The Effectiveness and Safety of the Thrombopoetin Agonist Romiplostim in the Treatment of Adults with Chronic Idiopathic Thrombocytopenic Purpura

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Abstract

Background: The treatment of chronic idiopathic thrombocytopenic purpura (ITP) has been a challenge for many hematologists and clinicians. Since the development of thrombopoietin (TPO) in 1994 there has been a new surge of research attempting to boost the platelet production potential in patients affected by this disorder. This new attempt is headed by TPO agonist medications, one of them being romiplostim.

Methods: An exhaustive search for studies analyzing the efficacy and safety of romiplostim in the treatment of chronic ITP was conducted. Studies must have had patients with a mean platelet count of 30 x 10^9/L and were otherwise medically uncompromised.

Results: Four studies were selected; two randomized control studies and two cohort studies were selected. Study A had two phases in their study. Phase I revealed that the target goal was not reached in all but one of the patients who received lower dose group (doses less than 1 μg/kg). In Phase II 16 patients evaluated in the 1 and 3 μg/kg cohorts, 10 had reached the target range while 2, who were from the 3 μg/kg cohort, had even exceeded this range. Study B demonstrated that the overall platelet response was 79% (33/42) in splenectomized patients and 88% (36/41) in non-splenectomized patients receiving romiplostim. Study C determined that the most effective way to achieve the target platelet response was to convert the dosage based on patient weight. The researchers in Study D determined that the best starting dose of romiplostim in a phase III trial for Japanese adults with chronic ITP was 3 μg/kg.

Conclusion: The new addition of romiplostim in the treatment of chronic ITP in these studies were effective in raising platelet counts while having only mild to moderate side effects in the majority of the patients. Serious adverse events were not attributed to the use of romiplostim.

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Biography

Sean Wilson is a native of Mission Viejo, California, which is located in the Southern part of Orange County. He was a competitive athlete in water polo goalie while playing in both high school and at a Division One University. He graduated with a Degree in Biological Sciences, with a focus in Physiology at the University of California Irvine in 2005. He spent a total of eight years working full time in the medical field such as in athletic training, physical therapy, surgery and emergency medicine before attending PA school. He has enjoyed an active lifestyle with mountain biking and playing the bass guitar in many bands. He has spent all of his life following the example of Jesus Christ which led him to meeting his wife Deanna while attending a post-college ministry group at Saddleback Church. Together they have two wonderful dogs; Jewels a boxer-greyhound mix, and Bella a Black Labrador Retriever. After graduating from PA school in 2010, Sean plans on returning back home to California to be near his family and to work with both Spanish speaking populations and the military. Serving others in missions alongside his wife and giving to those in need are great passions inside of his heart. He also looks forward to the children that he and his wife will one day have and love with all of their hearts.
Abstract

**Background:** The treatment of chronic idiopathic thrombocytopenic purpura (ITP) has been a challenge for many hematologists and clinicians. Since the development of thrombopoietin (TPO) in 1994 there has been a new surge of research attempting to boost the platelet production potential in patients affected by this disorder. This new attempt is headed by TPO agonist medications, one of them being romiplostim.

**Methods:** An exhaustive search for studies analyzing the efficacy and safety of romiplostim in the treatment of chronic ITP was conducted. Studies must have had patients with a mean platelet count of $30 \times 10^9/L$ and were otherwise medically uncompromised.

**Results:** Four studies were selected; two randomized control studies and two cohort studies were selected. Study A had two phases in their study. Phase I revealed that the target goal was not reached in all but one of the patients who received lower dose group (doses less than $1 \mu g/kg$). In Phase II 16 patients evaluated in the 1 and $3 \mu g/kg$ cohorts, 10 had reached the target range while 2, who were from the $3 \mu g/kg$ cohort, had even exceeded this range. Study B demonstrated that the overall platelet response was 79% (33/42) in splenectomized patients and 88% (36/41) in non-splenectomized patients receiving romiplostim. Study C determined that the most effective way to achieve the target platelet response was to convert the dosage based on patient weight. The researchers in Study D determined that the best starting dose of romiplostim in a phase III trial for Japanese adults with chronic ITP was $3 \mu g/kg$.

**Conclusion:** The new addition of romiplostim in the treatment of chronic ITP in these studies were effective in raising platelet counts while having only mild to moderate side effects in the majority of the patients. Serious adverse events were not attributed to the use of romiplostim.

**Keywords:** Chronic idiopathic thrombocytopenic purpura, adults, romiplostim.
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# Table of Contents

Biography ........................................................................................................................................... 2  
Abstract ........................................................................................................................................... 3  
Acknowledgements ......................................................................................................................... 4  
Table of Contents .......................................................................................................................... 5  
List of Tables ................................................................................................................................... 6  
List of Figures .................................................................................................................................. 7  
List of Abbreviations ......................................................................................................................... 8  
Background ...................................................................................................................................... 9  
Objectives and Methods .................................................................................................................. 17  
Results ........................................................................................................................................... 18  
Discussion ...................................................................................................................................... 25  
Conclusion ..................................................................................................................................... 28  
References ..................................................................................................................................... 30  
Tables ............................................................................................................................................ 36  
Figures ........................................................................................................................................... 39
List of Tables

Table I: Summary Matrix of the Evaluated Studies
Table II: Adverse Events of Study A
Table III: Adverse Events of Study B
Table IV: Adverse Events of Study C
Table V: Adverse Events of Study D
List of Figures

