

# Eltrombopag: the emerging evidence of its therapeutic value in thrombocytopenia

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## Abstract

**Introduction:** Idiopathic (immune) thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by low platelet counts and bleeding episodes. Current therapy options are associated with unwanted side effects, and although patients initially respond to treatment the platelet count is not sustained in many individuals. There is a need for safe and well-tolerated treatments that provide a sustained platelet response.

**Aims:** This review summarizes the emerging evidence for the potential use of eltrombopag in the treatment of ITP in adults.

**Disease and treatment:** Eltrombopag is a nonpeptide, small molecular weight thrombopoietin receptor agonist that is orally administered. It mimics the activity of thrombopoietin, a cytokine that promotes growth and production of platelets, primarily inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells.

**Profile:** Eltrombopag is still in the early stages of development but initial phase I and phase II results are promising. Potential advantages of eltrombopag may include a sustained platelet response and a good tolerability profile. Its once-daily oral dosing regimen would also be an advantage over many of the existing therapies. It is expected that patients who have failed first-line therapy with corticosteroids and wish to avoid the need for a splenectomy, and patients with chronic refractory ITP, may benefit from eltrombopag treatment.

**Key words:** eltrombopag, evidence, immune thrombocytopenic purpura, outcomes, SB497115, thrombocytopenia, treatment

## Core emerging evidence summary for eltrombopag in ITP

Outcome measure	Emerging evidence
<b>Patient-oriented evidence</b>	
Tolerability	Good tolerability in healthy volunteers
Convenience of administration	Oral, once-daily dosing
<b>Disease-oriented evidence</b>	
Platelet response	Dose-dependent increase in platelet count at doses of 30 mg and above
Safety	Does not induce platelet activation or enhance agonist-induced platelet aggregation
Specificity	Specific for human/chimpanzee thrombopoietin receptor

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## Scope, aims, and objectives

Eltrombopag (SB497115; GlaxoSmithKline & Ligand Pharmaceuticals Inc) is an oral thrombopoietin agonist in development for the treatment of thrombocytopenia. It is currently being evaluated in phase II trials in patients with chemotherapy-induced thrombocytopenia and chronic hepatitis C-related thrombocytopenia and phase III trials in patients with idiopathic (immune) thrombocytopenic purpura (ITP). The objective of this review is to evaluate the emerging evidence for the potential use of eltrombopag in the management of ITP in adults.

## Methods

English language medical literature databases were searched for appropriate articles related to the treatment of thrombocytopenia with eltrombopag. The searches were conducted on October 27, 2005 or November 10–11, 2005 using the search terms “Eltrombopag OR SB-497115 OR SB-497115-GR.” Further searches were conducted on December 15, 2005. The cut-off date was from the beginning of the database to the date of the search unless otherwise stated.

- PubMed, <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>
- EMBASE, <http://datastarweb.com>
- BIOSIS, <http://datastarweb.com>
- Database of Abstracts of Reviews of Effects (DARE), <http://www.york.ac.uk/inst/crd/darehp.htm>
- Cochrane Database of Systematic Reviews (CDSR), <http://www.cochrane.org/index0.htm>
- Clinical Evidence, <http://www.clinicalevidence.com>
- <http://www.clinicaltrials.gov>
- <http://www.clinicalstudyresults.org>. Search strategy “GSK AND Thrombocytopenia – chemotherapy induced OR immune thrombocytopenic purpura”
- National Institute for Health and Clinical Excellence (NICE), <http://www.nice.org.uk>
- National Guideline Clearing House, <http://www.guideline.gov>. Search strategy “thrombocytopenia”

No articles or systemic reviews were identified. ClinicalTrials.gov identified three ongoing phase II clinical trials. No treatment guidelines involving eltrombopag were identified. Guidelines for ITP were identified from the websites of the American Society of Hematology (ASH) and the British Society for Haematology (BSH).

Online abstracts from the following congresses were searched using the search strategy “Eltrombopag OR SB-497115 OR SB-497115-GR.”

**Table 1** | Evidence base included in the review (preclinical and phase I only)

Category	Number of records	
	Full papers	Abstracts
Initial search	0	6
records excluded	0	0
records included	0	6
Level 2 clinical evidence (RCT)	0	1

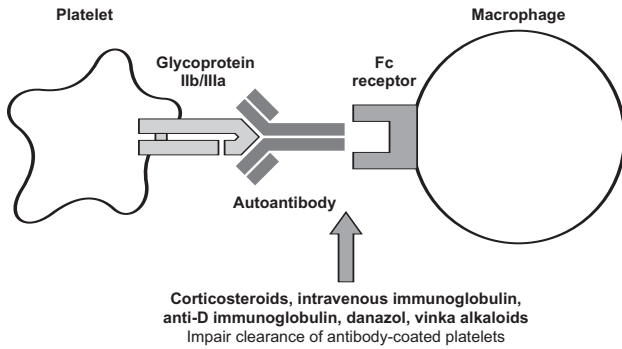
For definition of levels of evidence, see Editorial Information on inside back cover.  
RCT, randomized controlled trial.

