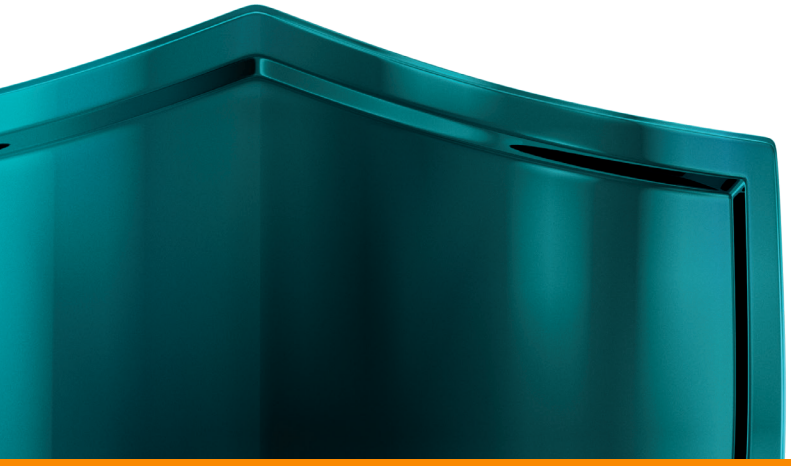


TAVALISSE AS SECOND-LINE THERAPY FOR IMMUNE THROMBOCYTOPENIA

Published in the *British Journal of Haematology*—
"Fostamatinib is an effective second-line therapy in patients with immune thrombocytopenia [ITP]"

A post hoc analysis of the TAVALISSE trial population by line of therapy

Boccia R, Cooper N, Ghanima W, et al. *Br J Haematol*. In press. Published online July 23, 2020. doi:10.1111/bjh.16959.

To view this publication online, visit

TAVALISSE2L.com

Indication

TAVALISSE is indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

Select Important Safety Information

Warnings and Precautions

· Hypertension can occur with TAVALISSE treatment. Patients with pre-existing hypertension may be more susceptible to the hypertensive effects. Monitor blood pressure every 2 weeks until stable, then monthly, and adjust or initiate antihypertensive therapy for blood pressure control maintenance during therapy. If increased blood pressure persists, TAVALISSE interruption, reduction, or discontinuation may be required.

Please see additional Important Safety Information throughout, complete Important Safety Information on the back cover, and accompanying full Prescribing Information.

Tavalisse®
(fostamatinib disodium hexahydrate) tablets

THE FIT-1, FIT-2, AND FIT-3 PHASE 3 CLINICAL TRIALS ASSESSED EFFICACY, SAFETY, AND DURABILITY[1,2]

The Fostamatinib in ITP (FIT) Program was designed to evaluate short- and long-term treatment effects, with an open-label extension study that followed 2 double-blind, placebo-controlled studies of 150 adults with chronic immune thrombocytopenia (ITP).[1]

Primary endpoint—stable response: 17%[2-4,*]

- Median post-baseline platelet count: 97 x 10^9/L
- Platelet counts ≥50 x 10^9/L during weeks 14-24 (at least 4 of 6 consecutive visits)

Post hoc endpoint—overall response: 43%[1,4,†]

- Median post-baseline platelet count: 49 x 10^9/L
- At least one platelet count ≥50 x 10^9/L during weeks 0-12

A post hoc analysis was conducted to evaluate patient response by line of therapy[‡]

In these studies of patients who had received ≥1 prior therapy, 32 of 145 patients received fostamatinib as 2nd-line therapy following steroids with or without immunoglobulins. The remaining patients received fostamatinib as 3rd-or-later-line therapy.

The 2 groups differed not only in number of prior therapies, but also in duration of ITP, proportion with persistent ITP, and baseline platelet count. Patients were representative of the general adult chronic ITP population, including exposure to prior therapies.

