Initiated Interventional Trials						
ETB115AUS01T / 116643 *NCT01623167* Pivotal study IL SAA filing	Epag added to standard immunosuppression in treatment-naive SAA	Epag + CsA + h-ATG	IST treatment-naive SAA	154	Ongoing/ enrolling 120-day cutoff date at 28-Feb-2018 with 154 patients (153 dosed) Study open at NIH for continued enrollment	• Primary CSR (data cutoff date of 30-Sep-2016) submitted with 1L SAA sNDA in Mar 2018 • 120-day Safety and Efficacy Update (data cutoff date of 28-Feb-2018) submitted Jul 2018

ETB115AUS28T / 112523 *NCT00922883* Pivotal study refractory SAA	A pilot study of a TPO-R agonist in aplastic anemia patients with immunosuppressive-therapy refractory thrombocytopenia	Epag	Refractory aplastic anemia	44	Closed to accrual; currently open for extended access treatment and follow-up only. CSR: 09-May-2014	• Primary CSR (data cutoff date of 01-Jun-2013) submitted with refractory sNDA in Feb 2014 • 120-day Safety Update (data cutoff date of 31-Mar-2104) submitted in Jun 2014 • Cytogenetic abnormality data from CSR submitted with 1L SAA sNDA
ETB115AUS18T / 116826 *NCT01891994* Supportive study refractory SAA	Extended dosing with epag in refractory SAA	Epag	Refractory SAA	40	Open - No Longer Recruiting - Follow-up only CSR on 04-May-2017	• Study summary (data cutoff date of 31-Mar-2014) submitted in Jun 2014 • Cytogenetic abnormality from Winkler et al 2017 publication submitted with 1L SAA sNDA
ETB115EDE03T / 200933 *NCT02099747*	(RACE) A prospective randomized multicenter study comparing hATG + CsA with or without epag as front-line therapy for SAA patients	h-ATG + CsA +/- Epag	IST treatment-naive SAA	146	Ongoing/ enrolling	2016 DSUR: 4 SUSARs reported in Table 10-6 2017 DSUR: 1 SUSAR reported in Table 10-1
ETB115AUS13T / 115895 *NCT01703169*	Efficacy and safety of epag in patients with severe and very severe aplastic anemia	Epag	Refractory /relapsed severe and very -SAA	13	Complete	N/A
2012-0334/NCI-2012-01096/NCI CTRP *NCT01624805*	Addition of epag to immunosuppressive therapy in patients with newly diagnosed aplastic anemia	h-ATG + CsA + Epag +/- GCSF	IST treatment-naive aplastic anemia	38 /100	Ongoing/ enrolling	N/A
NCPHOI-2016-01 *NCT03413306*	A phase II multicenter randomized study of epag combined with CsA and hATG versus hATG and CsA as first line treatment in pediatric patients with severe acquired aplastic anemia	h-ATG + CsA +/- Epag	IST treatment-naive SAA	UNK /100	Ongoing/ enrolling	N/A
MAAhmed *NCT03243656*	Randomized clinical trial of the use of epag in children with idiopathic aplastic anemia	h-ATG + CsA +/- Epag	IST treatment-naive idiopathic aplastic anemia	UNK /20	Ongoing/ enrolling	N/A

Case Report Ali et al 2017	Epag for secondary failure of platelet recovery post-allogeneic hematopoietic stem cell transplant in children	Epag	IST treatment-naive (post-AHSCT) SAA	1	Complete	N/A
ETB115AUS27T *NCT01328587*	A pilot study of a TPO-R agonist, epag, in moderate aplastic anemia patients	UNK	Moderate aplastic anemia	34/38	Active	N/A
ETB115XDE02T	Epag for moderate aplastic anemia.	UNK	Moderate aplastic anemia	29/116	Active	N/A
ETB115EUS30T	Epag for patients with Fanconi anemia and other inherited bone marrow failure syndromes	Epag, and permitted supportive care	Fanconi anemia and other inherited bone marrow failure syndromes	25	Planned	N/A
Hwang et al 2018	Eltrombopag in the management of aplastic anaemia: real-world experience in a non-trial setting	Epag/CsA	Aplastic anemia	20	UNK	N/A
Gill et al 2017	The thrombopoietin mimetics eltrombopag and romiplostim in the treatment of refractory aplastic anemia	Epag/ATG	Refractory aplastic anemia	10	UNK	N/A
Investigator-Initiated Non-interventional Trials						
ETB115EES02T	Observational study to evaluate the incidence and management of aplastic anemia in Spain	N/A	Aplastic anemia	UNK	N/A	N/A
Boddu et al 2017	Clinical outcomes in adult patients with aplastic anemia: A single institution experience	(**A**)hATG/ CsA/P; (**B**)hATG/ CsA/P/ GCSF; (**C**)hATG/ CsA/P/ GCSF/ epag; (**D**)rATG/ CsA/P; (**E**)rATG/ CsA/P/ GCSF	Aplastic anemia	126	N/A	N/A
Lengline et al 2018	Nationwide survey on the use of eltrombopag in patients with severe aplastic anemia: a report on behalf of the French Reference Center for Aplastic Anemia	N/A	Aplastic anemia	46	N/A	N/A
Review Article Willis et al 2014	Recent Developments in Drug Therapy for Aplastic Anemia	N/A	Aplastic anemia	N/A	N/A	N/A

[Source: Novartis submission on October 26, 2018]

The applicant stated that overall no new safety issues were reported from the trials listed in the above table. The 6 deaths in the SOAR study were due to intestinal hemorrhage, sepsis (the patient died during screening and did not receive the study medication), worsening of aplastic anemia, general physical health deterioration, sepsis (disease progression) and septic shock/ cardiorespiratory arrest. None of the deaths were assessed as related to the study treatment. In addition, in the SOAR study there was one patient who experienced drug induced liver injury (DILI) five days after the start of eltrombopag and cyclosporine. Liver function tests remained high despite eltrombopag discontinuation and decrease in cyclosporine dose. LFTs normalized 12 days after discontinuation of cyclosporine, suggesting that the event of DILI was likely due to cyclosporine.

Regarding the RACE trial, Novartis provided a Development Safety Update Report (DSUR) covering the period from June 24, 2017 to June 23, 2018 prepared by European Society for Blood and Marrow Transplantation (EBMT). A total of 146 patients were enrolled. Summary of safety information comparing the two arms was not provided. However, a total of 13 deaths (eltrombopag+h-ATG+CsA: 5 deaths, h-ATG+CsA: 8 deaths) were reported. The causes of the reported deaths are summarized in the table below.

Table 64 RACE Study: Reported Adverse Events Leading to Death (June 23, 2018 Cutoff)

	Eltrombopag+ h-ATG+CsA N=73*	**h-ATG+CsA N=73***
Deaths due to AE	5 (6.8%)	8 (11.0%)
Abdominal infection		1 (1.4%)
E. coli left hip arthritis		1 (1.4%)
Aplastic anemia	1 (1.4%)	
Acute respiratory syndrome/cerebral thrombosis	1 (1.4%)	
Sepsis/multi-organ failure		3 (4.1%)
Respiratory failure	1 (1.4%)	
Cardiac arrest	1 (1.4%)	
Peritoneal infection	1 (1.4%)	
Cerebral embolism		1 (1.4%)
Intracranial hemorrhage		2 (2.7%)

* Based on 1:1 randomization and enrollment of a total of 146 patients.
[Source: Adapted from Novartis submission on October 26, 2018; DSUR prepared by EBMT]

A total of 12 patients discontinued study treatment due to treatment failure (eltrombopag+h-ATG+CsA: 6 patients, h-ATG+CsA: 6 patients). No new safety issues were raised in the report. The overall safety assessment was as follows:

A total 146 subjects have been randomized and treated until 23 June 2018. There were no

SUSARs reported. There were 20 serious suspected adverse reactions (SSARs) reported (serious adverse events assessed as expected and either related to Eltrombopag, or ATGAM or CsA) and one pregnancy case. Out of 20 SSARs two SSARs were reported as related to Eltrombopag. The event terms reported for these SSARs were "Urinary tract infection" and "Toxidermia". The events are listed in the SmPC for Eltrombopag and therefore assessed as expected for Eltrombopag. There was a new pregnancy case reported in this reporting period. The partner of patient 66 was reported pregnant. So far, the pregnancy is progressing without complications.

For the SAE "Neoplasms-Other, adenocarcinoma ovary" which is reported as unresolved in this DSUR, latest FU was received on the 21st of June. The event is unresolved and it will be followed in the next reporting period.

Patient (b) (6) experienced the serious adverse event Oesophagitis while in the RACE trial. The event was unexpected for Eltrombopag, but Eltrombopag was given out of protocol as a commercial form, therefore does not require to be reported as a SUSAR, which was also confirmed by EMA.

Patient (b) (6) experienced the serious adverse event Atrial fibrillation. The event was reported as related to ATGAM and assessed as unexpected. ATGAM is not an IMP for the RACE trial. There is also no possible interaction with the IMP Eltrombopag as the patient was in the control arm A and didn't receive the IMP. Therefore, the SAE Atrial fibrillation does not require to be reported as a SUSAR.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Evolution to clonal hematologic diseases such as myelodysplastic syndrome (MDS) and leukemia is a serious complication of aplastic anemia and is usually associated with the appearance of a cytogenetic abnormality in bone marrow cells. In other studies, the risk was estimated to be approximately 15% at 5 years and the incidence of conversion to abnormal karyotype was about 50% within the first 30 months. Patients with clonal evolution involving chromosome 7 abnormalities in SAA fared as poorly as in primary MDS, with a high rate of conversion to acute leukemia. In the AUS01T trial, evolution to clonal hematopoiesis was to be defined by detection of new bone marrow cytogenetic abnormalities at landmark time points. Clonal evolution occurred in a total of 9 patients (7%) including 3 pediatric patients (IDs (b) (6) (b) (6)) in AUS01T. In 3 patients (IDs (b) (6)), chromosomal aberrations were of unclear significance; 5 patients (IDs (b) (6)) had the loss of chromosome 7, either alone or in combination with complex cytogenetic abnormalities and in 3 of the 5 patients; this was accompanied by morphologic evidence of dysplasia or full myeloid malignant transformation. In one patient (ID (b) (6)), chromosomal abnormality was deletion of chromosome 13, considered

having a good prognostic in aplastic anemia. It is not clear whether these evolutions occurred due to the underlying disease, the IST and/or eltrombopag.

The applicant provided the table below that summarizes the 9 cases of cytogenetic abnormalities that occurred during the AUS01T trial at the September 30, 2016 data cutoff.

Table 65 AUS01T: Clonal Evolution Observed During the Trial

Patient ID/ Cohort/age/ gender/ exposure to eltrombopag (months)	Cytogenetic analysis at baseline	Time to clonal evolution (months)	Cytogenetic analysis at the time of clonal evolution	Narrative	Outcome
Patient (b) (6) Cohort 1 17-yr/female 4.7 mos	46,XX[20]	48.3	46,XX,del(5)(q15q31)[2]/46,XX[19]	Patient received the first dose of study medication (h-ATG and CsA) on Day 1 (b) (6) and eltrombopag on Day 14 (b) (6). Patient received eltrombopag (b) (6). Eltrombopag was discontinued due to platelet count > 200x10^3 µL. On (b) (6)(Follow Up Year 4) patient was diagnosed with clonal evolution as demonstrated by the following bone marrow findings: new cytogenetic abnormality defining of clonal evolution per protocol based on bone marrow cytogenetics. The abnormality (partial deletion of chromosome 5) was further interrogated by FISH and was negative for the chromosome 5 abnormality associated with MDS. The bone marrow morphology did not show any evidence of MDS or AML. Therefore, this abnormality is of unknown clinical significance. Patient is not currently on any investigational medication associated with the research protocol.	Follow-up still ongoing
Patient (b) (6) Cohort 1 39-yr female 5.7 mos	46,XX[20]	24.0	48,XX,+6,+15[2]46,XX[18]	Patient received the first dose of study medication (h-ATG and CsA) on Day 1 (b) (6) and eltrombopag on Day 14 (b) (6). Patient received eltrombopag (b) (6). On (b) (6)(Follow Up Year 2) patient was diagnosed with clonal evolution as demonstrated by	Discont'd study (failure to f/u) Patient had a CR at 6

				new cytogenetic abnormality of clonal evolution based on bone marrow cytogenetics. The abnormality was described as trisomy 6 and trisomy 15, in 2 out of 20 metaphases. The bone marrow morphology did not have any abnormalities to MDS or AML. The clinical meaning of this abnormality is unclear and not defining of any disease.	months.
Patient (b) (6) Cohort 1 64-yr female 2.8 mos	46,XX[20]	3.0	45,XX,t(3;3)(q21;q26), -7[3]/ 46,XX[17]	Patient received the first dose of study medication (h-ATG and CsA) on Day 1 (b) (6) and eltrombopag on Day 14 (b) (6). Patient received eltrombopag (b) (6) On 11/20/12 (3 months evaluation) patient was diagnosed with clonal evolution as demonstrated by new cytogenetic abnormality defining of clonal evolution based on bone marrow cytogenetics. The abnormality was associated with MDS and involves loss of chromosome 7. The bone marrow morphology showed dysplastic cells and increased blasts concerning for the development of MDS. Patient discontinued study treatment on (b) (6) due to clonal evolution; evolved to MDS from (b) (6) bone marrow biopsy, received HSCT on (b) (6) and died post-HSCT on (b) (6)	Died due to HSCT related cause Patient Had a PR at 3 months.
Patient (b) (6) Cohort 1 68-yr female 2.8 mos	46, XX [20]	3.0	46,xx, del(13)(q12q22)[cp3] 46,XX[17]	Patient received the first dose of study medication (h-ATG and CsA) on Day 1 (b) (6) and eltrombopag on Day 14 (b) (6). Patient received eltrombopag from (b) (6). Eltrombopag was discontinued due to clonal evolution. On (b) (6) (3 Month Evaluation) patient was diagnosed with clonal evolution as demonstrated new cytogenetic abnormality defining of clonal evolution based on bone marrow cytogenetics. The abnormality was described as deletion 13q. The bone marrow morphology did not	Cytogenetics normalized

				have dysplasia or increased blasts to suggest MDS or AML. Deletion 13q is not an infrequent finding in aplastic anemia subjects and it is reported to be a good prognostic feature in aplastic anemia.	
Patient (b) (6) Cohort 1 69-yr male 5.7 mos	45,X-Y[10]/ 46,XY[10]	29.8	45,XY,-7[20]	Patient received the first dose of study medication (h-ATG and CsA) on Day 1 (b) (6) and eltrombopag on Day 14 (4/10/13). Patient received eltrombopag (b) (6). On (b) (6) (Unscheduled Visit 1) patient was diagnosed with clonal evolution as demonstrated new cytogenetic abnormality of clonal evolution based on bone marrow cytogenetics. The abnormality was associated with MDS and involves loss of chromosome 7.	Progressi on to MDS, monoso my 7
Patient (b) (6) Cohort 2 48-yr female 2.3 mos	No mitotic activity	6.1	46,XX del(7) (p13p15)[3] /46,XX,[19]	Patient received the first dose of study medication (h-ATG and CsA) on Day 1 (b) (6) and eltrombopag on Day 14 . Patient received eltrombopag (b) (6). Eltrombopag was discontinued due to platelet count>400x10^3 µL. On (b) (6) (6 Month Evaluation) patient was diagnosed with clonal evolution as demonstrated new cytogenetic abnormality defining of clonal evolution per protocol based on bone marrow cytogenetics. The abnormality was described as deletion of chromosome 7. The bone marrow presented mildly hypocellular for age with progressive trilineage hematopoiesis; there was no overt evidence of dysplasia; and no increase in CD34 positive cells. The bone marrow morphology did not show any overt dysplasia or increased blasts. However, loss or partial loss of chromosome 7 in subjects with aplastic anemia is associated with MDS.	Discont'd study due to clonal evolu-tion
Patient (b) (6) Cohort 2	Insufficient mitotic	24.1	46,XY, t(5,12)	Patient received the first dose of study medication (h-ATG and CsA) on Day 1	Follow-up still

7-yr male 2.5 mos	activity		(p10;p10)[2]/ 46XY[18]	(b) (6) and eltrombopag on Day 14 (b) (6). Patient received eltrombopag (b) (6). Eltrombopag was discontinued due to platelet count > 200x10^3 µL. On (b) (6)(Follow Up Year 2) patient was diagnosed with clonal evolution as demonstrated by new cytogenetic abnormality defining of clonal evolution based on bone marrow cytogenetics. The abnormality was described as translocation 5:12 seen in 2/20 metaphases. The bone marrow morphology did not have any abnormalities suggestive of MDS or AML. The clinical meaning of this abnormality is unclear and not defining of any disease.	ongoing
Patient (b) (6) Cohort 3 60-yr female 6.0 mos	46 XX[20]	6.0	45,XX,-7[7]/ 46,XX[16]	Patient received the first dose of study medication (h-ATG, CsA and eltrombopag) on Day 1 (b) (6). Patient received eltrombopag (b) (6) (b) (6). On (b) (6)(6 Month evaluation) patient was diagnosed with clonal evolution as demonstrated by new cytogenetic abnormality defining of clonal evolution based on bone marrow cytogenetic. The abnormality was described as monosomy 7. The bone marrow morphology showed dysplasia concerning for the development of MDS, but no increase in blasts. Monosomy 7 is clinically significant and is associated with high risk for progression to acute myeloid leukemia in aplastic anemia subjects.	Evolu-tion to MDS PR at 3 months
Patient (b) (6) Cohort 3 16-yr male 3.1 mos	46,XY[20]	2.9	45,XY,-7[6]/ 46,XY[14]	Patient received the first dose of study medication (h-ATG, CsA and eltrombopag) on Day 1 (b) (6). Patient received eltrombopag (b) (6) (b) (6).Eltrombopag was discontinued due to clonal evolution. On (b) (6)(3 Month Evaluation) patient was diagnosed with clonal evolution as demonstrated by new	Loss of chromos ome 7 with high risk of transfor-ming to AML; HSCT.

				cytogenetic abnormality defining of clonal evolution based on bone marrow cytogenetics. The abnormality was described as monosomy 7. The bone marrow morphology did not show any dysplasia or increased blasts. However, monosomy 7 in aplastic anemia is associated with MDS and progression to acute myeloid leukemia. Patient received a stem cell boost on (b) (6)	

*It has been reported that 2 patients with high-grade cytogenetic evolutions were found to have a cryptic inherited bone marrow failure disorder following enrollment consistent with a telomere disease (gene mutation in RTEL1).
[Source: AUS01T CSR]

According to the datasets, among the 9 patients with clonal evolution, 6 patients (Cohort 1: 4 patients, Cohort 2: 1 patients, Cohort 3+Extension Cohort: 1 patient) had progressed to MDS or AML in the AUS01T trial.

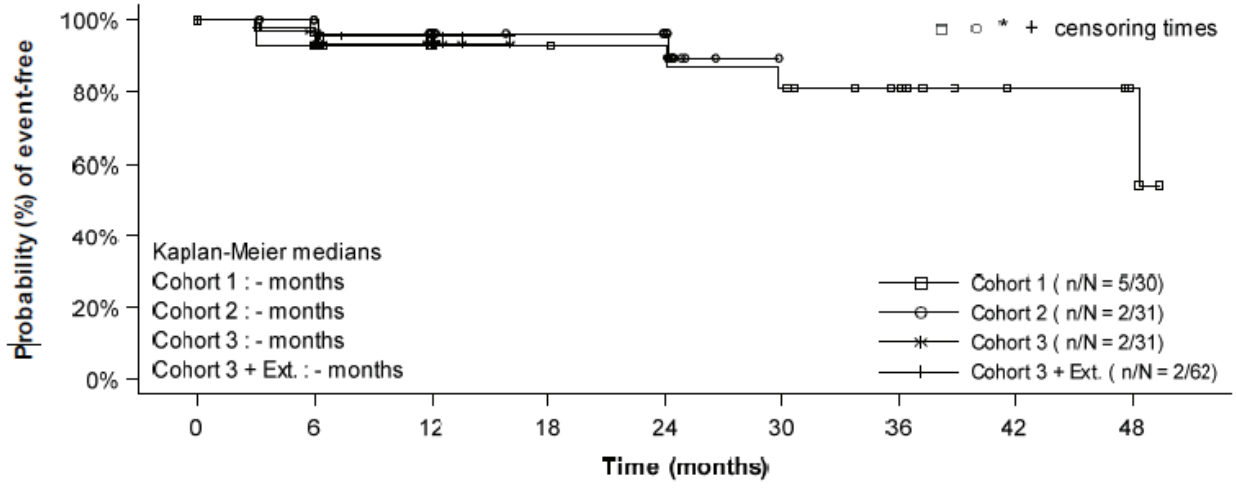
Table 66 AUS01T: Clonal Evolution (FAS)

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=62
Clonal Evolution	5 (17%)	2 (7%)	2 (7%)	2 (3%)
Evolution to MDS/AML	4 (13%)	1 (3%)	1 (3%)	1 (2%)
Other evolution	1 (3%)	1 (3%)	1 (3%)	1 (2%)
No evolution	25 (83%)	29 (94%)	29 (94%)	60 (97%)

[Source: ADTTE.xpt]

Of the 9 patients (7%) with clonal evolution, the clonal events occurred within 6.1 months in 5 patients of which 4 were in the chromosome 7. The median time to clonal evolution was not evaluable in all cohorts.

Figure 2 AUS01T: Kaplan-Meier Plot of Time to Clonal Evolution (FAS)



No. of patients still at risk

Time (months)	0	6	12	18	24	30	36	42	48
Cohort 1	30	25	17	17	16	14	10	5	3
Cohort 2	31	27	21	18	16	0			
Cohort 3	31	29	16	0					
Cohort 3 + Ext.	62	41	16	0					

[Source: AUS01T CSR]

Review comment: Pooled analysis of cytogenetic progression was conducted for the US18T and US28T trials (n=83) at 8 years of follow-up. These trials treated patients with refractory SAA with single-agent eltrombopag. Eighteen percent of patients had clonally evolved. Generally, clonal evolution occurred early after eltrombopag initiation: 81% occurred within 6 months. Among the 6 patients with high risk chromosome 7 abnormalities, 5 occurred within 3 months.

In the historical studies that treated SAA patients with standard IST (h-ATG + CsA) without eltrombopag as first-line therapy, the incidence of clonal evolution in Scheinberg et al. (2009) and Scheinberg et al. (2012) at a median follow-up of 3 years was 9.5% and 21%, respectively. In Rosenfeld et al (2003), clonal evolution was reported in 10.6% of patients.

According to Townsley et al. 2017, the frequency of clonal evolution in the historical experience with standard immunosuppressive therapy at 2 years was 8% [standard error, ±3%] with a median time to clonal evolution of 4-6 years. Therefore, at this time it does not appear that eltrombopag is associated with higher frequency, however, possibly there may be earlier onset. Longer follow-up is needed to fully assess the incidence of clonal evolution with eltrombopag therapy.

A total of 4 patients developed AEs in the neoplasms benign, malignant, and unspecified SOC

(basal cell carcinoma: 3 patients, squamous cell carcinoma: 2 patients) in the AUS01T trial. One patient developed both squamous and basal cell carcinoma.

8.8.2. **Human Reproduction and Pregnancy**

No cases of pregnancies were reported in the pivotal or supportive trials.

8.8.3. **Pediatrics and Assessment of Effects on Growth**

Promacta has an indication for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Assessments of effects on growth were not conducted.

8.8.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

No information about overdose was included in the submission. There is no known potential for abuse with eltrombopag. No events of recurrence of thrombocytopenia were reported after discontinuation of eltrombopag in the pivotal or supportive trials.

8.8.5. **120-Day Safety Update**

On July 25, 2018, the applicant submitted the 120-day safety update which contained updated safety and efficacy data from the pivotal study AUS01T with a clinical data cutoff date of February 28, 2018. The submission contained data from 30 additional patients, all enrolled in the Extension Cohort and 17 months of longer follow-up for those patients who were included in the original submission in the AUS01T trial. The median follow-up time (from the date of first study treatment to the clinical cut-off date) for Cohort 1, 2, 3 and combined Cohort 3+Extension Cohort was 61, 47, 33 and 22 months, respectively. With the update, a total of 154 patients were enrolled and 153 patients (Cohort 1: 30, Cohort 2: 31, Cohort 3: 31, Cohort 3+Extension Cohort: 92) received eltrombopag at the time of February 28, 2018 cut-off date. The updated evaluation of safety was concentrated on the combined Cohort 3+Extension Cohort.

<u>Overall Exposure:</u>
At the updated cutoff in Cohort 3+Extension Cohort, the median duration of treatment to eltrombopag, h-ATG and the therapeutic dose of CsA was 183 days (range: 12-204 days), 4 days (range: 1-5 days) and 186 days (range: 6-224 days), respectively, and was consistent with the original cutoff. A total of 64 patients (70%) received eltrombopag for longer than 24 weeks.