Figure I: Maximum Platelet Response for Phase 1 of Study A

Figure II: Overall Platelet Response for Study B

Figure III: Number of Weeks for Platelet Response in Study B

Figure IV: Patients Receiving Rescue Therapies in Study B
List of Abbreviations

AE .......................................................... Adverse Event
AMG-531 ..................................................... Romiplostim
DIC .......................................................... Disseminated Intravascular Coagulation
EDTA ......................................................... Ethylenediaminetetraacetic Acid
HIV .......................................................... Human Immunodeficiency Virus
ITP .......................................................... Idiopathic Thrombocytopenic Purpura
IVIG .......................................................... Intravenous Immunoglobulins
TPO .......................................................... Thrombopoietin
TTP-HUS ................................................. Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome
URI .......................................................... Upper Respiratory Infection
The Effectiveness and Safety of the Thrombopoetin Agonist Romiplostim in the Treatment of Adults with Chronic Idiopathic Thrombocytopenic Purpura

BACKGROUND

Idiopathic thrombocytopenic purpura (immune thrombocytopenic purpura, ITP) is a platelet deficiency disorder that affects both adults and children equally. It can present in patients as a symptom or during a routine blood screen with patients who are asymptomatic. The symptoms can vary in severity ranging from life threatening occurrences such as intracranial hemorrhage to small petechial lesions and bruising. Other common symptoms include bleeding of mucosal surfaces in the mouth, blood in the stool or urine, and heavy menstrual bleeding. In a Danish study in 1995, the incidence of this disorder in Denmark was reported to be about 22 per million per year. Current research shows the numbers to be closer to 100 per million per year in the United States. Another estimate of the annual incidence of ITP in the United States was 1.6/10,000. Approximately half of ITP cases occur in children between the ages of 2 and 6.

The etiology of this ITP is unclear, however, there have been many ideas postulated. The pathogenesis of ITP is accepted to be concurrent increase of platelet destruction with a decrease of platelet formation. Platelets are rapidly destroyed by platelet-specific antibodies bound to autologous platelets, which are then removed via macrophages along with B and T-helper cells. The Fcγ receptors, which predominate in the spleen and liver, are the target site for this destruction. The platelet production impairment seems to be attributable to both the inhibition of megakaryopoiesis and to the intramedullary destruction of platelets. Autoantibodies are developed and bind to platelets, thereby shortening platelet survival from a duration of two to three days to a matter of minutes. Disappearance of such autoantibodies correlates with the reestablishment of normal platelet counts. Thus, the treatment of this disease is not only seen to decrease the amount of, and rate of, platelet destruction, but to also increase platelet production.
Acute vs. Chronic

The idiopathic thrombocytopenic purpura is characterized as either acute or chronic. Acute ITP, which most often occurs in children and young adults, is defined as occurring for less than 6 months.\textsuperscript{20,42} In acute ITP, the onset of the disorder is abrupt with petichiae and bruising. A female to male ratio is seen to be 1:1. Parents often notice area of bruising from the ankles or waistline of clothing from minor contact. Acute forms of ITP in children are usually self-limited, require little or no treatment and have a spontaneous remission rate of up to 90\%.\textsuperscript{33} One source cites that complete remission is where platelet counts are greater than 150 x 10\(^9\)/L within 6 months of the initial diagnosis, and occur in 67\% of children without the need for platelet therapy.\textsuperscript{6} This article notes that indicators for early remission in children with acute ITP, are abrupt onset of illness, a preceding infection, wet purpura, and a platelet count of less than 5 x 10\(^9\)/L. Remission most often occurs in males under the age of ten.\textsuperscript{6} Although children most often experience acute ITP, as many as 7-28\% will have the disorder long enough for it to be considered chronic.\textsuperscript{27,32}

In chronic ITP individuals have ITP for greater than six months \textsuperscript{6,20,42} while some studies consider a duration beyond three months to be chronic.\textsuperscript{11,46} The majority of patients with chronic ITP are adults with median age of between 40 and 45.\textsuperscript{16} In another large study, however, approximately three quarters of the 934 cases were less than 40 years of age with the variance between 16 and 87 years of age.\textsuperscript{36} Older patients have a greater risk of bleeding due to a higher incidence of coexisting conditions such as hypertension, peptic ulcer disease, and cerebrovascular disease.\textsuperscript{21} In chronic ITP the female to male ratio is greater than that in the acute phase, with a ratio of almost 3:1.\textsuperscript{43} Spontaneous remission in chronic ITP is not common and most patients have a fluctuating course of this disease that may last for days or weeks at a time. If spontaneous remissions do however occur, they are often incomplete. The lower goal of 50 x 10\(^9\)/L or more platelets is satisfactory for the
treatment of patients with chronic ITP. Since most do not ever achieve remission status, the goal of treating chronic ITP has been to reduce the overall incidence of bleeding or clotting deficiencies.

There is no “gold standard” for diagnosing this disease. Since there is no gold standard for the diagnosis of this disease, the diagnosis is generally achieved by exclusion. A good approach is to perform a peripheral smear from a routine complete blood count. Abnormal findings on the slide does not definitively diagnose or rule out ITP as the result could be due to pseudothrombocytopenia or the presence of ethylenediaminetetraacetic acid (EDTA) in the collection tube or a drug such as heparin. Platelets seen with patients of ITP are also abnormally large and have a greater variance in their size and shape than those seen in a normal group of platelets. When measuring thrombopoetin in ITP, in most cases the concentration will not be increased. Although the presence of autoantibodies, can provide support for the diagnosis of ITP, the frequency of false negatives and false positives make this test rather limited. ITP does not cause any changes in the characteristics of bone marrow; therefore, an examination is not necessary, unless the question of differential diagnosis of ITP versus myelodysplastic syndrome in patients who are over 60 years of age presents itself. Moreover, once the diagnosis of ITP has been determined, it is important to investigate the cause of the disorder.