- Platelet response was assessed by the proportion of patients achieving platelet counts of ≥50 x 10^9/L and of ≥30 x 10^9/L at any visit (without rescue therapy within 4 weeks)
- Durability of response was calculated as the percentage of treatment days patients maintained their response, measured from the date of a qualifying platelet count to loss of response[§]

Select Important Safety Information

Warnings and Precautions (continued)

- Elevated liver function tests (LFTs), mainly ALT and AST, can occur with TAVALISSE. Monitor LFTs monthly during treatment. If ALT or AST increase to >3 x upper limit of normal, manage hepatotoxicity using TAVALISSE interruption, reduction, or discontinuation.

Please see additional Important Safety Information throughout, complete Important Safety Information on the back cover, and accompanying full Prescribing Information.

From the 2nd-line analysis of fostamatinib published in the *British Journal of Haematology*

The dominant pathophysiology of ITP involves autoantibody-mediated phagocytosis of platelets by macrophages through the Fcγ receptor complex, which requires signaling through SYK [spleen tyrosine kinase]. SYK-signaling in B cells and dendritic cells may also contribute to disease pathophysiology....

We hypothesize that early treatment of ITP with SYK inhibition may interrupt disease progression by blocking phagocytosis of antibody-coated platelets and thus subsequent events.

In the 2019 update of the International Consensus Report on ITP,

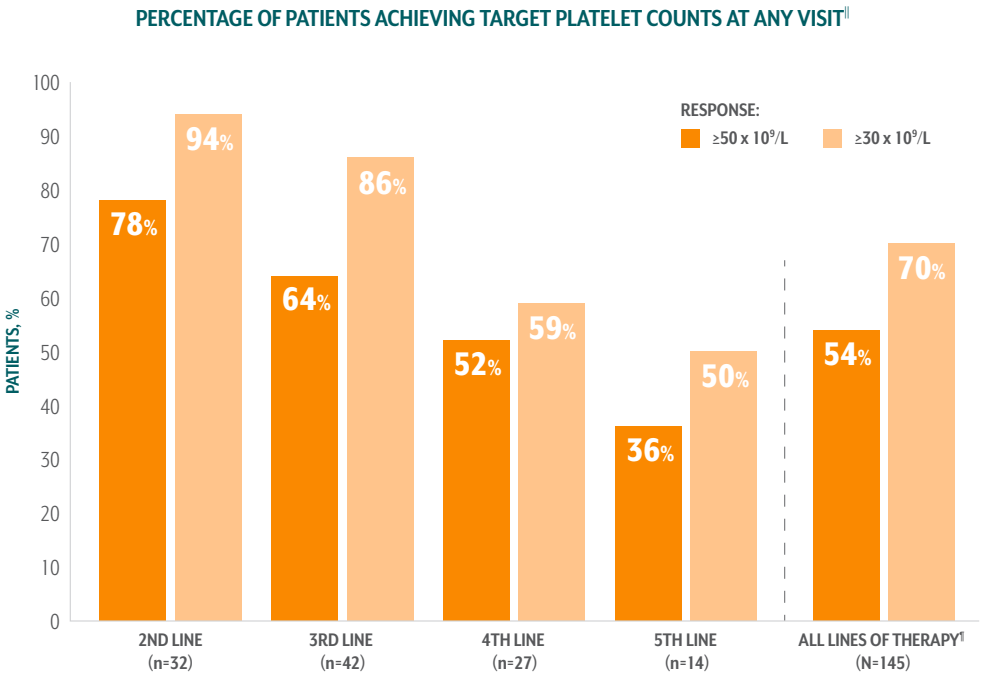
Fostamatinib is endorsed as a second-line treatment for adult chronic ITP

The clinical goals should be to resolve bleeding events or to prevent severe bleeding... [and] the platelet count should be improved to attain a minimum of 20 to 30 x 10^9/L....[5]

Additional references: 1. Bussel J, Arnold DM, Grossbard E, et al. Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: results of two phase 3, randomized, placebo-controlled trials. *Am J Hematol*. 2018;93(7):921-930. **2.** Bussel JB, Arnold DM, Boxer MA, et al. Long-term fostamatinib treatment of adults with immune thrombocytopenia during the phase 3 clinical trial program. *Am J Hematol*. 2019;94(5):546-553. **3.** TAVALISSE® [package insert]. South San Francisco, CA: Rigel Pharmaceuticals, Inc.; April 2018. **4.** Data on file, Rigel Pharmaceuticals, Inc. April 2018. **5.** Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. *Blood Adv*. 2019;3(22):3780-3817.

