Fostamatinib: a review of its clinical efficacy and safety in the management of chronic adult immune thrombocytopenia

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Management of chronic immune thrombocytopenia (ITP) is going through a transition, with the main driving forces being a better understanding of the disease, recognition that platelet count is less important than bleeding symptoms, and the availability of new therapies. The heterogeneity of chronic ITP makes treatment challenging, and highlights the need for a personalized approach. A key aspect of tailored treatment is the availability of agents to target specific underlying pathophysiological mechanisms. In this review, we examine the evidence for orally bioavailable fostamatinib and its active moiety, taminib (R406), which has been approved for the treatment of chronic adult ITP. Fostamatinib inhibits FcR-triggered, Syk-dependent cytoskeletal rearrangement during phagocytosis and, as such, represents an active therapy targeting a previously unexplored mechanism of ITP pathogenesis.

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Immune thrombocytopenia (ITP) is an autoantibody-mediated heterogeneous disorder characterized by a low platelet count ($<100,000/\mu\text{L}$) in the absence of other causes for the bleeding [1]. At presentation it can be asymptomatic, mildly symptomatic (mucocutaneous lesions/bleeding) or serious/life-threatening (intracranial and gastrointestinal bleeding with complications) [2–4]. Estimates of the average annual prevalence of ITP have varied relatively widely, with Kistangari & McCrae reporting a range of 4 to 23.6 per 100,000 person/year in adults [5]. In individual studies, rates for the prevalence of ITP per 100,000 included: 9.5 [6]; 8.1 in children and 12.1 in adults [7]; and 23.6 in adults (with annual rates of 7.1 and 9.5/100,000 reported in 2 separate years) [8]. Overall, the incidence of ITP has generally been reported to be between two and four cases per 100,000 person-years [3,5,9]. In adults, the prevalence of ITP increases with age and may be slightly higher in women of reproductive age and older males [5,9,10]. The inflammatory biology and relapse/refractory nature of ITP pose both physical and psychosocial challenges to patients who have to live with the disease for prolonged periods. As such, ITP has a negative impact on the patient's quality of life (QoL), particularly with respect to physical functioning and mental health [11].

ITP is a chronic heterogeneous disease and medical therapy is rarely curative [5]. Initial treatment comprises corticosteroids with or without intravenous immunoglobulin (IVIg) or intravenous anti-D immune globulin (IV-anti-D). However, the majority of patients will eventually require alternative therapy as a result of poor tolerability or relapse [12]. This has resulted in an unmet need for alternative therapeutic options and the evaluation of a range medical therapies, as alternatives to splenectomy, including rituximab, the thrombopoietin-receptor agonists (TPO-RA) eltrombopag, avatrombopag and romiplostim, and fostamatinib, which is a recently approved spleen tyrosine kinase (Syk) inhibitor and the focus of this review.

The Syk signaling pathway has emerged as a potential new target for treatment of autoimmune diseases, including ITP. As platelet destruction in ITP is mediated by Syk-dependent phagocytosis of Fc γ R-bound platelets [13], Syk inhibition represents a promising approach to the management of ITP. Here, we update the findings from our

Figure 1. Pathogenesis of immune thrombocytopenia. ITP is an autoimmune disease caused by antiglycoprotein autoantibodies that deplete platelets via destruction and inhibition of megakaryocyte production of new platelets. Autoantibody-coated platelets bind to antigen-presenting cells through the FcR, leading to Syk-dependent platelet engulfment and destruction by macrophages. Activated macrophages and dendritic cells induce proliferation of platelet-reactive CD4⁺ Th cells and Treg cells, which together amplify the production of antiplatelet antibodies from activated B cells.

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GP: Glycoprotein; ITP: Immune thrombocytopenia; PLT: Platelet.

previous review which evaluated much of the preclinical and early clinical data on fostamatinib [14] and focus on the clinical evidence for this novel orally administered pro-drug which is approved as a treatment for chronic ITP in adults. For this narrative review, a search of PubMed up to 22 June 2020 using the search term 'fostamatinib' (n = 178) was conducted to identify relevant articles assessing the clinical use of fostamatinib in chronic/persistent ITP in adults, and this was augmented with articles known to the authors and relevant to this topic.

Pathogenesis of ITP

ITP is believed to occur as a consequence of defects in immune tolerance. Two major mechanisms contribute to the development of ITP: increased platelet destruction and insufficient platelet production. The pathophysiology of the disease is complex and not fully understood, although both antibody-mediated and/or T cell-mediated platelet destruction are key processes (Figure 1). A common view is that autoantibodies are produced which bind to glycoproteins on the surface of platelets and mark them for phagocytic breakdown in the spleen and liver

through an interaction with Fc γ receptors [2,3,14]. In addition, autoantibodies have been reported to increase complement-mediated or desialylation-induced platelet destruction, and also inhibit megakaryocyte production of new platelets [3]. However, as many as 30–40% of patients with ITP have no detectable antibodies and other mechanisms must be involved [2].

As noted in our previous review, alterations in B- and T-cell tolerance can result in clonal expansion of platelet-reactive antibodies that arise through somatic mutations and these changes in tolerance can occur centrally, during differentiation, or peripherally. The latter is thought to result in a platelet-specific disorder (primary ITP) that is more sensitive to therapy [15]. Furthermore, a skewed Th1/Th2 ratio with increased levels of IFN- γ , IL-2 and IL-17, and decreased peripheral Th2 and Treg cells have also been observed in patients with primary ITP [16–18]. These changes favor the survival of autoreactive T-cell clones and drive T-cell-dependent, antigen-driven clonal expansion and somatic mutations of autoantibodies in ITP [19].

Autoantibodies initially target platelet surface glycoproteins, primarily GPIIb/IIIa (integrin α IIb β 3) and GPIb/IX [20], but epitope spreading enables the production of antibodies against additional targets [21]. Following binding of autoantibodies to the platelet surface they are cleared by splenic macrophages through Fc γ R-mediated phagocytosis, although alternative mechanisms for platelet clearance (e.g., complement-dependent lysis) have been reported [22]. More recently, GPV has also been shown to be an immune target in ITP and anti-GPV autoantibodies are of clinical relevance since they were able to remove platelets from the circulation [23]. In addition, abnormalities in megakaryocyte proliferation and differentiation attributed to the presence of autoantibodies may also diminish platelet production [24].