Table 67 UAS01T: Updated Exposure to Eltrombopag (Safety Set)

Cutoff date	Sept 30, 2016	Feb 28, 2018
	Cohort 3+Ext. N=62	Cohort 3+Ext. N=92
Duration of treatment (days)		
Median	180	183
Range	3-195	12-204
≤ 6 weeks	7 (11%)	6 (7%)
>6 to ≤12 weeks	8 (13%)	9 (10%)
>12 to ≤24 weeks	14 (23%)	13 (14%)
>24 weeks	33 (53%)	64 (70%)
Relative dose intensity (%)		
Median	99.2	98.9
Range	60.5-100	60.5-100

Relative dose intensity = 100 x [(Cumulative dose/Duration of exposure)/(Planned dose intensity)].
[Source: ADSL.xpt and ADEX.xpt]

The median duration of treatment to the maintenance dose of CsA increased from 167 days (range: 12-488 days) to 387 days (range: 22-646 days) in the combined Cohort 3+Extension Cohort.

Table 68 AUS01T: Updated Exposure to Maintenance Dose of CsA (Safety Set)

Cutoff date	Sept 30, 2016		Feb 28, 2018	
	Cohort 2 N=31	Cohort 3+Ext. N=62	Cohort 2 N=31	Cohort 3+Ext. N=92
Patients who received maintenance dose	15	38	15	67
Duration of treatment (days)				
Median	547	167	561	387
Range	13-739	12-488	13-891	22-646

[Source: ADSL.xpt]

The incidence of patients who required dose adjustment of eltrombopag in the combined Cohort 3+Extension Cohort (51%) was also similar to the original cutoff (50%).

Updated Safety Summary

The table provides a summary of the overall safety results at the original and the updated cutoff dates in the combined Cohort 3+Extension Cohort. At the updated cutoff, the incidences were higher except for AEs leading to treatment discontinuation. At the update, a higher

proportion of patients had completed the 6-month treatment with eltrombopag (5% [5/92] subjects were on-treatment at the updated cutoff, while 24% [15/62] subjects were on-treatment with eltrombopag at the original cutoff).

Table 69 AUS01T: Comparison of Overall Summary of Safety (Safety Set)

Cutoff date	Sept 30, 2016		Feb 28, 2018	
	Cohort 3+Ext. N=62		Cohort 3+Ext. N=92	
	All Grades	≥Grade 3	All Grades	≥Grade 3
All AEs	47 (76%)	39 (63%)	72 (78%)	59 (64%)
Related to eltrombopag	38 (61%)	32 (52%)	65 (71%)	54 (59%)
All deaths	0	-	3 (3%)	-
Deaths within 30 days of last dose of eltrombopag	0	-	0	-
SAEs	26 (42%)	22 (36%)	46 (50%)	40 (44%)
Related to eltrombopag	13 (21%)	10 (16%)	31 (34%)	25 (27%)
AEs leading to treatment discontinuation	4 (7%)	3 (5%)	4 (4%)	3 (3%)
AEs requiring dose interruption/adjustment	15 (24%)	15 (24%)	28 (30%)	27 (29%)

[Source: ADAE.xpt]

Deaths:

At the update, there were a total of 7 deaths (4 additional deaths to the original cutoff) in the AUS01T trial. All of the additional 4 deaths were reported during the follow-up and no deaths were assessed as related to the study treatment:

- Patient (b) (6) Cohort 2) was a 29-year old female who died on Day 971, during the follow-up 881 days after last dose of eltrombopag, due to infection (septic shock).
- Patient (b) (6) (Cohort 3) was a 72-year old female who died on Day 864, during the follow-up 676 days after last dose of eltrombopag, of unknown cause.
- Patient (b) (6) Extension Cohort) was a 65-year old male who died on Day 419, during the follow-up 225 days after last dose of eltrombopag, due to infection (septic shock).
- Patient (b) (6) (Extension Cohort) was a 65-year old male who died on Day 121, during the follow-up 109 days after last dose of eltrombopag, due to infection (pneumonia).

Serious Adverse Events:

The SAEs reported at the updated cutoff were similar to the original cutoff date in Cohort 3+Extension Cohort. SAEs that occurred ≥5% in Cohort 3+Extension Cohort were serum sickness, febrile neutropenia, upper respiratory infection and lung infection.

Table 70 AUS01T: Serious Adverse Events that Occurred in ≥ 2 Patients (Safety Set)

Cutoff date	Sept 30, 2016	Feb 28, 2018
	Cohort 3+Ext. N=62	Cohort 3+Ext. N=92
All SAEs	26 (42%)	46 (50%)
Serum sickness[a]	6 (10%)	8 (9%)
Febrile neutropenia	5 (8%)	8 (9%)
Upper respiratory infection	1 (2%)	6 (7%)
Lung infection	2 (3%)	5 (5%)
Bacteremia	0	4 (4%)
Rash[b]	3 (5%)	4 (4%)
Hypertension	1 (2%)	3 (3%)
Pharyngitis	2 (3%)	3 (3%)
Sinusitis	2 (3%)	3 (3%)
Infusion related reaction	2 (3%)	2 (2%)
Abdominal pain	1 (2%)	2 (2%)
Enterocolitis infectious	1 (2%)	2 (2%)
Headache	0	2 (2%)
Retinal vascular disorder	1 (2%)	2 (2%)
Tonsillitis	0	2 (2%)
Viral infection	0	2 (2%)

a. All cases of serum sickness were assessed as "unlikely" or "unrelated" to eltrombopag.
b. Includes rash maculo-papular.
[Source: ADAE.xpt]

Discontinuations due to Adverse Events:

At the updated cutoff, no additional patients discontinued treatment with eltrombopag due to an AE in Cohort 3+Extension Cohort.

Table 71 AUS01T: Adverse Events Leading to Treatment Discontinuation (Safety Set)

Cutoff date	Sept 30, 2016	Feb 28, 2018
	Cohort 3+Ext. N=62	Cohort 3+Ext. N=92
All AEs	4 (7%)	4 (4%)
Rash maculopapular	3 (5%)	3 (3%)
Colitis	1 (2%)	1 (1%)

[Source: ADAE.xpt]

In Cohort 3+Extension Cohort, the incidence of dose interruptions or adjustments of eltrombopag due to AEs at the update was also consistent with the original cut off. At the update, 30% of patients had eltrombopag dose interrupted or adjusted mostly due to ALT or AST increased.

Table 72 AUS01T: Adverse Events Requiring Dose Interruption/Adjustments of Study Treatment in ≥ 2 Patients in Cohort 3+Extension Cohort (Safety Set)

Cutoff date	Sept 30, 2016	Feb 28, 2018
	Cohort 3+Ext. N=62	Cohort 3+Ext. N=92
All AEs	15 (24%)	28 (30%)
ALT increased	11 (18%)	18 (20%)
AST increased	9 (15%)	13 (14%)
Blood bilirubin increased	0	2 (2%)

[Source: ADAE.xpt]

Treatment Emergent Adverse Events:

Generally, the incidences of AEs reported at the update in Cohort 3+Extension Cohort were consistent with the original update. The most frequently reported AEs (≥10%) were ALT increased, AST increased, blood bilirubin increased and febrile neutropenia.

Table 73 AUS01T: Adverse Events that Occurred in in ≥ 5% of Patients (Safety Set)

Cutoff date	Sept 30, 2016		Feb 28, 2018	
	Cohort 3+Ext. N=62		Cohort 3+Ext. N=92	
	All Grades	≥Grade 3	All Grades	≥Grade 3
All AEs	47 (76%)	39 (63%)	72 (78%)	59 (64%)
ALT increased	17 (27%)	17 (27%)	27 (29%)	26 (28%)
AST increased	12 (19%)	12 (19%)	16 (17%)	16 (17%)
Blood bilirubin increased	9 (15%)	9 (15%)	16 (17%)	16 (17%)
Febrile neutropenia	10 (16%)	10 (16%)	15 (16%)	15 (16%)
Serum sickness[a]	6 (10%)	5 (8%)	8 (9%)	6 (7%)
Rash[b]	4 (6%)	2 (3%)	8 (9%)	3 (3%)
Upper respiratory tract infection	1 (2%)	1 (2%)	7 (8%)	5 (5%)
Lung infection	3 (5%)	3 (5%)	6 (7%)	6 (7%)
Hypertension	1 (2%)	1 (2%)	5 (5%)	5 (5%)
Skin discoloration[c]	3 (5%)	0	5 (5%)	0

a. All cases of serum sickness were assessed as "unlikely" related to eltrombopag.
b. Includes rash maculo-papular and rash pustular.
c. Includes skin hyperpigmentation.
[Source: ADAE.xpt]

Safety Analyses by Demographic Groups:

Geriatric patients:

A total of 15 patients ≥ 65 years of age were enrolled as of the updated cutoff in Cohort 3+Extension Cohort (increased from the 10 patients ≥ 65 years at the original cutoff). The incidence of AEs in the patients ≥ 65 years (87%) was higher compared with patients <65 years of age (77%).

Table 74 AUS1T: Updated AEs by Age (<65 Years vs. ≥65 Years)

Cutoff date	Sept 30, 2016		Feb 28, 2018	
	Cohort 3+Ext. N=62		Cohort 3+Ext. N=92	
	<65 yrs (n=52)	≥ 65yrs (n=10)	<65 yrs (n=77)	≥ 65yrs (n=15)
All AEs	42 (81%)	8 (80%)	59 (77%)	13 (87%)
Serious AEs	23 (44%)	3 (30%)	38 (49%)	8 (53%)
AEs leading to withdrawal	3 (6%)	1 (10%)	3 (4%)	1 (7%)
AEs leading to death	0	0	0	0

[Source: ADAE.xpt]

Pediatric patients:
At the updated cutoff date, a total of 8 additional pediatric patients (all in the Extension Cohort) were enrolled. The incidences of AEs at the update in pediatric patients in Cohort 3+Extension Cohort were largely consistent with those at the original cutoff. The updated incidences of AEs in pediatric patients were also largely consistent with the adult patient population except the incidence of febrile neutropenia was higher in pediatrics <18 years (39%) compared with patients ≥18 of age (8%).

Table 75 AUS01T: Updated AEs by Pediatric Subgroup that Occurred in ≥ 2 Patients in cohort 3+Extension Cohort (Safety Set)

Cutoff date	Sept 30, 2016			Feb 28, 2018		
	Cohort 3+Ext.			Cohort 3 +Ext.		
	2-5 yrs N=1	6-11 yrs N=7	12-17 yrs N=10	2-5 yrs N=1	6-11 yrs N=11	12-17 yrs N=14
All AEs	0	5 (71%)	9 (90%)	0	10 (91%)	11 (79%)
Febrile neutropenia	0	3 (43%)	2 (20%)	0	7 (64%)	3 (21%)
ALT increased	0	1 (14%)	3 (30%)	0	3 (27%)	3 (21%)
Upper respiratory tract infection	0	0	0	0	3 (27%)	1 (7%)
AST increased	0	1 (43%)	1 (10%)	0	2 (18%)	1 (7%)
Blood bilirubin	0	0	2 (20%)	0	0	3 (21%)

increased						
Rash[a]	0	1 (14%)	1 (10%)	0	2 (18%)	2 (14%)
Headache	0	0	0	0	1 (9%)	2 (14%)
Lung infection	0	2 (29%)	0	0	2 (18%)	1 (7%)
Sinusitis	0	1 (14%)	1 (10%)	0	2 (18%)	1 (7%)
Enterocolitis	0	0	0	0	0	2 (14%)
Hypertension	0	0	0	0	0	2 (14%)
Bacteremia	0	0	0	0	1 (9%)	1 (7%)
Infusion related reaction	0	1 (14%)	1 (10%)	0	1 (9%)	1 (7%)
Nausea	0	0	0	0	1 (9%)	1 (7%)
Pharyngitis	0	0	0	0	2 (18%)	0
Serum sickness	0	0	1 (10%)	0	1 (9%)	1 (7%)
Tonsillitis	0	0	0	0	2 (18%)	0

a. Includes rash maculopapular and rash pustular.
[Source: ADAE.xpt]

The updated incidences of AEs and AEs leading to withdrawal in pediatric patients were similar to adult patients in Cohort 3+Extension Cohort. However, SAEs occurred at a higher rate in pediatric patients (69%) compared with adult patients (42%).

Table 76 AUS01T: Updated AEs by Age (<18 Years vs. ≥18 Years)

Cutoff date	**Sept 30, 2016**		**Feb 28, 2018**	
	Cohort 3+Ext. N=62		**Cohort 3+Ext. N=92**	
	<18 yrs (n=18)	≥ 18yrs (n=44)	<18 yrs (n=26)	≥ 18yrs (n=66)
All AEs	14 (78%)	36 (82%)	21 (81%)	51 (77%)
Serious AEs	10 (56%)	16 (36%)	18 (69%)	28 (42%)
AEs leading to withdrawal	2 (11%)	2 (5%)	2 (8%)	2 (3%)
AEs leading to death	0	0	0	0

[Source: ADAE.xpt]

Adverse Events of Special Interest:

The incidences of bleeding and hepatobiliary events in Cohort 3+Extension Cohort were consistent with the original cutoff. There were no new thromboembolic or renal events throughout the cohorts. No cases of malignancies, bone marrow fibrosis or recurrence of thrombocytopenia (after discontinuation of eltrombopag) adverse events were reported in the AUS01T trial.

The table below summarizes the incidences of hepatobiliary events at the two cutoff dates in Cohort 3+Extension Cohort.

Table 77 AUS01T: Updated Incidences of Hepatobiliary Events (Safety Set)

Cutoff date	Sept 30, 2016	Feb 28, 2018
	Cohort 3+Ext. N=62	Cohort 3+Ext. N=92
All	25 (40%)	38 (41%)
ALT increased	17 (27%)	27 (29%)
AST increased	12 (19%)	16 (17%)
Blood bilirubin increased	9 (15%)	16 (17%)
Blood ALP increased	1 (2%)	1 (1%)
Ascites	0	1 (1%)
Cholestasis	1 (2%)	1 (1%)
Liver injury	1 (2%)	1 (1%)
Ocular icterus[a]	1 (2%)	0

a. Per the applicant, the event ocular icterus was recorded in patient (b) (6) in the SOC hepatobiliary disorders at the original analysis, but has since been revised to the SOC eye disorder.
[Source: ADAE.xpt]

At baseline, all except 3 patients in study AUS01T had GPI negative neutrophil level of ≤50% (see table 16 above). With the update, the worst post-baseline level to >50% (from ≤50% at baseline) had shifted in 1 patient each in Cohort 1, Cohort 2 and Extension Cohort during the trial.

Laboratory Findings:

Hematology:
In the AUS01T trial, supportive care including transfusion support (blood and platelets) and administration of hematopoietic growth factors (e.g., G-CSF, GM-CSF, or erythropoietin) were permitted as clinically indicated at baseline and during the treatment period. The applicant notes that although transfusion could be given during the treatment period, the reporting of the worst grade post-baseline is likely to be recorded when the patient was not transfused.

The table below summarizes the shifts in hematology laboratory tests from baseline to worst grades that occurred at any time during treatment. The laboratory values could initially drop before improving. At the updated cutoff, the incidences of worsening from baseline for hematology abnormalities were similar to those observed at the original cutoff in Cohort 3+Extension Cohort. Most of the worsening of hematology abnormalities occurred during the first 13 days of treatment. There were no clinically meaningful differences between the cohorts.

Table 78 AUS01T: Updated Shifts in Hematology Laboratory Tests (Safety Set)

Cutoff date		Sept 30, 2016	Feb 28, 2018
	Worsening from baseline to	Cohort 3+Ext. N=62	Cohort 3+Ext. N=92
Hemoglobin	Grade 1	0	0
	Grade 2	2/11 (18%)	1/16 (6%)
	Grade 3	49/55 (86%)	69/78 (88%)
Neutrophils	Grade 1	1/1 (100%)	1/1 (100%)
	Grade 2	0	0
	Grade 3	2/5 (40%)	3/12 (25%)
	Grade 4	10/21 (48%)	14/32 (44%)
Platelets	Grade 1	0	0
	Grade 2	0	0
	Grade 3	0	0
	Grade 4	41/41 (100%)	57/57 (100%)

*The percentages= number of patients whose grade worsened/total number of patients (who had missing or less than grade x at Baseline and) with at least one post-Baseline value for the considered parameter.
[Source: CSR AUS01T and ADLB.xpt]

Biochemistry:
According to the applicant, in the original submission, the rules for reporting grade 3 and 4 LFT laboratory abnormalities as AEs were inconsistent. In the update, all grade 3 and 4 laboratory abnormalities were queried whether to report them as AEs.

Overall, the incidences of shifts in chemistry laboratory tests were similar to the original cutoff date. At the update, worst-grade shifts to ≥grade 3 AST, ALT and bilirubin occurred in 17%, 30% and 13% of patients, respectively, in Cohort 3+Extension Cohort.

The table below summarizes shifts in biochemistry by worsening grade from baseline for the two cutoff dates.

Table 79 AUS01T: Updated Shifts in Chemistry Laboratory Tests (Safety Set)

Cutoff date		Sept 30, 2016	Feb 28, 2018
	Worsening from baseline to	Cohort 3+Ext. N=62	Cohort 3+Ext. N=92
AST	Grade 1	17/56 (30%)	30/84 (36%)
	Grade 2	9/62 (15%)	12/92 (13%)
	Grade 3	10/62 (16%)	14/92 (15%)
	Grade 4	2/62 (3%)	2/92 (2%)
ALT	Grade 1	12/47 (26%)	19/71 (27%)

	Grade 2	16/58 (28%)	27/87 (31%)
	Grade 3	19/61 (31%)	24/91 (26%)
	Grade 4	2/62 (3%)	4 /92 (4%)
Bilirubin	Grade 1	13/46 (28%)	22/70 (31%)
	Grade 2	25/54 (46%)	38/81 (47%)
	Grade 3	9/62 (15%)	11/91 (12%)
	Grade 4	1/62 (2%)	1/92 (1%)
ALP	Grade 1	17/39 (44%)	34/62 (55%)
	Grade 2	11/62 (18%)	14/92 (15%)
	Grade 3	1/62 (2%)	1/92 (1%)
	Grade 4	0	0
Creatinine	Grade 1	16/61 (26%)	27/91 (30%)
	Grade 2	2/62 (5%)	3/92 (3%)
	Grade 3	0	0
	Grade 4	0	0
Hyperglycemia	Grade 1	27/48 (56%)	39/68 (57%)
	Grade 2	23/59 (39%)	35/89 (39%)
	Grade 3	3/61 (5%)	5/91 (6%)
	Grade 4	0	0
Hypoglycemia	Grade 1	11/62 (18%)	17/92 (19%)
	Grade 2	0	0
	Grade 3	0	0
	Grade 4	0	0

*The percentages= number of patients whose grade worsened / total number of patients (who had missing or less than grade x at Baseline and) with at least one post-Baseline value for the considered parameter.
[Source: CSR AUS01T 120-day safety update]

A total of 29 patients (32%) had increased ALT or AST ≥ grade 3 at any time in Cohort 3+Extension Cohort. Of the 29 patients, a total of 5 patients (IDs: (b) (6)) were pediatric patients less than 18 years of age (range: 9 to 16 years). All 5 patients developed ≥ grade 3 AST or ALT within the first 13 days on study and one patient (ID: (b) (6) had a repeat incidence of ≥ grade 3 occurring from Day 57 to Day 60. Of these 5 patients, 1 patient (ID: (b) (6)) developed grade 4 ALT on treatment; this patient had baseline ALT and AST grade 0 and developed grade 4 ALT elevation on Day 8 which lasted for 3 days and decreased to ≤ Grade 2 after 10 days in total. Eltrombopag therapy was interrupted in all 5 patients for a median period of 4 days (range, 2-10 days) and it has been reported that all 5 patients recovered to their baseline laboratory grade or to a lower grade. Among these 5 patients, one patient (ID: (b) (6)) also had grade 3 total blood bilirubin (>3 to 10 x ULN) during the time of ≥ grade 3 AST or ALT elevation.

Among the 24 adult patients who developed ≥ grade 3 ALT or AST elevation, 3 patients (IDs: (b) (6), (b) (6)) had grade 4 ALT/AST elevation. In 18 patients, the ≥ grade 3 ALT or AST elevation occurred within 13 days on study. The ALT or AST elevation decreased to ≤ grade 2 in all except one patient (b) (6)(who died due to infection 109 days after the last dose of eltrombopag and at

the time of the death, the event of ALT/AST increased was reported as ongoing). A total of 16 patients interrupted treatment with eltrombompag for a median period of 5 days (range, 1-21 days). The ALT/AST elevations were reported to have been recovered in all patients except patient (b) (6) and no patients had ≥ grade 3 ALT or AST elevation again after re-starting eltrombopag. Among the AEs that occurred in the 24 patients during the time of ≥ Grade 3 ALT or AST elevation, the following AEs were assessed as unlikely or possibly related to eltrombopag: grade 3 total blood bilirubin (3 events), grade 3 hypokalemia (1 event), grade 4 liver injury (1 event [patient (b) (6)]) and grade 2 nausea (1 event). The narrative for Patient (b) (6) is presented under section 8.5.2 and the LFT abnormalities did not meet the laboratory criteria for Hy's law.

All AEs were reported as recovered except the AE that occurred in patient (b) (6).

A total of 29 patients (32%) met the criteria of ALT or AST > 3xULN and TBIL > 2xULN and (ALP < 2xULN or missing) in Cohort 3+Extension Cohort, where the 3 laboratory parameters met the defined thresholds (ULN) within a 30 day period of each other. The cases of 13 patients are presented above in section 8.4.6. See table 81 for the remaining 16 cases.

The elevations of the LFTs were usually transient and it has been reported that most of the patients recovered completely while on eltrombopag treatment. Some patients had confounding medical history and some were also receiving concomitant drugs known to induce transient increases of the LFTs. None of the patients discontinued eltrombopag due to ≥ grade 3 ALT or AST elevations. It has been reported that most of the AEs of the elevation in transaminases were clinically manageable with dose adjustment or interruption, none led to treatment discontinuation. Overall, 20% and 14% of patients in Cohort 3+Extension Cohort had eltrombopag dose adjusted/interrupted due to ALT or AST increased, respectively. See table 72 above.