USE OF FOSTAMATINIB AS 2ND-LINE THERAPY RESULTED IN HIGHER RESPONSE RATES

The response to fostamatinib was seen in patients across all lines of therapy



Higher response rates were seen in patients exposed only to steroids (with or without immunoglobulins) prior to receiving fostamatinib

Time to response (platelet count ≥50 x 10^9/L) in responders to fostamatinib:

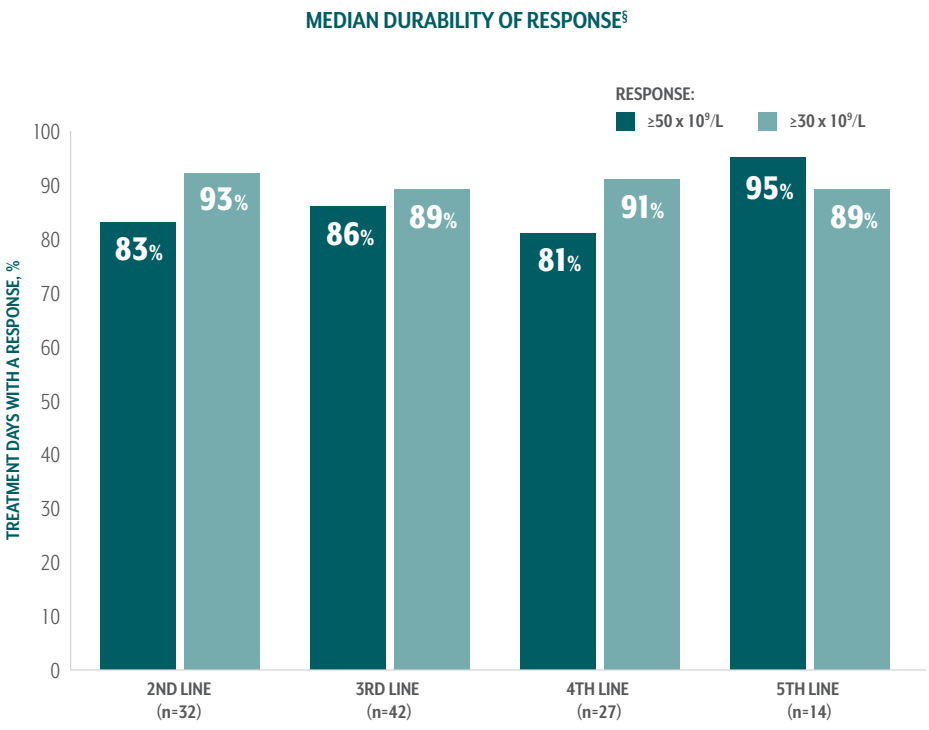
- **56%** of 2nd-line patients responded within 4 weeks
- **76%** of 2nd-line patients responded within 12 weeks
- **81%** of patients across all lines of therapy responded within 12 weeks

"Non-responders were more likely to have received more treatments and have a longer duration of ITP...."

*Stable platelet response: achievement of a platelet count ≥50 x 10^9/L on ≥4 of the 6 visits during weeks 14-24 without need for rescue treatment.
†Overall response: achievement of a platelet count ≥50 x 10^9/L at least once during the first 3 months/12 weeks without need for rescue treatment.
‡Data cutoff date: December 2019.
§Durability of response: median percentage of treatment days that patients maintained a response of ≥50 x 10^9/L or ≥30 x 10^9/L, with loss of response at the first of two platelet counts ≤30 x 10^9/L or ≤20 x 10^9/L, respectively, at least 4 weeks apart, or use of rescue therapy.
‖Platelet response was assessed by the proportion of patients achieving platelet counts of ≥50 x 10^9/L and of ≥30 x 10^9/L at any visit (without rescue therapy within 4 weeks).
¶Percentage of patients achieving platelet counts of ≥30 x 10^9/L calculated using data on file.[4]

RESPONSE WAS MAINTAINED FOR THE MAJORITY OF TIME ON THERAPY

This analysis measured the percentage of treatment days that patients maintained their response



The majority of 2nd-line patients with platelet counts ≥50 x 10^9/L maintained their response for >36 months

"Although rates of response varied, response, once achieved, was maintained (durable) irrespective of number of prior lines of therapy."