The current therapeutic approaches for the treatment of ITP have been developed to target distinct events that occur along the pathogenetic pathway, either through inhibition of immunological events that promote destruction or inhibit development of platelets (e.g. steroids, intravenous immunoglobulin (IVIg), anti-D, fostamatinib, rituximab, immunosuppressive agents) or by promoting the production of new platelets (e.g. TPO-RA).

Treatment of adults with chronic ITP

The management of adult patients with persistent/chronic ITP has markedly changed over the last 50 years and is currently going through a transition, with the main driving forces being a greater understanding of the disease per se, recognition that platelet count is less important than overall bleeding symptoms, and the availability of new therapies [12,25,26]. ITP is a heterogeneous disease and presentation can vary widely, particularly with regard to platelet count and level of bleeding, thus necessitating an individualized approach to treatment [25]. Factors impacting on treatment decisions include: extent of bleeding, age, comorbidities predisposing to bleeding, disease stage/duration and severity, activity/lifestyle, potential adverse effects, patient-related factors such as well-being/QoL, fatigue and expectations/concerns [12]. The numerous changes in treatment practices that have taken place in the last decade are reflected in recent guidance/guidelines documents, including those from the American Society of Hematology (ASH) [26], as well as an updated International Consensus Report produced by a global panel of expert investigators using clinical best evidence and expert opinion [12].

The recommended treatment goals in these evidence-based consensus reports include: treatment to prevent severe bleeding, maintenance of a target platelet level of $>20\text{--}30 \times 10^9/\text{l}$ (at least for symptomatic patients), minimal treatment-related toxicity and improvement in the individual's QoL [12]. **Figure 2** provides an overview of the treatment approach advocated in the International Consensus Report based upon a thorough review of clinical best evidence up to 2018 augmented with the expert opinion of the panel members [12].

For newly diagnosed patients, corticosteroids such as prednisone, prednisolone, methylprednisolone and dexamethasone, which are easily administered and relatively inexpensive, are the mainstay for the initial management of adults with ITP. IVIg or IV-anti-D may be appropriate initial treatment options in patients unresponsive to corticosteroids, and in those who have contraindications to steroid therapy (patients with insulin-dependent diabetes, uncontrolled diabetes, active infection and psychiatric disorders) or require a more rapid response [12]. These agents can be used to increase platelet count rapidly in emergency situations and are not intended for long-term use because of limited duration of response and potential toxicity. Other than a small number of patients who can be maintained on daily low doses of steroids, the majority of patients with ITP will eventually require alternative therapy. The agents with the most robust evidence supporting their use in the treatment of ITP include rituximab, the thrombopoietin-receptor agonists (TPO-RA) eltrombopag, avatrombopag and romiplostim, and the Syk inhibitor fostamatinib [**Figure 2**]. Agents with less robust evidence include azathioprine, cyclosporin, cyclophosphamide, mycophenolate, etc. Splenectomy, which was previously considered a second-line approach is now considered to

Figure 2. Overview of therapies available for the treatment of immune thrombocytopenia as advocated in the International Consensus Report.

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be 'Subsequent therapy: surgical' and it is generally recommended to wait ≥ 12 to 24 months after diagnosis before performing the splenectomy because of the possibility of stabilization or remission. Steroids, IVIg, TPO-RAs or other effective therapies may be used during this period to help increase platelet counts prior to splenectomy. It is also recommended that predictive studies assessing potential response using Indium labelled platelets are considered before surgery [12].

Fostamatinib

Background

Fostamatinib disodium hexahydrate (R788; Tavalisse[®], Riegel Pharmaceuticals) has the chemical formula N4-(2,2-dimethyl-4-[(dihydrogenphosphonoxy)methyl]-3-oxo-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxy-phenyl)-2,4-pyrimidinediamine disodium hexahydrate. It is an orally bioavailable prodrug that is metabolized to its biologically active form, tavalitinib [(R406) N4-2,2-dimethyl-3-oxo-4H-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine], a potent and selective small molecule inhibitor of Syk (Figure 3) [14]. R406 has poor aqueous solubility, and fostamatinib was designed as a methylene-phosphate prodrug which is cleaved by alkaline phosphatase at the apical brush-border membranes of intestinal enterocytes to its active moiety [14].

Pharmacology

Mechanism of action & pharmacodynamic properties

R406 is a spleen tyrosine kinase inhibitor with demonstrated activity against Syk and it has been shown to inhibit signal transduction of B-cell receptors and Fc-activating receptors, which play a key role in antibody-mediated

Figure 3. Metabolism of the orally bioavailable prodrug, fostamatinib, to its biologically active form, tamatinib (R406), by alkaline phosphatases at the apical brush-border membranes of intestinal enterocytes. Republished with permission of Future Medicine Ltd [14]; permission conveyed through Copyright Clearance Center, Inc.

cellular responses. These effects have been explored in autoimmune and inflammatory disease models, and in models of hematological malignancies (e.g., B-cell lymphomas and chronic lymphocytic leukemia), and R406 was found to inhibit or delay the onset of disease progression. In the context of ITP, R406 has been shown to reduce antibody-mediated destruction of platelets. These pharmacodynamic/preclinical studies were covered in greater detail in our previous review and some of the key findings were [14]:

- *In vitro* R406 inhibited Syk-mediated IgE- and IgG-mediated activation of FcR signaling and FCγR- and FCγR-dependent responses in a number of cell types, and it inhibited degranulation, cytokine production and FcR-mediated antigen internalization in mast cells, TNF-α production induced by FCγR-cross-linking in macrophages, anti-IgG-induced oxidative burst in TNFα-primed neutrophils and FCγR-dependent arachidonic acid release in dendritic cells in response to immune complexes [27,28].
- Inhibition of Syk by R406 inhibited all downstream phosphorylation events of the Syk pathway, including PLCγ1, Akt/PKB, Erk, p38 and JNK [27].
- The specificity of R406 for Syk is further supported by observations that the phenotype of R406-treated cells is similar to that observed after siRNA knockdown of Syk in a basophilic cell line [29].
- In platelets, Syk activation occurs through ITAM-containing GPVI (collagen receptor) and certain integrins (αIIbβ3; GPIIb/IIIa) and R406-treated mice did not show extended bleeding times compared with vehicle [30–32].
- Lack of detrimental effects on platelets was confirmed in studies of R406 in human platelets, with no impairment in platelet aggregation in treated platelets, this is consistent with prior studies showing little to no coagulation defect due to Syk-deficiency or GPVI deficiency [31,33].
- Development of thrombocytopenia and hemolytic anemia was also impeded by fostamatinib in disease models of ITP and warm antibody autoimmune hemolytic anemia [34].
- In animal models where antibodies against platelets and red cells were passively transferred to mice, fostamatinib treatment prevented the development of thrombocytopenia and hemolytic anemia [34].
- Fostamatinib (25–40 mg/kg) significantly protected mice from developing thrombocytopenia, compared with vehicle only, in a disease model for ITP (mice injected with platelet-targeting anti-integrin α-IIb antibodies) [34].

Pharmacokinetics

The pharmacokinetic properties of fostamatinib and its active metabolite, R406, have been investigated in healthy volunteers (including Japanese subjects), and in patients with renal disease, liver disease, non-Hodgkin lymphoma and rheumatoid arthritis (Table 1) [35–39].

Absorption

Preclinical studies confirmed that fostamatinib at single oral doses of 10 and 20 mg/kg was rapidly absorbed and highly bioavailable, with peak plasma levels for its active metabolite, R406 achieved within 1 h [40]. Fostamatinib was not detected in plasma samples in this animal model suggesting that it is completely converted to the active metabolite.

Table 1. Pharmacokinetic parameters for fostamatinib and its biologically active form (R406) in human studies.

Author		Pharmacokinetic parameters for R406						Ref.
		C _{max} (ng/ml)	t _{max} (h)	AUC (ng/ml·h)	t _{1/2} (h)	CL (l/min)	Vd (l)	
Healthy volunteers (n = 5 to 6 per group)								
Baluom <i>et al.</i> 2013	R406 80 mg	501 ± 128	1.3 ± 0.3	4410 ± 997	14.5 ± 3.9	0.32 ± 0.07	409 ± 175	[35]
	R406 250 mg	2030 ± 489	1.2 ± 0.3	18,100 ± 2930	14.9 ± 3.6	0.24 ± 0.04	306 ± 95	
	R406 400 mg	3410 ± 745	1.5 ± 0.5	34,900 ± 14,600	17.8 ± 10.6	0.22 ± 0.09	340 ± 276	
	R406 500 mg	3660 ± 713	1.1 ± 0.2	29,600 ± 6270	20.9 ± 5.8	0.29 ± 0.06	546 ± 249	
	R406 600 mg	3920 ± 888	1.3 ± 0.3	36600 ± 7760	12.9 ± 5.9	0.29 ± 0.09	316 ± 146	
	Fostamatinib 80 mg	306 ± 46	1.1 ± 0.2	3150 ± 982	14.8 ± 4.7	0.45 ± 0.13	557 ± 166	
	Fostamatinib 250 mg	1140 ± 122	1.6 ± 0.4	13,700 ± 3140	16.0 ± 2.8	0.32 ± 0.07	431 ± 82	
	Fostamatinib 400 mg	1220 ± 317	1.6 ± 0.4	13,400 ± 4360	12.1 ± 2.0	0.54 ± 0.15	545 ± 109	
Japanese and white subjects (n = 5 to 12 per dosage group)								
Martin <i>et al.</i> 2016	Fostamatinib 50 mg	163 ± 56	3	2170 ± 308	14.7	3.3 ± 1.2		[36]
	Fostamatinib 100 mg	338 ± 164	3	4150 ± 1460	19.3	3.0 ± 1.3		
	Fostamatinib 150 mg (white subjects)	431 ± 184	1.5	4620 ± 1390	14.6	4.0 ± 2.4		
	Fostamatinib 150 mg	626 ± 237	1.5	5870 ± 1660	12.8	3.7 ± 3.0		
	Fostamatinib 200 mg	395 ± 136	1.5	4430 ± 1560	14.3	2.6 ± 1.1		
Japanese healthy subjects (n = 12 per dosage group)								
	Fostamatinib 100 mg	477 ± 237	1	4640 ± 1460	13.3	3.0 ± 1.0		
	Fostamatinib 200 mg	955 ± 371	1.25	8620 ± 3270	13.6	3.0 ± 1.0		
Patients with renal disease (n = 8 per group)								
Martin <i>et al.</i> 2015	Fostamatinib 150 mg: CL _{CR} ≥80 ml/min	690	2.5	7380	20.5			[37]
	CL _{CR} ≥30–<50 ml/min	425	2.5	5790	23.8			
	ESRD post-dialysis	407	2.3	5450	19.6			
	ESRD predialysis	529	3.0	6810	22.1			
Patients with hepatic disease (n = 8 per group; Child-Pugh Class A, B and C)								
	Fostamatinib 150 mg: No hepatic impairment	692	1.5	8970	19.4			
	Mild hepatic impairment	615	2.5	6390	16.7			
	Moderate hepatic impairment	602	1.8	6860	16.1			
	Severe hepatic impairment	582	1.5	9490	19.2			
Patients with non-Hodgkin lymphoma								
Friedberg <i>et al.</i> 2010	Fostamatinib 200 mg	668 ± 258		1800 ± 602				[38]
	Fostamatinib 250 mg	1020 ± 781		2590 ± 1900				
Patients with rheumatoid arthritis (n = 12)								
Baluom <i>et al.</i> 2011	Fostamatinib 100 mg	397 ± 177	1.0 ± 0.4	3260 ± 990	14.5 ± 4.3			[39]
CL: Clearance; CL _{CR} : Creatinine clearance estimated by Cockcroft Gault equation; C _{max} : Maximum plasma concentration; ESRD: End-stage renal disease; t _{max} : Time to maximum plasma concentration; t _{1/2} : Half life; Vd: Volume of distribution.								