Since the diagnosis of ITP is a diagnosis of exclusion there are a number of disorders or diseases that must be ruled out before making a definitive diagnosis. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) and disseminated intravascular coagulation (DIC) are difficult to distinguish from ITP and misdiagnosis can occur. Schistocytes, which are not commonly seen in patients with ITP are seen in patients with TTP-HUS and in patients who are apslenic. Myelodysplasia, which is commonly seen in patients over 60 may present with the picture of pure thrombocytopenia, hence, the current recommendation of testing bone marrow in such patients. A study by Kuter has demonstrated that the use of romiplostim in the treatment of chronic ITP in humans and in rats has shown to produce a dose-dependent increase in bone marrow fibrosis. They
also showed, however, that the discontinuation of romiplostim from the patients resulted in the reduction of reticulin grading in bone marrow. Reticulin fibrosis is associated with many benign conditions, but also malignant disorders such as various forms of leukemia.29

**Immune vs. Secondary Causes**

There are two classifications of the causes of ITP, idiopathic immune thrombocytopenic purpura, and secondary forms of immune thrombocytopenic purpura. The latter is caused by infections such as HIV or other viruses in children, hepatitis C, or helicobacter pylori; collagen vascular diseases such as systemic lupus erythematosus; different forms of leukemia; or drugs such as trimethoprim-sulfamethoxazole or rifampin. The eradication of helicobacter pylori infections was shown in one systemic review to have a success rate of 51% versus 8% in those who were infected or were not infected, respectively (95% CI 4.2-83).1

**Treatment**

The treatment of ITP is generally reserved for those who are chronic or for those who are in emergent need of treatment due to extremely low platelet counts or uncontrolled bleeding. Initial first line approaches to therapy in non-emergent cases include the use of corticosteroids, intravenous immune globulin (IVIG), or anti-Rh(D). The goal of treatment in chronic ITP is not as much to obtain complete remission since the incidence of this is so low, but to eliminate symptoms of bleeding, and according to most studies, maintain a platelet count of at least 50 x 10⁹/L.

*First line treatments*

The use of steroids is the most commonly used approach to the treatment of ITP, and many hematologists differ in their opinions regarding the dose and strength of the steroids they use. Most adults will have a reoccurrence of thrombocytopenia once the prednisone has been either tapered or discontinued and will require further treatment. There is a concern for the chronic use of corticosteroids inducing osteoporosis, especially in the older population. Therefore, patients using
Corticosteroids are commonly treated simultaneously with calcium and vitamin D supplementation along with close monitoring of their bone mineral density. New studies have addressed the idea of using high-doses of either methylprednisolone or dexamethasone in hopes of having a better chance of achieving remission, having fewer side effects and requiring fewer days of treatment compared to the standard use of prednisone. Although there is no specific conclusion as to which treatment option is best, one systematic review recently suggested that high dose dexamethasone is the best treatment option after an initial diagnosis of ITP.38

The use of IVIG in the treatment of ITP was found by chance while clinicians were treating congenital hypogammaglobulinemia in a child with immune-mediated thrombocytopenia.23 It has since been proven to be a primary medication often for emergent cases or those who are immunocompromised. The downside to this medication is the cost of its use; however, another variation of this drug was developed and is now also widely utilized. This is the creation of an intravenous anti-red cell antibody, also known as anti-Rh(D), which only works with Rh-positive patients, costs one tenth of the use of IVIG, and demonstrates similar efficacy.9 Both IVIG and anti-Rh(D) have been seen to increase platelet counts within several days, making them an effective treatment for those requiring immediate increase of the level of platelets.18

Second Line

After first line treatments have failed, there have been a number of approaches made by hematologists and clinicians. Of these second line treatment options, a splenectomy approach, has been the most traditional, either laparoscopically or in a standard open procedure. One study estimated a complete remission rate as high as 65% post splenectomy in adult patients with chronic ITP.26 Despite the great efficacy of the splenectomy approach, there are risks such as those seen in surgical procedures compounded by an increased susceptibility to fulminant sepsis syndrome, often caused by streptococcus pneumonia. The fear and danger of such complications makes the decision to have a
splenectomy a difficult one. Other second line therapies include the use of immunosuppressive agents such as rituximab, cyclophosphamide, and azathioprine, which have shown promising results in the treatment of chronic ITP in small studies.\textsuperscript{35}

**Thrombopoietin (TPO) agonists**

It was not until recently that the drugs developed and utilized to treat ITP were aimed at reducing the amount of platelet destruction. The success of erythroid and myeloid growth factors has greatly stimulated the growth of erythrocytes and neutrophils, but finding comparable results in the development of hematopoietic growth factors to increase platelet production has been rather difficult. Since the discovery of thrombopoietin (TPO) in 1994, many efforts have been made to achieve the same results. TPO is the only physiologically relevant manager of platelet production by acting to "amplify" the basal production rate of megakaryocytes and platelets. The first generation of TPO agonist drugs developed (rHuTPO, PEG-rHuMGDF), were recombinant human TPO growth factors. They produced promising results in their early studies, but the development of antibodies resulting in thrombocytopenia in approximately 8\% of their patients, resulted in the discontinuation of their clinical development.\textsuperscript{41}

