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Sustained response off-treatment and thrombotic events in patients with immune thrombocytopenia treated with fostamatinib: a systematic review and meta-analysis

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Running head: Safety and efficacy of fostamatinib use in ITP

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Immune thrombocytopenia (ITP) is an acquired condition characterized by low platelet counts and a paradoxical thrombotic risk, with a potential for long-term remission following treatment. For this reason, there has been increasing interest in the thrombotic risk and chances of remission associated with ITP-specific treatments. Fostamatinib, an oral Syk inhibitor, has recently become available for the treatment of ITP.[1,2] Although some studies have shown the possibility of obtaining a sustained response off-treatment (SROT) in a subset of patients on fostamatinib,[3–5] the magnitude of this phenomenon is still not well understood. Recent research has detected a very low thrombotic event rate in users of fostamatinib.[6] However, data on this novel drug are still scarce. We have carried out a systematic review to investigate the rates of (1) SROT and (2) thrombosis of fostamatinib users.

We searched Medline and Embase up to September 17th, 2025, using a pre-defined research string ["Fostamatinib AND ((Immune Thrombocytopenic Purpura) OR (Autoimmune Thrombocytopenia) OR (Werlhof Disease) OR (Thrombocytopenia) OR (Thrombocytopenic))"] and a snowball strategy. Eligibility assessment was performed independently by two reviewers (S.S., C.M). Disagreements were solved by consensus or by a third reviewer (B.C.). We included peer-reviewed published studies in English describing adult ITP patients with known fostamatinib treatment status and available data on at least one of the primary outcomes. We excluded case series describing fewer than 5 patients. The primary efficacy outcome was the cumulative rate of SROT, extracted as study-defined SROT (fostamatinib discontinuation with sustained safe platelet counts). Study definitions are summarized in **Supplemental Table 1**. The primary safety outcome was the cumulative rate of thrombotic events, defined as any fatal or non-fatal thrombosis, either in the arterial or venous district. Secondary outcomes included the rates of arterial and venous thrombotic events analyzed separately. The diagnosis of ITP was based on

the authors' judgment. Data extraction was performed independently by two reviewers (S.S., C.M.) using a pre-defined electronic case report form (eCRF) set up on Microsoft Excel. We analyzed data from observational studies and randomized controlled trials (RCTs) separately. Categorical data were expressed as counts and percentages, with 95% confidence intervals (CI) calculated with the exact binomial method (GraphPad Prism 10). Where necessary, we performed data conversions (*e.g.*, years or days to months). We compared categorical data using the Fisher's exact test and chi square test, as appropriate. The assessment of the risk of bias was performed independently by B.C. and C.M. using the RoB2 tool for RCTs and the ROBINS-I version 2 tool for observational studies, with results visualized using the *robvis* tool. We performed meta-analysis of data using the random intercept logistic regression model and logit transformation; heterogeneity was measured using the I^2 statistic and the Wald test (R Core Team software, 2023). We performed a *post-hoc* subgroup analysis, comparing the frequency of SROT between patients with primary and secondary ITP. Two-tailed p-values <0.05 were considered statistically significant. Institutional review board approval was not required. The study conduct was in accordance with the declaration of Helsinki.

We retrieved 630 studies, with 11 studies (9 observational studies and 2 RCTs) included in the final analysis (**Figure 1**). Three studies provided data on SROT and ten on thrombosis. Altogether, the eligible studies reported on SROT for 294 patients and thrombosis for 613 patients, for a total of 674 individual adults with ITP treated with fostamatinib (123 in RCTs and 551 in observational studies). Additionally, 61 patients received placebo in the context of RCTs. Eligible patients' characteristics are detailed in **Supplemental Table 2**.