CL: Clearance; CL_{CR}: Creatinine clearance estimated by Cockcroft Gault equation; C_{max}: Maximum plasma concentration; ESRD: End-stage renal disease; t_{max}: Time to maximum plasma concentration; t_{1/2}: Half life; Vd: Volume of distribution.

In human healthy volunteers, absorption was rapid with peak R406 levels occurring between 1 and 2 h after administration of fostamatinib (R406 in one study) and having a median value of 1.5 h in all the studies included in Table 1. Absorption appeared to be slightly delayed in patients with renal insufficiency/failure (2.3–3.0 h) [37]. Dose proportional C_{max} and AUC_{0–∞} levels were observed at doses up to 400 mg in healthy volunteers [35].

Distribution

R406 is highly bound to plasma proteins (98.3% in human plasma) and distributes reversibly into blood cells [41]. The mean (±SD) apparent volume of distribution (V_Z/F) following single dose administration ranged between 306 ± 95 and 557 ± 166 l [Table 1] and at steady-state it was 256 ± 92 l [41].

Elimination

Fostamatinib is metabolised in the gut by alkaline phosphatase to its main active metabolite R406. Subsequently, R406 is extensively metabolised, primarily through pathways of CYP450-mediated oxidation (by CYP3A4) and glucuronidation (by UDP glucuronosyltransferase [UGT]1A9). R406 is the predominant moiety in the systemic circulation, and there is minimal exposure to any of its metabolites [29].

Following absorption, R406 undergoes slow bi-phasic elimination with a terminal half-life ($t_{1/2}$); ranging between 12 and 21 h across the majority of groups, but between 20 and 24 h in patients with renal disease (Table 1). Approximately 20% of an administered dose is recovered in the urine, primarily as N-glucuronide R406. About 80% of the dose was eliminated in the feces, mainly as R406 and 3,5-benzene diol R406 (with wide individual variation in the amounts of these metabolites recovered) [42].

Food interactions

Administration of fostamatinib with a high-calorie, high-fat meal (deriving approximately 150, 250 and 500–600 calories from protein, carbohydrate and fat, respectively) increased R406 AUC by 23% and C_{max} by 15%, indicating fostamatinib can be administered with or without food [41].

Special populations

Population analyses indicate that the pharmacokinetics of fostamatinib/R406 are not altered based on age, gender, race/ethnicity [41]. Nor are they altered in subjects with renal impairment (creatinine clearance [CL_{Cr}] = 30 to <50 ml/min, estimated by Cockcroft Gault equation and end stage renal disease requiring dialysis), or hepatic impairment (Child-Pugh Class A, B and C) [37]. In line with the SmPC, fostamatinib should not be used in patients with severe hepatic impairment, and in patients with mild or moderate hepatic impairment, monitoring of liver function should be performed regularly during fostamatinib therapy [41].

Clinical experience with fostamatinib in persistent/chronic immune thrombocytopenia

In patients with persistent/chronic ITP the safety and efficacy of fostamatinib has been evaluated in individual cases in everyday clinical practice [43], in a Phase II open-label study [34] and in the FIT clinical trials programme comprising two double-blind, randomized, placebo-controlled, Phase III studies (FIT1 and FIT2; NCT02076399 and NCT02076412, respectively) [44,45], an on-going open-label extension study (FIT3; NCT02077192) [46–48] and two *post hoc* analyses [49,50] (Table 2). The FIT1 and FIT2 studies were of identical design and included a total of 150 adults with chronic ITP treated for 24 weeks. A total of 123 patients continued treatment with fostamatinib in the open-label on-going extension study (FIT3) which was the subject of an interim analysis after a median 6.7 (range 1–31) months [48].

Case reports & open-label study

In a Phase II open-label pilot study, the clinical efficacy and tolerability/safety of escalating doses (75–175 mg twice daily) of fostamatinib was evaluated in 16 adult patients with refractory chronic ITP [34]. All patients were required to have failed at least 2 typical treatments prior to entry (including corticosteroids, 100%; IVIg, 94%; rituximab, 88%; splenectomy, 69%; anti-D, 56%; danazol, 50%) and have at least 3 separate platelet counts of $<30 \times 10^9/l$ over a 3-month period. Treatment was initiated with fostamatinib 75–150 mg twice daily and this could be increased every 2 weeks, by 25 mg twice daily, up to a maximum of 175 mg twice daily. The dosage was escalated until a persistent response was achieved, the maximum dosage was reached or toxicity occurred. Response assessment were made weekly for the first 7 weeks and then every 1–4 weeks depending on the patient's response. The key findings are outlined in Table 2. Eight of the 16 patients (50%) achieved a sustained response with a reduced need for IVIg and tapering of steroid therapy; four patients had transient nonsustained responses; and four patients did not respond to treatment.

Real-world experience in treating patients with chronic ITP at the Boston Medical Center Health System were presented at the 2019 American Society of Hematology (ASH) meeting [43]. Four patients were retrospectively identified and all were refractory to, or could not tolerate, previous treatment with corticosteroids, IVIg and rituximab, and two also failed treatment with the thrombopoietin agonists romiplostim and eltrombopag. Fostamatinib was started at a dosage of 100 mg orally twice daily and titrated up to 150 mg twice daily if the platelet count was $<50 \times 10^9/l$. The duration of follow-up was 2 to 9 months. After 4 weeks, three patients had platelet counts

Table 2. Clinical studies/trials with oral fostamatinib in patients with primary persistent/chronic immune thrombocytopenia.