Table 80 AUS01T: Updated Elevations in Liver Function Tests (Safety Set)

Cutoff date	**Sept 30, 2016**	**Feb 28, 2018**
	Cohort 3+Ext. N=62	**Cohort 3+Ext. N=92**
ALT or AST > 3xULN	40 (65%)	58 (63%)
ALT or AST > 5xULN	22 (36%)	29 (32%)
ALT or AST > 8xULN	12 (19%)	17 (19%)
ALT or AST > 20xULN	2 (3%)	4 (4%)
TBIL > 2xULN	25 (40%)	41 (45%)
ALT or AST > 3xULN and TBIL > 1.5xULN	29 (47%)	40 (44%)
ALT or AST > 3xULN and TBIL > 2xULN	17 (27%)	29 (32%)

ALT or AST > 3xULN and TBIL > 2xULN and (ALP < 2xULN or missing)	17 (27%)	29 (32%)

Based on worst post-Baseline value for each parameter, obtained from samples collected within maximum 30 days of each other.
[Source: CSR AUS01T 120-day safety update]

Table 81 AUS01T: Additional Cases of Patients with ALT or AST > 3xULN and TBIL > 2xULN and (ALP < 2xULN or missing) During Treatment with Eltrombopag (Safety Set)

	Elevated LFTs or TBIL occurred at			LFTs or TBIL elevation led to eltrombopag interruption	Recovered while on eltrombopag
Patient/ Age/ Cohort	**Base-line**	**Day on eltrombopag**	**Relevant medical history or concomitant med while on eltrombopag**		
(b) (6)/29 yo Extension Cohort	Grade 1 AST Grade 2 ALT	Increased transaminases started on Day 2 and returned to baseline on Day 3. Bilirubin elevation started on Day 4 and recovered on Day 9.	Ceftazidime Ivermectin Cyclobenzaprine Oxycodone Valacyclovir Pantoprazole Acetaminophen	No	Yes
(b) (6)/73 yo Extension Cohort	No	Transaminase elevation began on Day 2 and resolved on Day 4. Bilirubin elevation started on Day 20 and remained intermittently elevated until Day 188 when recovered.	Cetirizine HCL Ondansetron Ceftazidime Valacyclovir Pantoprazole Acetaminophen	No	No
(b) (6)/16 yo Extension Cohort	Grade 2 ALT	Transaminase elevation started on Day 2, returned and recovered on Day 22. Elevated Bilirubin started on Day 3 and recovered on Day 5; Bilirubin elevated again on Day 15 and recovered on Day 28. Elevated ALT reoccurred on Day 57 and recovered on Day 60.	Chikungunya virus Infection. Acyclovir Pantoprazole Acetaminophen Ondansetron Ceftazidime Micafungin Ivermectin Voriconazole Amphotericin B	Interrupted from Day 3 to Day 6 and again from Day 57 to Day 59.	Yes.
(b) (6)/38 yo Extension Cohort	No	Bilirubin elevation started on Day 15 and persisted through Day 169. Transaminases elevation	No	No	Yes

		started on Day 153 and for one time was reported concomitantly with Bilirubin elevation. In the following assessment on Day 162, transaminases were reported as grade 1. Subject presented a viral infection reported on Day 153, and a disseminated subcutaneous Staphylococcus Aureus infection reported on Day 176, both infection were reported as SAEs.			
(b) (6)/9 yo Extension Cohort	Grade 1 ALT	Bilirubin and transaminase were reported as elevated concomitantly on Day 14 only. Both laboratory parameters continued to fluctuate independently between grade 0 to 3 until Day 186, then both recovered.	Hepatitis B (inactive) Valacyclovir	Interrupted on Day 13 for 2 days.	Yes.
(b) (6)/26 yo Extension Cohort	Grade 2 AST Grade 4 ALT Grade 2 TBL	Baseline elevated values for bilirubin and transaminases continued to decrease and normalized while on eltrombopag.	Hepatitis B (inactive) DILI due to prior treatment with hydroxycut Hyperbilirubinemia and transaminitis at baseline. Valacyclovir	No	Yes
(b) (6)/44 yo Extension Cohort	Grade 1 AST Grade 3 ALT	Transaminases elevation were observed at baseline and continued to progress up to Grade 4, and recovered on Day 22. Bilirubin elevation started on Day 22 and intermittently remained elevated.	Valacyclovir pantoprazole	No	Yes
(b) (6)/26 yo Extension Cohort	No	Bilirubin and transaminase were reported as elevated concomitantly on Day 4	Valacyclovir pantoprazole acetaminophen	No	Yes

		only. Both laboratory parameters recovered.			
(b) (6)/14 yo Extension Cohort	Grade 1 ALT	Bilirubin and transaminase were reported as elevated concomitantly on Day 42 only. Both labs recovered.	Autoimmune hepatitis	No	Yes
(b) (6)/20 yo Extension Cohort	No	Bilirubin elevated and transaminases were reported as elevated concomitantly from Day 34 to 37. Both lab parameters recovered.	Valacyclovir	Dose interrupted from Day 37 to Day 52.	Yes
(b) (6)/15 yo Extension Cohort	Grade 1 ALT Grade 3 TBL	Bilirubin elevation was observed at baseline and continued elevated through Day 17, and then recovered. An isolated increase of ALT occurred on Day 24.	Valacyclovir Levofloxacin	No	Yes
(b) (6)/7 yo Extension Cohort	No	Elevated transaminases and bilirubin started on Day 49 and resolved on Day 50 and 51, respectively. Subject presented events of febrile neutropenia from Day 41 to Day 91, and pharyngitis from Day 44 to Day 51, both events were reported as SAEs.	Hepatitis B (inactive)	No	Yes
(b) (6)/23 yo Extension Cohort	No	Elevated transaminases started on Day 16 and recovered on Day 26. Intermittent bilirubin elevation started on Day 33 and recovered on Day 57. Isolated ALT increase on Day 181 and recovered on Day 188.	Acetaminophen Pantoprazole	Dose was interrupted from Day 182 to Day 184, due to isolated ALT.	Yes.
(b) (6)/9 yo Extension Cohort	No	Bilirubin elevated and transaminases were reported as elevated concomitantly on Day 49 and 50. Both lab parameters recovered.	Acetaminophen	Dose interrupted from Day 8 to Day 17 due to isolated transaminitis.	Yes
(b) (6)/33 yo Extension	Grade 3 ALT	Transaminase elevation was observed at baseline and	Vancomycin Pantoprazole	No	Yes

Cohort		continued elevated up to Day 13. Increased Bilirubin started on Day 22 and continued through Day 155.			
(b) (6)/38 yo Extension Cohort	No	Bilirubin elevated and transaminases were reported as elevated concomitantly from Day 5 to Day 16. Both lab parameters recovered.	Hepatitis B (inactive) Dengue Fever Acetaminophen	Dose was interrupted from Day 4 to Day 14	Yes

[Source: CSR AUS01T 120-day safety update]

The applicant also conducted an evaluation to assess the relationship between ALT/AST > 3x ULN and the dose and extent of eltrombopag exposure for patients enrolled in Cohort 3+ Extension Cohort. The dose of eltrombopag was 150 mg and 75 mg in 74 and 16 patients, respectively. In addition, one patient each was on 50 mg and 37.5 mg. In patients treated with 150 mg, 51 patients (69%) developed ALT/AST elevation > 3xULN with a median time to onset of 0.4 months. In patients treated with 75 mg, 7 patients (45%) developed ALT/AST elevation > 3xULN during the treatment period (median time to onset was not evaluable). No patients treated with 37.5 mg and 50 mg were reported with an ALT/AST elevation. The results in the pediatric patients were consistent with the overall patient population in Cohort 3+Extension Cohort. In the 13 pediatric patients on 150 mg, 9 patients (69%) developed ALT/AST elevation > 3xULN with a median time to onset of 0.4 months; and in the 11 pediatric patients on 75 mg, 4 patients (36%) developed ALT/AST elevation > 3xULN during the treatment period (median time to onset was not evaluable).

For concomitant (within 30 days) elevation of ALT and/or AST > 3xULN and total bilirubin > 1.5xULN, the reported incidences in patients taking 150 mg and 75mg were 46% (median time to onset: NE) and 38% (median time to onset: NE), respectively. In the pediatric patients, the reported incidences in patients taking 150 mg and 75mg were 62% (median time to onset: 0.4 months) and 27% (median time to onset: NE), respectively, indicating that increased dose of eltrombopag is associated with higher incidence of liver toxicity.

When comparing the incidences of LFTs abnormalities during the first 13 days of treatment between Cohorts 1+2 versus Cohort 3+Extension Cohort as analyzed by the applicant, in general the incidences were higher in the combined Cohorts 1+2 compared to Cohort 3+Extension Cohort (see table below). Considering that in Cohorts 1 and 2, eltrombopag was added to h-ATG+CsA treatment starting on Day 14 and in Cohort 3+Extension Cohort the eltrombopag/h-ATG+CsA combination treatment was started on Day 1, it is not clear what elements contributed to these results.

Table 82 AUS01T: Elevations in Liver Function Tests Collected Within the First 13 Days (February 28, 2018 Cutoff Date)

	Cohort 1+Cohort 2 N=61	Cohort 3+Ext. N=92
ALT or AST > 3xULN	35 (57%)	50 (54%)
ALT or AST > 5xULN	25 (41%)	23 (25%)
ALT or AST > 8xULN	13 (21%)	7 (8%)
ALT or AST > 20xULN	5 (8%)	2 (2%)
TBIL > 2xULN	13 (21%)	10 (11%)
ALT or AST > 3xULN and TBIL > 1.5xULN	20 (33%)	20 (22%)
ALT or AST > 3xULN and TBIL > 2xULN	10 (16%)	6 (7%)
ALT or AST > 3xULN and TBIL > 2xULN and (ALP < 2xULN or missing)	9 (15%)	5 (5%)

ALP = Alkaline phosphatase, ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, TBIL = Total Bilirubin.
[Source: Novartis submission on July 17, 2018]

The applicant also conducted an analysis of liver-related AEs from the Novartis Safety Database. A total of 1,259 patients were identified with a liver-related AE. Of the reported 1,259 patients, a total of 123 events occurred in 101 patients with aplastic anemia/bone marrow failure/anemia (children 3-12 years: 2 patients, 18-64 years: 37 patients, >65 years: 30 patients, not reported: 32 patients). Of the 123 events (serious: 55 [45%], non-serious: 68 [55%]), the outcome was reported for 72 events (fatal: 5 events [none were assessed as not related to eltrombopag, the specific causes of death were not provided], completely recovered: 42 events, improving: 7 events, condition unchanged: 18 events). Most of the liver AE that occurred in the 101 patients did not have enough information to assess the relationship to eltrombopag. Of the 101 patients, the AEs that occurred in 30 patients (including one pediatric patient) were excluded from further analysis as there were no events suggesting drug-induced liver injury or information. Time-to-onset was reported in 27 of 71 patients with 74% occurring in the first 3 months and 92% within 6 months of therapy. At the 150 mg dose, an increase in severity was not observed. In the SAA indication, a total of 2 pediatric cases were reported: both patients were on concomitant medications that cause LFT abnormality. Only in a total of 17 of the 123 events, there was temporal association with eltrombopag and in 8 events (serious: 1 event, non-serious: 7 events), there was a positive dechallenge along with positive rechallenge in two cases. Time to onset was available in 6 of the 8 cases (range: 1 week to 3 months). The dose of eltrombopag ranged from 50 mg to 150 mg (with half of the patients on 50 mg once daily). In all 8 cases, it has been reported that the hepatic function abnormality completely resolved after discontinuation of eltrombopag. Of the 17 cases, the details in 9 cases were provided by the applicant (see the table below). There were no significant clinical

symptoms in most of the LFTs increase in the 9 cases. Time to onset ranged from 6 days to 512 days in 7 of the 9 cases with 78% of events occurring within 3 months of eltrombopag treatment. There was one case of drug-induced liver injury: the patient was concomitantly on cyclosporine and pantoprazole therapy known to cause hepatotoxicity or elevation in liver enzymes. Of the 9 cases, the AEs were resolving/resolved following reduction/ discontinuation of eltrombopag in 6 cases, the condition was ongoing in 1 case, final outcome was not reported in 2 cases.

Table 83 Liver-related AEs in Patients with Severe Aplastic Anemia (from Novartis Safety Database)

Case number, age, gender, time to onset, dose	Concomitant medications, medical history	Preferred Term, action taken, outcome	Comments
Pediatric case			
(b) (6) (Study E2201), 9 yo, female, 8 days, 50 mg once daily	Cyclosporine, voriconazole	Liver function test increased, treatment with eltrombopag discontinued, event resolved	Baseline LFTs were within normal range. Patient developed elevated AST and ALT (grade 3) 8 days after initiation of eltrombopag and cyclosporine. The patient had been on voriconazole at the time of study entry. Laboratory tests showed elevated blood levels of cyclosporine at 726 ng/ml (50 to 400 ng/ml) (grade 3), at which time the cyclosporine dose was reduced and eltrombopag was discontinued. Elevated LFTs normalized 14 days after dose reduction of cyclosporine and discontinuation of eltrombopag. Following normalization of elevated LFTs, treatment with eltrombopag was reinitiated at 50% dosing, and dose escalation continued as per protocol. The increase in LFT levels was assessed as likely due to the increased plasma levels of cyclosporine due to the interaction between cyclosporine and voriconazole. Voriconazole inhibits CYP3A4 which increases the plasma level of cyclosporine. Increase in cyclosporine blood levels can increase the likelihood of hepatic function abnormality and the event of hepatotoxicity is listed as a warning in the prescribing information for cyclosporine (Neoral).
Adult cases			

(b) (6), 73 y, male, not reported, 150 mg once daily	None	AST increased, treatment discontinued and event resolved, restarted at lower dose, final outcome not provided	Increase in AST observed to 180 IU/l. Eltrombopag discontinued and AST returned to baseline (positive dechallenge). Rechallenge with reduced dose of 100 mg resulted in increase in AST to 100 IU/L (positive rechallenge). Treatment with eltrombopag was continued at this dose.
(b) (6) Study 200926; refractory SAA, 71 y, female, 512 days, 100 mg once daily	Rabeprazole, thyroid neoplasm	Hepatic function abnormal, treatment discontinued, complete recovery	Increase in ALT to grade 3, bilirubin grade 1 and ALP grade 1. Serology for HAV, HBV, HCV, and HBE was negative. Positive dechallenge and event resolved upon discontinuation of eltrombopag.
(b) (6), 40 y, female, not reported, 100 mg once daily	Not reported	Hepatic enzyme increased, dose reduced, condition Improving	Increase in ALT grade 3 was observed subsequent to dose increase to 100 mg once daily. Event improved subsequent to reduction in dose to 50 mg. Dechallenge was positive and event was reported as recovering.
(b) (6), 48 y, female, 26 days, 50 mg	Tramadol, paracetamol	Hepatic function abnormal, AST and ALT increased, treatment discontinued, not reported	Baseline values of AST and ALT were 29 and 25 IU/L, respectively, that increased to AST 57 IU/l and ALT 124 IU/l subsequent to increase in eltrombopag dose to 50mg once daily. Eltrombopag was discontinued but was restarted after 11 days at an increased dose of 75 mg once daily. AST and ALT values continued to rise (lab values not reported) and eltrombopag was permanently discontinued. Outcome for events was not reported.
(b) (6), 85 y, male, approximately 1.5 month, 50 mg	Cyclosporine	LFT abnormal, Treatment discontinued, completely recovered	Baseline AST and ALT values were 40-50 IU/L. After 1.5 months of eltrombopag treatment, both AST and ALT were 290 IU/L. Eltrombopag was discontinued and LFT values returned to baseline after 4 days. Dechallenge was positive.
(b) (6), 70 y, female, 2.5 month, 75 mg	None	Hepatic function abnormal, treatment ongoing,	Patient had normal baseline LFTs. Eltrombopag dose was gradually increased to 75 mg and after 2.5 months of therapy initiation patient had ALT increased to grade

		condition unchanged	2. Treatment with eltrombopag was ongoing without improvement in the LFTs.
(b) (6), 71 y, male, 3 weeks, unknown	None	ALT increased, treatment discontinued, completely recovered	Baseline ALT was normal. Gradual increase in ALT values was observed after 3 weeks of therapy. ALT increased to 100 IU/L after 6 weeks of therapy and eltrombopag was discontinued. ALT values returned to baseline within 15 days of therapy discontinuation. Dechallenge was positive.
(b) (6), Study E2403, first-line SAA), 60 y, male, 6 days, 150 mg	Cyclosporine pantoprazole	Drug-induced liver injury, Unknown, Condition unchanged	Baseline LFT values were normal. Patient experienced AST, ALT, and bilirubin increased to grade 3 after 6 days on therapy with cyclosporine and eltrombopag 150 mg once daily. Eltrombopag was discontinued after 4 days of therapy and cyclosporine was discontinued 11 days after the event. AST elevation recovered while total bilirubin, direct bilirubin and ALT levels improved to grade 1.

[Source: Novartis submission on July 17, 2018]

Cytogenic Abnormalities Including Clonal Evolution:

At the updated cutoff in study AUS01T, a total of 15 patients (10%) had clonal evolution: 6 additional adult patients from the September 30, 2016 data cutoff (Cohort 1: 1 patients at Year 5 assessment, Extension Cohort: 5 patients) and none in pediatric patients. According to the applicant, of the 15 patients, 4 patients (IDs (b) (6) had chromosomal aberrations of unclear significance and 7 patients (IDs (b) (6)) had loss of chromosome 7, either alone or in combination with complex cytogenetic abnormalities. In 3 of the 7 patients with loss of chromosome 7, morphologic evidence of dysplasia or full myeloid malignant transformation was observed and in 6 of the 7 patients the alteration in chromosome 7 occurred within 6.1 months. In 3 of 15 patients (IDs (b) (6)) deletion of chromosome 13 was reported, considered to be a good prognostic factor in patients with aplastic anemia. One patient (ID: (b) (6) in Cohort 1) had a follow-up bone marrow assessment at 5 years which was markedly changed compared to previous bone marrow assessment, with features of dysplasia and hypercellularity concerning for potential development of MDS. The table below summarizes the 6 additional cases of clonal evolution reported at the update.

Table 84 AUS01T: Additional Clonal Evolution Observed During the Trial (February 28, 2018 Cutoff Date)

Patient ID/ Cohort/age/ gender/ exposure to eltrombopag (months)	Cytogenetic analysis at baseline	Time to clonal evolution (months)	Cytogenetic analysis at the time of clonal evolution	Narrative	Outcome
Patient (b) (6) Cohort 1 41-yr male 5.6 mos	6, XY [20]	60.5	Dysplasia with hyper-cellularity concerning for a potential developing MDS/MPN.	Patient received the first dose of study medication (h-ATG and CsA) on Day 1 (b) (6) and received eltrombopag from (b) (6) On (b) (6) (Follow Up Year 5) patient was diagnosed with clonal evolution: new cytogenetic abnormality defining of clonal evolution based on BM cytogenetics. Although cytogenetics remains normal on the bone marrow from (b) (6) both show consistent abnormal features that support a diagnosis of MDS/MPN unclassificable over that of aplastic anemia in remission.	Follow up ongoing.
Patient (b) (6) Extension 70 -yr male 6.0 mos	46,XY[2]	12.0	46,XY,del(13)(q12q22)[5]/45,X,-Y[4]/46,XY[11]	Patient received the first dose of study medication (h-ATG, CsA, eltrombopag) on Day 1 (b) (6) received eltrombopag from (b) (6). On (b) (6) (Follow up Year 1), patient was diagnosed with clonal evolution: new cytogenetic abnormality defining of clonal evolution based on BM cytogenetics. The abnormality was deletion of chromosome 13. BM morphology was normal and lacked dysplasia or increased blasts to suggest MDS. Loss of Y chromosome was considered a normal age/related change in men. Deletion of chromosome 13 is of uncertain significance in aplastic anemia and it is reported to be a good prognostic feature in aplastic anemia. In view of this changes, it was decided to repeat BM evaluation in 6 months or sooner if his blood counts decline. The patient	Repeat BM Evalua-tion at Month 6 or sooner if blood counts decline.

				remained on low dose cyclosporine.	
Patient (b) (6) Extension 57-yr male 6.0 mos	46,XY[20]	6.0	46,XY,del(7)(p13)[3]/46,XY[17]	Patient received the first dose of study medication (h-ATG, Cs, eltrombopag) on Day 1 (b) (6); received eltrombopag from (b) (6) to (b) (6). Treatment with eltrombopag was stopped due to a new cytogenetic abnormality. On (b) (6) (At Month 6), patient was diagnosed with clonal evolution: a new cytogenetic abnormality defining of clonal evolution per protocol based on BM cytogenetics. The abnormality was deletion of chromosome 7. The morphology did not show any overt dysplasia or elevated blasts that would be consistent with MDS. It was reported that cytogenetic abnormality was due to progression of disease (SAA) and the type of mutation (short arm of chromosome 7) was unusual for SAA (which normally has a mutation in the long arm of chromosome 7 or monosomy 7).	HSCT
Patient (b) (6) Extension 50-yr female 3.3 mos	46,XX[14]	3.0	47,XX,+8[5]/46,XX[15]	Patient received the first dose of study medication (h-ATG, CsA, eltrombopag) on Day 1 (b) (6); received eltrombopag from (b) (6). Treatment with eltrombopag was stopped due to a new cytogenetic abnormality. On (b) (6) (at Month 3), subject was diagnosed with clonal evolution: a new cytogenetic abnormality defining of clonal evolution based on BM cytogenetics. The abnormality was trisomy 8 in 5 out of 20 metaphases on standard cytogenetic analysis. On an unknown date the patient underwent a BM biopsy which showed improved cellularity overall with some atypical megakaryocytes noted, but no increase in blasts or other dysplasia or definitive evidence to change her diagnosis from aplastic anemia to MDS. Trisomy 8 is of uncertain	HSCT CR at 3 months

				significance, and although can be transient, the possibility of a low grade MDS cannot be excluded.	
Patient (b) (6) Extension 78-yr female 3.3 mos	46,XX [20]	3.0	46,XX,del(13)(q12q22)[3]/46,XX[17]	Patient received the first dose of study medication (h-ATG, CsA, eltrombopag) on Day 1 (b) (6); received eltrombopag (b) (6). Treatment with eltrombopag was stopped due to a new cytogenetic abnormality. On (b) (6) (at Month 3), patient was diagnosed with clonal evolution: a new cytogenetic abnormality defining of clonal evolution per protocol based on BM cytogenetics. The abnormality was deletion 13q in 3 out of 20 metaphases. The BM morphology did not show any evidence of dysplasia or increased blasts to support a diagnosis of MDS or leukemia. At the Month 3 visit, counts showed a partial response. The investigator instructed the subject to stop eltrombopag and advised to continue to remain on the study and on CsA. The next BM biopsy at Month 6 was reported as normal - 46, XX [20].	Stopped eltrombopag, on treatment with CsA. PR at 3 months. Normal BM at 6 months.
Patient (b) (6) Extension 65-yr male 6.1 mos	46,XY[11]	6.1	46,XY,inv(7)(q21q31)[5]/46,XY[15]	Patient received the first dose of study medication (h-ATG, CsA, eltrombopag) on Day 1 (b) (6); received eltrombopag from (b) (6). On (b) (6) (Month 6) patient was diagnosed with clonal: new cytogenetic abnormality defining of clonal evolution based on BM cytogenetics. The abnormality was (7)(q21q31) in 5 out of 20 metaphases. It was reported that, chromosome 7 is a poor prognostic indicator, but this was an unusual rearrangement. Morphologically the BM did not show any evidence of dysplasia or increased blasts to support a diagnosis of MDS or leukemia.	Follow up ongoing.

[Source: CSR AUS01T 120-day safety update]

With the update, among the 15 patients with clonal evolution, a total of 9 patients (Cohort 1: 5 patients, Cohort 2: 1 patient, Cohort 3+Extension: 3 patients) had progressed to MDS/AML. The incidence of evolution to MDS/AML was 17%, 3% and 3% in Cohort 1, Cohort 2 and Cohort 3+Extension Cohort, respectively, with overall median follow time of 61, 47, and 22 months, respectively. The higher incidence of clonal evolution in Cohort 1 might be due to longer follow up time.

Table 85 AUS01T: Updated Time to Evolution (February 28, 2018 Cutoff Date)

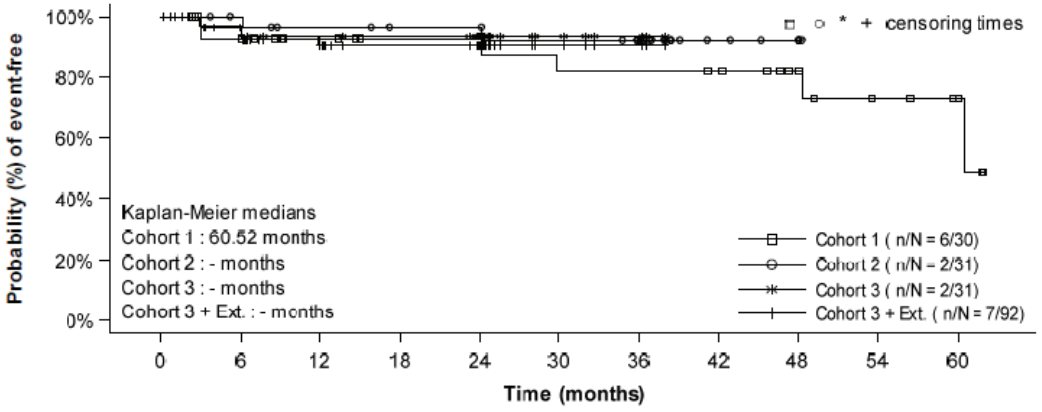
	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3+Ext. N=92
Clonal Evolution	6 (20%)	2 (7%)	2 (7%)	7 (8%)
Evolution to MDS/AML	5 (17%)	1 (3%)	1 (3%)	3 (3%)
Other evolution	1 (3%)	1 (3%)	1 (3%)	4 (4%)
No evolution	24 (80%)	29 (94%)	29 (94%)	85 (92%)

[Source: ADTTE.xpt]

The median time to clonal evolution in Cohort 1 was 60.5 months (95% CI: 48.3, NE) and not evaluable in other cohorts.

Review comment: In the historical studies that treated SAA patients with standard IST (h-ATG + CsA) without eltrombopag as first-line therapy, the incidence of clonal evolution in Scheinberg et al. (2009) and Scheinberg et al. (2012) at a median follow-up of 3 years was 9.5% and 21%, respectively. Therefore, it does not appear that the addition of eltrombopag to h-ATG +CsA is associated with higher risk of clonal progression.

Figure 3 AUS01T: Updated Kaplan-Meier Plot of Time to Clonal Evolution (2/28/2018 Cutoff)



No. of patients still at risk

Time (months)	0	6	12	18	24	30	36	42	48	54	60
Cohort 1	30	26	20	17	17	15	15	14	10	6	4
Cohort 2	31	29	26	24	24	22	18	6	4	0	
Cohort 3	31	30	27	26	22	6	3	0			
Cohort 3 + Ext.	92	74	44	34	29	6	3	0			

[Source: CSR AUS01T 120-day safety update]

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

No new safety signals were identified through postmarket experience.

