Clinical trials of 2 oral TPO-RAs in ITP[1,2]:

- PROMACTA® (eltrombopag): Persistent or chronic
- Doptelet® (avatrombopag): Chronic

ITP, immune thrombocytopenia; TPO-RAs, thrombopoietin receptor agonists.
DOPTELET is a registered trademark of AkaRx, Inc.

Indication and Important Safety Information

Indication for PROMACTA® (eltrombopag)

PROMACTA is indicated for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with persistent or 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.

Limitations of Use

PROMACTA is not indicated for the treatment of patients with myelodysplastic syndromes (MDS).

Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection.

Important Safety Information for PROMACTA® (eltrombopag)

WARNING: RISK FOR 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.

RISK OF HEPATOTOXICITY
PROMACTA may increase the risk of severe and potentially life-threatening hepatotoxicity. Monitor hepatic function and discontinue dosing as recommended.

Please see additional Important Safety Information for PROMACTA throughout, and click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

PROMACTA® (eltrombopag)
12.5mg, 25mg, 50mg, 75mg tablets
12.5mg, 25mg oral suspension

Overview of clinical trials

Adult and pediatric pivotal trials[1-12]

	PROMACTA® (eltrombopag)	Doptelet® (avatrombopag)*
Total adult	730 adult patients with persistent or chronic ITP[1]	205 adult patients with chronic ITP[6-8,12]
Short term (28 days-6 months)[3-8]	• TRA100773A (N=117, phase 2)[3] • TRA100773B (N=114, phase 3)[4] • RAISE (N=197, phase 3)[5]	• NCT00441090 (phase 2)[6] – Core study (N=64)[6] – Rollover study NCT00625443 (N=53 patients who completed 28 days in core study)[7] • NCT01438840 (phase 3)[8] – Core study (N=49)[8]
Long term (>1 year)[1,8]	• EXTEND long-term study (N=302, phase 3)[11]	– Extension phase (n=39)[12]
Total pediatric	159 pediatric patients with persistent or chronic ITP[1]	0 pediatric patients with chronic ITP[2,6-8,12]
Pediatric (31 weeks and 37 weeks)[9,10]	• PETIT (N=67, phase 2)[9] • PETIT 2 (N=92, phase 3)[10]	• N/A[2,6-8,12]
Total patients studied	• 889[1]	• 205[2,6-8,12]

The products shown here are not interchangeable. No conclusion regarding comparative safety or efficacy can be drawn from this information.

*Avatrombopag is indicated for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to previous treatment.[2]

Important Safety Information for PROMACTA® (eltrombopag) (continued)

Hepatotoxicity

PROMACTA may increase the risk of severe and potentially life-threatening hepatotoxicity.

Treatment of ITP, chronic hepatitis C, and refractory severe aplastic anemia

- Measure serum alanine aminotransferase (ALT), aspartate aminotransferase (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 UGT1A1 and OATP1B1, 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 ≥3 times the upper limit of normal in patients with normal liver function or ≥3 times baseline in patients with pretreatment elevations in transaminases and are progressively increasing; or persistent for ≥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 outweighs 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

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Design of 6-month trials

Six-month randomized, double-blind, placebo-controlled studies in adult patients[1,12]

	PROMACTA® (eltrombopag) RAISE, NCT00370331[1,5,13,14]	Doptelet® (avatrombopag) NCT01438840 (Core Study)[8,12]
Population	Total: N=197 → PROMACTA: n=135, Placebo: n=62 75 sites in 23 countries, including the US	Total: N=49 → Avatrombopag: n=32, Placebo: n=17 27 sites in 11 countries, excluding the US
Inclusion criteria		
Baseline platelet count	• <30,000/mcL	• <30,000/mcL
Prior ITP therapies	• ≥1	• ≥1
Exclusion criteria	• Previous PROMACTA study participation • Cardiovascular disease • History of arterial or venous thrombosis, in the presence of ≥2 additional risk factors • Chronic or active hepatitis • Concurrent malignant disease and/or history of cancer treatment with cytotoxic chemotherapy and/or radiotherapy • Evidence of HIV infection	• Gastric atrophy • Cardiovascular disease • Arterial or venous thrombosis • Secondary ITP • Active chronic hepatitis • Cirrhosis • Malignant disease • Myelodysplastic syndromes • Pernicious anemia • Portal hypertension • Use of romiplostim or eltrombopag within 4 weeks of randomization
Baseline characteristics		
Patients with history of splenectomy, %	• 37% for eltrombopag; 34% for placebo	• 34% for avatrombopag; 29% for placebo
Patients receiving concomitant ITP medications, %	• 47% for eltrombopag; 50% for placebo	• 47% for avatrombopag; 41% for placebo
Patients who received ≥5 prior ITP therapies, %	• 26% for eltrombopag; 18% for placebo	• ~30% (prior medications only)
Primary end point	• Odds of response (platelet count ≥50,000/mcL to ≤400,000/mcL) to PROMACTA vs placebo	• Median cumulative weeks of platelet response (≥50,000/mcL) in the absence of rescue therapy (Week 1 through Week 26)
Secondary end points	• Median platelet counts (Day 8 through Week 26) • Percentage of patients requiring rescue therapy (Day 1 through Week 26) • Maximum and total weeks of platelet response (Day 1 through Week 26) • Percentage of patients with a reduction in use of concomitant ITP medication (Day 1 through Week 26) • Severity of bleeding events on the WHO Bleeding Scale • Patient-reported HRQoL outcomes (through Week 26)	• Proportion of patients with a response at Day 8 • Proportion of patients with a reduction in use of concomitant ITP medication (Week 1 through Week 26)

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HRQoL, health-related quality of life; WHO, World Health Organization.