Study design [no. pts]	Fostamatinib dosage (oral) [duration of Rx]	Response end point	Main efficacy findings	Reference	Ref.
Case reports and open-label study					
Open-label, Phase II study [n = 16],	75 mg bid escalated at doses of 25 bid up to 175 mg bid [3–53 w]	↑ in platelet count by $>20 \times 10^9/l$ from baseline to $\geq 30 \times 10^9/l$ with no rescue treatment	Efficacy: 12/16 pts (75%) achieved a positive response which was sustained in eight pts. Median platelet count peaked at $105 \times 10^9/l$ from a baseline of $16 \times 10^9/l$. A total of eight pts had a persistent response (platelet count $>50 \times 10^9/l$ for a median of 95% study visits and a median peak platelet count of $188 \times 10^9/l$). Four pts had a nonsustained transient response and 4 pts did not respond to treatment Safety: Overall, the tolerability of fostamatinib was good, but three pts discontinued treatment because of toxicity (one case each of: deep vein thrombosis (unrelated); vomiting and diarrhea; and elevated transaminase levels). Other, mostly mild to moderate AEs probably related to fostamatinib included GI events, elevated SBP, headache and weight gain	Podolanczuk <i>et al.</i> 2009	[34]
Individual cases	100 mg bid increased to 150 mg bid if platelet count was $<50 \times 10^9/l$ [2–9 m]	Fostamatinib suitability in 4 pts at an Academic Medical Center refractory to previous therapy	Efficacy: Three pts received fostamatinib because of side effects or inconvenience with ROM. After 4 w, three pts had a platelet count of $>50 \times 10^9/l$ and in 1 pt it was $<30 \times 10^9/l$. For two pts who have been on therapy for 7–8 m platelet counts were $>100 \times 10^9/l$. Two pts discontinued fostamatinib; 1 due to an inadequate response and 1 because an adverse event Safety: Two pts developed diarrhea (1 discontinued treatment) and one pt experienced elevated BP	Hughes <i>et al.</i> 2019	[4,43]
FIT (1,2,3) clinical trials programme					
MC, R (2:1), D-B, PC, Phase III study [n = 76]	100 mg bid with an increase to 150 mg bid allowed depending on platelet count and tolerability (n = 51) or placebo (n = 25) [24 w]	Overall response (platelet count $\geq 50 \times 10^9/l$ between weeks 1 and 12) Primary end point: Stable platelet response by week 24 ($\geq 50 \times 10^9/l$ on at least 4 of the last six visits between weeks 14 and 24)	Efficacy: Overall response: fostamatinib 37% vs PL 8% ($p < 0.01$) Stable platelet response: fostamatinib 18% vs PL 0% ($p < 0.05$)	FIT1 NCT02076399	[44]
MC, R (2:1), D-B, PC, Phase III study	100 mg bid with an increase to 150 mg bid allowed depending on platelet count and tolerability (n = 50) or placebo (n = 24) [24 w]		Efficacy: Overall response: fostamatinib 48% vs PL 21% ($p < 0.05$) Stable platelet response: fostamatinib 18% vs PL 4% (NS)	FIT2 NCT02076412	[45,74]
MC, R (2:1), D-B, PC, Phase III studies pooled [n = 150]	100 mg bid with an increase to 150 mg bid allowed depending on platelet count and tolerability (n = 101) or placebo (n = 49) [24 w]	As above	Efficacy: Overall response: fostamatinib 43% vs PL 14% ($p = 0.0006$) Stable platelet response: fostamatinib 18% vs PL 2% ($p = 0.0003$) Moderate and severe bleeding-related events were more frequent in the PL group vs the fostamatinib group (16 vs 9% in those with an overall response to fostamatinib and 6% in those with a stable response). Patients in the fostamatinib group required less rescue medication (30 vs 45%; $p = 0.07$). Safety: Any AE reported in 83% of fostamatinib pts vs 75% PL pts. The most common were: diarrhea (31 vs 15%), hypertension (28 vs 13%), nausea (19 vs 8%), dizziness (11 vs 8%), ALT increased (11 vs 0%), respiratory infection (11 vs 6%), AST increased (9 vs 0%) and rash (9 vs 2%), neutropenia (6 vs 0%). And abdominal pain/fatigue/chest pain (all 6 vs 2%, respectively). Most AEs were mild or moderate (fostamatinib 81% vs PL 81%). Serious AEs were reported in 13% of pts in the fostamatinib group and 21% of pts in the PL group. There were similar rates for AEs leading to treatment withdrawal (fostamatinib 10% vs PL 8%). AEs reported in 146 fostamatinib-treated pts across the FIT (1,2,3) clinical trials programme are presented in Table 3	Pooled results FIT1 and FIT2 Bussel <i>et al.</i> 2018, 2019.	[44,45, 47,48]
AE: Adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; RTI: Respiratory tract infection; bid: Twice daily; D-B: Double-blind; m: Months; MC: Multicentre; PC: Placebo-controlled; W: Week; PL: Placebo; R: Randomized; ROM: Romiplostim; Rx: Treatment; SAE: Serious AE; SBP: Systolic blood pressure; TCP: Thrombocytopenia.					

Table 2. Clinical studies/trials with oral fostamatinib in patients with primary persistent/chronic immune thrombocytopenia (cont.).

Study design [no. pts]	Fostamatinib dosage (oral) [duration of Rx]	Response end point	Main efficacy findings	Reference	Ref.
Open-label extension study from FIT1 and FIT2 [n = 123]	100 mg bid with an increase to 150 mg bid allowed depending on platelet count and tolerability [1.5–41.3 m]	Achievement and maintenance of a stable platelet count $\geq 50 \times 10^9/l$ for 12 m.	Efficacy: Median duration of fostamatinib treatment was 8.9 m and median compliance was 98%. 42 of 123 pts were continuing fostamatinib treatment. Of 27 pts with a stable response, 21 (78%) had maintained the response for 1 year and 15 (56%) for 2 years. A total of 32 pts had data after 2 years and the median platelet count was $81 \times 10^9/l$. An overall platelet response was achieved by 57/123 (46%) of patients Safety: AEs were reported by 95 (77%) pts and were mild/moderate in 92 (75%) of cases. The most common AEs were diarrhea and hypertension which were manageable with appropriate treatment, dose modification or treatment discontinuation (5 pts). SAEs were reported by 28 pts (23 unrelated to fostamatinib) and these included 11 with bleeding-related events, TCP in six pts, epistaxis in three, sepsis in two and increased liver enzymes in two. In this long-term study no new safety signals were observed	FIT3 Bussel <i>et al.</i> 2019, Duliege <i>et al.</i> 2018	[46,48,49]
<i>Post hoc</i> analysis from FIT1 and 2 to assess second-line [n = 32] and early use [n = 29]	Dosage as per FIT1 and 2. Only pts who had failed treatment with steroids $\pm$ immunoglobulins and no other therapies (i.e. second-line therapy, and those treated early in the disease)	Platelet responses in pts receiving fostamatinib early (<2 years) and as second-line therapy	A total of 32 of 145 pts received fostamatinib as second-line therapy and 25 (78%) had an overall platelet response (platelet count $\geq 50 \times 10^9/l$) which compares very favorably with the 47% response rate in the 113 pts who received it as $\geq 3^{\text{rd}}$ line therapy. In the subgroup of 29 pts who received fostamatinib early (<2 years), 9 of 10 pts (90%) who received the drug <1 year and 11 of 19 (57%) who received it between 1 – <2 years responded. These compare favorably with the response rate of 50% in pts with ITP for 2–53 years. AEs were consistent with the main study	Boccia <i>et al.</i> 2020	[51]