In the later part of 2008, the FDA approved the use of two new thrombopoietin (TPO) mimetic agents romiplostim and eltrombopag. These mimetic agents have been shown to have no sequence homology with TPO, and therefore, the patients do not produce antibodies as seen with the first generation recombinant TPO growth factors.\textsuperscript{19} A key attribute of these TPO mimetic drugs is their ability to dimerize and thereby activate the thrombopoietin receptors. The half lives of the initial mimetic TPO agonist drugs were too short to be clinically active and PEGylation has been employed to prolong the effectiveness of these drugs. The current TPO agonist drugs being studied are either peptide or non peptide mimetics. The overall structure of non peptide mimetics (i.e. eltrombopag) are much smaller than peptide mimetics (i.e. romiplostim) and enable oral dosing versus intravenous and
subcutaneous dosing. Peptide and non peptide mimetics have been found to function by utilizing different signaling pathways and a head to head study of the comparison of these two drugs has not yet been conducted.

Although the ability of using oral dosing method is enticing, there are far more studies studying the efficacy of treating chronic ITP in adult patients with romiplostim rather than eltrombopag. Romiplostim is a peptide mimetic that consists of two identical peptide sequences that are covalently bound and pygylated to increase the half life of the drug. This drug increases megakaryocyte proliferation and differentiation while utilizing the STAT5 and JAK2 signaling pathways. The first-in-human study to test the pharmacodynamics, pharmacokinetics, and overall platelet response in healthy volunteers with romiplostim, was published in 2004 with promising results. This double-blind, placebo-controlled study with 48 subjects, all men, was conducted. It looked at the effects of dosing romiplostim both intravenously (IV) and subcutaneously (SC) in doses ranging from 0.1µg/kg to 10µg/kg in eight equal numbered cohorts. The results of this study determined that the affinity for the Mpl receptor of romiplostim was greater than they anticipated and that the dose of 10µg/kg IV had an increased platelet count as high as 6 fold the baseline count for that individual patient, with a total count being 1.38 million platelets. Fortunately, all patients included in this study, did not have any serious events despite such high platelet counts. The study determined future studies will utilize the SC mechanism of delivery as it was revealed to have a much lower drug exposure as compared to IV treatments. They also concluded that the most effective dose for future treatments of ITP and thrombocytopenia should start at 2.0 µg/kg.

Romiplostim is administered as a subcutaneous injection weekly. Romiplostim has been shown to increase platelet counts starting at day five and peaking at days 12 to 15 in healthy volunteers. Romiplostim has been used to increase platelet counts in patients with chemotherapy-induced thrombocytopenia and one researcher poses the question of romiplostim being an alternative
treatment for patients with chronic ITP other than rituximab who are refractory to steroid use. Such questions and studies have shown the promise of treating patients with chronic ITP in hopes of achieving a minimum platelet goal of 50 x 10^9/L.
Objective

The objective of this study is to evaluate the efficacy and safety of the treatment of adult patients with chronic ITP using romiplostim.

METHODS

An exhaustive literature search using the following search engines was performed: Medline, UpToDate, CINAHL, and Evidence Based Medicine Reviews Multifile using search term key words “idiopathic thrombocytopenic purpura”, “chronic”, “TPO agonists”, “AMG-531”, “romiplostim”, “eltrombopag”, “thrombocytopenia”, “adult”, “refractory”, and “treatments”. The criteria for inclusion in this study were adults, who were diagnosed with chronic ITP and in papers that were published in the English language. They also must have had a mean platelet count of 20 x10⁹/L or less, with normal liver and creatinine enzymes. Papers that conducted long term studies beyond 6 months were not included in this review. The one paper that was found to be longer than 6 months did not have specific patient numbers for AEs that could be utilized in this study. Those also excluded from this study were children, those with a platelet count above 30 x 10⁹/L at the time of enrollment, and patients who were still adjusting ITP medication doses and having no IVIG, IV anti-D, alkylating agents or rituximab treatments in past 2 weeks. Patients with conditions or histories of cardiovascular disease, having a known risk factor for a thrombotic events, active cancer, history of bone marrow disorder, HIV, Hep C or B, and nursing or pregnant women. Two cohort studies and two randomized control trials were selected.
RESULTS

Upon meeting the inclusion and exclusion criteria there were a total of four available studies found for evaluation in this review, discussed below in chronological order. A summary of these studies is provided in Table 1.