8.10. Integrated Assessment of Safety

The evaluation of safety of eltrombopag in combination with standard immunosuppressive therapy (h-ATG and cyclosporine) for patients with SAA as first-line therapy was primarily based on a total of 153 patients who received eltrombopag in the AUS01T trial and more specifically on the 92 patients enrolled in the Cohort 3+Extension Cohort who received the recommended dosing regimen of the combination therapy (eltrombopag on Day 1 to Month 6 plus h-ATG+ cyclosporine followed by low cyclosporine maintenance dose for 18 additional months in patients who achieved a hematologic response at Month 6).

The safety review was supplemented with supportive trials in Japanese patients treated with different regimens and limited safety information from historical control studies that treated patients with h-ATG and CsA without eltrombopag.

In the AUS01T trial, the median duration of eltrombopag therapy in Cohort 3+Extension Cohort was 183 days (range: 12-204 days) with 70% of patients receiving eltrombopag longer than 24 weeks. The median exposure to the cyclosporine therapeutic dose was 186 days (range: 6-224 days) and 387 days (range: 22-646 days) for the maintenance dose in Cohort 3+Extension Cohort. The safety findings are as follows:

- A total of 7 patients (Cohort 1: 3 patients, Cohort 2: 1 patient, Cohort 3+Extension Cohort: 3 patients) died in the AUS01T trial. All 7 deaths were assessed as unrelated to study treatment. One patient in Cohort 1 died on-treatment with eltrombopag and CsA, due to toxic metabolic encephalopathy and central respiratory failure attributed to thymoma that existed before the study entry. The other two patients in Cohort 1 died due to HSCT-related cause during follow-up approximately 1 and 2 years after the end of therapy, respectively. The remaining 4 deaths also occurred during follow-up (109-881 days after the last dose of eltrombopag).
- In Cohort 3+Extension Cohort, 50% of patients experienced SAEs which was higher than the incidences in Cohorts 1 (43%), 2 (39%) and 3 (42%). The most frequently reported SAEs (≥5%) in Cohort 3+Extension Cohort were serum sickness, febrile neutropenia, upper respiratory infection and lung infection.
- A higher proportion of patients in Cohort 3+Extension Cohort (64%) experienced ≥ grade 3 AEs compared to Cohort 1 (53%) or Cohort 2 (58%). The most frequently reported ≥ grade 3 AEs (≥5%) in Cohort 3+Extension Cohort were ALT increased, AST increased, blood bilirubin increased, febrile neutropenia, serum sickness, lung infection, upper

respiratory tract infection and hypertension.

- The incidence of AEs in Cohort 3+Extension Cohort was 78% and was higher than in Cohort 1 (63%) or Cohort 2 (68%). The differences were mostly due the higher incidences of ALT increased and AST increased. The most frequently reported AEs (≥10%) in Cohort 3+Extension Cohort were ALT increased, AST increased, blood bilirubin increased and febrile neutropenia.
- A total of 15 patients (10%) (Cohort 1: 6 patients, Cohort 2: 2 patients, Cohort 3+Extension Cohort: 7 patients) had clonal evolution. Of the 15 patients with clonal evolution, 9 patients had progressed to MDS or AML. The median time to clonal evolution in Cohort 1 was 60.5 months (95% CI: 48.3, NE) and not evaluable in other cohorts. The incidence of clonal evolution in the historical experience with standard IST (h-ATG + CsA) without eltrombopag as first-line therapy in SAA range from 9.5% to 21%. Therefore, it does not appear that eltrombopag is associated with higher frequency.
- The AUS01T trial enrolled a total of 37 pediatric patients (24%) <18 years of age (Cohort 1: 5 patients, Cohort 2: 6 patients, Cohort 3: 8 patients, Cohort 3+Extension Cohort: 26 patients). In general, the safety profile of pediatric patients was largely consistent with the adult patients except the incidence of febrile neutropenia was higher in pediatrics <18 years (39%) compared with patients ≥18 of age (8%). In addition, SAEs occurred at a higher rate in pediatric patients (69%) compared with adult patients (42%).
- The following toxicities are listed in the current Warnings and Precautions section of the eltrombopag prescribing information: hepatotoxicity, increased risk of death and progression of MDS to AML, thrombotic/thromboembolic complications, and cataracts. No new safety signals were observed in the AUS01T trial.

9. Advisory Committee Meeting and Other External Consultations

Advisory committee or any other external consultations were not required for this sNDA.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The following are recommended major changes to the fostamatinib prescribing information based on this review:

10.2. Nonprescription Drug Labeling

This section is not applicable.

11.Risk Evaluation and Mitigation Strategies (REMS)

REMS is not required for this application.

12.Postmarketing Requirements and Commitments

No clinical PMCs or PMRs are deemed necessary for this sNDA.

13.Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): AUS01T

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 17		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HYON-ZU LEE
11/02/2018

KATHY M ROBIE SUH
11/02/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22291Orig1s021

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	sNDA 022-291
Supplement #:	21
Drug Name:	Eltrombopag
Indication(s):	For the treatment of severe aplastic anemia (SAA)
Applicant:	Novartis
Submission Date:	March 29, 2018
PDUFA Date:	December 29, 2018
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Cindy Gao, Ph.D.
Concurring Reviewers:	Yuan-Li Shen. Dr. P.H., Team Leader
	Thomas Gwise, Ph.D., Division Director
Medical Division:	Division of Hematology Products II
Clinical Reviewer:	Hyon-Zu Lee, M.D.
Clinical Team Leader:	Kathy Robie Suh, M.D.
Clinical Division Director:	Albert Deisseroth, M.D.
Project Manager:	Kimberly Scott

Keywords: severe aplastic anemia

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1. EXECUTIVE SUMMARY

The purpose of this submission is to obtain approval for the use of eltrombopag in combination with standard immunosuppressive therapy for the *first-line treatment* of adult and pediatric patients 2 years and older with severe aplastic anemia.

The proposed new indication was supported primarily on findings from the pivotal Study AUS01T, a single center, single arm, non-randomized, Phase I/II trial investigating the efficacy and safety of horse antithymocyte globulin (h-ATG) + cyclosporine in combination with eltrombopag as experimental therapy in patients with severe aplastic anemia who have not received prior definitive immunosuppressive therapy.

The primary endpoint was Investigator assessment of complete response (CR) rate at 6 months which was analyzed by the proportion and 95% CI from exact binomial method.

The data and analyses provided by the sponsor tend to support the assertion that Eltrombopag is effective in combination with standard immunosuppressive therapy for the *first-line treatment* of adult and pediatric patients 2 years and older with severe aplastic anemia.

The results of the analysis are summarized as follows:

The study data submitted were obtained from patients receiving a combination of horse antithymocyte globulin (h-ATG) + cyclosporine and the study drug, eltrombopag. The CR rate at 6 months in Cohort 3 + Extension Cohort is 43.7% (95% CI, 33.1%, 54.7%) with data cut off date Febuary 2018.

The sponsor also submitted historical data to use as a control to estimate the effect of eltrombopag alone. The sponsors comparison to the historical control data with earlier data cut off September 2016 provide the following, while the sponsor did not submit the analysis results when compared with historical control using updated data with cut off date February 2018.

Table 1 Sponsor's Analysis Results of CR at 6 Months (Data cutoff September 2016)

Endpoint	Data	Historical studies (h-ATG+CsA arm pooled)	Method	Treatment effect[3] (95% CI)
Complete response at Month 6	Subject-level	Scheinberg et al 2009 (03-H-0193) Scheinberg et al 2011 (06-H-0034)	Propensity score matching	38.10 (20.69, 55.50)
			IPTW propensity score	39.75 (21.25, 58.25)
	Study summary	Scheinberg et al 2009 (03-H-0193) Scheinberg et al 2011 (06-H-0034) Tisdale et al 2000 (97-H-0117)	Fixed effects[1]	35.44 (19.54, 51.35)
			Bayesian MAP[2]	33.01 (9.19, 51.59)

CR= Complete response, IPTW=Inverse Probability of Treatment Weighting, MAP=Meta-Analytic Predictive
[1] Random effects model led to the same results as the fixed effects model, because given the small number of studies and their similarity, the estimated variance between studies variance was equal to zero.
[2] For Bayesian MAP, the posterior mean and its 95% credible interval using a priori half-Normal(0.5) distribution for the between study standard deviation
[3] Treatment effect: Difference in CR for Study AUS01T Cohort 3 and Extension (eltrombopag+h-ATG+CsA) -. historical studies (h-ATG + CsA arm)

Source: Table 3-3, Summary of Clinical Efficacy, module 2, SDN 866 SN 227

This FDA reviewer agreed with the sponsor that the CR rate at 6 month is in Cohort 3 + Extension Cohort is 43.7% (95% CI, 33.1%, 54.7%) with data cut off date February 2018. In addition, FDA reviewer performed several addional exploratory analyses. The results are summarized as follows:

Table 2 Reviewer's Analysis Results of CR at 6 Months (Data cut off Feb 2018)

	Study AUS01T	Historical Control
Unadjusted Analysis		
# of patients included the analysis	87	102
CR, n (%)	38 (43.7)	17 (16.7)
CR rate difference (95% CI)	27.0 (14.3, 39.7)	
Propensity Score Matching Analysis		
# of patients included the analysis	68	68
CR rate difference (95% CI)	28.4 (12.99, 43.73)	
IPTW Analysis		
# of patients included the analysis	87	102
CR rate difference (95% CI)	27.1 (12.0, 42.2)	
Fixed Effect Analysis		
# of patients included the analysis	87	102
CR rate difference (95% CI)	27.0 (14.57, 39.33)	

Taken in total, the analysis showed that the combination of all three therapies has benefits of the treatment. The exploratory analyses provide some evidence, although possibly biased and weaker than evidence from a randomized controlled trial, that the addition of eltrombopag to the (h-ATG) + cyclosporine provides added benefit compared to (h-ATG) + cyclosporine without eltrombopag.

2. INTRODUCTION

2.1 Overview

Eltrombopag is an orally bioavailable, small-molecule thrombopoietin (TPO)-receptor agonist that interacts with the transmembrane domain of the human TPO-receptor and initiates signaling cascades that induce proliferation and differentiation from bone marrow progenitor cells. Eltrombopag has been investigated in multiple clinical development programs and is currently approved in the United States, the European Union, and other countries for use in chronic immune thrombocytopenia, chronic hepatitis C virus associated thrombocytopenia, and *refractory* severe aplastic anemia.

The purpose of this submission is to obtain approval for the use of eltrombopag in combination with standard immunosuppressive therapy for the *first-line treatment* of adult and pediatric patients 2 years and older with severe aplastic anemia.

The proposed new indication was supported primarily on findings from the pivotal Study AUS01T, a single center, single arm, non-randomized, Phase I/II trial investigating the efficacy and safety of horse antithymocyte globulin (h-ATG) + cyclosporine in combination with eltrombopag as experimental therapy in patients with severe aplastic anemia who have not received prior definitive immunosuppressive therapy. The table below summarizes the study features of the pivotal study. The Study AUS01T was sponsored by the National Heart Lung, and Blood Institute (NHLBI). The following table summarized the key features of the Study AUS01T.

Table 3 Pivotal Study AUS01T

Phase and Design	Non randomized, single center, pilot phase I/II study investigating the standard (immunosuppressive therapy) IST regimen of h-ATG+CsA, in combination with eltrombopag as experimental therapy in subjects with SAA who have not received prior definitive IST. Each of the cohort 1, 2, 3 was designed with Simon two-stage design. The subjects were treated with immunosuppressive therapy, h-ATG+CsA, combined with eltrombopag as experimental therapy. The cohorts differed only by the starting day of eltrombopag, the duration of eltrombopag, and by the addition of a CsA maintenance regimen.
Treatment Period	Cohort 1: h-ATG on day 1-4 from day 1 to month 6 + eltrombopag from day 14 to month 6 Cohort 2: h-ATG on day 1-4 from day 1 to month 6 + eltrombopag from day 14 to month 3 Cohort 3 and Extension Cohort: all 3 drugs started concurrently on day 1: h-ATG on day 1-4, CsA and eltrombopag from day 1 to month 6. Responding subjects received low dose of CsA (maintenance dose) from month 6 to month 24.
Follow-up Period	All subjects were followed at the NHLBI at month 3 and month 6 visits. Subsequent follow up visits at the NHLBI were scheduled at month 12 and then annually for up to 5 years. The subjects were also followed between landmark visits by their referral physicians at their discretion.
# of Subjects per Arm	Cohort 1: 31 Cohort 2: 31 Cohort 3: 31 Extension Cohort: 61
Study Population	Subjects with SAA who have not received prior definitive IST, both adult and pediatric patients

2.2 Regulatory History

In November 2013, FDA granted eltrombopag orphan-drug designation request for treatment of aplastic anemia.

In April 2017, the sponsor had a Type C meeting with FDA, and discussed plans to utilize historical data in the planned sNDA. During the discussion, the Agency commented that "*In general, we recommend that the analysis plan involving historical control patients should be finalized during the design stage of the studies without the knowledge of efficacy of the treatment group. We acknowledge that your proposed analyses will be considered for exploratory purpose including both analyses using summary level data and patient level data*."

In this meeting, the sponsor also explained that for durability of response, they do not have the data (from historical studies) to support comparison of durability of response between Study US01T and the historical control controls. The Sponsor proposes that CR in Study US01T is a sufficiently strong endpoint for supporting durability of response and they will present durability in that context. The Agency acknowledged this approach but commented that depending on the findings at review, additional data on durability may be needed.

In January 2018, FDA granted eltrombopag Breakthrough Thearapy Designation for the treatment of patients with severe aplastic anemia in combination with standard immunosuppressive therapy.

2.3 Data Sources

Material reviewed for this application include the protocol and the amendments, statistical analysis plan, clinical study report and the submitted datasets for the pivotal Study US01T. Individual patient-level data for study Scheinberg 2011 and Scheinberg 2009 were also included in the analysis.

Reviewed data for US01T were provided electronically with the standard analysis data formats located at: \\CDSESUB1\evsprod\NDA022291\0227\m5\datasets\etb115aus01t-primary.
Reviewed data for historical studies were provided electronically located at:
\\CDSESUB1\evsprod\NDA022291\0227\m5\datasets\ise-first-line-saa.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data from the Study AUS01T were provided electronically in the format of ADaM and SDTM. Documentations on datasets and programming were included with sufficient details for verification of key study results.

3.2 Evaluation of Efficacy

3.2.1 Pivotal Study AUS01T

3.2.1.1 Study Design and Endpoints

Study AUS01T is a phase I/II, non-randomized, single-arm, single center study designed to evaluate the efficacy and safety of eltrombopag treatment, in combination with the regimen of h-ATG and CsA, in definitive immunosuppressive therapy-naïve subjects with severe aplastic anemia (SAA). The study was conducted at NHLBI of the National Institutes of Health (NIH).

The protocol was initially designed for 95 subjects in Cohort 1, 2 and 3, and amended to add the Extension Cohort to gain more experience with the recommended regimen. The actual number of patients enrolled in the study is more than planned, as an extension cohort was added. The subjects were enrolled sequentially in eltrombopag combined with h-ATG + CsA. The cohorts 1

to 3 used the Simon two stage design and differed only by the starting day and duration of eltrombopag and the addition of a low dose of CsA (maintenance dose) for responders:

- Cohort 1, h-ATG (Day 1-4) + CsA (Day 1-6) + eltrombopag (Day 14-Month 6).
- Cohort 2, h-ATG (Day 1-4) + CsA (Day 1-6) + eltrombopag (Day 14-Month 3). Responding subjects who did not relapse at month 6 received maintenance dose of CsA from month 6 to month 24.
- Cohort 3, h-ATG (Day 1-4) + CsA (Day 1-6) + eltrombopag (Day 1-Month 6). Responding subjects who did not relapse at month 6 received maintenance dose of CsA from month 6 to month 24.
- Extension Cohort, same treatment regime with Cohort 3

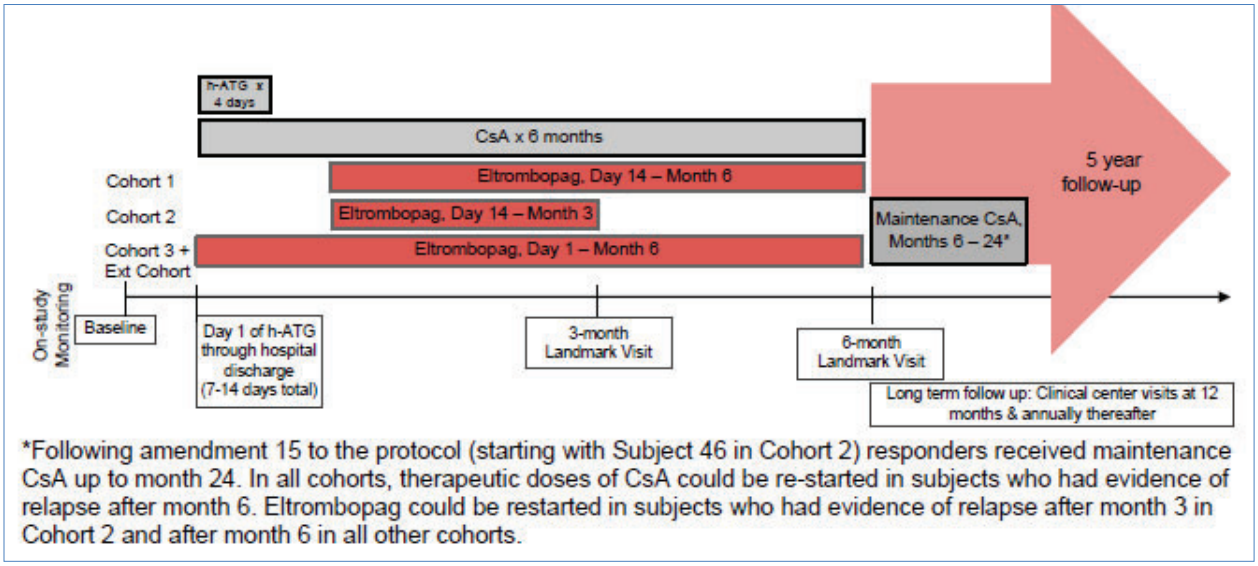
Reviewer Comment

As the applicant stated that the addition of extension cohort was recruit more subjects with the same dosing regimen as Cohort 3, and collect more data for the analysis of the secondary endpoints within the target regimen.

The treatment phase with CsA + eltrombopag was 6 months, with CsA maintenance from Month 6-24, with the possibility of re-initiation of CsA + eltrombopag at therapeutic dose in the case of relapse.

All subjects were followed at the NHLBI at month 3 and month 6 visits. Subsequent follow-up visits at the NHLBI were at month 12 then annually for up to 5 years. The subjects were followed between landmark visits by their referral physicians at their discretion.

Figure 1 Study Design



Source: Figure 9-1, Clinical Study Report, Study AUS01T

Protocol amendment allowed for maintenance administration of CsA for responders from Month 6 to Month 24. This applied to approximately half of the subjects in Cohort 2, and all of the subjects in Cohort 3 and the extension Cohort.

Cohorts 1, 2 and 3 were each designed as a Simon two-stage design to test the null hypothesis H_0: rate of complete responder (CR) at month 6 $\leq$ 10% versus the alternative, H_1: rate of CR at month 6 $\geq$ 30%. At least 3 complete responders at the first stage and at least 7 at the end of second stage were required to reject the null hypothesis.

3.2.1.2 Statistical Methodologies

Study Population

The full analysis set (FAS) was used as primary analysis set, defined as all subjects who received at least one dose of the study drug eltrombapag. Because the dosing sought is the one used with patients in Cohort 3 and Extension Cohort, the efficacy analysis was focusing on Cohort 3 and Extension Cohort only.

The per protocol set (PPS) was used as sensitivity analysis set, including a subset of subjects in the FAS without any major protocol deviation and who have completed a minimum exposure requirement.

Primary Efficacy Endpoint

The primary endpoint was Investigator assessment of complete response (CR) rate at 6 months following h-ATG + CsA + eltrombopag, based on hemoglobin (Hgb) count, absolute neutrophil count (ANC), and platelet count. A complete responder is defined as (all 3 were to be met):

- ANC > 1 x 10^3/uL
- Platelet count > 100 x 10^3/uL
- Hgb > 10 g/dL

Secondary Efficacy Endpoints

- CR rate at 3 and 12 months and yearly thereafter up to 5 years
- Overall response (OR: CR + partial response [PR]) rates at 3, 6, 12 months and yearly thereafter up to 5 years, where PR was defined as blood counts no longer meeting the standard criteria for severe pancytopenia in SAA, equivalent to at least 2 of the 3 criteria obtained on 2 consecutive serial blood measurements at least one week apart (ANC > 500/uL, platelet count > 20x10^3/uL, and reticulocyte count > 60x10^3/uL)
- Duration of CR
- Duration of OR
- Overall survival (OS)
- Change from baseline to post-baseline assessments in PROMIS Global Health, Sleep Disturbance, Applied Cognition-Abilities, Anxiety and Depression scores

- Change from baseline to post-baseline assessments in FACT-Anemia, Thrombocytopenia and Neutropenia scores

As for CR, improvement in blood counts following administration of growth factors within the 21 days preceding the assessment of response, were not considered as fulfilling the criteria for PR. Similarly, improvement in platelet counts following platelet transfusions within the 7 days preceding the assessment, was not considered for the assessment of PR. However, reticulocyte and neutrophil counts were not affected by transfusions and were used for the assessment of PR.

PROMIS is an initiative based on an NIH grant to establish and provide the public free, reliable and validated commonly used measures of subject-reported outcomes.

The FACT instruments are a health assessment instrument designed to measure multi-dimensional quality of life in chronic illness and its associated therapy. The different subscales selected for this study are specific for subjects with diseases or treatments with hematological effects.

Subjects enrolled in Cohorts 1 to 3 answered questionnaires at Baseline, pre-eltrombopag Day 14 (Cohorts 1 and 2 only), months 3, 6, 12 and yearly visits. Missing questionnaires due to subject's clinical status (e.g. critically ill) were reported as a protocol deviation.

Primary Analysis Method

Cohorts 1, 2 and 3 were each designed as a Simon two-stage design to test the null hypothesis H_0: rate of complete responder (CR) at month 6 $\leq$ 10% versus the alternative, H_1: rate of CR at month 6 $\geq$ 30%. At least 3 complete responders at the first stage and at least 7 at the end of second stage were required to reject the null hypothesis.

For each cohort, the rate of CR was calculated, defined as the number of subjects who achieved a CR at month 6 landmark, divided by the total number of subjects enrolled into that cohort who had reached the month 6 landmark or had withdrew earlier for any reason and including non-evaluable subjects. The two-sided 95% confidence interval (CI) based on the exact method.

Subjects in Cohort 2 who relapsed after the end of month 3 treatment period, could have eltrombopag restarted at the Investigator's discretion. The subjects who required treatment with eltrombopag prior to month 6 were considered as non-responders at month 6 for the statistical analyses.

Sensitivity Analysis Method

Sensitivity analyses included repeating the primary efficacy analysis using the PPS and using a more stringent definition of CR (ANC $\geq$ 1500/μL, platelet count $\geq 150\times10^3$/μL, hemoglobin $\geq$ 12g/dL for female or $\geq$ 13 g/dL for male).

The supportive analysis included a subgroup analysis of CR rate at 6-months by age (< 18 years, 18-64 years, ≥ 65 years), gender, race, Glucose phosphate isomerase (GPI) negative neutrophils level (≤ 50% vs. > 50%), and severity of aplastic anemia.

Analysis Method for Quality of Life Endpoint

PROMIS and FACT scores and changes from Baseline were summarized over time by cohort, and by cohort and response (responders vs. non-responders) at landmark month 6 visit, using statistics for continuous variables. Answers to all items as well as derived scores were listed. Missing assessments due to subjects' clinical status was also listed. All HRQL summaries were based on the FAS.

Sample Size Determination

The sample size was determined using Simon 2-Stage Minmax Design, based on the assumption that the CR probability at 6 months is between 10%-12% with h-ATG/CsA treatment and 30% with eltrombopag treatment.

With Simon Minmax 2 Stage Design, for each cohort 1, 2 or 3, 24 subjects were planned to be accrued and to test the null hypothesis, and the null hypothesis H_0 was accepted (i.e. the treatment had to be terminated) if no more than 2 subjects demonstrated a CR to the treatment within 6 months. If 3 or more subjects had a CR to the treatment within 6 months at the first stage, an additional 7 subjects were accrued (total N = 24 + 7 = 31). The null hypothesis of $p \leq$ 10% was accepted if the total number of subjects having a CR within 6 month was 6 or less. The study was powered against an alternative hypothesis H_1 $p > 30\%$ at two-sided 0.05 significance level and 0.865 for power.

Once accrual to Cohort 1 was completed it was proposed to treat another cohort (Cohort 2), and once accrual to Cohort 2 was completed it was proposed to treat another cohort (Cohort 3). An extension to Cohort 3 will improve precision of exploratory analysis of secondary endpoints.