Among 294 patients treated with fostamatinib in observational studies (166 females, 21 patients with secondary ITP and 216 with chronic ITP), SROT was reported in 14 patients (meta-analyzed frequency: 5%, 95% CI 2-10; I^2 71%, p=0.04) over a median

follow-up since discontinuation, based on available data, of 263 days (IQR, 247-313) (**Table 1;** see **Supplemental Table 1** for SROT definitions). SROT was not reported in any of the eligible RCTs. There were no significant differences in the rates of SROT of primary and secondary ITP patients (primary: 11/183, 6%, 95% CI 3-11; secondary: 1/15, 7% 95% CI 0-32; *p*=1). The causes of secondary ITP, as reported by the authors, were lymphoproliferative disorders (n=4), monoclonal gammopathy of undetermined significance (MGUS; n=3), immune deficiency (n=3), systemic lupus erythematosus (n=2), antiphospholipid antibody syndrome (n=2) and COVID-19 (n=1). The patient with secondary ITP who achieved SROT had ITP secondary to MGUS.

Among 490 patients treated with fostamatinib in observational studies (55% females, 21 patients with secondary ITP and 337 patients with chronic ITP), 5 patients developed thrombosis over a follow-up ranging from 4 to 60 months (meta-analyzed frequency: 1%, 95% CI 0-2; I^2=0%, *p*=0.94) (**Table 2**). In the 2 eligible RCTs, none of the patients treated with fostamatinib or placebo (all with primary ITP) developed thrombosis throughout a study duration of 6 months (meta-analyzed frequency for fostamatinib: 0%, 95% CI 0-100; I^2=0%; *p*=1) (**Table 2**). Among the 490 patients treated with fostamatinib in observational studies, the meta-analyzed frequencies of arterial and venous thrombosis were low and comparable (**Supplemental Table 3**). None of the RCT patients developed arterial or venous thrombosis (**Supplemental Table 3)**.

All observational studies eligible for SROT and six of the observational studies eligible for thrombosis were at critical risk of bias due to uncontrolled confounding of treatment selection. The remaining two observational studies, both extension cohorts of previous RCTs, were considered at serious risk of bias due to confounding (**Supplemental Figure 1**). Results on thrombosis remained consistent considering only studies at lower risk of bias (**Supplemental Table 4**). The two RCTs eligible for the analysis of thrombosis displayed some concerns regarding the presence of bias (**Supplemental Figure 1**).

In our systematic review of published studies, we have found that the cumulative frequency of thrombosis is low and that a non-negligible proportion of treated patients may achieve a lasting SROT upon discontinuation of fostamatinib. Direct comparisons of our results with data on other ITP treatments are impossible. Moreover, data on SROT are significantly limited by the few eligible studies and heterogeneity in how drug discontinuation was reported and achieved. Nevertheless, spontaneous remission of chronic ITP in adults occurs only sporadically. Splenectomy is a one-time intervention with a modest excess risk of infection and venous thromboembolism and reported durable remissions over 10-12 years.[7] Although thrombotic events have been reported in thrombopoietin receptor agonist (TPO-RA) users,[8] a meta-analysis from 2021 found no statistically significant increase in thrombosis among ITP patients treated with TPO-RAs.[9] On the other hand, following tapering and discontinuation of TPO-RAs, SROT has been reported in 25 to 32% of patients in prospective studies.[10,11] Responses to rituximab generally last one year. In an RCT of rituximab versus placebo 4% of patients receiving rituximab experienced thrombosis versus none in the placebo group.[12]

The results of our study align with the mechanistic rationale for fostamatinib use, as fostamatinib selectively impairs immune-mediated platelet destruction without promoting prothrombotic pathways. Syk inhibition has been shown to inhibit platelet activation and thrombus formation without significantly impairing primary hemostasis[13] and may reduce the release of neutrophil extracellular traps[14] and contrast atherothrombosis. Moreover, Syk inhibition attenuates autoantibody and proinflammatory cytokine production, underscoring the possibility of obtaining a durable remission.[15] Taken together, our results suggest that fostamatinib may be a suitable option in patients at high thrombotic risk and support continued efforts to investigate optimal discontinuation strategies.