- ASH, all conferences from 2002 to 2005,
  - [http://www.abstracts2view.com/hem\\_ash05atlanta/](http://www.abstracts2view.com/hem_ash05atlanta/)
  - [http://www.abstracts2view.com/hem\\_sandiego2004/](http://www.abstracts2view.com/hem_sandiego2004/)
  - <http://www.abstracts2view.com/hem/>
  - <http://www.abstracts2view.com/hemphiladelphia02/>
- European Hematology Association, all conferences from 2004 to 2005,
  - <http://www.eurocongres.com/eha2005/abstracts.htm>
  - [http://eurocongres.com/eha2004/eha\\_scientific.html](http://eurocongres.com/eha2004/eha_scientific.html)

Eltrombopag is currently in phase III development. Therefore, the availability of clinical data for eltrombopag is limited. A total of six abstracts were identified, of which five reported on the outcomes of preclinical studies in animals or *in-vitro* studies, and one on clinical data from healthy volunteers (Table 1). Phase II data, which was presented at a symposium at the 47th Annual Meeting of ASH (2005), but otherwise unpublished, was identified by a news report and also included.

## Disease overview

ITP is a disorder in which the host's immune system destroys platelets. The pathogenesis of ITP remains to be fully elucidated. It has been proposed that it is an autoimmune disorder in which autoantibodies play a major role by binding to platelet antigens causing their premature destruction by the reticuloendothelial system, in particular the spleen (Woods et al. 1984 a,b) (Fig. 1). Recent evidence suggests that platelets are also destroyed by cytotoxic T cells (Olsson et al. 2003). If bone marrow megakaryocytes are not able to increase production and maintain a normal number of circulating platelets, persistent thrombocytopenia (decreased number of circulating platelets) develops. Individuals who suffer from ITP may have symptoms such as easy bruising on skin and gums, purpura, nosebleeds, or mucosal bleeding. The most serious risk in patients who develop ITP is intracranial hemorrhage.



**Fig. 1 |** Pathogenesis of idiopathic (immune) thrombocytopenic purpura

Most autoantibodies are directed against epitopes on the platelet-surface antigen glycoprotein IIb/IIIa. Antibody-coated platelets bind to antigen-presenting cells (macrophages) through Fc receptors and are then internalized and degraded (Cines & Blanchette 2002).

There are limited data on the incidence and prevalence of ITP due to a lack of large sample studies. The Platelet Disorder Support Association (PDSA) estimates that there are approximately 20 000 individuals with ITP in the USA alone (PDSA 2005). It is estimated that there are around 100 new cases of ITP per million people each year in the USA, and about half of those affected are children (PDSA 2005). In adults, this disease is more common in women than men (Stasi & Provan 2004; Table 2). It was initially suggested that ITP affects approximately three times more women than men, and that these women were generally aged 20–40 years (Waters 1992). However, more recent studies in Denmark and the UK have suggested that the female–male ratio was 1.7 and 1.2, respectively (Frederiksen & Schmidt 1999; Neylon et al. 2003). In addition, these studies showed that the incidence of ITP was greatest in adults older than 60 years.

The acute and abrupt onset of ITP in children often follows a viral illness (e.g. rubella, mumps, upper respiratory tract infection) or immunization (Stasi & Provan 2004). In children, the prevalence is the same among boys and girls and is most prevalent in children aged 2–6 years. The majority of cases do not require treatment and the disorder usually resolves within 2 to 8 weeks in 80–90% of cases (Dickerhoff & von Ruecker 2000; Kuhne et al. 2001). In contrast, the onset of ITP in adults is insidious and has a chronic course (Table 2).

There are limited studies assessing the morbidity and mortality associated with ITP. It has been shown that ITP has a stable and benign course in adults with mild and asymptomatic thrombocytopenia, and that fewer than 10% of patients develop severe thrombocytopenia that requires treatment (Stasi et al. 1995). Hemorrhage is the primary cause of long-term morbidity and mortality in patients with ITP. Data from 1817 patients with ITP showed that the rate of fatal hemorrhage was between 0.0162 and 0.0389 cases per patient-year at risk (Cohen et al. 2000). This

**Table 2 |** Characteristics of immune thrombocytopenic purpura in children and adults (adapted with permission from Stasi & Provan. *Mayo Clin Proc.* 2004;79:504–522)

	Children	Adults
Peak age incidence (years)	2–6	>50
Sex incidence (M : F)	1 : 1	1 : 1.7
Onset	Acute	Insidious
Preceding infection	Common	Unusual
Usual duration	2–4 weeks	Years
Clinical course (%)		
spontaneous remissions	>80	2
chronic disease	24	43

risk of fatal bleeding was greater in patients older than 60 years (0.130 cases per patient-year) compared with patients younger than 40 years (0.004 cases per patient-year). Predicted 5-year mortality rates were also greater for patients older than 60 years compared with patients younger than 40 years (47.8 vs 2.2%) (Cohen et al. 2000).