Study A

In October of 2006 Bussel et al\textsuperscript{11} published a randomized control trial with phases I and II. Phase I was an open-label, dose escalation trial with sequential cohorts of patients. It states its primary objective as to assess the safety and tolerability of 2 injections of romiplostim in adult patients with ITP. Its secondary objective was to determine what dose would result in a platelet count between 50 x 10\textsuperscript{9}/L and 450 x 10\textsuperscript{9}/L (its target dose) and that was double the baseline, and to determine the adequacy of administering 2 romiplostim injections within a 2-3 week time frame in which to achieve this target dose range. They assigned 4 patients each to cohorts receiving 0.2, 0.5, 1, 3, 6, and 10 µg/kg for a total of 24 patients involved in the study. Of the 24 patients in the study 17 were women, 22 were white, and had a mean age of 45 years. Their mean baseline count was 11 x 10\textsuperscript{9}/L with a median time since their initial diagnosis being 6.2 years. Before the study 19 (79\%) had undergone a splenectomy, while 7 (29\%) were concurrently receiving corticosteroid therapy. The patients were to receive their first injection at day 1, followed by observations for another 14. If at day 15 they had a count less than 50 x 10\textsuperscript{9}/L then they were eligible to receive a second identical dose. If their count was above 50 x 10\textsuperscript{9}/L they were to wait until day 22 and reassessed to whether they had a count above 50 x 10\textsuperscript{9}/L. If still not above 50 x 10\textsuperscript{9}/L, then no second dose was given. The study revealed the results in groups of between doses 0.2, 0.5, and 1 µg/kg (lower dose group) and doses of 3, 6, and 10 µg/kg (higher dose group). The results of the study revealed that the target goal was not reached in all but one of the patients who received lower dose group, and that this patient had received treatment with rituximab 4 weeks prior to the start of the trial. The mean peak counts for the 3, 6, and 10 µg/kg groups were 163 x 10\textsuperscript{9}/L (day
11), 309 x 10⁹/L (day 10), and 746 x 10⁹/L (day 14), respectively (Figure 1). Of the higher dose group, only 4 reached the target range while an additional 3 exceeded it. A list of the most frequent AEs seen with a 10% or greater frequency is provided in Table 2. There were also 3 serious AEs noted in the study, where the investigators determined that only one of them was related to romiplostim. This patient experienced a transient platelet count below their baseline after the discontinuation of the treatment.¹¹

Phase II of the study was a double-blind, placebo-controlled evaluation of romiplostim with ITP patients. Its primary objective was to evaluate the safety of romiplostim and to determine a weekly dose that would result in a platelet count within the target range as previously stated in phase I. There were a total of 21 patients in this study, 4 receiving placebo, 8 receiving 1µg/kg, 8 receiving 3µg/kg and 1 receiving 6µg/kg. Of the 21 patients, 15 were women, 14 were white, and they had a mean age of 49 years. Their mean platelet count at baseline was 16 x 10⁹/L, and 5.2 years had passed since their initial diagnosis of ITP. There was total of 14 (67%) who had previously undergone a splenectomy, and 7 (33%) who were receiving concurrent corticosteroid therapy. The patients were randomly assigned to receive either 1, 3, or 6 µg/kg of romiplostim or placebo in a 4:1 romiplostim to placebo ratio, respectively. The researchers later removed the 6 µg/kg patient from the study as they determined that this would be too high of a dose. The study also withheld doses from patients if during treatment their platelet count exceeded 350 x 10⁹/L. They were then followed up for an additional 6 weeks after the study. The mean time until the first dose peaked the count was seen at 18, 19, and 63 days for the 1 µg/kg, 3 µg/kg and placebo cohorts, respectively. Of the 16 patients evaluated in the 1 and 3 µg/kg cohorts, 10 had reached the target range while 2, who were from the 3 µg/kg cohort, had even exceeded this range. The most frequent AEs can be seen in Table 2. Of the 3 patients with severe AEs, only one as the investigators determined, was due to treatment as a patient had vaginal bleeding with severe, but transient thrombocytopenia 19 days after discontinuation of the treatment.¹¹
Study B

Kuter et al\textsuperscript{30} published a 24 week double blinded randomized control trial study of 125 patients in 2008. The patients were randomly assigned 2:1 to receive weekly subcutaneous injections of romiplostim or placebo, respectively. Before being eligible for the study, the patients had to have had a mean platelet count of less than $30 \times 10^9/L$, with none $\geq 35 \times 10^9/L$. Patients were further analyzed according to by those who had undergone a splenectomy and those who had not. The participant’s characteristics were comparable in the placebo and romiplostim groups, however, in the splenectomized groups the patients had received increased previous ITP treatments, had a lower baseline platelet count, and had higher baseline thrombopoietin concentrations than the non-splenectomized group. The goal of the study was to reach a durable response, defined as weekly platelet responses during 6 or more weeks of the final 8 weeks of treatment. They also looked for the incidence of a transient response, defined as four or more weekly platelet responses without a durable platelet response between weeks 2 to 25. Other important endpoints examined in this study were the frequency of overall platelet response, both transient and durable responses, the proportion of patients requiring rescue drugs, and the number of weekly platelet responses. Rescue drugs were defined as an increased dose of concurrent ITP therapy, or the added use of a new ITP drug to increase platelet counts. The platelet response is seen to be between $50 \times 10^9/L$ and $200 \times 10^9/L$. The groups were initially started with a dose of $1\mu g/kg$ per week and were adjusted as stated in the following:

\textquote{\textbf{2 $\mu g/kg$ every week if the count was $\leq 1 \times 10^9/L$ or less and 2 $\mu g/kg$ every 2 weeks if 11$\times 10^9/L$ to 50$\times 10^9/L$. Once platelets reached more than 50$\times 10^9/L$, the maintenance algorithm was used: dose was increased by 1 $\mu g/kg$ every week if $1 \times 10^9/L$ or less; increased by 1 $\mu g/kg$ after 2 weeks if 11$\times 10^9/L$ to 50$\times 10^9/L$; reduced by 1 $\mu g/kg$ after 2 consecutive weeks at 201$\times 10^9/L$ to 400$\times 10^9/L$; withhold if more than 400$\times 10^9/L$ and subsequent doses reduced by 1 $\mu g/kg$ and given after count was less than 200$\times 10^9/L$.The maximum allowed dose was 15 $\mu g/kg$.}}\textsuperscript{30}