Interim Analysis

For each cohort 1,2 and 3, an interim analysis was conducted at the end of the first stage once 24 subjects had reached 6-months and, if 3 or more complete responses (CR) were observed, accrual continued until the planned total number of subjects was reached. At least 7 out of 31 subjects at the end of second stage were required for the null hypothesis of CRR ≤ 10% to be rejected.

Handling of Missing Data/Censoring

For the analysis of CR and OR, subjects who were still ongoing but had not reached the considered timepoint yet were not included in the analysis of response at that timepoint. However, subjects with a missing or 'Non-evaluable' response for other reasons were treated as non-responders at that timepoint in the calculation of the OR and CR rate.

Subjects who were complete or partial responders were included in the analysis of the duration of response. Complete and partial responders who did not relapse at the data cut-off date were censored at the date of the last assessment of response with a known outcome.

Subjects who were complete responders were included in the analysis of the duration of CR. Complete responders who did not relapse at the data cut-off date were censored at the date of the last assessment of response with a known outcome.

Comparison with Historical Control – Post hoc, Exploratory Analyses

Selection of Historical Studies

The

The applicant reviewed the literature in PubMed using the following search criteria:
(aplastic anemia OR aplastic anaemia) AND clinical trials) AND
("2001/01/01"[Date - Publication]: "2016/09/23"[Date - Publication]) after January 2001.
Among the publications filtered out, 71 met the criteria for inclusion that patients were with severe aplastic anemia. These 71 trials were further evaluated for inclusion using the following criteria:

- IST-naïve patients included in the trial
- IST consisting of h-ATG+CsA for at least one arm
- Definition of complete and/or overall responses based on similar criteria than US01T and response rate at month 6 reported
- IST regimen comparable to US01T in terms of doses and durations

The final search resulted in 4 studies selected out. The characteristic of these 4 studies are summarized in the following table

Table 4 Summary of Historical Studies

	Scheinberg 2011 (06-H-0034) N = 60 [1]	Scheinberg 2009 (03-H-0193) N = 42 [1]	Tisdale et al 2000 (97-H-0117) N = 16 [1]	Rosenfeld et al. 2003 (90-H-0146) N = 122 [1]	Study AUS01T Cohort 3 + Extension N = 92
Design	RCT, parallel arms, 60 patients in each treatment arm of h-ATG+CsA and r-ATG+CsA. Median follow up = 28 months	RCT, parallel arms, 42 patients in the h-ATG+CsA arm and 35 patients in the h-ATG+CsA + sirolimus arm.	RCT, parallel arms, 15 patients in cyclophosphamide +CsA arm vs. 16 patients in h-ATG+CsA arm. Median follow up = 21.9 months	Single arm, median follow up – 7.2 years	Non-randomized, 31 patients in each of 3 cohorts and an extension cohort, median follow up = 12 months in cohort 3 + extension
Pediatric or adult population	Pediatric and adult	Pediatric and adult	Adult	Pediatric and adult	Pediatric and adult

Treatment regime	h-ATG (day 1-4) + CsA (day 1 – month 6) vs. r-ATG (day 1-5) + CsA (day 1- month 6)	h-ATG (day 1-4) + CsA (day 1 – month 6) vs. h-ATG (day 1-4) +CsA (day 1 – month 6) + sirolimus (day 1 – month 6)	Cyclophosphamide (day 1-4) + CsA (day 1 – month 6) vs. h-ATG (day 1-4) + CsA (day 1 – month 6)	h-ATG (day 1-4) +CsA (day 1 – month 6)	Cohort 1: h-ATG (day 1-4) + CsA (day 1-m 6) + eltrombopag (day 14-m 6); cohort 2: h-ATG (day 1-4) + CsA (day 1-m 6) + eltrombopag (day 14-m 3); cohort 3 + Extension: h-ATG (day 1-4) + CsA (day 1-m 6) + eltrombopag (day 1-m 6); maintenance CsA for responders from m 6 – m 24
Dose in arm of interest	h-ATG (day 1-4): 40 mg/kg/day; CsA (day1 -month 6) starting dose: age ≥12 years with 6 mg/kg/day, age < 12 years with 12 mg/kg/day	h-ATG (day 1-4): 40 mg/kg/day; CsA (day 1-month 6) starting dose: age ≥12 years with 10 mg/kg/day, age < 12 years with 15 mg/kg/day	h-ATG (day 1-4): 40 mg/kg/day; CsA (day 1-month 6) starting dose: 12 mg/kg/day	h-ATG (day 1-4): 40 mg/kg/day; CsA (day 1-month 6) starting dose: adults with 10 mg/kg/day, children with 15 mg/kg/day	h-ATG (day 1-4): 40 mg/kg/day; CsA (day 1-month 6) starting dose: age ≥12 years with 6 mg/kg/day, age < 12 years with 12 mg/kg/day; eltrombopag (day 1 – month 6) depends on age and ethnicity, maximum 150 mg/day
CR at month 3, n (%) [2]	7 (11.7)	3 (7.1)	2 (12.5)	NA	19 (35.2)
CR at month 6, n (%) [2]	12 (20.0)	5 (11.9)	4 (25.0)	NA	24 (52.2)
OR at month 3, n (%) [2]	37 (61.7)	24 (57.1)	11 (68.8)	73 (59.8)	43 (79.6)
OR at month 6, n (%) [2]	41 (68.3)	26 (61.9)	9 (56.3)	75 (61.5)	39 (84.8)

[1] number of patients in the h-ATG+CsA arm, which were included in the analysis of the review
[2] from the paper

Source: adapted from Table 1-1 in Summary of Clinical Efficacy in first line severe aplastic anemia.

Reviewer Comments

- *There is only adult population in the study Tisdale et al. 2000, while the Study AUS01T has both adult and pediatric population. The heterogeneity in patients' age between the studies may challenge the balance between the treatment cohorts in the analysis.*

- *The Study Scheinberg 2011 was conducted between 2005 and 2010, and the Study Scheinberg 2009 was conducted between 2003 and 2005. The Study AUS01T was conducted between 2012 and 2016. Because Study AUS01T and the historical studies are not conducted at the similar time, then the relationships observed between treatment and outcome might be affected. Changes in disease or diagnostic definitions, exposures over time and treatments could all contribute to non-contemporaneous bias.*

Analysis Methods

Data from cohort 3 and extension cohort from Study US01T were pooled to form a dataset with triplet h-ATG-CsA+eltrombopag and compared to historical control data in patients treated with h-ATG+CsA. The efficacy outcomes consisted out complete response (CR) and overall response (OR) rates at month 6. Two types of retrospective analyses were performed:

- Analysis using patient-level data from the studies 03-H-0193 and 06-H-0034 using propensity score matching method or inverse probability treatment weighting (IPTW) with stabilized weights.
- Analysis using summery-level data from the 4 selected historical control studies (note: only 3 selected historical control studies had the available data for month 6 CR rate, so only these 3 historical controls studies were used in the analysis for the primary endpoint).

Reviewer Comments:

- *Extension cohort has the same population and same regime of therapy. After the planned enrollment of 31 patients, other patients were enrolled into extention cohort. It appears reasonable to combine the extension cohort and cohort 3 for the analysis of primary efficacy endpoint response rate.*

Analysis using patient-level data

1. *Propensity Score Matching*

Propensity scores (Rosenbaum and Rubin 1983) were estimated using a logistic regression model with the binary variable of the treatment versus control as dependent variable and adjusted for baseline covariates including demographic characteristics (age and gender) and baseline hematological counts (platelets, neutrophils, and reticulocytes). The hematological counts were log-transformed. Null values were replaced by 0.1 to allow the log-transformation.

Matched pairs were formed (1:1 matching without replacement) of treated and control patients with a similar propensity score using greedy matching algorithm with caliper width of 0.2 of the standard deviation of the logit of the propensity scores (Austin 2011).

To check the balance of the distributions of propensity scores, graphical displays including boxplots were used to compare the distribution of the propensity scores in treated (US01T) vs. control (historical data) patients with a visual inspection.

To assess the quality of matching, examination of the balance of baseline covariates between treated and control patients in the matched sample were performed. This was done by computing the absolute standardized mean difference between the two groups for both dichotomous as well as continuous covariates. Standardized differences that were less than 25% (Austin 2009) indicated balance on these covariates between the treated and control patients. Refer to the Appendix for details of the formulation of the absolute standardized mean difference.

Then estimation of treatment effect (e.g., difference in proportions of CR or OR) were performed with 95% confidence interval using the method appropriate for computing variance of the difference in matched data (Agresti and Min 2004)

2. Inverse probability treatment weighting (IPTW) method using stabilized weights

Using the same method as in the propensity score matching method, a propensity score was estimated from the fitted logistic regression model adjusted for the baseline covariates and the propensity score were examined to assess the overlap of the propensity score distribution between the treatment and control groups.

A stabilized weight is calculated for each patient by multiplying the inverse of the probability of receiving the treatment that the patient actually received (i.e. the weights for treated patients are the inverse of their propensity score whereas the weights for patients in the historical control are the inverse of the complement of their propensity scores) by the expected value of receiving treatment the treatment that the patient actually received. Refer to the Appendix for details of the formulation of the IPTW estimates.

Analysis using Summary Level Data

3. Frequentist fixed effects model

The fixed effects model assumes that all historical studies share the same true response rate. The estimate of response rate for the hypothetical h-ATG+CsA arm in the US01T study, pai star, is derived as the weighted mean of all observed response rate from all historical studies. The weights are the inverse of the corresponding within-study variance.

To examine heterogeneity of the study results, a forest plot was used to display the individual study results (response rate and 95% confidence interval) and help understanding the magnitude, precision and direction of the results from study to study.

4. Frequentist random effects model

The random effects model assumes that the response rate may vary across historical studies but are all sampled from the same distribution.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

The first subject first visit was on (b) (6). The data cutoff date for the submitted report is 9/30/2016. The study enrolled 124 subjects as of the data cut-off date. One subject in Cohort 1 discontinued from the trial after enrollment due to disease misdiagnosis at study entry and did not receive treatment with eltrombopag, therefore this subject was excluded from the analysis.

Treated subjects included

- Cohort 1 (N = 30), h-ATG (Day 1-4) + CsA (Day 1-6) + eltrombopag (Day 14-Month 6)
- Cohort 2 (N = 31), h-ATG (Day 1-4) + CsA (Day 1-6) + eltrombopag (Day 14-Month 3)
- Cohort 3 (N = 31), h-ATG (Day 1-4) + CsA (Day 1-6) + eltrombopag (Day 1-Month 6)
- Extension to Cohort 3 (N = 61), same treatment regime with Cohort 3

The extension cohort enrollment was still ongoing, and 5 subjects already enrolled at data cutoff were still receiving treatment with eltrombopag, but had not reached the month 6 visit yet.

The main reason for ending treatment was “completed per protocol”. The other reasons to end treatment for high platelet count (> 400 x 10^3/uL) was 12.9% in Cohort 3.

Table 5 Patient Disposition

Cutoff date	30-Sep-2016				28-Feb-2018			
	Cohort 1 N=31 n (%)	Cohort 2 N=31 n (%)	Cohort 3 N=31 n (%)	Cohort 3 + Extension N=62 n (%)	Cohort 1 N=31 n (%)	Cohort 2 N=31 n (%)	Cohort 3 N=31 n (%)	Cohort 3 + Extension N=92 n (%)
Subject enrolled								
Treated with eltrombopag	30 (96.8)	31 (100)	31 (100)	62 (100)	30 (96.8)	31 (100)	31 (100)	92 (100.0)
Not treated with eltrombopag	1 (3.2)[a]	0	0	0	1 (3.2)[a]	0	0	0
Subject treated with eltrombopag								
End of treatment with eltrombopag	30 (96.8)	31 (100)	31 (100)	47 (75.8)	30 (96.8)	31 (100)	31 (100)	87 (94.6)
Treatment with eltrombopag ongoing	0	0	0	15 (24.2)[b]	0	0	0	5 (5.4)[b]
Primary reason to end eltrombopag								
Completed per protocol	19 (61.3)	27 (87.1)	23 (74.2)	32 (51.6)	19 (61.3)	27 (87.1)	23 (74.2)	64 (69.6)
Platelet count > $400x10^3/\mu L$	3 (9.7)	1 (3.2)	4 (12.9)	5 (8.1)	3 (9.7)	1 (3.2)	4 (12.9)	6 (6.5)
Platelet count > $200x10^3/\mu L$	3 (9.7)	0	2 (6.5)	4 (6.5)	3 (9.7)	0	2 (6.5)	5 (5.4)
Adverse event	0	1 (3.2)	1 (3.2)	4 (6.5)	0	1 (3.2)	1 (3.2)	4 (4.3)
Clonal evolution	2 (6.5)	0	1 (3.2)	1 (1.6)	2 (6.5)	0	1 (3.2)	3 (3.3)
Investigator decision	1 (3.2)	0	0	0	1 (3.2)	0	0	3 (3.3)
Subject decision	1 (3.2)	1 (3.2)	0	1 (1.6)	1 (3.2)	1 (3.2)	0	2 (2.2)
Death	1 (3.2)	0	0	0	1 (3.2)	0	0	0
Protocol deviation	0	1 (3.2)	0	0	0	1 (3.2)	0	0
Subject status after end of eltrombopag treatment								
Post-eltrombopag follow-up ongoing[c]	16 (51.6)	23 (74.2)	26 (83.9)	37 (59.7)	7 (22.6)	20 (64.5)	20 (64.5)	58 (63.0)
Completion/ withdrawal from study	14 (45.2)	8 (25.8)	5 (16.1)	10 (16.1)	23 (74.2)	11 (35.5)	11 (35.5)	29 (31.5)
Primary reason for study completion or study withdrawal								
Initiation of additional IST other than steroids or CsA	9 (29.0)	0	2 (6.5)	3 (4.8)	9 (29.0)	2 (6.5)	5 (16.1)	9 (9.8)
Insufficient response	1 (3.2)	3 (9.7)	1 (3.2)	3 (4.8)	1 (3.2)	3 (9.7)	1 (3.2)	8 (8.7)
Transplant	1 (3.2)	1 (3.2)	0	0	2 (6.5)	1 (3.2)	2 (6.5)	6 (6.5)
Clonal evolution or progression to MDS/AML	1 (3.2)	1 (3.2)	2 (6.5)	2 (3.2)	1 (3.2)	1 (3.2)	2 (6.5)	3 (3.3)
Persistent hepatotoxicity	0	0	0	1 (1.6)[e]	0	0	0	1 (1.1)[e]
Subject decision	0	1 (3.2)	0	1 (1.6)	0	1 (3.2)	0	1 (1.1)
Completion of protocol participation	0	0	0	0	6 (19.4)	0	0	0
Death	1 (3.2)	0	0	0	1 (3.2)	0	0	0
Failure to follow up	0	0	0	0	2 (6.5)	0	0	0
Never started eltrombopag	1 (3.2)[a]	0	0	0	1 (3.2)[a]	0	0	0
Patient's non-compliance	0	0	0	0	0	1 (3.2)	1 (3.2)	1 (1.1)
Relapse	1 (3.2)	1 (3.2)	0	0	1 (3.2)	1 (3.2)	0	0
Toxicity	0	1 (3.2)[d]	0	0	0	1 (3.2)[d]	0	0

a. Subject (b) (6) was misdiagnosed at Baseline, and had AML and not SAA. The subject received h-ATG (4 days) and CsA (2 weeks) but did not start eltrombopag.
b. 15 subjects in the Extension Cohort had not yet reached Month 6 treatment with eltrombopag at cutoff 30-Sep-2016 and 5 subjects at cutoff 28-Feb-2018.
c. Subjects still followed-up for yearly assessments at data cut-off.
d. Subject (b) (6) completed the course of h-ATG and of eltrombopag (3 months) as per protocol, however discontinued CsA and withdrew from the study because of nephrotoxicity 2 weeks after the last dose of eltrombopag.
e. Subject (b) (6) discontinued eltrombopag on Day 12 due to typhlitis (SAE) and CsA on Day 22 due to elevated liver function tests. On Day 71, the subject withdrew from the study due to persistent hepatotoxicity.

Source: Table 2-2, 120 day efficacy and safety update, Study AUS01T

Demographic and Baseline Characteristics

Patients demographic are summarized in Table 4. In Cohort 3 + Extension Cohort (N = 92), the median age of subjects 28.0 (range 5 - 82) years, 26 (28.3%) subjects were pediatric, 50 (54.3%) subjects were female, and 57 (62.0%) were White.

Table 6 Demographics Characteristics

	Cohort 1 (N = 30)	**Cohort 2** (N = 31)	**Cohort 3** (N = 31)	**Cohort 3 + Extension** (N = 92)
Age (years)				
Mean (SD)	39.7 (18.94)	33.8 (18.65)	36.2 (21.9)	35.0 (22.10)
Median (range)	39.0 (12, 72)	28.0 (3, 68)	29.0 (5, 82)	28.0 (5, 82)

< 18	5 (16.7)	6 (19.4)	8 (25.8)	26 (28.3)
2 – 5	0	1 (3.2)	0	1 (1.1)
6 – 11	0	1 (3.2)	1 (3.2)	11 (12.0)
12 – 17	5 (16.7)	4 (12.9)	7 (22.6)	14 (15.2)
18 – 64	20 (66.7)	23 (74.2)	18 (58.1)	51 (55.4)
≥ 65	5 (16.7)	2 (6.5)	5 (16.1)	15 (16.3)
Gender, n (%)				
Female	14 (46.7)	14 (45.2)	14 (45.2)	50 (54.3)
Male	16 (53.3)	17 (54.8)	17 (54.8)	42 (45.7)
Race, n (%)				
White	16 (53.3)	19 (61.3)	23 (74.2)	57 (62.0)
Black of African American	6 (20.0)	7 (22.6)	4 (12.9)	16 (17.4)
Asian	3 (10.0)	4 (12.9)	1 (3.2)	8 (8.7)
Other	3 (10.0)	0	3 (9.7)	6 (6.5)
Unknown	2 (6.7)	1 (3.2)	0	5 (5.4)

Source: Table 11-2, Clinical Study Report; Table 2-3, 120 day efficacy and safety update; Study AUS01T

The hematological parameters at baseline are summarized in Table 5. In summary, in each of cohort 1, 2 and 3 and extension cohort, over one third of the subjects were diagnosed with very severe aplastic anemia (ANC < 200/Ul) except for cohort 3. Three subjects in total had glucose phosphate isomerase (GPI) negative neutrophil > 50% at Baseline. In Cohort 3 + extension, approximately 45% of the subjects had normal cytogenetic analysis at baseline. However, almost the rest of the subjects were not evaluable for this parameter.

Table 7 Hematological Parameters

	Cohort 1 (N = 30)	**Cohort 2** (N = 31)	**Cohort 3** (N = 31)	**Cohort 3 + Extension** (N = 92)
Absolute Neutrophil Count (10^3/uL)				
Mean (SD)	0.41 (0.40)	0.34 (0.25)	0.36 (0.36)	0.35 (0.37)
Median (range)	0.28 (0, 1.38)	0.33 (0, 0.90)	0.31 (0, 1.81)	0.27 (0, 1.93)
Platelet Count (10^3/uL)				
Mean (SD)	11.0 (7.69)	7.6 (3.83)	9.8 (2.67)	9.3 (6.44)
Median (range)	10.0 (2, 37)	8.0 (1, 14)	9.0 (1, 27)	8.0 (0, 40)
Absolute Reticulocyte Count (10^3/uL)				
Mean (SD)	23.2 (16.67)	19.4 (14.90)	28.1 (17.93)	27.0 (19.70)
Median (range)	22.5 (2, 52)	15.0 (2, 53)	24.0 (2, 60)	21.0 (2, 97)
Severity of Aplastic Anemia				
Severe	19 (63.3)	19 (61.3)	22 (71.0)	51 (55.4)
Very Severe	11 (36.7)	12 (38.7)	9 (29.0)	41 (44.6)

GPI Negative Neutrophil				
Median (Q1, Q3)	1.0 (1.0, 1.2)	1.0 (1.0, 3.3)	1.0 (1.0, 7.5)	1.0 (1.0, 6.3)
≤ 50%	27 (90.0)	29 (93.5)	25 (80.6)	77 (83.7)
> 50%	1 (3.3)	1 (3.2)	1 (3.2)	3 (3.3)
Missing	2 (6.7)	1 (3.2)	5 (16.1)	12 (13.0)
Cytogenetic Analysis				
Normal	20 (66.7)	22 (71.0)	16 (51.6)	41 (44.6)
Abnormal	1 (3.3)	2 (6.5)	0	4 (4.3)
Not evaluable	9 (30.0)	7 (22.6)	15 (48.4)	44 (47.8)
Missing	0	0	0	3 (3.3)

Source: Table 11-3, Table 11-4, Clinical Study Report; Table 2-4, Table 2-5, 120 efficacy and safety update; Study AUS01T

3.2.1.4 Results and Conclusions

3.2.1.4.1 Primary Endpoint - Complete hematological response at month 6

Primary Analysis

The complete hematological response rate at month 6 is 33.3% in Cohort 1, 25.8% in Cohort 2, 43.7% in Cohort 3 + Extension Cohort.

Table 8 Complete Response at 6 Months – Primary Analysis (Data cut off Feb 2018)

	Cohort 1 (N = 30)	**Cohort 2** (N = 31)	**Cohort 3** (N = 31)	**Cohort 3 + Extension** (N = 92)
Evaluable Patients, n	30	31	31	87
CR, n (%), 95% CI	10 (33.3)	8 (25.8)	18 (58.1)	38 (43.7)
	17.3, 52.8	11.9, 44.6	39.1, 75.5	33.1, 54.7

Source: reviewer's analysis

Sensitivity Analysis

The same analysis was performed for the complete hematological response at month 6 using the PPS and each cohort. The results showed similar complete hematological response at 6 months, which is consistent with the primary analysis using the FAS. Similarly, a sensitivity analysis was performed using a more stringent definition for complete response (i.e. (ANC ≥ 1500/μL, platelet count ≥ 150×10^3/μL, hemoglobin ≥ 12g/dL for female or ≥ 13 g/dL for male). The results are shown in the following table.

Table 9 Complete Response at Month 6 – Sensitivity Analysis Based on PPS (Data Cut-off Feb 2018)

	Cohort 1 N = 30	Cohort 2 N = 31	Cohort 3 N = 31	Cohort 3 +Extension N = 88
PPS Analysis Population				
Evaluable Patients, n	30	30	31	87
CR, n (%), 95% CI	10 (33.3)	8 (26.7)	18 (58.1)	38 (43.7)
	17.3, 52.8	12.3, 45.9	39.1, 75.5	33.1, 54.7

Source: reviewer's analysis

Comparison with Historical Control

The study data submitted were obtained from patients receiving a combination of horse antithymocyte globulin (h-ATG) + cyclosporine and the study drug, eltrombopag. The sponsor submitted historical data to use as supportive information of the control to estimate the effect of eltrombopag alone.

(a) Unadjusted Analysis

With subject-level data from the study Scheinberg 2011 (Study 06-H-0034) and study Scheinberg 2009 (Study 03-H-0193) pooled as a historical control cohort, the CR at Month 6 from study US01T was compared with the historical control cohort.

The following table summarized the treatment effect with adjusting for any baseline covariates. The unadjusted difference is 27.0% (95% CI, 14.3, 39.7) in the CR rate and 13.6% (95% CI, 1.1, 26.2) in the OR rate.

Table 10 Unadjusted Analysis of Complete Response and Overall Response at Month 6 (Data cut off Feb 2018)

	Treatment Cohort (N = 87) [1]	Historical Control Cohort (N = 102)
CR, n (%)	38 (43.7)	17 (16.7)
CR rate difference, % (95% CI) [2]	27.0 (14.3, 39.7)	
OR, n (%)	69 (79.3)	67 (65.7)
OR rate difference, % (95% CI) [3]	13.6 (1.1, 26.2)	

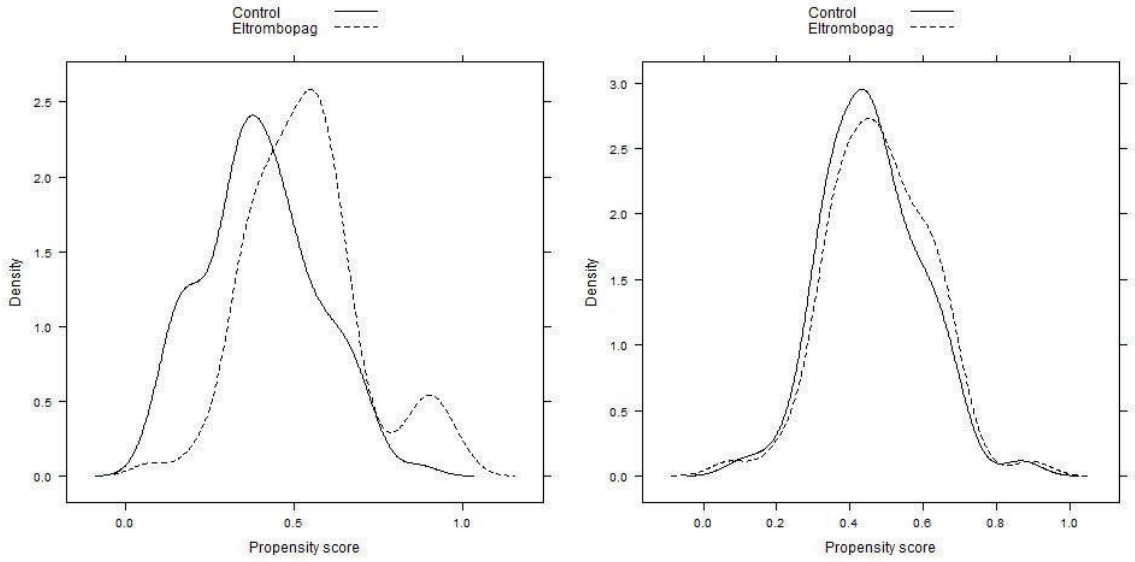
[1] Evaluable number of patients
[2] CR rate difference = CR rate in treatment cohort – CR rate in historical control cohort
[3] OR rate difference = OR rate in treatment cohort – OR rate in historical control cohort

(b) Propensity Score Matching Analysis

Using baseline covariates age, gender, log(ANC), log(ARC) and platelet count, propensity score was calculated for each patient using logistic regression.