Portielje et al. (2001) also reported that most adult patients with ITP have a good outcome with infrequent hospital admissions and no excess mortality compared with the general population. However, patients with severe thrombocytopenia who did not respond to therapy within the first 2 years (persistent low platelet count below  $30 \times 10^9/L$ ) had a four-fold increased mortality compared with the general population (Portielje et al. 2001).

There are no published clinical trials reporting the impact of ITP on the quality of life of patients. However, frequent bruising and bleeding episodes (e.g. nosebleeds that are difficult to stop and bleeding gums during normal dental care), that are symptomatic of ITP symptoms, are often distressing to the patient and their families. In addition, these bleeding episodes are inconvenient (e.g. removing blood stains from clothes), and may disrupt the patient's lifestyle by preventing them from partaking in everyday activities. ITP is often accompanied by fatigue and muscle aches which also impact on the patient's quality of life, especially those patients who normally lead an active lifestyle. Some patients with ITP also report being depressed. This depression may be caused by a lack of platelets which carry the neurotransmitter serotonin to the brain (PDSA 2005).

### Current therapy options

The goal of treatment is to achieve a safe platelet count to prevent major bleeding, while minimizing the adverse effects of the therapy. The ultimate goal of therapy is spontaneous or treatment-induced remission. Currently there are no evidence-based guidelines for the management of thrombocytopenia and limited data are available regarding the relative risks and benefits of various treatment options.

**Table 3** | Current first- and second-line therapy options for immune thrombocytopenic purpura

Therapy	Mechanism of action	Dosage and administration	Response	Duration of treatment or response	Adverse effects/disadvantages
<b>First line</b>					
Oral corticosteroids – prednisone	Not fully elucidated Increase platelet count by impairing ability of macrophages within bone marrow to destroy platelets and decreasing synthesis of autoantibodies has been proposed (Gernsheimer et al. 1989; Fujisawa et al. 1993)	Oral (1 mg/kg per day)	Approximately two-thirds of patients achieve a complete or partial response within the first few wks of treatment (Cines & Blanchette 2002; Stasi & Provan 2004)	No consensus Once platelet count normalizes, prednisone tapered off over approximately 4 wks (BCSH 2003; Stasi & Provan 2004). Long-term remission in 10–20% of patients (Ben-Yehuda et al. 1994; Stasi et al. 1995)	Acute adverse events include hypertension, hyperglycemia, activation of tuberculosis, systemic fungal infection, or acute psychosis Long-term use associated with osteoporosis and manifestations of hypercortisolism (i.e. Cushing syndrome, facial swelling, acne, cataracts, weight gain)
Intravenous immunoglobulin (IVIg) <sup>a</sup>	Not fully elucidated Presence of antiidiotype antibodies in IVIg block Fc receptors on macrophages, preventing them from binding to platelets has been proposed	Slow (several hours) intravenous 1 g/kg per day for 2–3 consecutive days	Approximately 75% of patients respond (Stasi & Provan 2004)	Sustained remission is infrequent, lasting no longer than 3–4 wks	Postinfusion headache – occasionally severe and associated with nausea and vomiting Rare occurrence of renal failure and pulmonary insufficiency Anaphylaxis in recipients with congenital deficiency of IgA Expensive Slow infusion
Anti-D immunoglobulin <sup>b</sup>	Induces immune red blood cell hemolysis, causing decreased function of mononuclear macrophages, preventing splenic destruction of platelets	Single intravenous infusion (50 mg/kg)	Approximately 70% of patients respond (Stasi & Provan 2004)		Fever/chill reactions Lacks efficacy in Rh D-negative and splenectomized patients Hemolytic anemia
<b>Second line</b>					
Splenectomy	Removal of spleen which is the site of platelet destruction and autoantibody synthesis	Surgical procedure	Approximately two-thirds of patients have a sustained response to splenectomy and 10–15% have a partial response (George et al. 1996; Cines & Blanchette 2002; BCSH 2003; Kojouri et al. 2004)	Approximately 75% achieve complete remission 2 case studies (7-year follow-up) demonstrated relapse (Fabris et al. 2001; Schwartz et al. 2003) Bell (2000) suggested that relapse may occur in most patients if the follow-up period is sufficiently long e.g. >7 years	Lifelong reduced natural defence against acute bacterial infections (e.g. sepsis). Risk of fatal infection attributed to absence of a spleen estimated to be 0.73 per 1000 patient-years (Schilling 1995) 26% of patients had postoperative complications (e.g. pulmonary embolism) resulting in prolonged hospitalization or readmission (Portielje et al. 2001)
<p><sup>a</sup>Used to treat internal bleeding when platelet count remains &lt;5 x 10<sup>9</sup>/L despite treatment with corticosteroids or when extensive purpura are present.</p> <p><sup>b</sup>For Rh D-positive patients only.</p> <p>d, day; Rh, rhesus; IgA, immunoglobulin A; wk, week.</p>					