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Design of trials longer than 1 year

Single-arm, open-label extension studies in adult patients[1,12]

	PROMACTA® (eltrombopag) EXTEND, NCT00351468[1,11,15]	Doptelet® (avatrombopag) NCT01438840 (Extension Phase)[8,12]
Population	PROMACTA: N=302	Avatrombopag: n=39
Length of study	• 7 years	• 1.5 years
Inclusion criteria	• Adults with ITP who had previously been enrolled in TRA100773A, TRA100773B, RAISE, or REPEAT	• Adults with ITP who had previously been enrolled in the NCT01438840 core study
Exclusion criteria	• Patients who had experienced drug intolerance or toxicity related to eltrombopag in their previous study	• Patients with significant safety or tolerability concerns related to avatrombopag in the core study
Primary end point	• Safety and tolerability parameters	• Safety and tolerability parameters
Secondary end points	• Percentage of patients with a platelet count ≥30,000/mcL or ≥50,000/mcL in the absence of rescue medication • Percentage of patients who responded to eltrombopag in a previous study and who respond to retreatment with a rise in platelet count to either ≥30,000/mcL or ≥50,000/mcL • Percentage of patients with a reduction in use of concomitant ITP medications • Percentage of patients requiring rescue therapy • Maximum bleeding score at any time during the study • Best postbaseline change in HRQoL	• Median platelet count • Percentage of patients requiring use of rescue therapy • Severity of bleeding events on the WHO Bleeding Scale

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Design of a head-to-head comparison of PROMACTA and Doptelet (study 305)

Six-month randomized noninferiority study[16,17]

	PROMACTA® (eltrombopag)	Doptelet® (avatrombopag)
Population N=23	n=11	n=12
Mean duration of drug exposure, weeks	10.5	15.6

Baseline characteristics

The 2 treatment arms were similar with regard to:

- Age
- Sex
- Ethnicity
- Baseline platelet count
- Splenectomy status
- Use of concomitant ITP medications

The trial was stopped early due to enrollment challenges and a limited study population.[16]

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Important Safety Information (continued)

Important Safety Information for PROMACTA® (eltrombopag) (continued)

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
- Portal vein thrombosis has been reported in patients with chronic liver disease receiving PROMACTA
- 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

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

- In a clinical trial of patients with intermediate- to high-risk MDS and thrombocytopenia receiving PROMACTA, an increased number of progressions from MDS to AML and deaths have been observed compared to placebo
- PROMACTA is not indicated for the treatment of patients with MDS

Cataracts

- Development or worsening of cataracts with PROMACTA has been reported with a frequency of 5% to 11% in 6 clinical studies
- Perform a baseline ocular examination prior to initiating PROMACTA. Regularly monitor patients for signs and symptoms of cataracts while on PROMACTA

Laboratory Monitoring

- Monitor serum liver tests
- During therapy with PROMACTA, assess complete blood counts (CBCs) with differentials, including platelet counts, weekly until a stable platelet count has been achieved. Monitor platelet counts monthly thereafter
- Obtain CBCs with differentials, including platelet counts, weekly for at least 4 weeks following discontinuation of PROMACTA
- When switching between the oral suspension and tablet, assess platelet counts weekly for 2 weeks, then follow standard monthly monitoring

Drug/Drug and Drug/Food Interactions

- PROMACTA must be taken 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
- Take PROMACTA without a meal or with a meal low in calcium (≤50 mg)

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.

The most common adverse reactions in 3 placebo-controlled clinical trials in patients with persistent or chronic ITP (≥3% and greater than placebo) for PROMACTA were nausea (9%), diarrhea (9%), upper respiratory tract infection (7%), vomiting (6%), increased ALT (5%), myalgia (5%), urinary tract infection (5%), oropharyngeal pain (4%), increased AST (4%), pharyngitis (4%), back pain (3%), influenza (3%), paresthesia (3%), and rash (3%).

The most common adverse reactions in 2 placebo-controlled clinical trials in patients with persistent or chronic ITP 1 year and older (≥3% and greater than placebo) for PROMACTA were upper respiratory tract infection (17%), nasopharyngitis (12%), cough (9%), diarrhea (9%), pyrexia (9%), abdominal pain (8%), oropharyngeal pain (8%), toothache (6%), ALT increased (6%), rash (5%), AST increased (4%), and rhinorrhea (4%).

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PROMACTA® (eltrombopag)
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