Throughout the first 12 weeks, the mean dose increase for the placebo group was more than 10 $\mu g/kg$ compared to the 3-4 $\mu g/kg$ seen with those who were treated with romiplostim. Within the first
week 25% of the patients receiving romiplostim in both splenectomized and non-splenectomized patients had achieved a platelet response and by the third week this percentage had increased to 50%. The median durable response achieved in the experimental splenectomized patients was between $56 \times 10^9/L$ and $85 \times 10^9/L$, while in the non-splenectomized patients it was between $63 \times 10^9/L$ and $96 \times 10^9/L$. Patients who were receiving placebo achieved a median weekly platelet count during these weeks (18-25 weeks) was $13 \times 10^9/L$ and $21 \times 10^9/L$ for splenectomized patients and $29 \times 10^9/L$ and $38 \times 10^9/L$ for non-splenectomized patients. The overall platelet response was 79% (33/42) in splenectomized patients and 88% (36/41) in non-splenectomized patients receiving romiplostim, compared to 0% of the splenectomized patients and 14% (3/21) non-splenectomized patients receiving placebo (Figure 4). The mean number of weeks with a platelet response was achieved to be 13.8 weeks for the romiplostim treated group and 0.8 weeks for the placebo group. The non-splenectomized groups achieved a better response with 15.2 weeks for the romiplostim group and 1.3 weeks for the placebo group as opposed to 12.3 and 0.2 weeks, respectively (Figure 5). The placebo groups were shown to have required rescue drugs in 59.5% of their patients compared to 21.7% in the treatment groups. The mean number of weeks that achieved the desired platelet response was 13.8 weeks and 0.8 weeks for the romiplostim treated groups and those receiving placebo, respectively. The most common AEs were headaches (35%), fatigue (33%), epistaxis (32%), arthralgias (26%), and contusions (25%) (Table 3). The study concluded that 2.4% (2/83) of the romiplostim treated patients AEs could be attributed to the treatment. One splenectomized patient assigned to romiplostim, who had an increased baseline bone marrow reticulin level, developed additional reticulin after 7 weeks of treatment. The patient’s bone marrow reticulin level returned to baseline 14 weeks later at the next biopsy sample measurement as romiplostim was terminated for this patient. One 82 year old patient, receiving romiplostim, with a history of extensive peripheral vascular disease and atrial fibrillation who had underwent a radial artery thromboemboectomy 8 months prior to the experiment developed a
right popliteal artery thrombosis and a platelet count of $11 \times 10^9$/L. He was able to continue the study after being treated with an embolectomy and anticoagulation. The use of rescue medications was required in 21.7% of the patients in the romiplostim groups. It was noted that only 17.1% of the patients who were non-splenectomized required rescue drugs, while in patients who were splenectomized 26.2% required the assistance of rescue drugs. The placebo groups utilized rescue medications in 57.1% of the splenectomized group, 61.9% of the non-splenectomized group with an overall average of 59.5% (Figure 6).

**Study C**

Newland et al\textsuperscript{34} published their cohort study in 2006, by evaluating a total of 16 adults with chronic ITP and treating them with 30, 100, 300 or 500 µg of romiplostim, subcutaneously. Ten of the sixteen patients were female and fifteen of the sixteen patients were white. Before the start of their study the patients had a mean platelet count of $14.5 \times 10^9$/L with a mean duration of eight years since their initial diagnosis of ITP. Of the 16 patients in the study, 13 had previously undergone a splenectomy procedure, and three were using prednisone concurrently during the study. The study clearly states its two goals, which are to evaluate the safety of romiplostim and to evaluate the efficacy of this drug to achieve their targeted therapeutic platelet levels: stated as doubling the baseline amount and having a count between 50 and $450 \times 10^9$/L. The study lasted for three weeks and patients were followed for an additional eight weeks for an observation period. Two administrations of the assigned dosages were required in this study and patients received their first dose on day one and their second dose on either day 15 or 22. Patients received the second dose on day 22 if, at day 15, they had a platelet count higher than $50 \times 10^9$/L. Of the total 16 patients, 2 were withdrawn from the study after the first injection, one from the 500µg cohort and one from the 300µg cohort, as a result potentially dangerous counts of $1536 \times 10^9$/L and $1062 \times 10^9$/L, respectively.
All 16 patients involved in the study had at least one adverse event (AE). Such AEs were not severe enough to cause any of the patients to withdraw themselves from the study. The most common AEs included headaches (50%), arthralgia (31%), fatigue (25%), contusions (25%), epistaxis (25%), petechiae (25%), ecchymosis (19%), injection site hemorrhage (19%), peripheral edema (19%), and nasopharyngitis (19%) (Table 4). Of the total 4 serious AEs noted in the study, only 2 were treatment induced. The study determined that the most effective way to achieve the target platelet response was to convert the dosage based on patient weight. It was determined that 8 of the 11 patients who received a dosage-equivalent of ≥ 1 µg/kg achieved the target response. The first dose of romiplostim had the highest percentage of reaching the target platelet response as compared to the second dose.