AE: Adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; RTI: Respiratory tract infection; bid: Twice daily; D-B: Double-blind; m: Months; MC: Multicentre; PC: Placebo-controlled; W: Week; PL: Placebo; R: Randomized; ROM: Romiplostim; Rx: Treatment; SAE: Serious AE; SBP: Systolic blood pressure; TCP: Thrombocytopenia.

$>50 \times 10^9/l$ and in one patient it was $<30 \times 10^9/l$. For two pts who have been on therapy for 7–8 months, platelet counts were $>100 \times 10^9/l$ (Table 2).

FIT (1, 2, 3) clinical trials programme

The efficacy of fostamatinib in ITP has been confirmed in 2 identically designed double-blind, randomized, placebo-controlled, Phase III studies [44,45], an open-label, on-going extension study [46] and in a pooled analysis from these studies [47–49]. The FIT1 (patients from N. America, Australia and Europe) and FIT2 (Europe only) studies were conducted in 150 adults with chronic ITP over 24 weeks, and the FIT3 study in 123 of these patients treated for between an additional 1.5 and 41.3 months (Table 2). The patients were refractory to previous ITP therapy which included three unique prior regimens including corticosteroids, splenectomy, TPO-RAs and/or rituximab (93% had received corticosteroids, 51% IVIg or IV Anti-D, 47% TPO-RAs, 34% had received rituximab and 34% had undergone splenectomy). At baseline, the median duration of disease was 8.5 years (and about 75% had a ≥ 3 -year history of ITP), and all patients had at least three platelet counts $<30 \times 10^9/l$ including 2 measurements within the preceding 3 months. These demographic data highlight that this was a difficult-to-treat ITP cohort. Fostamatinib was administered orally at a starting dose of 100 mg twice daily which could be titrated to 150 mg twice daily (depending on platelet count and tolerability) after week 4. By the end of the study period, 88% of patients were receiving 150 mg twice daily.

Results for the primary end point, a stable response which was defined as a platelet count of $\geq 50 \times 10^9/l$ on at least four of six visits during weeks 14 through 24, are presented in Table 2. Combined results from the FIT1 and FIT2 studies demonstrated a stable response rate of 18% with fostamatinib versus 2% with placebo ($p = 0.0003$), and an overall response rate (defined as a platelet count of $\geq 50 \times 10^9/l$ during weeks 1 to 12 and a *post hoc* analysis) of 43% with fostamatinib versus 14% with placebo ($p = 0.0006$). In patients with more severe ITP at baseline as defined by a platelet count of $<15 \times 10^9/l$, an increase to $30 \times 10^9/l$ at weeks 12 and 24 was achieved

Figure 4. Median platelet counts in overall and stable responders over time.

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by 21 and 15% of patients in the fostamatinib group versus 5 and 0% of the placebo group. Median platelet counts from baseline levels over 24 weeks were $95 \times 10^9/\text{l}$ in stable responders, $49 \times 10^9/\text{l}$ in overall responders, $14 \times 10^9/\text{l}$ in nonresponders and $18 \times 10^9/\text{l}$ with placebo [47]. Platelet responses to fostamatinib were relatively rapid, and both overall and stable responders achieved an initial platelet threshold of $\geq 50 \times 10^9/\text{l}$ after a median of approximately 15 days. However, in some individuals a slower but steady response was observed and the platelet count that exceeded $50 \times 10^9/\text{l}$ during weeks 2 to 12 or after the initial 12-week treatment period. A positive response to fostamatinib was demonstrated across all subgroups; age, gender; prior therapy; baseline platelet count and duration of ITP.

In the Phase III clinical trials and open-label extension trial a total of 146 patients were treated with fostamatinib, and 64 patients (44%) achieved an overall response. This included 43 of 101 (43%) initially treated with fostamatinib, and 21 of 44 (48%) patients who transitioned to fostamatinib after initially receiving placebo. The overall response to fostamatinib was maintained during treatment and median platelet counts remained $\geq 50 \times 10^9/\text{l}$ at all visits; with a median post-baseline platelet count of $63 \times 10^9/\text{l}$ (range 15 to $277 \times 10^9/\text{l}$) (Figure 4) [48]. The majority of patients maintained their response to fostamatinib for a median duration >28 months (range <1 to >28 months). In patients who had an insufficient response to TPO-RAs ($n = 69$), 24 (35%) had an overall response to fostamatinib and 14 of these maintained platelet counts consistently above $30 \times 10^9/\text{l}$ [48].

In the FIT1 and FIT2 randomized studies, 17 patients (17%) achieved the primary end point (a stable response to fostamatinib), and 10 of 44 (23%) patients who switched from the placebo group also achieved this end point with fostamatinib in the open-label extension study. Thus, a stable response was recorded in 18% of patients (27 of 146) in the fostamatinib-treated population [50]. The response to fostamatinib was durable with 18 of 27 (67%) patients maintaining a stable response for ≥ 1 year. An additional seven stable responders (26%) remained on fostamatinib for >1 -year as a result of continued clinical benefit (this was despite having ≥ 1 platelet count drop $< 50 \times 10^9/\text{l}$), and five of these patients regained their response. The other two patients with a stable response had not reached 12 months of therapy as of the data cut-off date. Overall, after 12 months of treatment, 93% of stable responders maintained their clinical response or continued to derive benefit on fostamatinib treatment. The median duration of the first stable response was not reached in this study and the authors estimated that it was >28 months. These patients continue to be monitored in the on-going FIT3 study [46–50].