Our study has limitations. Firstly, the risk of bias of the eligible observational studies was at least serious due to uncontrolled confounding of treatment selection. Moreover,

because of the few retrieved results (<10 for each endpoint), we could not formally assess publication bias. Nevertheless, the analyzed studies capture real-world experience with fostamatinib, and we therefore pooled estimates to detect possible safety signals. Moreover, a sensitivity analysis including only observational studies at lower risk of bias yielded comparable results for thrombosis. Secondly, there was considerable heterogeneity in the duration of follow-up and the annualization of thrombosis rates was not possible. Finally, our results regarding SROT are limited by many factors. Firstly, we retrieved only three observational studies suitable for the analysis of SROT, resulting in high heterogeneity of the meta-analyzed data. This reflects the still limited and emerging experience with fostamatinib tapering and discontinuation strategies, based on prior studies on TPO-RAs. Finally, with the available data, we were only able to compute the frequency of SROT among all treated patients. This is probably the greatest factor limiting the clinical relevance of our findings: computing the rates of SROT over the number of patients who were considered candidates for drug tapering with the goal of discontinuation would have probably led to more clinically meaningful estimates.

The results of our systematic review, although limited by the low quality of eligible studies and by the heterogeneity of follow-up duration, show that treatment with fostamatinib is characterized by a favorable safety profile and by the possibility of obtaining remission in a non-negligible and possibly underestimated proportion of treated patients, supporting its use as a valuable second-line option for patients with ITP.

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Table 1. Sustained response-off treatment (SROT) in immune thrombocytopenia (ITP) patients treated with fostamatinib in observational studies

Sustained response off-treatment (SROT)			
Study	Patients with events/Patients	Rate (%, 95% CI)	I^2; p-value
Gonzàlez-López, 2024	5/138	4 (1-8)	
Mingot-Castellano, 2024	7/61	12 (5-22)	
Lucchini, 2025	2/95	2 (0-7)	
Pooled estimate	14/294	**5 (2-10)**	71%; 0.04

Abbreviations: CI, confidence interval.
Treatment duration prior to fostamatinib discontinuation was not available in the study by Gonzàlez-López et al: four of the 5 patients who achieved a sustained response off-treatment, however, had a complete response prior to discontinuation. In the study by Mingot-Castellano et al, patients were eligible for tapering and discontinuation of fostamatinib if they had a platelet count greater than $100x10^9$/L (complete response) for at least 6 months OR if they had a platelet count greater than $250x10^9$/L, irrespective of the duration of their complete response. In the study by Lucchini et al, two patients discontinued fostamatinib within 6 months of treatment initiation, while in response, without tapering the drug.
The median length of follow-up since discontinuation was 263 days (interquartile range, 247-313) in one study, and unavailable for the other two. The median duration of SROT, based on available data, was 9 months.

Table 2. Thrombosis in immune thrombocytopenia (ITP) patients treated with fostamatinib in observational studies and in randomized controlled trials