**Study D**

The incidence of chronic ITP in adults in Japan has a rate similar to that seen in Western countries. The recent phase I study shows that the efficacy of romiplostim in healthy Japanese men promoted the continuation of their study. Shirasugi et al published their paper in 2009, as a phase II, open-label, sequential-cohort, dose-escalation study in six Japanese centers as a follow up to the phase 1 study. The study was designed to look at 4 cohorts, with 4 patients in each, and evaluate the efficacy of once weekly dose romiplostim in the sequential dose amounts of 1, 3, 6, and 10 µg/kg over the course of 5 weeks, three of which were follow-up. During the dose-escalation phase a patient receiving a 6 µg/kg dose had a markedly elevated platelet count of 980 x 10⁹/L, and therefore, the 10 µg/kg dose trial was not conducted. A total of 12 Japanese patients were evaluated, 8 of whom were female. They were between the ages of 20 and 70 and had a mean platelet count of less than 30 x 10⁹/L or if they were receiving concurrent steroid therapy less than 50 x 10⁹/L. The goal of the study was to look at the safety and tolerability of romiplostim and its effect on platelet counts in Japanese patients with chronic ITP, and to identify the appropriate starting dose for a phase III trial. Of these patients, those who achieved a platelet response of doubling their count to over 50 x 10⁹/L were
eligible to continue in the treatment-continuation phase. The 12 patients in the study received the scheduled dosing of romiplostim and none discontinued the study. Of the desired platelet responses, 7 of the 12 patients (58.3%) achieved this goal; 1 in the 1 µg/kg cohort, 2 in the 3 µg/kg cohort, and all 4 in the 6 µg/kg cohort. The mean peak platelet response seen in the study ranged from 44 x 10^9/L in the 1 µg/kg cohort to, as high as, 374 x 10^9/L in the 6 µg/kg cohort. None of the patients received rescue medications during the study. Of the 12 patients enrolled in the study, 67% of the patients reported having mild AEs while no serious AEs were recorded during the study and the most common mild AEs were headaches seen in 25% of the total patients in the study.

Of the original patients, 5 of the 12, met the qualifications to enter the treatment-continuation phase, one from the 3µg/kg cohort and all four from the 6µg/kg cohort. They continued the same treatments that they had received in the previous phase for an additional 2 weeks. The patient from the 3µ/kg cohort entered this portion of the study with a baseline platelet count of 6 x 10^9/L. The patient achieved platelet values during the continuation-treatment phase between 19 to 115 x 10^9/L, with half of their weekly counts being over 50 x 10^9/L. All four patients from the 6µg/kg group maintained values over 100 x 10^9/L for 13 additional weeks (with noted variances) until week 14 where 12 weeks after discontinuation of treatment, their mean platelet counts had dropped down to 24 x 10^9/L. The same minor AEs were noted in this phase with no serious AEs accounted for. There was at least one AE in 75% of the 6 µg/kg group and 50% of this group had treatment-related AEs, while the 3 µg/kg group had no such AEs. These AEs were seen both patients were malaise, arthralgia, and contact dermatitis. All five of these patients opted to enter an open-label study to continue the romiplostim treatment. This trial has yet to be published. The researchers in the end determined that the best starting dose of romiplostim in a phase III trial for Japanese adults with chronic ITP was 3 µg/kg.
As seen in Figure 4 there is a compiled list of the most frequent AEs seen in the studies. However, this list does not pertain 100% of the data, since some of the specific AEs were made unavailable in the studies.

**DISCUSSION**

The development of romiplostim was generated to provide an alternative treatment to immunomodulatory therapy, by directing its role in the production of platelets in treating patients with ITP. The most common medical agents such as corticosteroids, IVIG, anti-Rh(D), cyclophosphamide, and rituximab are aimed at decreasing the destruction of platelets in such patient populations, but come with a risk of immunosuppression. Although the risk of sepsis or other such severe infections is rare, finding an effective alternative therapy may become vital in the treatment of patients with chronic ITP, and potentially down the line with acute ITP as often seen in children. The binding of romiplostim to the TPO Mpl receptor has been shown in numerous studies\textsuperscript{11, 34, 47} to stimulate megakaryocytopoiesis and thrombocytopoiesis, thereby increasing platelet numbers. The addition of PEGylating drugs has been proven to promote longer half life in romiplostim as well as the predecessor recombinant TPO growth factors such as PEG-rHuMGDF.

This review of the current research available on the new drug romiplostim, evaluates its efficacy and safety, in the treatment of adults with chronic ITP. Although there have only been a few studies this drug, it has long been used in treating chemotherapy induced thrombocytopenia, immunodeficient induced thrombocytopenia such as occurs in HIV and hepatitis C, and is now being explored in the treatment of chronic ITP. Romiplostim, unlike the first TPO agonist drugs developed, has had no incidence of antibody production in any of its studies as it shares no homology with TPO.
The results of study A revealed that the target goal was not reached in all but one of the patients who received lower dose group (1 µg/kg and lower), and that this patient had received treatment with rituximab four weeks prior to the start of the trial. This provided evidence for this study as well for studies following this, that a dose of less than 1 µg/kg would not produce effective results.

As shown in study B, the overall response rate of romiplostim was shown to be greater than 80%. This is as high a reported efficacy as corticosteroids and intravenous immunoglobulins, and has proven even more effective than other second line treatments such as anti-D, azathioprine, danazol and splenectomy. A large percentage of the subjects in the study, including 63 who underwent a splenectomy as well as other treatments, are considered to be a chronic refractory group. Vesley et al provides the definition of chronic refractory ITP as persistent ITP lasting for more than 3 months, having a failed response to splenectomy and having a platelet count of less than 50 x 10⁹/L. An international committee’s definition even goes as far as establishing the platelet count to be \( \leq 20 \times 10^9/L \).