The following two figures plot the distribution of propensity score by treatment or historical control cohort, before or after matching. With the 1 to 1 greedy matching method, there were 68 patients from the treatment cohort matched with 68 patients matched from the historical control cohort. The difference was reduced after matching (Figure 2). There were 19 out of 87 patients (21.8%) in the treatment arm and 34 out of 102 patients (33.3%) in the control arm who were unmatched in the analysis.

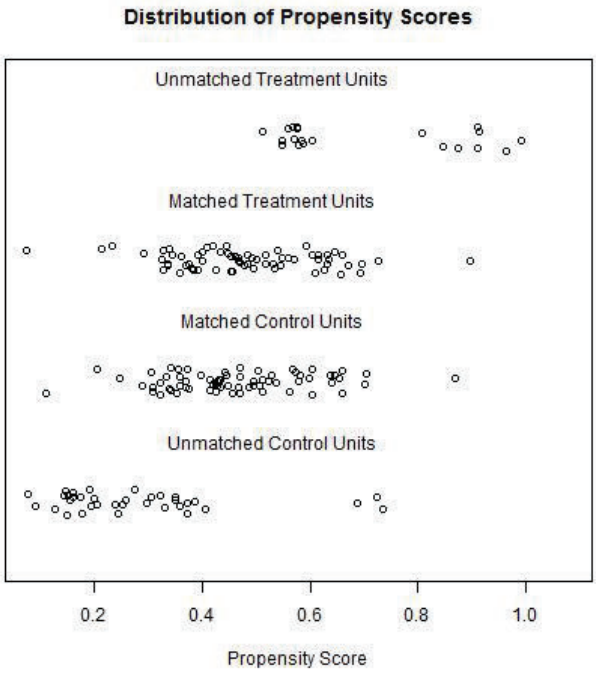
Figure 2 Distribution of Propensity Score Before and After Matching (Data cutoff: Feb 2018)



(a) before matching (b) after matching

Source: Reviewer analysis

Figure 3 Distribution of Propensity Scores including Matched and Unmatched Patients (Data cutoff Feb 2018)



Source: reviewer analysis

The table below compares the standardized difference of the 5 baseline covariates before propensity matching with after propensity score matching. The standardized difference in all of the 5 covariates reduced after the propensity score matching except for the variable age.

Table 11 Covariates Balance Before and After Propensity Score Matching (Data cut off Feb 2018)

	Log(plt)	Log(arc)	Log(anc)	age	gender	Log(plt)	Log(arc)	Log(anc)	age	gender
	Before Matching					After Matching				
Mean (Treatment)	8.76	9.92	4.53	35.16	0.45	8.96	9.921	5.29	35.46	0.51
SD (Treatment)	1.64	0.78	3.12	22.53	0.05	0.72	0.76	1.61	22.48	0.06
Mean (Control)	8.92	9.50	5.28	34.63	0.56	8.96	9.89	5.52	33.45	0.46
SD (Control)	0.90	1.06	1.89	20.35	0.05	0.84	0.88	1.72	20.88	0.06
Standardized mean difference	12.04	44.65	29.31	2.49	0.49	0.60	3.36	13.49	9.27	0.18

Source: reviewer analysis

With propensity score matching method, the treatment effect in CR rate at month 6 and OR rate at month 6 are shown in the following table. Compared with the unadjusted analysis, the treatment effect from propensity score matching analysis is close in terms of the CR rate, and is

smaller in terms of OR rate. The lower 95% CI for the CR rate difference based on the propensity score matching method rules out 0%, but not for the OR rate difference.

Table 12 Propensity Score Matching Analysis of CR and OR rates at Month 6 (Data cutoff Feb 2018)

	Treatment Effect
CR rate difference, % (95% CI)	28.4 (12.99, 43.73)
OR rate difference, % (95% CI)	10.4 (-0.03, 24.25)

Source: reviewer analysis

Reviewer's Comments on the Propensity Score Matching Method

- *With propensity score analysis, 19 out of 87 patients (21.8%) in the Study AUS01T and 34 out of 102 patients (33.3%) in the pooled historical control cohort were unmatched, and therefore excluded in the analysis. The resulting analysis population may not fully represent the target study population, and therefore the estimated treatment effect may not represent the true treatment effect in the target study population.*

- *The standardized mean difference for the covariate platelet count, ANC, and age are very high. With the pre-specified model checking criteria that standardized differences should be less than 25%, the results indicate that the propensity score model and the matching method did not create adequate well balanced treatment and control cohorts with the available covariates and the statistical model.. The functional form of the propensity score model or the covariates adjusted in the model needs to be changed.*

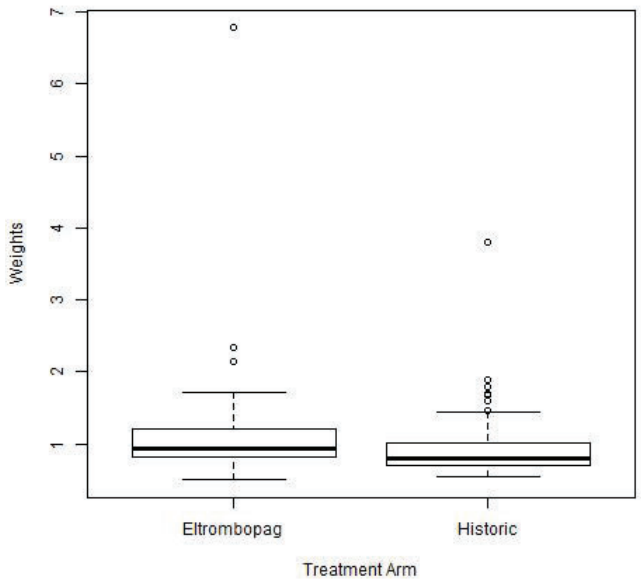
- *In general, propensity score matching analysis may only provide justification for the observed covariated included in the propensity score model. Potential bias may still exist if propensity score model is misspecified or there is unobserved confounders.*

(c) Inverse Probability Treatment Weighting Propensity Score Analysis

The IPTW propensity score analysis using patient-level data was also performed. It consists of estimation of the propensity scores, the weights, and the average treatment effect. The variables adjusted in the IPTW analysis were the same as those in the propensity score matching analysis.

The distribution of weights by treatment arm used in the IPTW analysis were plotted in Figure 4. The weights were bounded between -1 and 7.

Figure 4 Distribution of Weights (Data cutoff Feb 2018)



Source: reviewer analysis

The CR and OR difference between the treatment arms at Month 6 by IPTW propensity score analysis method are summarized in the following table. The CR difference between the treatment arms is similar to that from propensity score matching analysis.

Table 13 IPTW Propensity Score Analysis of CR and OR rates at Month 6 (Data cut off Feb 2018)

	Treatment Effect
CR rate difference, % (95% CI)	27.1 (12.0, 42.2)
OR rate difference, % (95% CI)	9.9 (-2.1, 21.9)

Reviewer Comments

- *With IPTW analysis, compared with propensity score matching analysis, all patients in the Study AUS01T and all patients in the historical control cohort were included in the analysis. However, the analysis results may still subject to the potential bias due to the extreme weights. With either stabilized or unstablized weights, there is one patient in each treatment arm with weight close to greater than 4. The weight of these two patients are much larger than the weights of other patients, and thus these two patients may have a large impact on the analysis results.*

- *Similar to the propensity score matching method, in general, IPTW analysis may only provide justification for the observed covariated included in the propensity score model. Potential bias may still exist if propensity score model is misspecified or there is unobserved confounders.*

(d) Fixed Effect Analysis

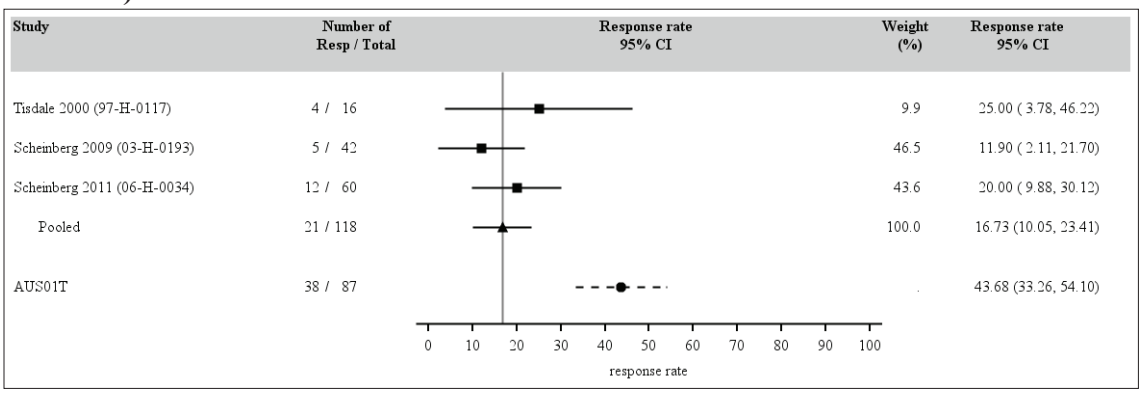
The complete response rate at Month 6 from AUS01T was compared with those from historical studies 06-H-0034, 03-H-0193, and 97-H-0117. The results from the fixed effect analysis are summarized in the following table. The forest plot of CR and OR in historical control studies, pooled historical control cohort, and study AUS01T are showed in the following two figures.

Table 14 Fixed Effect Analysis (Data cut off Feb 2018)

	Treatment N = 87	Historical Control N = 118 [1]
CR at Month 6, 95% CI	43.7% (33.26%, 54.10%)	16.7% (10.05%, 23.41%)
CR rate difference	27.0% (14.57%, 39.33%)	
OR at Month 6, 95% CI	79.3% (70.80%, 87.82%)	63.1% (56.97%, 69.15%)
OR rate difference	16.3% (5.79%, 26.72%)	

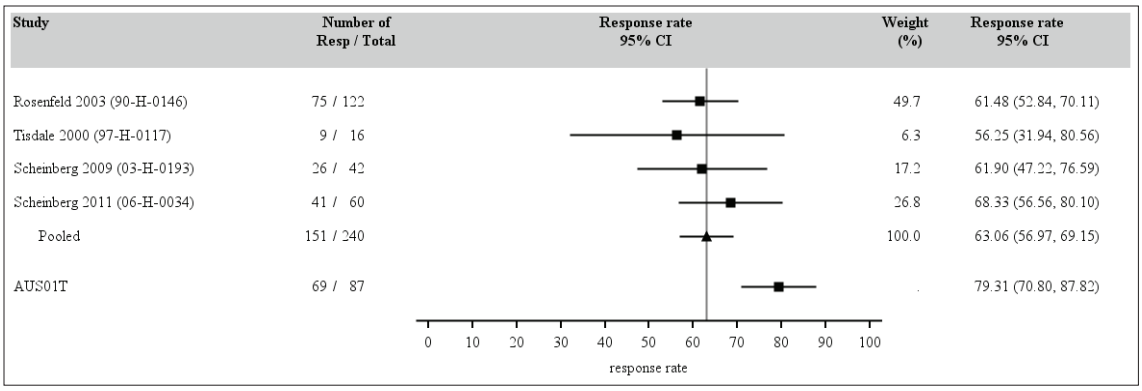
[1] Combined data from studies 06-H-0034, 03-H-0193, and 97-H-0117 only for CR analysis
Resource: reviewer analysis

Figure 5 Forest Plot of CR in Historical Control Studies and Study AUS01T (Data cut off Feb 2018)



Source: reviewer analysis

Figure 6 Forest Plot of OR in Historical Control Studies and Study AUS01T (Data cut off Feb 2018)



Source: reviewer analysis

Reviewer's comments:

The CR rate estimate and its 95% CI based on this fixed effect analysis appears to be similar to those from the patient evel analysis, but with a narrower CI. However, the ORR estimates and the 95% CI are not similar to the propensity score matched or weighted analyses after adding one more summary data result from the additional study. However this fixed effect analysis does not address the comparability issues between study AUS01T and the historical control data.

(e) Random Effect Analysis

The complete response rate and overall respone rate at Month 6 from the historical control cohort were compared with those from the AUS01T with random effect model for data with either cut off Sep 2016 or Feb 2018. However the estimated variance between the studies were estimated closed to zero, which may be due to the small sample size and therefore the random effect analysis results are identical to the fixed effects analysis results. Please refer to analysis (d) for more detailed analysis results.

3.2.1.4.2 Secondary Endpoints

Hematological Response by Assessment Time

The hematological response by assessment time at times other than month 6 are summarized in Table 13 and Table 14. As patients were continuously enrolled in the cohorts, some patients had not yet reached the scheduled assessment time by the cut off date Feb 2018.

At 1 Year, all the patients in the Cohort 3 and 78 patients in Cohort 3 + Extension Cohort reached this assessment time. At this assessment time, CR rate and OR rate in the Cohort 3 + Extension cohort were lower than those in the Cohort 3 only.

Table 15 CR and OR Rate by Assessment Time before 2 Years (Data cut off Feb 2018)

	Cohort 1 N = 30	Cohort 2 N = 31	Cohort 3 N = 31	Cohort 3 + Extension N = 92
Month 3				
Evaluable n	30	31	31	88
OR	23 (76.7) 57.7, 90.1	24 (77.4) 58.9, 90.4	27 (87.1) 70.2, 96.4	66 (75.0) 64.6, 83.6
CR	5 (16.7) 5.6, 34.7	7 (22.6) 9.6, 41.1	15 (48.4) 30.2, 66.9	24 (27.3) 18.3, 37.8
PR	18 (60.0)	17 (54.8)	12 (38.7)	42 (47.7)
No response	5 (16.7)	7 (22.6)	4 (12.9)	17 (19.3)
Withdrawal	2 (6.7)	0	0	5 (5.7)
Month 6				
Evaluable n	30	31	31	87
OR	24 (80.0) 61.4, 92.3	27 (87.1) 70.2, 96.4	29 (93.5) 78.6, 99.2	69 (79.3) 69.3, 87.3
CR	10 (33.3) 17.3, 52.8	8 (25.8) 11.9, 44.6	18 (58.1) 39.1, 75.5	38 (43.7) 33.1, 54.7
PR	14 (46.7)	19 (61.3)	11 (35.5)	31 (35.6)
No response	3 (10.0)	2 (6.5)	1 (3.2)	10 (11.5)
Withdrawal	3 (10.0)	2 (6.5)	1 (3.2)	8 (9.2)
1 Year				
Evaluable n	30	31	31	78
OR	9 (30.0) 14.7, 49.4	18 (58.1) 39.1, 75.5	23 (74.2) 55.4, 88.1	44 (56.4) 44.7, 67.6
CR	5 (16.7) 5.6, 34.7	10 (32.3) 16.7, 51.4	16 (51.6) 33.1, 69.8	30 (38.5) 27.7, 50.2
PR	4 (13.3)	8 (25.8)	7 (22.6)	14 (17.9)
Relapse	15 (50.0)	7 (22.6)	4 (12.9)	12 (15.4)
Withdrawal	6 (20.0)	5 (16.1)	4 (12.9)	22 (28.2)
Missing	0	1 (3.2)	0	0
2 Years				
Evaluable n	30	31	31	62
OR	8 (26.7) 12.3, 45.9	17 (54.8) 36.0, 72.7	20 (64.5) 45.4, 80.8	24 (38.7) 26.6, 51.9
CR	7 (23.3) 9.9, 42.3	13 (41.9) 24.5, 60.9	17 (54.8) 36.0, 72.7	19 (30.6) 19.6, 43.7
PR	1 (3.3)	4 (12.9)	3 (9.7)	5 (8.1)
Relapse	15 (50.0)	8 (25.8)	7 (22.6)	16 (25.8)
Withdrawal	7 (23.3)	6 (19.4)	4 (12.9)	22 (35.5)

Source: reviewer analysis

Table 16 CR and OR Rate by Assessment Time before 2 Years (Data cut off Feb 2018)

	Cohort 1 N=30		Cohort 2 N=31		Cohort 3 N=31		Cohort 3 + Extension N=92	
Response	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Year 3 , Total n	30		31		17		44	
Overall Response	7 (23.3)	9.9, 42.3	10 (32.3)	16.7, 51.4	2 (11.8)	1.5, 36.4	2 (4.5)	0.6, 15.5
Complete Response	5 (16.7)	5.6, 34.7	8 (25.8)	11.9, 44.6	2 (11.8)	1.5, 36.4	2 (4.5)	0.6, 15.5
Year 4 , Total n	30		22		14		41	
Overall Response	7 (23.3)	9.9, 42.3	3 (13.6)	2.9, 34.9	0	0.0, 23.2	0	0.0, 8.6
Complete Response	6 (20.0)	7.7, 38.6	2 (9.1)	1.1, 29.2	0	0.0, 23.2	0	0.0, 8.6
Year 5 , Total n	27		19		14		41	
Overall Response	4 (14.8)	4.2, 33.7	0	0.0, 17.6	0	0.0, 23.2	0	0.0, 8.6
Complete Response	3 (11.1)	2.4, 29.2	0	0.0, 17.6	0	0.0, 23.2	0	0.0, 8.6

Overall Response = Complete or Partial Response
'Total n' is the number of subjects in the treatment group who reached this timepoint or withdrew earlier. It is the denominator for percentage (%) calculation. The 95% CI were computed based on the exact method of Clopper-Pearson.

Source: adapted from Table 2-10, 120 efficacy and safety update; Study AUS01T

Duration of Complete Response

The duration of complete response in each cohort are summarized in Table 15. The Kaplan meiers of the duration of response in each cohort are plotted in Figure 9. Using KM method, the median of duration of complete response for cohort 3 + extension cohort is 24.3 months (95% CI: 23.0, NE).

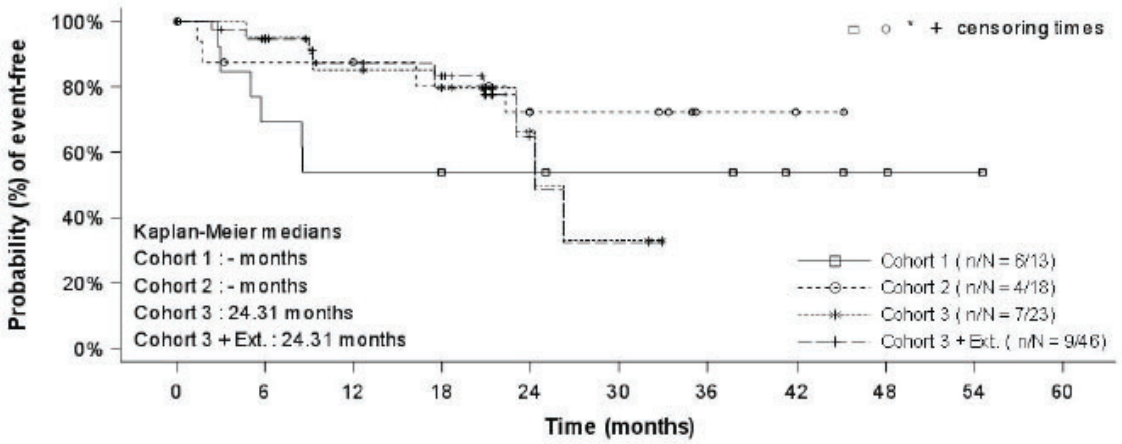
Table 17 Median of Duration of Complete Response

	Cohort 1 N = 30	Cohort 2 N = 31	Cohort 3 N = 31	Cohort 3 + Extension N = 92
Number of CR #	13 (43.3%)	18 (58.1%)	23 (74.2%)	46 (50.0%)
Median (95% CI), months	NE (5.1, NE)	NE (22.3, NE)	24.3 (23.0, NE)	24.3 (23.0, NE)

number of CR at any time

Source: Table 2-12, 120 day update, Study AUS01T

Figure 7 Kaplan Meier Curves of Duration of Complete Response



No. of patients still at risk

Time (months)	0	6	12	18	24	30	36	42	48	54	60
Cohort 1	13	9	7	6	6	5	5	3	2	1	0
Cohort 2	18	13	12	11	6	6	2	1	0		
Cohort 3	23	19	17	14	4	2	0				
Cohort 3 + Ext.	46	33	22	18	4	2	0				

'n/N' are the total number of events / total number of patients in that group.

Source: Figure 2-2, 120 day update, Study AUS01T

Duration of Overall Response

The duration of overall response in each cohort are summarized in Table 16. The Kaplan meiers of the duration of response in each cohort are plotted in Figure 10. Using KM method, the median of duration of complete response for cohort 3 + extension cohort is also 24.3 months (95% CI: 23.0, NE).

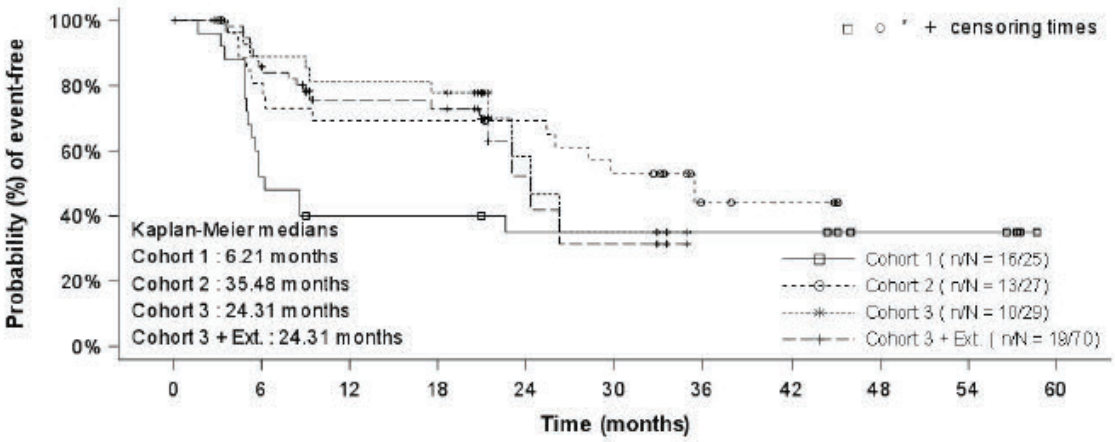
Table 18 Median of Duration of Overall Response

	Cohort 1 N = 30	**Cohort 2** N = 31	**Cohort 3** N = 31	**Cohort 3 + Extension** N = 92
Number of OR #	25 (83.3%)	27 (87.0%)	29 (93.5%)	70 (76.1%)
Median (95% CI), months	6.2 (5.1, NE)	35.5 (9.5, NE)	24.3 (21.4, NE)	24.3 (21.4, NE)

number of OR at any time

Source: Reviewer analysis

Figure 8 Kaplan Meier Curves of Duration of Overall Response



No. of patients still at risk

Time (months)	0	6	12	18	24	30	36	42	48	54	60
Cohort 1	25	13	9	9	7	7	7	7	4	4	0
Cohort 2	27	21	18	18	17	13	4	3	0		
Cohort 3	29	24	22	21	5	3	0				
Cohort 3 + Ext.	70	48	27	26	5	3	0				

'n/N' are the total number of events / total number of patients in that group

Source: Figure 2-2, 120 day update, Study AUS01T

Overall Survival

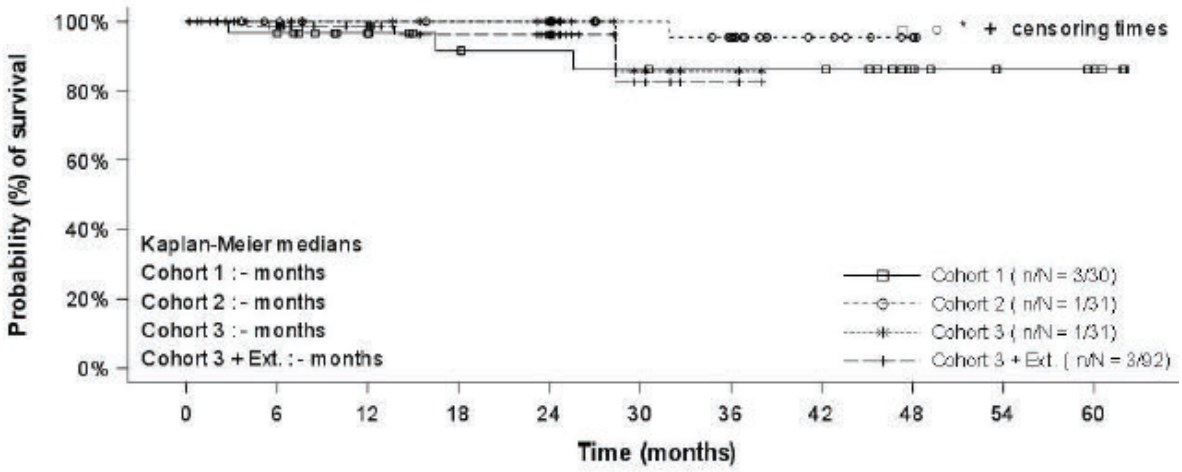
Overall, 7 subjects died in the study by the data cut off date, and 3 of them were in cohort 3 + extension cohort. The overall survival are summarized in Table 17 and the Kaplan Meier curves are plotted in Figure 11.