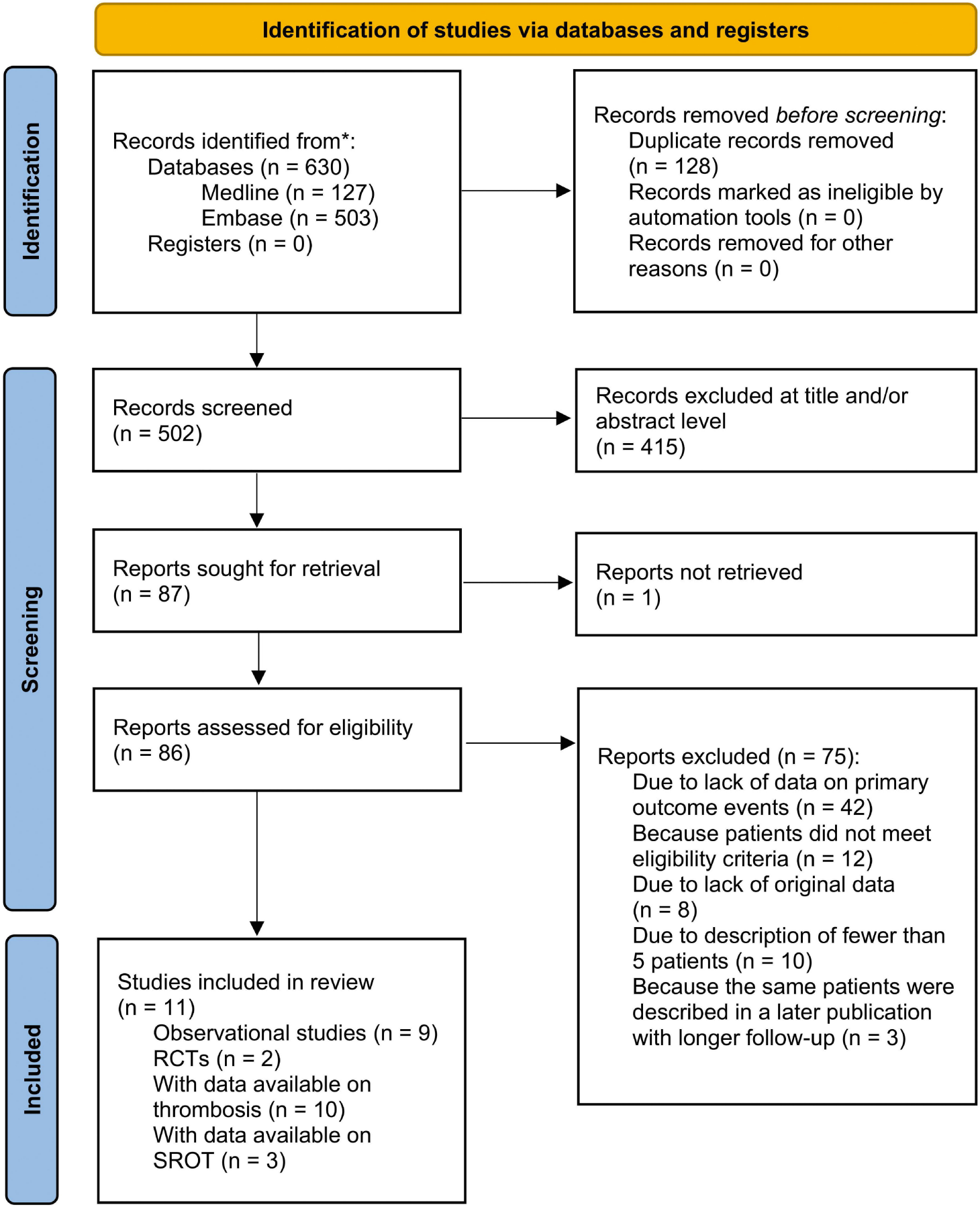
Thrombosis – Observational studies			
Study	Patients with events/Patients	Rate (%, 95% CI)	I^2; p-value
Lucchini, 2025	0/95	0 (0-4)	
Kuwana, 2025	0/22	0 (0-15)	
Gonzàlez-López, 2024	2/138	2 (0-5)	
Dranitsaris, 2024	2/51	4 (1-14)	
Mingot-Castellano, 2024	0/18	0 (0-19)	
Passucci, 2024	0/15	0 (0-22)	
Mehta, 2022	0/5	0 (0-52)	
Cooper, 2021	1/146	1 (0-4)	
Pooled estimate	5/490	**1 (0-2)**	**0%; 0.94**
Thrombosis – Randomized controlled trials			
Study	Patients with events/Patients	Rate (%, 95% CI)	I^2; p-value
Kuwana, 2025	0/22	0 (0-15)	
Bussel, 2018	0/101	0 (0-4)	
Pooled estimate	0/123	**0 (0-100)**	**0%; 1**

Abbreviations: CI, confidence interval.
The length of follow-up ranged from 4 to 60 months in observational studies, whereas treatment duration was 6 months in randomized controlled trials.
Regarding observational studies: the temporal association between thrombosis and fostamatinib treatment initiation was not consistently reported. The reported thrombotic events included 2 deep vein thromboses (DVT), 1 superficial vein thrombosis (SVT), 1 acute myocardial infarction (AMI) and 1 transient ischemic attack (TIA). Whenever specified, we considered thrombotic events eligible for the analysis only if occurred while on treatment with fostamatinib. The study by Lucchini et al reported a thrombotic event which occurred 5 months after discontinuation of fostamatinib and, thus, was not included in this analysis.