ADVERSE EVENTS

Rates among patients in these subgroups were consistent with those in patients in the placebo-controlled trials

- The most common adverse events, including those classified as severe, were similar between 2nd-line and later-line patients
- Bleeding events were less frequent in second-line (28%) versus later-line (45%) patients

INDICATION AND IMPORTANT SAFETY INFORMATION

Indication

TAVALISSE is indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

Important Safety Information

Warnings and Precautions

- Hypertension can occur with TAVALISSE treatment. Patients with pre-existing hypertension may be more susceptible to the hypertensive effects. Monitor blood pressure every 2 weeks until stable, then monthly, and adjust or initiate antihypertensive therapy for blood pressure control maintenance during therapy. If increased blood pressure persists, TAVALISSE interruption, reduction, or discontinuation may be required.
- Elevated liver function tests (LFTs), mainly ALT and AST, can occur with TAVALISSE. Monitor LFTs monthly during treatment. If ALT or AST increase to >3 x upper limit of normal, manage hepatotoxicity using TAVALISSE interruption, reduction, or discontinuation.
- Diarrhea occurred in 31% of patients and severe diarrhea occurred in 1% of patients treated with TAVALISSE. Monitor patients for the development of diarrhea and manage using supportive care measures early after the onset of symptoms. If diarrhea becomes severe (≥Grade 3), interrupt, reduce dose or discontinue TAVALISSE.
- Neutropenia occurred in 6% of patients treated with TAVALISSE; febrile neutropenia occurred in 1% of patients. Monitor the ANC monthly and for infection during treatment. Manage toxicity with TAVALISSE interruption, reduction, or discontinuation.
- TAVALISSE can cause fetal harm when administered to pregnant women. Advise pregnant women the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose. Verify pregnancy status prior to initiating TAVALISSE. It is unknown if TAVALISSE or its metabolite is present in human milk. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during TAVALISSE treatment and for at least 1 month after the last dose.

Drug Interactions

- Concomitant use of TAVALISSE with strong CYP3A4 inhibitors increases exposure to the major active metabolite of TAVALISSE (R406), which may increase the risk of adverse reactions. Monitor for toxicities that may require a reduction in TAVALISSE dose.
- It is not recommended to use TAVALISSE with strong CYP3A4 inducers, as concomitant use reduces exposure to R406.
- Concomitant use of TAVALISSE may increase concentrations of some CYP3A4 substrate drugs and may require a dose reduction of the CYP3A4 substrate drug.
- Concomitant use of TAVALISSE may increase concentrations of BCRP substrate drugs (eg, rosuvastatin) and P-Glycoprotein (P-gp) substrate drugs (eg, digoxin), which may require a dose reduction of the BCRP and P-gp substrate drug.

Adverse Reactions

- Serious adverse drug reactions in the ITP double-blind studies were febrile neutropenia, diarrhea, pneumonia, and hypertensive crisis, which occurred in 1% of TAVALISSE patients. In addition, severe adverse reactions occurred including dyspnea and hypertension (both 2%), neutropenia, arthralgia, chest pain, diarrhea, dizziness, nephrolithiasis, pain in extremity, toothache, syncope, and hypoxia (all 1%).
- Common adverse reactions (≥5% and more common than placebo) from FIT-1 and FIT-2 included: diarrhea, hypertension, nausea, dizziness, ALT and AST increased, respiratory infection, rash, abdominal pain, fatigue, chest pain, and neutropenia.

Please see accompanying full Prescribing Information.

To report side effects of prescription drugs to the FDA, visit www.fda.gov/medwatch or call 1-800-FDA-1088 (1-800-332-1088).

LEARN MORE ABOUT THE CLINICAL BENEFIT OF TAVALISSE AT **TAVALISSEhcp.com**

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