### Current guidelines for ITP

It is well established that current treatment guidelines for ITP from ASH (George et al. 1996; ASH 1997; George & Davidoff 1997) and the BSH (BCSH 2003) are based on expert opinion rather than evidence because of a lack of high-quality clinical trials and long-term outcome data. Due to the lack of evidence-based guidelines, Stasi and Provan (2004), Cines and Bussel (2005), and Chong and Ho (2005) have also published their opinions on the management of ITP based upon literature reviews and their clinical experience. Although these guidelines discuss recommendations for the management of ITP in adults, children, and during pregnancy, this review will focus on the guidelines for ITP in adults.

In adults, it is unusual for ITP to spontaneously remit. Therefore, in cases of ITP associated with a high risk of bleeding, treatment to increase platelet counts should be started. Adults with platelet counts  $<30 \times 10^9/L$  are likely to have significant purpura and some mucosal bleeding. Therefore, BSH guidelines do not recommend treatment in patients with platelet counts  $>30 \times 10^9/L$  unless they are undergoing a procedure which is likely to result in blood loss (i.e. surgery or operative dentistry). In comparison, ASH guidelines recommend treatment in patients with platelet counts  $<20$  to  $30 \times 10^9/L$  (*sic*), or those with counts  $<50 \times 10^9/L$  and significant mucous membrane bleeding or risk factors for bleeding (e.g. hypertension, peptic ulcer disease) (George et al. 1996; ASH 1997). The patient's lifestyle should also be taken into consideration when planning therapy.

Currently, there are three treatment options which are commonly used for initial therapy of ITP; prednisone, intravenous immunoglobulin (IVIg), and anti-D immunoglobulin (Table 3). Splenectomy is a common second-line option. The most convenient and inexpensive option is prednisone. No difference has been demonstrated between these three treatment options in terms of response rate, duration of response or the requirement for a splenectomy at 1 year (Jacobs et al. 1994; George et al. 2003). None of these treatments are particularly effective; for example in patients treated with prednisone, fewer than 10% have a sustained normal platelet response (Stasi et al. 1995). High-dose dexamethasone (40 mg per day for 4 consecutive days) has also been investigated as an initial therapy for adults with ITP (Cheng et al. 2003). The data from this study are promising. Eighty-five percent of patients responded to high-dose dexamethasone, and approximately 42% had a sustained response.

Both the US and British guidelines recommend initial treatment for ITP with oral prednisone (1 mg/kg per day) or oral prednisone in combination with IVIg, dependent upon the platelet count and the presence of bleeding. Alternatively, anti-D immunoglobulin may be used instead of IVIg. However, it is only effective in rhesus (Rh) D-positive patients. Neither of these treatments have been shown to provide long-term remission of ITP. Stasi and Provan (2004) remarked that a "wait-and-see" policy may be preferable in patients without bleeding symptoms to avoid the long-term toxicities associated with treatment. Adults with platelet counts

$<5 \times 10^9/L$  are at high risk of serious hemorrhage and it is recommended that they are treated with intravenous methylprednisolone 1 g/day for 3 days and either anti-D immunoglobulin or IVIg.

If the patient fails to maintain a safe platelet count with prednisone, intravenous anti-D immunoglobulin, and/or IVIg after 3–6 months, both the US and British guidelines recommend a splenectomy as a second-line treatment option, which is associated with a high risk of postoperative complications (Table 3). An alternative to an open splenectomy is a laparoscopic splenectomy which has a quicker recovery and reduced length of hospitalization (Park et al. 2000). Mortality rates for open and laparoscopic splenectomy are 1.0 and 0.2%, respectively (Kojouri et al. 2004). Splenectomy-sparing strategies, including rituximab or danazol, are considered by Cines and Bussel (2005) to defer or avoid the need for splenectomy.