FIGURE LEGENDS

Figure 1. Flow-chart of study selection

Abbreviations: RCTs, randomized controlled trials; SROT, sustained response off-treatment


Identification of studies via databases and registers
Identification
Records identified from*:
Databases (n = 630)
Medline (n = 127)
Embase (n = 503)
Registers (n = 0)
Records removed *before screening*:
Duplicate records removed (n = 128)
Records marked as ineligible by automation tools (n = 0)
Records removed for other reasons (n = 0)
Screening
Records screened (n = 502)
Records excluded at title and/or abstract level (n = 415)
Reports sought for retrieval (n = 87)
Reports not retrieved (n = 1)
Reports assessed for eligibility (n = 86)
Reports excluded (n = 75):
Due to lack of data on primary outcome events (n = 42)
Because patients did not meet eligibility criteria (n = 12)
Due to lack of original data (n = 8)
Due to description of fewer than 5 patients (n = 10)
Because the same patients were described in a later publication with longer follow-up (n = 3)
Included
Studies included in review (n = 11)
Observational studies (n = 9)
RCTs (n = 2)
With data available on thrombosis (n = 10)
With data available on SROT (n = 3)

SUPPLEMENTARY DATA

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Supplemental Table 1. Operational definitions of sustained response off-treatment (SROT) across eligible studies

Eligible study	Provided definition of sustained response off-treatment
Gonzàlez-López, 2024	Successful and durable discontinuation of fostamatinib for over 9 months.
Mingot-Castellano, 2024	Possibility to discontinue chronic ITP treatment and maintain a safe platelet count for a prolonged period of time [not pre-specified].
Lucchini, 2025	N/A.

Abbreviations: N/A, not available.

Supplemental Table 2. Characteristics of eligible studies. Section A shows the characteristics of observational studies and Section B the characteristics of randomized controlled trials

Section A

Study	Country	Eligible patients (fostamatinib/ total)	Comparator	Length of treatment duration/ follow-up (months)	Females (n/N, %)	Age (years; median, IQR)	Primary ITP (n/N, %)	Disease duration (years; median)	Number of prior treatments (median, IQR)
	Observational studies with data available on thrombosis								
Kuwana, 2025	Japan	22/22	No	NA/ 36	NA	NA	22/22 (100%)	NA	NA
González-López, 2024	Spain	138/138	No	7 (median)/ 27	77/138 (56%)	66 (56-80)	123/138 (89%)	4.25	4 (2-5)
Dranitsaris, 2024	USA	51/179	Yes (TPO-RA)	3 (median)/ 42	NA	NA	NA	NA	NA
Mingot-Castellano, 2024	Spain, Norway	18/18*	No	NA/ 8.5 (median)	4/18 (22%)	60 (37-69)	NA	1.50	4.5 (4-7)
Passucci, 2024	Italy	15/15	No	4 (median)/ 4 (median)	9/15 (60%)	55 (50–63)	NA	20.3	4 (2-7)
Mehta, 2022	USA	5/5	No	12 (median)/ 12 (median)	1/5 (20%)	79 (63-82)	NA	NA	2 (1-4)
Cooper, 2021	North America, Australia, Europe	146/146	No	19 (mean)/ 60	88/146 (60%)	53 (20-88)	146/146 (100%)	8	3 (1-13)
Lucchini, 2025	Italy	95/95	No	7 (median)/ 6	56/95 (58%)	64 (21-86)	89/95 (93%)	7.7	4 (1-24)
	Observational studies with data available on SROT								
González-López, 2024	Spain	138/138	No	7 (median)/ 27	77/138 (56%)	66 (56-80)	123/138 (89%)	4.25	4 (2-5)
Mingot-Castellano, 2024	Spain	61/61	No	4 (median)/ 9 (median)	33/61 (54 %)	59 (49–78)	61/61 (100%)	1.50	4 (1-9)

Lucchini, 2025	Italy	95/95	No	7 (median)/ 6	56/95 (58%)	64 (21-86)	89/95 (93%)	7.7	4 (1-24)

Abbreviations: IQR, interquartile range; ITP, immune thrombocytopenia; NA, not available; USA, United States of America; TPO-RA, thrombopoietin receptor agonist; SROT, sustained response off-treatment.
*All patients were on a combination therapy with fostamatinib and avatrombopag.