Table 19 Overall Survival

	Cohort 1 N = 30	Cohort 2 N = 31	Cohort 3 N = 31	Cohort 3 + Extension N = 92
Death, n (%)	3 (10.0%)	1 (3.2%)	1 (3.2%)	3 (3.3%)
Censor, n (%)	27 (90.0%)	30 (96.8%)	30 (96.8%)	89 (96.7%)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (28.4, NE)	NE (28.4, NE)

Source: reviewer analysis

Figure 9 Kaplan-Meier Plot of Overall Survival



No. of patients still at risk

Time (months)	0	6	12	18	24	30	36	42	48	54	60
Cohort 1	30	29	22	18	17	16	15	15	9	6	5
Cohort 2	31	29	27	26	26	22	18	8	4	0	
Cohort 3	31	30	28	26	22	5	2	0			
Cohort 3 + Ext.	92	77	48	37	30	5	2	0			

'n/N' are the total number of events / total number of subjects in that group.

Source: Figure 2-5, 120 efficacy and safety update, Study AUS01T

3.2.1.4.3 Analysis of Quality of Life

Subject-reported outcomes showed that parameters measured by Health questionnaires were stable or were improved at month 6.

For PROMIS scores, change from baseline to post-baline assessments were summarized in the table below. For global physical health score and global mental health score, higher scores represent better quality-of-life outcomes, whereas on the symptom scales, a higher score represents a worse outcome e.g. more sleep disturbance, more anxiety and.or more depresson. However, interpretation should be done with caution due to the very small number of non-responders.

At month 3 and month 6, changes in mean PROMIS scores were less than 10 on the global physical health, global mental health, and cognition subscale among both responders and non-responders and overall in each cohort. Changes in sleep disturbance were unremarkable. At month 6, both anxiety and depression mean scores worsened in subjects who were nonresponders and remained stable or improved in responding subjects. In summary, the PROMIS assessments seemed to show a mean improvement in anxiety for responders in Cohort 3. Other subscales seemed to be stable and similar between responders and non-responders.

Table 20 PROMIS T-scores Change from Baseline to Month 3 or Month 6

	Month 3			Month 6		
	Responders N = 22	**Non-responders N = 1**	**All N = 23**	**Responders N = 22**	**Non-responders N = 1**	**All N = 23**
Global physical health						
Mean (SD)	0.1 (11.13)	-2.4 (NA)	0 (-10.88)	4.9 (10.79)	11.0 (NA)	5.2 (10.62)
Global mental health						
Mean (SD)	-4.9 (7.81)	1 (NA)	-5.2 (7.74)	-0.4 (8.44)	-2.7 (NA)	-0.5 (8.26)
Sleep disturbance						
Mean (SD)	-1.2 (10.04)	8.1 (NA)	-0.8 (10.00)	-3.4 (9.49)	-8.7 (NA)	-3.6 (9.34)
Anxiety						
Mean (SD)	-3.2 (9.25)	0 (NA)	-3.0 (9.06)	-5.8 (9.07)	15.5 (NA)	-4.9 (9.91)
Depression						
Mean (SD)	1.2 (8.41)	12.9 (NA)	1.7 (8.57)	0.2 (7.66)	12.9 (NA)	0.7 (7.94)
Applied cognition abilities						
Mean (SD)	2.5 (8.13)	8.5 (NA)	2.8 (8.05)	4.0 (8.59)	9.9 (NA)	4.2 (8.49)

Source: adapted from Table 11-4, Table 11-5, CSR, Study AUS01T

For FACT scores, higher FACT scores are indicative of better functioning and better quality of life. Similar to the PROMIS score, for FACT scores, interpretation should be done with caution due to the very small number of non-responders in each cohort. Overall, by month 3, FACT scores were improved for responders in all the categories, but got worse for non-responders. By month 6, FACT scores were improved for both responders and non-responders in all the categories.

Table 21 FACT scores Change from Baseline to Month 3 or Month 6

	Month 3			Month 6		
	Responders	**Non-responders**	**All**	**Responders**	**Non-responders**	**All**
Global total score						
N	17	4	21	21	1	22
Mean (SD)	3.0 (13.4)	-6.3 (10.8)	1.2 (13.3)	3.0 (15.7)	9.0 (NA)	3.2 (15.4)
Anemia trial outcome index						
N	16	4	20	21	1	22
Mean (SD)	10.3 (27.1)	-3.0 (19.3)	7.6 (25.9)	5.8 (20.4)	15.0 (NA)	6.2 (20.0)
Thrombocytopenia trial outcome index						
N	17	4	21	21	1	22
Mean (SD)	10.5 (17.2)	-0.5 (7.6)	8.4 (16.3)	11.3 (16.5)	10.0 (NA)	11.2 (16.1)
Thrombocytopenia total score						

N	17	4	21	21	1	22
Mean (SD)	10.6 (20.3)	-2.5 (14.3)	8.1 (19.7)	11.5 (22.0)	11.0 (NA)	11.5 (21.5)
Neutropenia trial outcome index						
N	16	4	20	21	1	22
Mean (SD)	9.1 (20.3)	-5.8 (13.6)	6.1 (19.8)	8.8 (18.3)	9.0 (NA)	8.8 (17.8)
Neutropenia total score						
N	16	4	20	21	1	22
Mean (SD)	9.0 (23.4)	-7.8 (20.5)	5.7 (23.4)	9.0 (23.5)	10.0 (NA)	9.1 (22.9)

Source: adapted from Table 11-6, Table 11-7, CSR, Study AUS01T

3.2.1.5 Results and Conclusions

In summary, efficacy and safety of eltrombopag were investigated in the Study AUS01T, which was a phase I/II, non-randomized, single-arm, single center study designed to evaluate the efficacy and safety of eltrombopag treatment, in combination with the regimen of h-ATG and CsA, in definitive immunosuppressive therapy-naïve subjects with severe aplastic anemia (SAA).

The study enrolled 92 patients in Cohort 3 + Extension Cohort. There were 87 patients who reached the assessment time for the primary endpoint CR at 6 months. Among these evaluable patients, there were 38 patients (43.7%) reaching CR at 6 months, and 69 patients (79.3%) reaching OR at 6 months. The median duration of response for CR and that for OR are the same. Both of them are 24.3 months.

The applicant submitted data from 4 historical trials with h-ATG (day 1-4) + CsA therapy to compare with eltrombopag plus h-ATG (day 1-4) + CsA therapy. Two of the historical trials have individual patient level data. The other two trials have summary level data only from literature. Among these four trials, three trials included both pediatric and adult population, and the other one included adult population only.

Various statistical analysis methods were applied to the data from compare the CR and OR rate at 6 months between the eltrombopag therapy in the Study AUS01T with those from the historical data. These analysis results were considered exploratory, so no formal hypothesis testing was performed. Even though there are statistical concerns of the adequacy of using historical control data for comparative purposes, the results, however, appears to be supportive. The difference of CR rate at 6 months in these analyses are consistent, suggesting the benefit of adding eltrombopag to the therapy of h-ATG (day 1-4) + CsA.

3.3 Evaluation of Safety

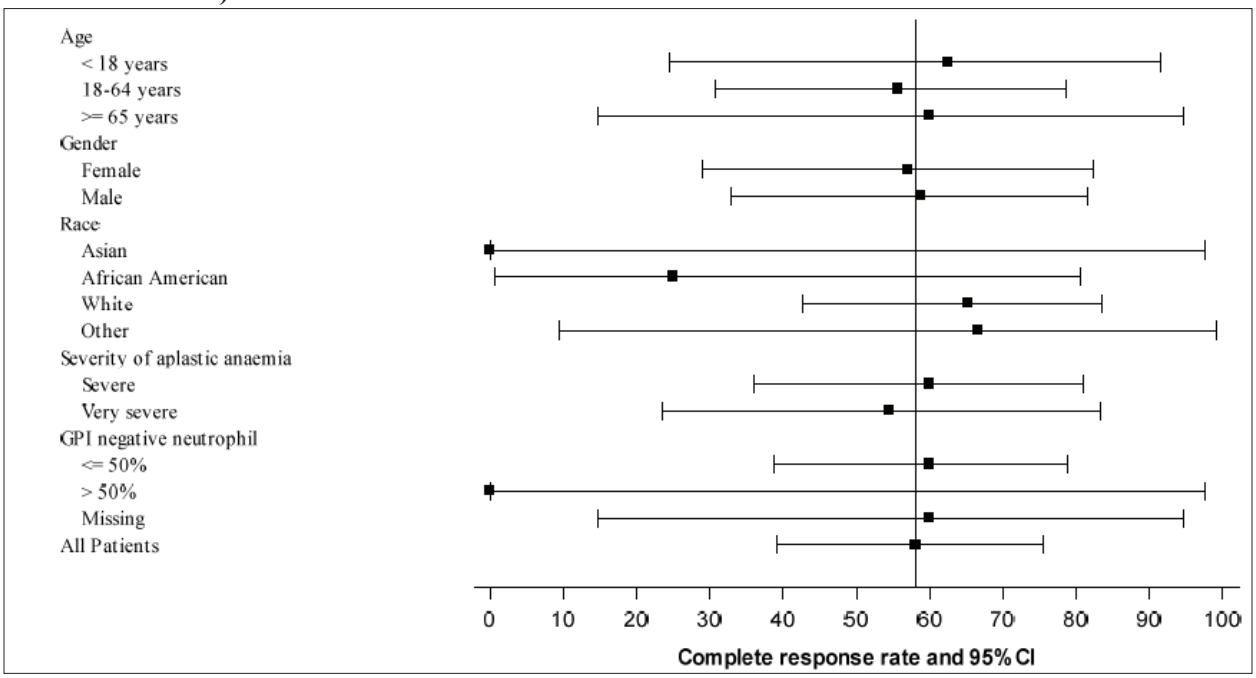
Please refer to the clinical review for more information about evaluation of safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

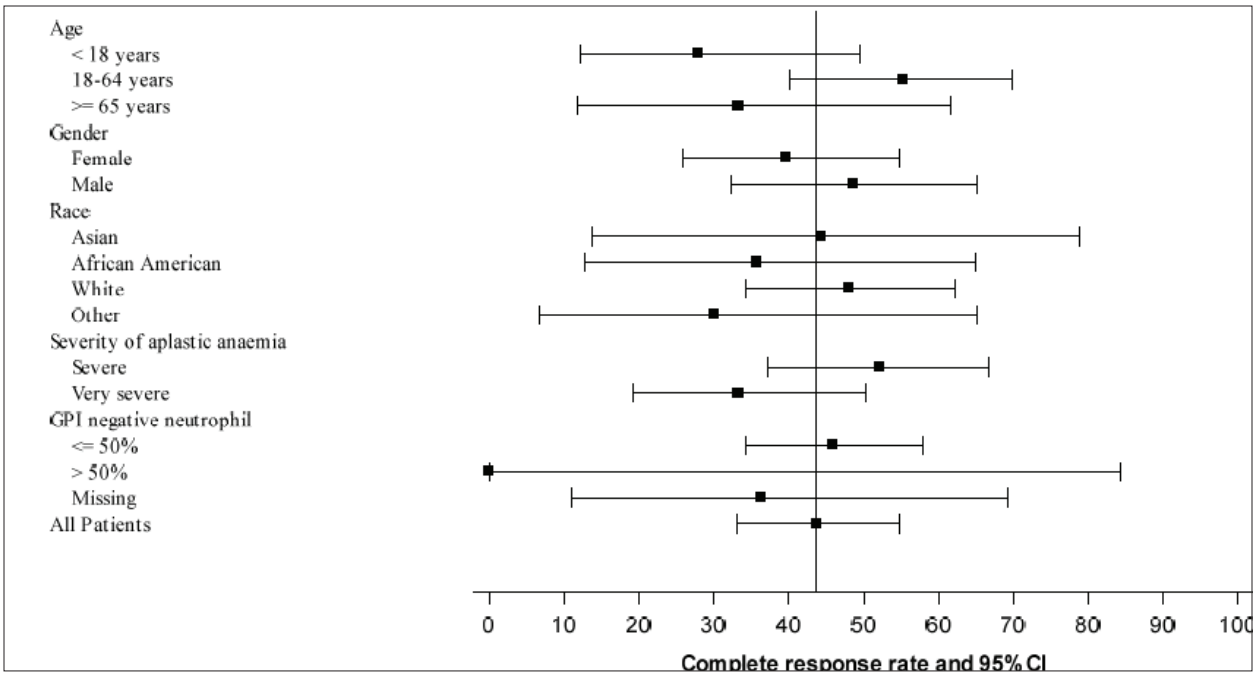
The primary endpoint CR at month 6 were analyzed by subgroups of age, gender and race. The results in each cohort are plotted in Figure 12 – 13. Limited by the sample size, the results in some subgroups have wide confidence interval and the results need to be interpreted with cuation.

Figure 10 Forest plot of CR at month 6 with 95% Confidence Interval for Cohort 3 (Data cut off Feb 2018)



Source: Figure 14.2-1.1u, 120 efficacy and safety update, Study AUS01T

Figure 11 Forest plot of CR at month 6 with 95% Confidence Interval for Cohort 3 and Extension Cohort (Data cut off Feb 2018)



Source: Figure 14.2-1.1u, 120 efficacy and safety update, Study AUS01T

4.2 Other Special/Subgroup Populations

The primary endpoint CR at 6 months were analyzed in the subgroups of severity of aplastic anemia and GPI negative neutrophil. Please refer the section 4.1 for analysis results. Similarly due to the small sample size in some subgroups, the confidence interval are wide in some subgroups.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

In summary, there is no major statistical issues identified in the review.

The applicant collected historical conrol data. The reviewer identified the following statistical issues with the analysis using historical control data.

In terms of historical studies included in the analysis:

- *There is only adult population in the study Tisdale et al. 2000, while the Study AUS01T has both adult and pediatric population. The heterogeneity in patients' age between the studies may lead to imbalance between the treatment cohorts in the analysis.*

- *The Study Scheinberg 2011 was conducted between 2005 and 2010, and the Study Scheinberg 2009 was conducted between 2003 and 2005. The Study AUS01T was conducted between 2012 and 2016. Because Study AUS01T and the historical studies are not conducted at the similar time, then the relationships observed between treatment and outcome might be*

affected. Changes in disease or diagnostic definitions, exposures over time and treatments could all contribute to non-contemporaneous bias.

- *The regime and dose in the backbone therapy h-ATG + CsA in the pivotal trial are heterogeneous from the historical trials. Therefore it is difficult to separate out the treatment effect of eltrombopag when comparing the pivotal study AUS01T with the historical trials.*

In terms of propensity score matching analysis:

- *With propensity score analysis, 19 out of 87 patients (21.8%) in the Study AUS01T and 34 out of 102 patients (33.3%) in the pooled historical control cohort were unmatched, and therefore excluded in the analysis. The resulting analysis population may not fully represent the target study population, and therefore the estimated treatment effect may not represent the true treatment effect in the target study population.*

- *The standardized mean difference for the covariate platelet count, ANC, and age are very high. With the pre-specified model checking criteria that standardized differences should be less than 25%, the results indicate that the propensity score model and the matching method did not create adequate well balanced treatment and control cohorts with the available covariates and the statistical model.. The functional form of the propensity score model or the covariates adjusted in the model needs to be changed.*

- *In general, propensity score matching analysis may only provide justification for the observed covariated included in the propensity score model. Potential bias may still exist if propensity score model is misspecified or there is unobserved confounders.*

In terms of IPTW analysis:

- *With IPTW analysis, compared with propensity score matching analysis, all patients in the Study AUS01T and all patients in the historical control cohort were included in the analysis. However, the analysis results may still subject to the potential bias due to the extreme weights. With either stabilized or unstablized weights, there is one patient in each treatment arm with weight close to greater than 4. The weight of these two patients are much larger than the weights of other patients, and thus these two patients may have a large impact on the analysis results.*

- *Similar to the propensity score matching method, in general, IPTW analysis may only provide justification for the observed covariated included in the propensity score model. Potential bias may still exist if propensity score model is misspecified or there is unobserved confounders.*

In terms of fix effect analysis:

- *The CR rate estimate and its 95% CI based on this fixed effect analysis appears to be similar to those from the patient evel analysis, but with a narrower CI. However, the ORR estimates and the 95% CI are not similar to the propensity score matched or weighted analyses after adding one more summary data result from the additional study. However this fixed effect analysis does not address the comparability issues between study AUS01T and the historical control data.*

5.2 Conclusions and Recommendations

In summary, efficacy and safety of eltrombopag were investigated in the Study AUS01T, which was a phase I/II, non-randomized, single-arm, single center study designed to evaluate the efficacy and safety of eltrombopag treatment, in combination with the regimen of h-ATG and CsA, in definitive immunosuppressive therapy-naïve subjects with severe aplastic anemia (SAA).

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The applicant submitted data from 4 historical trials with h-ATG (day 1-4) + CsA therapy to compare with eltrombopag plus h-ATG + CsA therapy. Two of the historical trials have individual patient level data. The other two trials have summary level data only from literature. Among these four trials, three trials included both pediatric and adult population, and the other one included adult population only.

Various statistical analysis methods were applied to the data from compare the CR and OR rate at 6 months between the eltrombopag therapy in the Study AUS01T with those from the historical data. These analysis results were considered exploratory, so no formal hypothesis testing was performed. Even though there are statistical concerns of the adequacy of using historical control data for comparative purposes, the results, however, appear to be supportive. The difference of CR rate at 6 months in these analyses are consistent, suggesting the benefit of adding eltrombopag to the therapy of h-ATG (day 1-4) + CsA. The overall efficacy results showed supportive evidence of the benefits of adding altrombopag to the h-ATG + CsA therapy. However, the Study AUS01T is designed as a single arm study, alpha was not controlled and there is no formal statistical hypothesis applied.

The subgroup analysis showed consistent positive trend of the results with the primary analysis for CR and OR at 6 months even though there are some variation of some subgroups due to relatively small sample sizes in the subgroup.

Overall there is no major statistical issues identified in the review. The final decision of approving altrobopag for the proposed indication is deferred to the clinical reviewer.

5.3 Labeling Recommendations

There is no major labeling changes during the review.

APPENDICES

Reference

Agresti A., Min Y. Effects and non-effects of paired identical observations in comparing proportions with binary matched-pairs data. Statistics in Medicine, 2004; 23: 65-75.

Austin, P. C. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in Medicine, 2009; 28: 3083–3107.

Austin P.C. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharmaceutical Statistics, 2011; 10: 150-161

Rosenbaum, P.R., Rubin D.B. The central role of the propensity score in observational studies for causal effects. Biometrika, 1983; 70(1): 41–55.

Rosenbaum, P.R., Rubin D.B. Reducing bias in observational studies using subclassification on the propensity score. Journal of the American Statistical Association, 1984; 79 (387): 526–524.

DerSimonian R., Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials, 1986; 7, 177-188.

Scheinberg P., Wu C.O., Nunez O. et al. Treatment of severe aplastic anemia with a combination of horse antithymocyte globulin and cyclosporine, with or without sirolimus: a prospective randomized study. Haematologica, 2009; 94 (3): 348-354.

Scheinberg P., Nunez O., Weinstein B. et al. Horse versus Rabbit Antithymocyte Globulin in Acquired Aplastic Anemia. N Engl J Med , 2011; 365 (5): 430-438.

Formulation of the absolute standardized mean difference in the propensity score analysis

For a continuous baseline covariates x, let xbar trt and xbar control be the sample means in treated and control patients, respectively. Let S2trt and S2control be the sample variances in treated and control patients, respectively. The standardized difference is

$$d = 100 \times \frac{|(\bar{x}_{trt} - \bar{x}_{control})|}{\sqrt{\frac{s^2_{trt} + s^2_{contol}}{2}}}$$

For a binary baseline covariates, let phat trt and phat control be the sample proportions of the variable in treated and control patients, respectively. The standardized difference is

$$d = 100 \times \frac{|(\hat{p}_{trt} - \hat{p}_{control})|}{\sqrt{\frac{(\hat{p}_{trt}(1-\hat{p}_{trt}) + \hat{p}_{control}(1-\hat{p}_{control}))}{2}}}$$

IPTW

The IPTW estimate of the treatment effect was calculated as weighted difference in response rates between h-ATG+CsA+eltrombopag and h-ATG+CsA using the stabilized weights. The 95% confidence interval of the treatment effect was provided.

Suppose we have data on n patients and let a binary response vector Y=(Y1, Y2, …, YN), a patient treatment indicator vector Z=(z1, z2, …, zn), and measured baseline covariate matrix X=(x1, x2, …, xn). The propensity score $e(X_i, \beta) = P[z_i=1 | x_i]$ were estimated from the fitted logistic regression model adjusted for the baseline covariates. The normalized estimator for treatment effect delta using stabilized weights was

$$\hat{\Delta}_{IPTWN} = \frac{\sum_{i=1}^{n} \frac{P(Z_i=1)Z_i Y_i}{e(X_i, \beta)}}{\sum_{i=1}^{n} \frac{P(Z_i=1)Z_i}{e(X_i, \beta)}} - \frac{\sum_{i=1}^{n} \frac{P(Z_i=0)(1-Z_i)Y_i}{1-e(X_i, \beta)}}{\sum_{i=1}^{n} \frac{P(Z_i=0)(1-Z_i)}{1-e(X_i, \beta)}}$$

The (1-alpha)100% confidence interval of the estimated treatment effect was $\hat{\Delta}_{IPTWN} \pm Z_{(1-\alpha/2)} SE(\hat{\Delta}_{IPTWN})$ where the estimated of the sampling variance of the treatment effect was obtained by bootstrapping with 1000 replications.