Post hoc analyses from the FIT1 and FIT2 trials were undertaken to assess second-line and early use of fostamatinib in patients with ITP [51]. Only patients who had failed treatment with steroids $\pm$ immunoglobulins and no other therapies ($n = 32$), and those treated early in the course of the disease (<2 years) were included in these analyses. When used as second-line therapy 25 (78%) fostamatinib-treated patients had an overall response (platelet count $\geq 50 \times 10^9/\text{l}$), which compares very favorably with the 48% response rate in the 113 pts who received it as $\geq 3^{\text{rd}}$

line therapy. In the subgroup of 29 patients with early stage disease, nine of ten patients (90%) with persistent ITP (disease duration <1 year) and 11 of 19 (58%) with ITP for between 1 and <2 years responded to fostamatinib. These rates compare favorably with the response rate of 51% in patients with ITP for 2–53 years. These results suggest that higher response rates may be achieved when fostamatinib is used as second-line treatment for ITP and in patients with early (<2 years) disease, compared with later lines of therapy and more chronic disease (>2 years) [51].

Bleeding-related end points & need for rescue medication

In patients treated with fostamatinib, moderate to severe bleeding-related events were reported by four of 43 (9%) overall responders and six of 58 (10%) non-responders, versus eight of 49 (16%) patients on placebo [47]. Serious bleeding-related events did not occur in any of the 43 overall responders to fostamatinib compared with 4 of 58 (7%) of non-responders and five of 49 (10%) of placebo-treated patients. Rescue medication was used by 16% of responders and 34% of nonresponders to fostamatinib, compared with 45% of patients receiving placebo. In stable responders, three of 18 (17%) used rescue medication, and only during the first week of treatment, whereas nonresponders and placebo patients used rescue medication throughout the study (up to week 24) [47]. Types of rescue medication included IVIg, corticosteroids, and platelet transfusion, as recommended by clinical guidelines.

In population-based cohort studies, ITP was associated with thromboembolic events at a rate estimated to be twofold higher than the general population [52]. Analysis of data from the FIT 1, 2, 3 studies identified a single transient ischemic attack (0.7%) in patients treated with fostamatinib. This involved a patient with pre-existing atherosclerosis and the case resolved spontaneously [53]. This low incidence of thromboembolism with fostamatinib may relate to its mechanism of action (Syk inhibition) and deserves further evaluation.

Tolerability & safety

In patients with ITP, fostamatinib has generally been well tolerated in Phase III studies. Approximately, 10% of fostamatinib-treated patients discontinued treatment compared with 8% of patients receiving placebo [47]. The most commonly reported AEs for fostamatinib are consistent with those previously reported for Syk inhibitors, including gastrointestinal disorders, hypertension, and transaminase elevation (Table 3) [48]. The majority of AEs were mild/moderate in severity and were manageable with appropriate monitoring and standard therapeutic approaches, including appropriate treatment of the AE, dose reduction/treatment interruption, and infrequently discontinuation of fostamatinib [50]. In total, 31% of patients treated with fostamatinib versus 17% on placebo required modification of their treatment: interruption (18 vs 10%), dose reduction (9 vs 2%), or withdrawal (10 vs 8%). Serious AEs (SAEs) were reported in 13% of patients in the fostamatinib group and 21% of patients in the placebo group; 4 vs 2%, respectively, were considered to be drug-related [47,48]. There were two deaths, one in the placebo group (from probable sepsis 19 days after discontinuing the study) and one in the fostamatinib group (plasma cell myeloma which led to withdrawal from the study and death 71 days later), but causality was not ascribed. Only 3 SAEs were reported in more than one patient: epistaxis (2% fostamatinib vs 2% placebo), menorrhagia (0 vs 4%) and thrombocytopenia (1 vs 4%).

In an interim report of the long-term extension study that is ongoing, AEs were reported by 95 (77%) patients and were mild to moderate in 92 (75%) of cases [49]. The most common AEs were diarrhea and hypertension which were manageable with appropriate treatment, dose modification/interruption, or treatment discontinuation (five patients). SAEs were reported by 28 pts (23 unrelated to fostamatinib) and these included 11 bleeding-related events (thrombocytopenia $n = 6$, epistaxis $n = 3$ and sepsis $n = 2$). In this long-term study no new safety signals were observed and the overall safety profile of fostamatinib in ITP clinical trials was consistent with its use in other indications such as rheumatoid arthritis [14,50].

Conclusions / place in therapy (meeting unmet needs)

It is widely acknowledged that over the last decade management of ITP has markedly improved but it is not optimal, and a key reason for this is the heterogeneity of the disorder with regards to its underlying pathophysiology, variable presentation and the differing individual responses to treatment. This highlights the need for a personalized approach to treatment with management tailored to the needs of the individual, taking into consideration factors such as age, extent of bleeding, comorbidities predisposing to bleeding, bleeding risks with necessary concomitant medications, complications associated with the treatments being considered, possible adverse effects, lifestyle considerations, patient concerns/worries and accessibility to care [12]. These factors were taken into consideration by an expert panel that produced an updated International Consensus Report based on clinical best evidence available up to July

Table 3. The most common adverse events (%) reported during fostamatinib treatment in the FIT (1, 2, 3) clinical trials programme (n = 146).

Type of AE	Mild AEs	Moderate AEs	Severe AEs	Total AEs
Total AEs	21	41	23	86
Serious AEs	38 (26%) pts had serious AEs which were judged to be related to drug treatment			
Diarrhea	18	16	1	35
Hypertension	10	10	1	21
Nausea	17	2	0	19
Epistaxis	11	6	0	17
Petechiae	10	4	1	15
Headache	9	4	0	13
Dizziness	9	1	1	11
Upper RTI	7	3	0	10
Elevated ALT	6	4	0	10
Fatigue	8	1	0	9
Vomiting	8	0	0	8
Contusion	6	1	1	8
Elevated AST	4	3	0	7
Abdominal pain	3	2	0	6
Nasopharyngitis	6	0	0	6
Cough	4	1	0	6
Dyspnea	3	1	1	6
Rash	6	0	0	6
Chest pain (non-cardiac)	3	2	1	6
Neutropenia	2	3	1	6
Thrombocytopenia	0	1	5	6

AE: Adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; RTI: Respiratory tract infection.
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2018. For adult patients requiring initial treatment for newly-diagnosed ITP they recommended corticosteroids along with the immunoglobulins IVIg and IV-anti-D, and as subsequent therapy the recommended choices (with the most robust evidence) were TPO-RAs, fostamatinib and rituximab [12]. During this period there has been a move away from splenectomy, which is now recommended upon failure of medical therapies [12]. Treatment is also recommended on the basis of clinical need rather than the platelet count alone, or the artificial definition into newly presented, persistent or chronic categories.