Section B

Study	Country	Patients (fostamatinib/ total)	Comparator	Study duration (months)	Females (n/N, %)	Age (years; median, IQR)	Primary ITP (n/N, %)	Disease duration (years; median, IQR)	Number of prior treatments (median, IQR)
	Randomized controlled trial with data available on thrombosis								
Bussel, 2018	North America, Australia and Europe	101/150	Yes (placebo)	6	91/150 (61%)	NA	150/150 (100%)	NA	NA
Kuwana, 2023	Japan	22/34	Yes (placebo)	6	26/34 (76%)	63 (25-81)	34/34 (100%)	12 (1-41)	2 (1-10)

Abbreviations: IQR, interquartile range; ITP, immune thrombocytopenia; NA, not available.
None of the eligible randomized controlled trials had data available on sustained response off-treatment (SROT).

Supplemental Table 3. Arterial and venous thrombotic events in immune thrombocytopenia (ITP) patients treated with fostamatinib in observational studies and randomized controlled trials

Arterial thrombosis – Observational studies			
Study	Patients with events/Patients	Rate (%, 95% CI)	I^2; p-value
Lucchini, 2025	0/95	0 (0-4)	
Kuwana, 2025	0/22	0 (0-15)	
Gonzàlez-López, 2024	1/138	1 (0-4)	
Dranitsaris, 2024	0/51	0 (0-7)	
Mingot-Castellano, 2024	0/18	0 (0-19)	
Passucci, 2024	0/15	0 (0-22)	
Mehta, 2022	0/5	0 (0-52)	
Cooper, 2021	1/146	1 (0-4)	
Pooled estimate	2/490	**0 (0-2)**	**0%; 1**
Venous thrombosis – Observational studies			
Study	Patients with events/Patients	Rate (%, 95% CI)	I^2; p-value
Lucchini, 2025	0/95	0 (0-4)	
Kuwana, 2025	0/22	0 (0-15)	
Gonzàlez-López, 2024	1/138	1 (0-4)	
Dranitsaris, 2024	2/51	4 (1-14)	
Mingot-Castellano, 2024	0/18	0 (0-19)	
Passucci, 2024	0/15	0 (0-22)	
Mehta, 2022	0/5	0 (0-52)	
Cooper, 2021	0/146	0 (0-3)	
Pooled estimate	3/490	**0 (0-3)**	**0%; 0.96**
Arterial thrombosis – Randomized controlled trials			
Study	Patients with events/Patients	Rate (%, 95% CI)	I^2; p-value
Kuwana, 2025	0/22	0 (0-15)	
Bussel, 2018	0/101	0 (0-4)	
Pooled estimate	0/123	**0 (0-100)**	**0%; 1**
Venous thrombosis – Randomized controlled trials			
Study	Patients with events/Patients	Rate (%, 95% CI)	I^2; p-value
Kuwana, 2025	0/22	0 (0-15)	
Bussel, 2018	0/101	0 (0-4)	

Pooled estimate	0/123	**0 (0-100)**	**0%; 1**

Abbreviations: CI, confidence interval.

No significant differences were observed between the raw frequencies of patients with arterial and venous thrombotic events (p=0.65) in observational studies.

Supplemental Table 4. Sensitivity analysis of thrombosis in immune thrombocytopenia (ITP) patients treated with fostamatinib in observational studies at lower risk of bias