A retrospective analysis of 139 patients with ITP has reported that the age of the patient affects the response to, and adverse effects of, therapy with corticosteroids, splenectomy, and danazol (Andrés et al. 2003). Patients aged  $\geq 60$  years reported a higher incidence of adverse events with corticosteroids, and a lower success rate of splenectomy with more frequent postoperative complications compared with patients aged  $<60$  years. In contrast, patients aged  $\geq 60$  years had a greater response rate to danazol treatment.

### Chronic refractory ITP

Approximately 11–35% of adults with ITP are refractory to conventional treatment (BCSH 2003). These patients are at the greatest risk of death (Portielje et al. 2001). ASH (1997), BSH (BCSH 2003), Stasi and Provan (2004), and Cines and Bussel (2005) recommend several treatment options for chronic refractory ITP (often following a splenectomy), although there is no consensus regarding preferred regimens and the majority often have serious, toxic side effects (Table 4). The therapies most commonly recommended by ASH, dependent on platelet count and the presence of bleeding symptoms, included IVIg, accessory splenectomy, high-dose corticosteroids, danazol, and azathioprine (ASH 1997).

### Unmet needs

As stated previously, current guidelines for the treatment of ITP are generally based on personal opinion rather than clinical evidence. Therefore, to improve the management of ITP there is a need for clinical trials with well-defined outcomes to assist with the development of evidence-based treatment guidelines. Important outcome measures may include platelet count, frequency and severity of bleeding episodes, mortality from bleeding, duration of response, safety and tolerability, quality of life, and cost effectiveness. In addition, there is limited published evidence of the cost effectiveness of current therapy options for ITP. Despite this lack of data, it is evident from existing studies that there is an unmet need for safe and well-tolerated therapies that provide a sustained platelet response.

**Table 4** | Adverse effects of current first- and second-line therapy options for chronic refractory immune thrombocytopenic purpura (adapted with permission from Stasi & Provan. *Mayo Clin Proc.* 2004;79:504–522)

	Adverse effects
<b>First line</b>	
Rituximab <sup>a</sup>	First-infusion reactions
High-dose corticosteroids (methylprednisolone; oral or i.v. dexamethasone)	Diabetes, fluid retention (methylprednisolone), osteoporosis, psychosis, avascular necrosis of femoral head (dexamethasone)
Danazol <sup>a</sup>	Weight gain, hirsutism, liver function disturbances
Immunosuppressive agents (including azathioprine <sup>a</sup> and i.v. cyclophosphamide <sup>b</sup> )	Immunosuppression, neutropenia, liver function disturbances (azathioprine), leukemia, cytopenia, teratogenicity (i.v. cyclophosphamide)
Vinca alkaloids	Neuropathy
Combination chemotherapy <sup>c</sup>	Leukemia, cytopenia, teratogenicity
Dapsone	Hemolysis, nausea, abdominal pain
Cyclosporin <sup>b</sup>	Nephrotoxicity, immunosuppression
<b>Second line</b>	
Campeth-1H	Rigors, fever, lymphopenia
<sup>a</sup> Considered a first-line therapy in patients failing splenectomy (Cines & Bussel 2005), and in the USA it may be considered instead of splenectomy in patients failing initial treatment with steroids (George JN, personal communication 2006). <sup>b</sup> Considered a second-line therapy in patients failing splenectomy (Cines & Bussel 2005). <sup>c</sup> Considered a third-line therapy in patients failing splenectomy (Cines & Bussel 2005). i.v., intravenous.	

The majority of patients with ITP initially respond to short-term treatment with corticosteroids and IVIg. However, in many patients the increase in platelet count is not sustained and they require further treatment. Although corticosteroids are inexpensive and are administered orally, their long-term use is associated with adverse effects such as Cushing syndrome and osteoporosis. In comparison, the use of IVIg is expensive and the time taken for intravenous administration is inconvenient. Anti-D immunoglobulin is less expensive than IVIg and is more convenient to administer because it has a shorter infusion time. However, approximately 16% of the general population are Rh D-negative, and anti-D immunoglobulin is ineffective in this population (National Blood Service 2006). Therefore, splenectomy is generally indicated as a second-line treatment option for those patients failing first-line therapy. Due to the frequent burden of postoperative complications, both to the patient and healthcare systems, and the risk of mortality associated with this treatment, alternative options are required.

In addition to the need for alternatives to splenectomy, there is also a need for safe and effective options for those patients who relapse following a splenectomy (i.e. chronic refractory ITP). Current therapies recommended for chronic refractory ITP are limited. There is no consensus on their use and the majority of treatments are potentially toxic with a low probability of a sustained response (Chong & Ho 2005). Stasi and Provan (2004) highlighted that the treatment of ITP is almost as dangerous as the disease itself due to the similar number of deaths resulting from treatment-related infections compared with hemorrhages.