Fostamatinib as a prodrug, and R406 as its active moiety, represent a novel treatment approach which can be orally administered and requires minimal titration; reducing both clinical time and the need for professional healthcare support. It was shown to produce a rapid, durable response among patients with long-standing ITP who were considered difficult to treat having previously received rituximab, and/or TPO-RAs or had undergone splenectomy [48]. Subgroup analyses illustrate good overall responses independent of duration of ITP, baseline platelet count, previous TPO-RA or rituximab therapy, and prior splenectomy. These results demonstrate that fostamatinib is able to improve platelet numbers among diverse types of patients, including those with and without multiple exposures to prior ITP treatments, and those with longer and shorter durations of ITP [47]. The findings from the FIT (1,2,3) clinical trials programme resulted in the approval of fostamatinib by the US FDA in April 2018 and the EMA in Europe in January 2020. Patients who responded to fostamatinib demonstrated good control of hemostasis.

Overall, fostamatinib was well tolerated, and adverse effects were generally predictable for a Syk inhibitor (including gastrointestinal effects such as diarrhea, hypertension and liver transaminase elevations) and could be managed with dose reduction/interruption, appropriate treatment or infrequently by discontinuation. Wider usage in everyday clinical practice, following its relatively recent approvals in the US and Europe, will provide a more grounded and comprehensive understanding of the efficacy and safety profile of fostamatinib in ITP and will help us define those patients most likely to benefit from this novel new therapeutic approach.

In the Phase III clinical trials, a stable platelet response (platelet count of $>50 \times 10^9/l$) was significantly higher for fostamatinib versus placebo (18 vs 2%; $p = 0.0003$). The median platelet count in fostamatinib stable responders ($95 \times 10^9/l$) and overall responders ($49 \times 10^9/l$) was markedly higher than that for placebo ($18 \times 10^9/l$). A positive response to fostamatinib was demonstrated across all subgroups for example, age, gender, prior therapy baseline platelet count and duration of ITP.

Across the 2 Phase III clinical trials and open-label extension study, 64 of 146 patients (44%) achieved an overall response. Overall, 93% of patients who achieved a stable response continued to respond and/or derive clinical benefit after 12 months of treatment.

The safety profile of fostamatinib in clinical trials involving patients with ITP is consistent with its safety profile in other indications, with most common AEs including gastrointestinal-related reactions (diarrhea, nausea and vomiting) and elevated blood pressure; most AEs have been mild to moderate, self-limited and did not lead to treatment discontinuation.

Compared with placebo, elevated liver transaminase levels and hypertension events were recorded in some fostamatinib-treated patients, but these could generally be managed with appropriate treatment or dose reductions.

Conclusion

Preclinical and Phase II and III clinical studies have shown fostamatinib to be a promising new approach to ITP that may be effective in heavily pretreated patients.

Executive Summary

Overview of immune thrombocytopenia

- Primary immune thrombocytopenia (ITP) is a heterogeneous autoimmune bleeding disease resulting in autoantibody-mediated premature destruction/clearance of platelets and reduced platelet production by megakaryocytes.
- Disruption of T- and B-cell tolerance mechanisms, as a result of somatic mutations, lead to the development of platelet reactive autoantibodies that contribute to the pathogenesis of ITP.
- Most patients with ITP have a skewed Th1/Th2 ratio that favors the survival of autoreactive T-cell clones that produce anti-GPIIb/IIIa and Ib/IX antibodies; these attach to the surface of platelets which are, in turn, cleared by splenic macrophages through Syk-dependent phagocytosis.

Unmet medical need

- Despite the availability of several different therapeutic approaches, with drugs having different mechanisms of action. ITP is able to persist for a number of years.
- Corticosteroids (with or without IVIg and anti-D) are recommended as first-line therapy in treatment guidelines while second-line choices include drugs such as the TPO-RAs, fostamatinib and rituximab. It is generally recommended to wait ≥ 12 to 24 months before considering splenectomy, which is viewed as 'subsequent therapy: surgical.'

Overview of fostamatinib disodium

- Fostamatinib disodium is a first-in-class selective orally active spleen tyrosine kinase inhibitor indicated for the treatment of ITP by protecting platelets from destruction by inhibiting FcR-triggered cytoskeletal rearrangements needed for phagocytosis.
- Fostamatinib has been studied clinically in studies involving patients with autoimmune hemolytic anemia, ITP, lymphoma, nephropathy and rheumatoid arthritis; as well as in preclinical models of autoimmune disease.

Preclinical studies of fostamatinib in ITP

- Fostamatinib is a highly bioavailable prodrug that is metabolized to tamatinib (R406), its active metabolite, in the presence of alkaline phosphatase or human intestinal microsomes *in vitro*.
- R406 was a selective and potent inhibitor of Syk in both *in vitro* and cell-based assays. It was found to bind to the catalytic domain of Syk and acted as a competitive inhibitor of ATP.
- The onset/progression of autoimmune and inflammatory diseases were inhibited or delayed by fostamatinib in several animal models.
- Fostamatinib is rapidly absorbed, and its active metabolite (R406) has a terminal half-life ranging from 12 to 21 h, and the majority of a dose ($\sim 80\%$) is eliminated in the feces.

Clinical studies of fostamatinib in ITP

- In patients with persistent/chronic ITP, fostamatinib has been evaluated in one Phase II trial ($n = 16$), two Phase III clinical trials ($n = 75$ each), and an open-label extension study involving 124 patients previously enrolled in the Phase III studies.
- In the Phase II study, 50% of patients had sustained responses to fostamatinib and 25% had transient responses.

Financial & competing interests disclosure

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