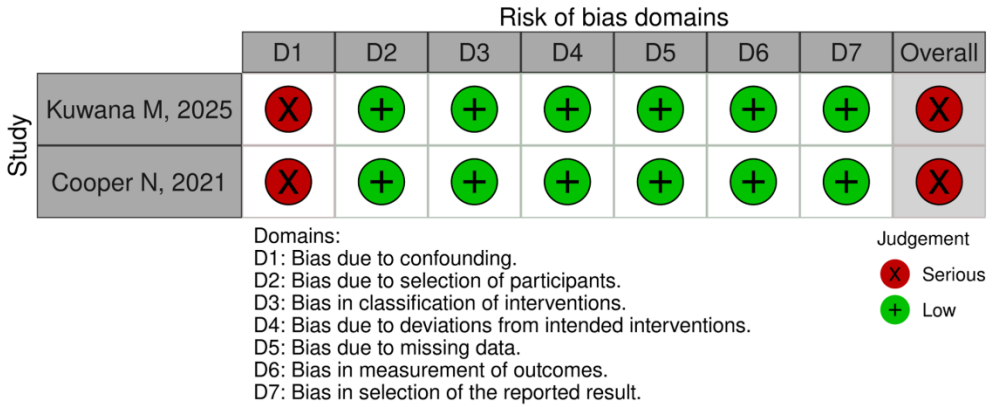
Thrombosis			
Study	Patients with events/Patients	Rate (%, 95% CI)	I^2; p-value
Kuwana, 2025	0/22	0 (0-15)	
Cooper, 2021	1/146	1 (0-4)	
Pooled estimate	1/168	**1 (0-4)**	**0%; 1**
Arterial thrombosis			
Study	Patients with events/Patients	Rate (%, 95% CI)	I^2; p-value
Kuwana, 2025	0/22	0 (0-15)	
Cooper, 2021	1/146	1 (0-4)	
Pooled estimate	1/168	**1 (0-4)**	**0%; 1**
Venous thrombosis			
Study	Patients with events/Patients	Rate (%, 95% CI)	I^2; p-value
Kuwana, 2025	0/22	0 (0-15)	
Cooper, 2021	0/146	0 (0-3)	
Pooled estimate	0/168	**0 (0-100)**	**0%; 1**

Abbreviations: CI, confidence interval.

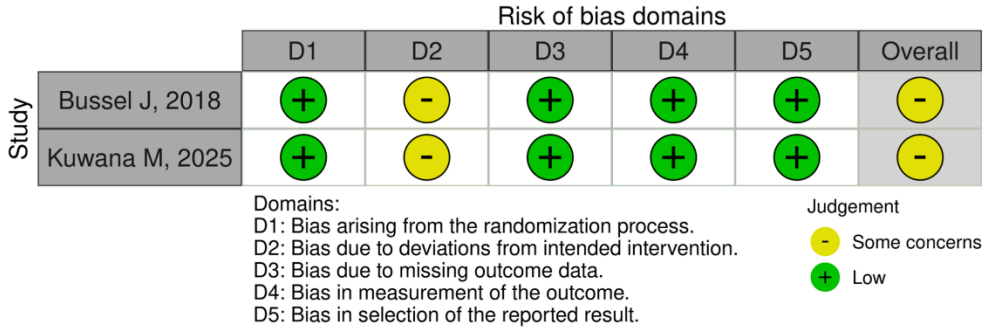
No significant differences were observed between the raw frequencies of patients with arterial and venous thrombotic events (p=0.32) in observational studies at lower risk of bias.

Supplemental Figure 1. Assessment of the risk of bias of the studies eligible for the evaluation of thrombosis in immune thrombocytopenia (ITP) patients treated with fostamatinib in observational studies and in randomized controlled trials

Panel A.
Risk of bias,
observational studies



Panel B.
Risk of bias,
randomized
controlled trials



Panel A visualizes data regarding observational studies and Panel B visualizes data regarding randomized controlled trials.
Risk of bias assessment was performed independently by two researchers using separate tools for observational studies (ROBINS-I version 2) and randomized controlled trials (RoB2).
Results of complete risk of bias assessments were visualized using the *robvis* tool.
In accordance with the instructions for the use of the ROBINS-I version 2 tool ("Decide whether to proceed with a risk-of-bias assessment"), all observational studies eligible for the analysis of sustained response off-treatment and six observational studies eligible for the analysis of thrombosis did not undergo a complete risk of bias assessment, because they displayed baseline critical risk of bias due to uncontrolled confounding.

Full references of the eligible studies

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