The symptoms of ITP and the adverse events associated with its treatment may impact on the quality of life of the patient. There is a lack of data for quality of life outcomes in patients with ITP so the effect of current treatment on this outcome remains to be established. Results from an ITP Support Association questionnaire completed by 171 patients with ITP showed that more than 50% of individuals have a fear of bleeding and found the treatment side effects difficult to live with (Watson & Bolton-Maggs 2000). Many individuals feared the side effects of corticosteroids and the risk of sepsis with splenectomy. In particular, adolescents were concerned about the restrictions imposed on their lifestyle.

**New therapies in development**

A number of novel treatment options for thrombocytopenia are currently in development (Table 5). Many of the current therapy options for ITP act by reducing platelet destruction. However, inadequate platelet production is also a contributing factor to thrombocytopenia and has been observed in up to two-thirds of patients with ITP (Stoll et al. 1985; Heyns Adu et al. 1986; Ballem et al. 1987). Aledort et al. (2004) suggested that this inadequate platelet production may occur as a result of accelerated endogenous thrombopoietin (eTPO) clearance and that eTPO replacement therapy may be a potential therapy for the management of ITP.

Thrombopoietin is a cytokine responsible for regulating megakaryopoiesis and the production of platelets. Binding of thrombopoietin to its receptor (Mpl) induces the formation of a Mpl dimer and tyrosine phosphorylation, resulting in the

**Table 5** | Novel treatment options being developed for thrombocytopenia

Therapy	Manufacturer	Phase	Mechanism of action
Eltrombopag	GlaxoSmithKline	Phase III	Low molecular weight, nonpeptidyl thrombopoietin receptor agonist (Luengo et al. 2004)
AMG531	Amgen	Phase III	Recombinant protein with action similar to that of endogenous thrombopoietin. Stimulates the growth and maturation of megakaryocytes by action on the Mpl receptor, resulting in an increase in platelet production (Broudy & Lin 2004)
VB22B ("minibody" agonist antibody)	Chugai	Preclinical	Dimeric covalent antibody fragment, induces dimerization of the thrombopoietin receptor (Orita et al. 2005)

phosphorylation and activation of numerous signaling molecules, including those of the Janus Kinase (JAK) and signal transducers and activators of transcription (STAT) pathway, the mitogen-activated protein kinase (MAPK) pathway, and the phosphoinositide 3-kinase (PI3K) pathway (Ezumi et al. 1995; Geddis et al. 2002). This series of signaling pathways ultimately leads to the stimulation of megakaryocyte development and the production of platelets. However, the complete signal transduction pathway of thrombopoietin has not been fully elucidated.

Several recombinant forms of human thrombopoietin have been investigated, but many companies have abandoned clinical trials with these agents due to the risk of immunogenicity and the need for prolonged administration over 2–3 weeks (Anon. 2005a).

### AMG531

Results from two phase II studies have reported that AMG531 administered by subcutaneous injection once a week or once a fortnight significantly increased platelet counts, and was safe and generally well tolerated (Kuter et al. 2004; Newland et al. 2004; Stepan et al. 2005). However, a number of patients have experienced serious adverse events with AMG531 including bone pain and diffuse reticulon formation in the bone marrow reported as myelofibrosis (Bussel et al. 2005; Stepan et al. 2005). The response to treatment was highly variable between patients which may suggest that individual dose adjustment may be required to achieve the desired outcome (Kuter et al. 2004).

## Drug review

Eltrombopag is an agonist of the thrombopoietin receptor (Mpl) currently in development for the treatment of ITP. The discovery of eltrombopag from a library of 260 000 small molecule compounds, based upon activation of STATs in BAF-3/TPO-R cells, is discussed elsewhere (Luengo et al. 2004).

### Specificity

#### Preclinical evidence

*In-vitro* studies of human bone marrow cells have shown that eltrombopag demonstrated a lack of activity in cell lines that did not express the thrombopoietin receptor (Erickson-Miller et al. 2004a; Table 6). Furthermore, this agonist has demonstrated

species specificity *in vitro* and only activates signaling pathways in human and chimpanzee platelets (Erickson-Miller et al. 2004b; Table 6). Data from sequencing studies suggested that thrombopoietin receptor agonists interact with the histidine 499 and threonine 496 residues to either change the conformation of the receptor or induce dimerization, resulting in activation of the signal transduction pathways of the thrombopoietin receptor (Erickson-Miller et al. 2004b). The species specificity was confirmed *in vivo* by the lack of effect of eltrombopag on platelet count in rats and dogs, in contrast to chimpanzees (Sellers et al. 2004).