Efficacy with Data Cut off Date Sep 28, 2016

Table 22 Complete Response at 6 Months – Primary Analysis (Data cut off Sep 2016)

	Cohort 1 (N = 30)	Cohort 2 (N = 31)	Cohort 3 (N = 31)	Cohort 3 + Extension	
				Sep 30, 2016 (N = 62)	Feb 28, 2018 (N = 92)
Evaluable n	30	31	31	46	87
CR, n (%), 95% CI	10 (33.3)	8 (25.8)	18 (58.1)	24 (52.2)	38 (43.7)
	17.3, 52.8	11.9, 44.6	39.1, 75.5	36.9, 67.1	33.1, 54.7

Source: reviewer analysis

Table 23 Complete Response at Month 6 – Sensitivity Analysis (Data Cut-off Feb 2018)

	Cohort 1 N = 30	Cohort 2 N = 31	Cohort 3 N = 31	Cohort 3 +Extension N = 62
PPS Analysis Population				
Evaluable n	30	30	31	46
CR, n (%), 95% CI	10 (33.3)	8 (26.7)	18 (58.1)	24 (52.2)
	17.3, 52.8	12.3, 45.9	39.1, 75.5	36.9, 67.1
More Stringent Definition for Complete Response				
Evaluable n	30	31	31	46
CR, n (%), 95% CI	2 (6.7)	1 (3.2)	2 (6.5)	2 (4.3)
	0.8, 22.1	0.1, 16.7	0.8, 21.4	0.5, 14.8

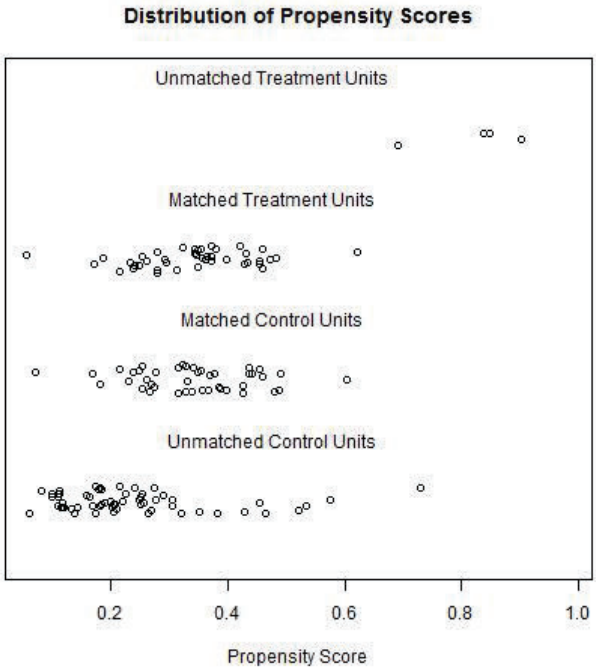
Source: reviewer analysis

Table 24 Unadjusted Analysis of Complete Response and Overall Response (Data cut off Sep, 2016)

	Treatment Cohort (N = 46) [1]	Historical Control Cohort (N = 102)
CR, n (%)	24 (52.2)	17 (16.7)
CR rate difference, % (95% CI) [2]	35.5 (19.36, 51.65)	
OR, n (%)	39 (84.4)	67 (65.7)
OR rate difference, % (95% CI) [3]	19.1 (5.22, 32.98)	

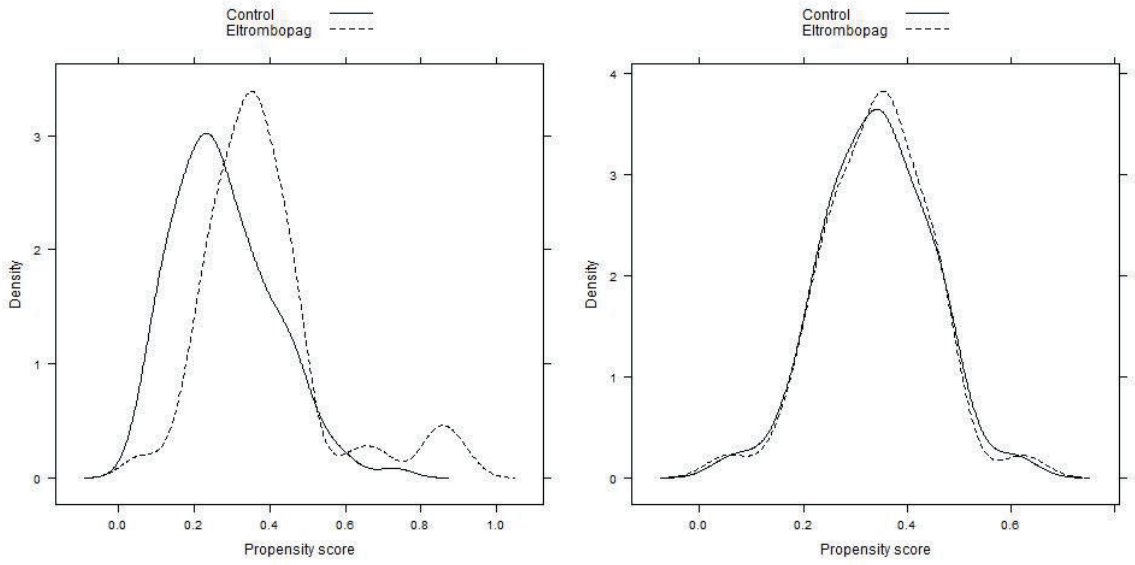
[1] Evaluable number of patients
[2] CR rate difference = CR rate in treatment cohort – CR rate in historical control cohort
[3] OR rate difference = OR rate in treatment cohort – OR rate in historical control cohort
Resource: reviewer analysis

Figure 12 Distribution of Propensity Scores including Matched and Unmatched Patients (Data cutoff Sep 2016)



Source: reviewer analysis

Figure 13 Distribution of Propensity Score Before and After Matching (Data cutoff: Sep 2016)



(a) before matching (b) after matching

Source: Reviewer analysis

Table 25 Covariates Balance Before and After Propensity Score Matching (Data cut off Sep 2016)

	lplt	larc	lanc	AGE	gender	lplt	larc	lanc	AGE	gender
			Before Matching					After Matching		
mean.trt	8.95	9.91	4.58	35.13	0.52	8.93	9.99	5.46	34.83	0.52
sd.trt	0.78	0.82	3.07	21.76	0.07	0.78	0.80	1.15	21.27	0.08
mean.ctrl	8.92	9.50	5.28	34.63	0.56	8.93	10.02	5.52	33.03	0.55
sd.ctrl	0.90	1.06	1.89	20.35	0.05	0.71	0.86	1.91	19.75	0.08
std.diff.x	2.71	43.37	27.48	2.39	0.15	0.58	3.56	4.09	8.77	0.09

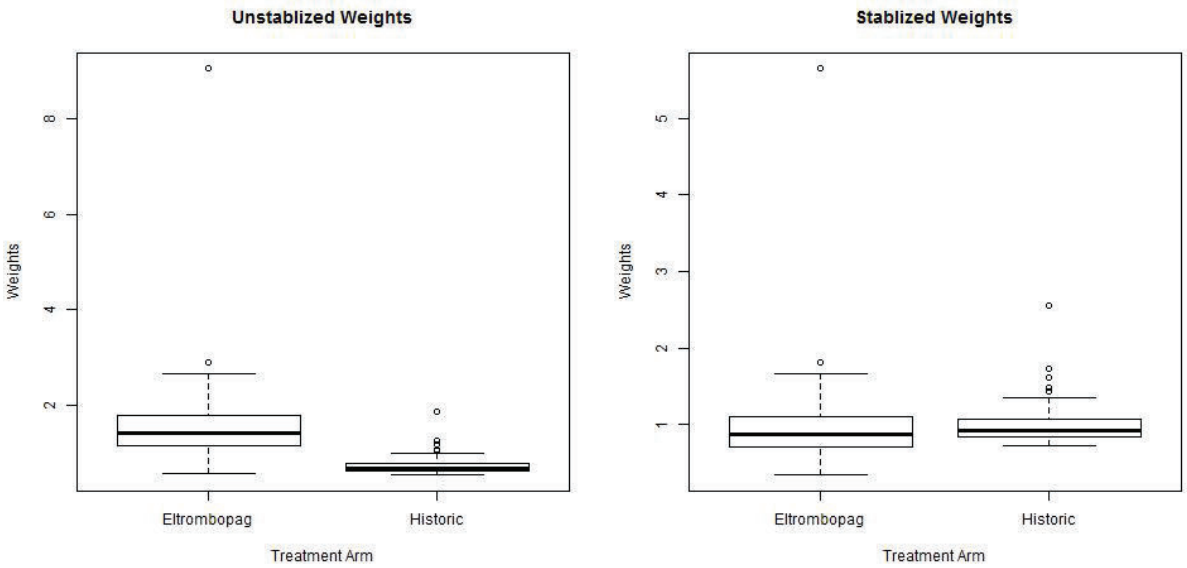
Source: Reviewer analysis

Table 26 Propensity Score Matching Analysis (Data cutoff Sep 2016)

	Treatment effect, 95 % CI
CR at month 6	38.1 (20.69, 55.50)
OR at month 6	11.9 (-4.53, 28.34)

Source: Reviewer analysis

Figure 14 Distribution of Weights (Data cutoff Sep 2016)



Source: Reviewer analysis

Table 27 IPTW Propensity Score Analysis (Data cut off Sep 2016)

	Weight	Treatment effect, (95 % CI)
CR at month 6	unstablized	39.7 (20.83, 58.66)
	stablized	39.7 (21.05, 58.45)
OR at month 6	unstablized	20.0 (7.25, 32.85)
	stabilized	20.0 (7.89, 32.20)

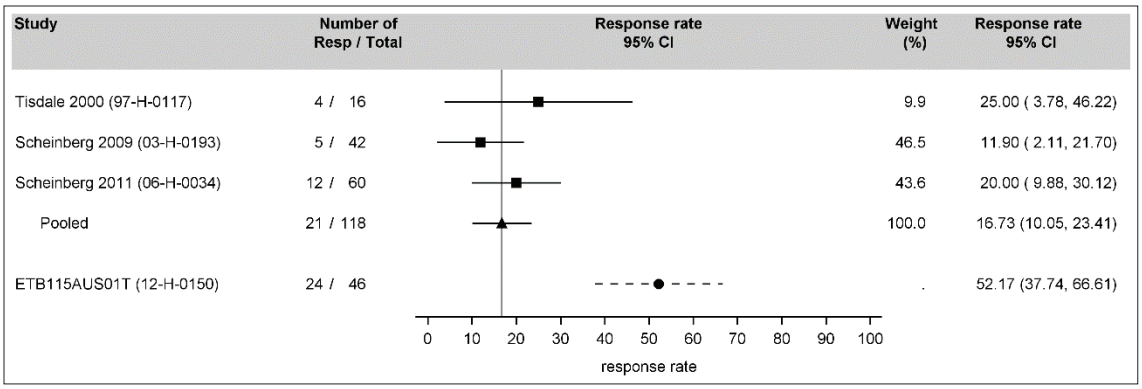
Resource: reviewer analysis

Table 28 Fixed Effect Analysis (Data cut off Sep 2016)

	Treatment N = 46	Historical Control N = 118 [1]
CR at Month 6, 95% CI	52.2 (37.74, 66.61)	16.7 (10.05, 23.41)
CR rate difference	35.4 (19.54, 51.35)	
OR at Month 6, 95% CI	84.8 (74.40, 95.16)	63.1 (56.97, 69.15)
OR rate difference	21.7 (9.69, 33.76)	

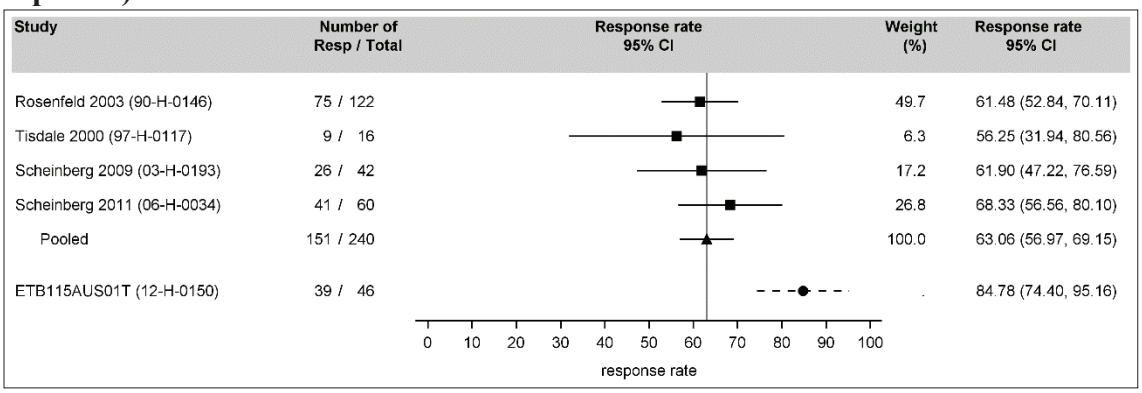
[1] Combined data from studies 06-H-0034, 03-H-0193, and 97-H-0117 only for CR analysis
Source: reviewer analysis

Figure 15 Forest Plot of CR in Historical Control Studies and Study AUS01T (Data cut off Sep 2016)



Source: reviewer analysis

Figure 16 Forest Plot of OR in Historical Control Studies and Study AUS01T (Data cut off Sep 2016)



Source: reviewer analysis

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/s/

XIN GAO
11/01/2018

YUAN L SHEN
11/01/2018

THOMAS E GWISE
11/01/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22291Orig1s021

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 7, 2018
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Robert Nguyen, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	PROMACTA (eltrombopag)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 022291
Supplement Number:	S-021
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On March 30, 2018, Novartis Pharmaceuticals Corporation, submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their approved New Drug Application (NDA) 022291/S-021 for PROMACTA (eltrombopag) tablets. With this supplement, the Applicant proposes a new indication for PROMACTA (eltrombopag) in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on June 14, 2018, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) PROMACTA (eltrombopag) tablets and PROMACTA (eltrombopag) for oral suspension, and Instructions for Use (IFU) for PROMACTA (eltrombopag) for oral suspension.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft PROMACTA (eltrombopag) tablets MG received on March 30, 2018, further revised on October 23, 2018, and received by DMPP and OPDP on October 25, 2018.
- Draft PROMACTA (eltrombopag) tablets Prescribing Information (PI) received on March 30, 2018 received on March 30, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 1, 2018.
- Approved PROMACTA (eltrombopag) tablets and PROMACTA (eltrombopag) for oral suspension labeling dated September 27, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
11/07/2018

ROBERT L NGUYEN
11/07/2018

SHARON R MILLS
11/07/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 6, 2018

To: Kimberly Scott, Regulatory Project Manager, Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for PROMACTA® (eltrombopag) tablets, for oral use and for oral suspension

NDA: 022291/Supplement-021

In response to DHP's consult request dated June 14, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and Instructions for Use (IFU) for Promacta. This supplement (S-021) pertains to the proposed indication for the use of Promacta in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Kimberly Scott) on November 1, 2018 and are provided below.

Medication Guide/IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide and IFU will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

34 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ROBERT L NGUYEN
11/06/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 21, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 22291/S-21
Product Name and Strength:	Promacta (eltrombopag) Tablets 12.5 mg, 25 mg, 50 mg, and 75 mg Promacta (eltrombopag) Oral suspension 25 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis
FDA Received Date:	March 29, 2018, July 25, 2018, July 31, 2018, and August 20, 2018
OSE RCM #:	2018-698
DMEPA Safety Evaluator:	Leeza Rahimi, Pharm.D.
DMEPA Team Leader:	Hina Mehta, Pharm.D.

1 REASON FOR REVIEW

Novartis Pharmaceuticals submitted a supplemental New Drug Application, NDA 22291/S-021 for Promacta (eltrombopag) Tablets. In this supplement, the Applicant is proposing the use of Promacta in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia. In addition, the Applicant has updated the Prescribing Information (PI) based on the approved revisions for NDA 22291/S-020.

The Division of Hematology Products (DHP) requested that we review the revised PI, Medication Guide (MG), and Instructions for Use (IFU).

1.1 Background Information

Promacta (eltrombopag) tablets NDA 22291 were approved on November 20, 2008 and Promacta oral suspension (NDA 207027) was approved on August 24, 2015 for the treatment of chronic immune (idiopathic) thrombocytopenia (ITP). Currently, Promacta is used for three different indications:

1) Treatment of chronic immune thrombocytopenia (ITP) in adult and pediatric patients 1 year and older who have insufficient response to corticosteroids, immunoglobulins, or splenectomy

2) Treatment of thrombocytopenia in patients with Hepatitis C infection

3) Treatment of severe aplastic anemia who have had insufficient response to immunosuppressive therapy

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA evaluated the revised PI, MG, and IFU for areas of vulnerability in regards to medication error. We note that our previous recommendations for NDA 22291/S-20 has been implemented.

We identified areas of improvement in the PI that should be revised to improve the clarity of information presented. We provide recommendations for the Division in section 4.1.

4 CONCLUSION & RECOMMENDATIONS

We identified areas on the proposed PI that can be improved to increase clarity of information and promote the safe use of the product.

4.1 RECOMMENDATION FOR THE DIVISION

A. Highlights of Prescribing Information
    1. Dosage and Administration
        a. We recommend revising the information presented for the First-line Severe Aplastic Anemia for increased clarity. Revise to:
        First-line Severe Aplastic Anemia: Initiate Promacta in adults and adolescents 12 to 17 years at 150 mg once daily, in pediatrics 6 to 11 years at 75 mg once daily, and in pediatrics 2 to 5 years at 2.5 mg/kg once daily. Administer concurrently with standard immunosuppressive therapy. Dose adjustment, reduction, or discontinuation may be required. (2.3, (b) (4)).

B. Full Prescribing Information
    1. Dosage and Administration
        a. Section 2.3 Severe Aplastic Anemia: To enhance the clarity of information and promote the safe use of the product, we recommend revising the first two sentences of the first paragraph. We suggest revising the sentences to read: “Initiate Promacta concurrently with standard immunosuppressive therapy. Do not exceed the initial dosing regimen of Promacta”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Promacta received on July 25, 2018, July 31, 2018, August 17, 2018, and August 20, 2018 from Novartis.

Table 2. Relevant Product Information for Promacta		
Initial Approval Date	November 20, 2008	August 24, 2015
Active Ingredient	eltrombopag	
Indication	• Thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. • Thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. • Patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. *PROMACTA is indicated in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.*	
Route of Administration	Oral	
Dosage Form	Tablets	Powder for Suspension
Strength	Tablets: 12.5 mg, 25 mg, 50 mg, 75 mg	25 mg packet
Dose and Frequency	-75 mg/day in chronic ITP; 100 mg/day in chronic hepatitis C-associated thrombocytopenia; 150 mg/day in severe aplastic anemia, according to the prescribing information. - **First-line Severe Aplastic Anemia:** PROMACTA should be initiated at 2.5 mg/kg, 75 mg, or 150 mg for most patients, concurrently with standard immunosuppressive therapy. Reduce initial dose in patients of Asian ancestry. The initial dose of PROMACTA should not be exceeded. Dose interruption, reduction, or discontinuation may be required.	
How Supplied	30 count bottle	30 packets/kit

Storage	20 and 25 degrees C (68 and 77 degrees F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 13, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, Promacta. Our search identified 6 relevant reviews[a], and we confirmed that our previous recommendations were implemented.

[a] Rahimi, L. Label and Labeling review for Promacta, NDA 207027/S-006. Silver Spring (MD) FDA, CDER, OSE, DMEPA (US); 2018 SEP 06. RCM # 2018-1401.

Rahimi, L. Label and Labeling review for Promacta, NDA 207027/S-005, NDA 022291/S-020. Silver Spring (MD) FDA, CDER, OSE, DMEPA (US); 2018 MAY 07. RCM # 2018-268.

Rahimi, L. Label and Labeling review for Promacta, NDA 207027/S-004. Silver Spring (MD) FDA, CDER, OSE, DMEPA (US); 2018 APR 18. RCM # 2017-2542.

Rychlick, I. Label and Labeling Review for Promacta, NDA 207027. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 SEP 16. ODS consult # 2016-2066.

Rutledge, M. Labeling Review Memorandum for Promacta (Eltrombopaq) Powder for Oral Suspension, NDA 207027. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 AUG 20. ODS consult # 2015-492.

Rutledge, M. Label and Labeling and Human Factors Review for Promacta (Eltrombopaq) Powder for Oral Suspension, NDA 207027. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 JUL 14. ODS consult # 2015-492.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On September 13, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR Long-Term Care Advise-ERR
Search Strategy and Terms	Match Any of the Words: Promacta

D.2 Results

The search retrieved no relevant articles associated with label and labeling for Promacta.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Promacta labels and labeling submitted by Novartis.

- Instructions for Use received on July 25, 2018, July 31, 2018, August 17, 2018, and August 20, 2018
- Medication Guide received on July 25, 2018, July 31, 2018, August 17, 2018, and August 20, 2018
- Prescribing Information (Image not shown) received on July 25, 2018, July 31, 2018, August 17, 2018, and August 20, 2018

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LEEZA RAHIMI
09/24/2018

HINA S MEHTA
09/24/2018

U.S. FOOD & DRUG ADMINISTRATION

Neal S. Young, M.D.
National Institutes of Health
9000 Rockville Pike, Building 10 Room CRC 3-5142
10 Center Drive
Bethesda, MD 20892

Dear Dr. Young:

This letter informs you of the findings of a U.S. Food and Drug Administration (FDA) inspection conducted at your site between June 27, 2018, and July 2, 2018. Investigator David L. Chon, representing the FDA, reviewed your conduct of a clinical investigation (Protocol **ETB115AUS01T**, "Eltrombopag Added to Standard Immunosuppression in Treatment-Naïve Severe Aplastic Anemia") of the investigational drug Promacta® (eltrombopag), performed for Novartis Pharmaceuticals Corporation.

This inspection was conducted as a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects have been protected.

We have reviewed the FDA Establishment Inspection Report and the documents submitted with that report, and we did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance.

No response to this letter is necessary. However, if you have any questions or concerns about this letter or the inspection, please write to me at the address given below.

Sincerely,

{See appended electronic signature page}

CDR LaKisha Williams, USPHS
Regulatory Health Project Manager
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
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LAKISHA M WILLIAMS
11/20/2018

CLINICAL INSPECTION SUMMARY

Date	July 30, 2018
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Hyon-Zu Lee Pharm.D., Clinical Analyst Kathy Robie Suh, M.D., Ph.D. Clinical Team Leader Kimberly Scott, R.N., B.S.N., Regulatory Project Manager Division of Hematology Products
NDA	022291 S-021
Applicant	Novartis Pharmaceuticals Inc.
Drug	eltrombopag
NME	No
Therapeutic Classification/Status	thrombopoietin receptor agonist (TPO)
Proposed Indication	Treatment of pediatric and adult aplastic anemia
Consultation Request Date	May 3, 2018
Summary Goal Date	August 29, 2018 (Priority Review)
Action Goal Date	September 28, 2018
PDUFA Date	September 29, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

A single clinical site (Dr. Neal Young) was selected by the Division of Hematology Products (DHP) for inspection in support of NDA 022291 S-021. The study data from this clinical site, as reported by the sponsor to the BLA, is considered to be reliable in support of the requested indication.

The final inspectional classification of Dr. Young is No Action Indicated.

2. BACKGROUND

Severe aplastic anemia (SAA) is a life-threatening bone marrow failure disorder characterized by pancytopenia and a hypocellular bone marrow. Allogeneic bone marrow transplantation offers the opportunity for cure in younger patients, but most are not suitable candidates for transplantation due to advanced age or lack of a histocompatible donor. Comparable long-term survival in SAA is attainable with immunosuppressive treatment with horse anti-thymocyte globulin (h-ATG) and cyclosporine (CsA). However, of those patients treated with h-ATG/CsA, up to 40% of responders relapse.

Eltrombopag is a hematopoietic thrombopoietin receptor agonist (TPO), orignally approved for the treatment of immune thrombocytopenia. For this supplement, the applicant proposes eltrombopag in combination with standard immunosuppressive therapy for the treatment of adult and pediatric patients two years of age and older with severe aplastic anemia as a first-line treatment.

A single study forms the basis for the regulatory decision making process for this application supplement.

ETB115AUS01T

ETB115AUS01T was a non-randomized, single-arm, single-center, Phase 1 to Phase 2 pilot study investigating eltrombopag as experimental therapy in combination with immunosuppressive therapy (IST) of h-ATG + CsA, in subjects with severe aplastic anemia (SAA) who have not received prior definitive IST. The primary study objective was to evaluate the safety and activity profile of eltrombopag in combination with horse anti-thymocyte globulin (h-ATG) and cyclosporine A (CsA) in treatment naïve SAA. Those with aplastic anemia who were entered into the study had bone marrow cellularity < 30%. Two of these three additional laboratory criteria were also required: (1) absolute neutrophil count (ANC) < 500/µL, (2) platelet count < 20x103/µL, or (3) absolute reticulocyte count < 60x103/µL. The primary study endpoint is complete response rate at six months.

A total of 124 subjects (Cohort 1: N=31; Cohort 2: N=31; Cohort 3: N=31 and Extension Cohort: N=31) were enrolled; 123 study subjects were analyzed:

The first patient was enrolled on (b) (6). The study is ongoing.

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	Protocol #/ Site #/# Subjects enrolled	Inspection Dates	Classification
Dr. Neal Young Warren Grant Magnuson Clinical Center Building 10 CRC 3E-5140 10 Center Drive, MSC 1202 NIH Bethesda, Maryland 20892-1202	ETB115AUS01T Site # 1 (single center study) 161 enrolled (124 enrolled prior to cutoff date of 9/30/16)	June 27 to July 2, 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
* Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Investigator

1. Neal Young, MD

A total of 161 subjects were screened and were enrolled. The study is ongoing for this five year follow-up study.

The inspection evaluated the following documents: protocol and amendments, source records, enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents, IRB correspondence, and sponsor-generated correspondence were also inspected.

Source documents for 12 enrolled subjects were reviewed comprehensively. Review included documentation of informed consent, eligibility criteria, electronic medical records, and safety reporting. A total of 60 subject records were reviewed and verified against the case report forms and NDA subject data line listings for the primary efficacy endpoint. Source data for the following laboratory endpoints were verified: ANC, absolute reticulocyte counts, platelet counts, hemoglobin, transfusion dates, and sample dates. Random records were reviewed and verified for reported SAEs and protocol deviations, under-reporting of AEs or protocol deviations There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

{See appended electronic signature page}

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