### Increased platelet count

#### Preclinical evidence – *in vitro* and *in vivo*

Preliminary *in-vitro* data showed that eltrombopag demonstrated maximal efficacy of thrombopoietin both in the proliferation of BAF-3/TPO-R cells ( $EC_{50} = 30$  nM) and an increase in the number of CD4+ cells, a marker of megakaryocyte differentiation, in human bone marrow cell cultures ( $EC_{50} = 100$  nM) (Luengo et al. 2004). In addition, the proliferative response of eltrombopag was assayed by thymidine incorporation in the human thrombopoietin cell line UT7-TPO and an  $EC_{50}$  of 30 nM was demonstrated (Erickson-Miller et al. 2004a). *In-vitro* studies comparing the biologic activity of eltrombopag with thrombopoietin are detailed in Table 7 (Erickson-Miller et al. 2004a).

The *in-vivo* activity of eltrombopag was initially demonstrated in chimpanzees (Sellers et al. 2004). There was a 1.3- to 2.4-fold increase in platelet count in three chimpanzees following five daily doses of eltrombopag (10 mg/kg per day). Subsequently, the ability of eltrombopag to activate the human thrombopoietin receptor was confirmed by phase I clinical trials.

#### Phase I clinical data

Data from a randomized, single-blind, placebo-controlled study in 72 healthy male volunteers showed that eltrombopag, administered as oral capsules once daily, for 1 day and after a 1 week washout for 10 days increased platelet counts in a dose-dependent manner at oral doses of 30 mg and above (Jenkins et al. 2004; Table 8).

### Safety and tolerability

Data from *in-vitro* studies with platelets obtained from human volunteers showed that eltrombopag does not induce platelet

**Table 6** | Selectivity and specificity of eltrombopag *in vitro* (Erickson-Miller et al. 2004a,b)

Method	Results
<b>Receptor selectivity</b>	
Panel of transfected and nontransfected cell lines in which other cytokines were active (G-CSF, Epo, IL-3, interferon-alfa, or interferon-gamma)	In those cell lines that did not express the thrombopoietin receptor, eltrombopag was inactive over a three-fold concentration range in proliferation, receptor gene, or STAT activation assays
<b>Species specificity</b>	
Electrophoretic mobility shift assay	No signaling in response to eltrombopag detected using platelets of cynomolgus macaques, cat, mouse, rat, pig, ferret, or tree shrew
HepG2 cells transiently infected with human thrombopoietin receptor, murine, or cynomolgus monkey receptor	Only cells transfected with human thrombopoietin receptor had STAT-activated reporter gene activity
Sequencing of thrombopoietin transmembrane domains of mice, dogs, and ferrets	In mice, dogs, and ferrets, thrombopoietin receptor contains Leu 499 Human and chimpanzee thrombopoietin receptor contains His 499
Point mutation replacing Leu with His 499 in thrombopoietin receptor of cynomolgus macaques	Conferred thrombopoietin receptor activity
Point mutation replacing His with Leu 499 in transmembrane domain of human thrombopoietin receptor	Inactive thrombopoietin receptor
HepG2 cells transiently infected with mutated murine G-CSF receptor (point mutation corresponding to His 499)	Conferred thrombopoietin receptor activity
HepG2 cells transiently infected with mutated murine G-CSF receptor (double point mutation corresponding to His 499 and Thr 496)	Conferred thrombopoietin receptor activity
Epo, epoetin; G-CSF, granulocyte colony-stimulating factor; His, histine; IL-3, interleukin-3; Leu, leucine; STAT, signal transducers and activators of transcription; Thr, threonine.	

activation or enhance agonist-induced platelet aggregation (Erhardt et al. 2004).

*In-vivo* eltrombopag was well tolerated in chimpanzees, rats, and dogs at all doses tested (Sellers et al. 2004). Phase I data in healthy volunteers have shown that eltrombopag was well tolerated over a 16-day period with no serious adverse events reported. In addition, there were no significant changes in laboratory or cardiovascular safety parameters (Jenkins et al. 2004). The majority of adverse events were reported to be mild in intensity and self-limiting (no further details reported).

#### Phase II clinical data

Preliminary data from a randomized, double-blind, phase II study in 104 adult patients with ITP (platelet count  $<30 \times 10^9/L$ ), who had failed one prior therapy, demonstrated that eltrombopag (50 or 75 mg) once daily for 6 weeks significantly increased and maintained platelet counts ( $>50 \times 10^9/L$ ) compared with placebo ( $P<0.001$ ) (Anon. 2005b). Of these responders, 87% achieved a platelet counts  $>50 \times 10^9/L$  by day 15. Eltrombopag was well tolerated throughout the study.

Three ongoing phase II trials are currently determining the efficacy and safety of eltrombopag in adults with chronic hepatitis C-related thrombocytopenia, cancer patients receiving multiple cycles of chemotherapy, and adults with refractory ITP.

#### Resource utilization

At this stage in its development, there is no evidence on which to base an assessment of the impact of eltrombopag on resource utilization in the management of ITP, although there are some areas where it could offer an advantage.

Corticosteroids are inexpensive. Therefore, it is likely that they will continue to be used as an initial therapy option for short-term treatment of ITP, despite tolerability issues. Alternative therapies, IVIg and anti-D immunoglobulin, which may be used as first- or second-line therapies, are relatively expensive to produce, and IVIg is inconvenient to administer. Eltrombopag may potentially have resource utilization benefits as a result of better tolerability than corticosteroids, and a lower cost of production and easier route of administration than IVIg and anti-D immunoglobulin.

Existing therapies have a different mode of action to eltrombopag. Corticosteroids, IVIg, and anti-D immunoglobulin act to prevent platelet destruction, whereas eltrombopag increases platelet production. Therefore, eltrombopag may potentially be used alone or in combination with these agents to increase the rate of remission and avoid the need for a splenectomy. It is expected that avoiding the requirement for hospitalization and the potential complications and risk of mortality associated with a splenectomy would be of benefit to the patient and healthcare systems.



**Table 7** | Activity of eltrombopag *in vitro* (Erickson-Miller et al. 2004a)

Method	Results
Western blot analysis for activation of STAT and MAPK pathways using phospho-specific antibodies on lysates of UT7-TPO cells (a thrombopoietin-dependent, megakaryocytic cell line) treated with eltrombopag	Kinetics and level of induction of pathway phosphorylation events with eltrombopag similar to that seen with thrombopoietin
mRNA expression of several early response genes associated with proliferation and thrombopoietin activation (i.e. Fos, EGR-1, and thyroid-like receptor 3) were measured in response to eltrombopag treatment	Kinetics and level of induction of gene expression with eltrombopag similar to that seen with thrombopoietin
Differentiation of normal human bone marrow progenitors (CD34) into CD41+ cells of the megakaryocyte lineage	Eltrombopag activity equal to or better than recombinant thrombopoietin (EC <sub>50</sub> = 100 nM)

EC<sub>50</sub>, the molar concentration of an agonist, which produces 50% of the maximum possible response for that agonist; EGR-1, early growth response-1; MAPK, mitogen-activated protein kinase; mRNA, messenger ribonucleic acid; STAT, signal transducers and activators of transcription.

There are very limited data regarding the economic burden of a splenectomy and the resulting complications on healthcare resources. An economic model with a theoretical cohort of 100 patients was developed to predict the cost of treating ITP patients with anti-D immunoglobulin for 1 year versus an immediate splenectomy (Bennett et al. 2000). The cost of a splenectomy was estimated to be \$US16 000 compared with \$US1213 per anti-D infusion. This predictive cost analysis suggested that a minimum of 47 patients would need to avoid a splenectomy with anti-D immunoglobulin to result in a cost saving. Therefore, it may also be expected that avoidance of splenectomy with eltrombopag would have a beneficial effect on the cost of treatment.

Eltrombopag may also have utility in patients with chronic refractory ITP who have failed a splenectomy. Compared with currently recommended therapies which are associated with toxic effects, eltrombopag is expected to be a safer alternative.

## Drug profile

Eltrombopag is in the early stages of clinical development, and phase I and phase II data reported so far are encouraging.

*In-vitro* and *in-vivo* data have demonstrated the species specificity of eltrombopag and its selectivity for the

thrombopoietin receptor. Results from phase I studies in healthy volunteers showed that eltrombopag  $\geq 30$  mg increased platelet counts to clinically relevant levels ( $>30 \times 10^9/L$ ) and was generally well tolerated. However, long-term data with clinically relevant outcomes in patients with ITP are required to assess the duration of response and long-term safety profile of eltrombopag. Current evidence suggests that eltrombopag will be administered orally once daily which would be an advantage over many of the existing therapies. In order to determine eltrombopag's place in therapy, the outcomes of phase II and phase III trials are required to determine its potential clinical impact.

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**Table 8** | The dose-dependent effect of eltrombopag on mean platelet count in 72 healthy male volunteers (Jenkins et al. 2004)

Oral dose of eltrombopag (mg)	Mean platelet count at baseline/day 1 (platelets/uL)	Maximum mean platelet count at day 14 or 16 (platelets/uL)	Mean increase from baseline (platelets/uL)
Placebo	234 000	255 000	21 000
5	217 000	249 000	32 000
10	251 000	291 000	40 000
20	236 000	279 000	43 000
30	249 000	323 000	74 000
50	254 000	356 000	102 000
75	239 000	357 000	118 000

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