Study B, also had some serious treatment-related AEs that were not seen in the other three studies. One splenectomized patient assigned to romiplostim, who had an increased baseline bone marrow reticulin level, developed additional reticulin after 7 weeks of treatment. The patient’s bone marrow reticulin level returned to baseline 14 weeks later by the next biopsy sample measurement and romiplostim was terminated for this patient. One 82 year old patient, receiving romiplostim, with a history of extensive peripheral vascular disease and atrial fibrillation who had undergone a radial artery thromboemboectomy 8 months prior to the trial, developed a right popliteal artery thrombosis and a platelet count of 11 x 10⁹/L. He was able to continue the study after being treated with an embolectomy and anticoagulation. Study B did not have a direct AE as a result of treatment with romiplostim, rather, there were AEs as a result of its discontinuation. One patient who had been
receiving the 10 µg/kg dose in phase I saw their platelet count drop below baseline, while one patient in phase II suffered vaginal bleeding and a severe, yet transient episode of thrombocytopenia.

Of the total 4 serious AEs noted in study C, only 2 were treatment induced. These were seen in the 300 µg and 500µg dose cohorts with worsening thrombocytopenia and headache with a transient increase of lactic dehydrogenase, respectively. From looking at the results of this study the researchers determined that the most effective way to achieve the target platelet response was to convert the dosage based on patient weight. It was determined that 8 of the 11 patients who received a dosage-equivalent of ≥ 1 µg/kg achieved the target response.

Study D concluded their study that their study showed that romiplostim for the treatment of Japanese adults with chronic ITP was a safe and well tolerated treatment option. All four of the patients treated with 6µg/kg and one half of the patients treated with 3 µg/kg achieved platelet responses, defined as a doubling of the platelet count above baseline to a level ≥ 50 x 10⁹/L. Although there was a higher response rate with the 6 µg/kg dose than the 3 µg/kg dose, the study concluded that phase III would use the 3 µg/kg dose instead of the higher dose. This appears to be supported by the fact that there was at least one AE in 75% of the 6 µg/kg group and 50% of this group had treatment-related AEs, while the 3 µg/kg group had no such AEs. These AEs were seen both patients were malaise, arthralgia, and contact dermatitis.

Despite the great potential that romiplostim has in treating patients with chronic ITP, there are some drawbacks to using this medication. Minor AEs such as headaches, arthralgias, fatigue, epistaxis and contusions have been commonly seen in all of these studies. In both studies, A and D, there were no serious AEs or rescue medications used, while in study B, 21.7% of the patients treated, required the use of rescue medications. It was noted that only 17.1% of the patients who were non-splenectomized required rescue drugs, while in patients who were splenectomized 26.2% required the assistance of rescue drugs.
Limitations of this Study

Given that such a small number of patients have been involved these studies using romiplostim, small outlier factors may have heavily influenced the results. All of the studies did not look at the overall activity levels of their patients during the experiments. There could be a possible discrepancy between the treatment groups or the control groups. This could result in having one group being more physically active resulting in a lower average platelet count during the prospective study. In study B some of the patients underwent frequent dosage changes as their platelet counts held a narrow range from 50 to 200 x 10^9/L. These patients also could reduce their dosage amount during the study, but never increase it, which could result in a smaller proportion of the patients achieving the target goal for the study. Study B also noted that although the patients in the study fulfilled the American Society of Hematology criteria for ITP, there may have been some who inherited a defect in their platelet production that could have mimicked ITP. It is also important to note that all of the studies were funded and co-written by Amgen Inc, the developer of romiplostim located in Thousand Oaks, CA. In study B, a section states, that Amgen designed the study, did the statistical analysis, collected the data and interpreted it. The coauthors were Dietmar Berger, who co-wrote studies B and D and Janet Nichol who co-wrote all of the studies who both are employed by Amgen, therefore, there is significant potential for bias in these results.

CONCLUSION

Since the development of romiplostim is relatively new, like all of the 2nd generation TPO agonists, the studies on the efficacy and safety of this drug are not numerous enough to become a first line treatment for chronic ITP. As with any new medications with breakthrough potential, there continues to be a need for further evaluation and long term assessment. In spite of the fact that romiplostim, in the treatment of chronic ITP, has only been used in the past few years in very few
patient trials, it still produces promising results. This study looked at two randomized control trials and two cohort studies including 112 patients. It still remains to fully access the possibility of minor and major AEs. There are studies currently under way which will shed some more light on the full potential of this drug and its contribution to the treatment of adults with chronic ITP and to address and fill any unanswered questions. It would be positive if these studies were without the influence of a pharmaceutical company and conducted by independent researchers.
REFERENCES


### TABLE 1: Summary Matrix

<table>
<thead>
<tr>
<th>Author/ Title/ Journal</th>
<th>Yr. published</th>
<th>Patients/ Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome(s)</th>
<th>Study type</th>
<th>Validity (Jadad score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>James B. Bussel et al./ AMG 531, a Thrombopoiesis-Stimulating Protein, for Chronic ITP/ The New England Journal of Medicine</td>
<td>2006</td>
<td>Phase 1: had a total of 24 patients with groups of 4 in six different progressive doses of AMG 531 Phase 2: had a total of 21 patients with 4 assigned to the placebo group and 17 to the experimental group</td>
<td>Phase 1: AMG 531 doses of 0.2, 0.5, 1, 3, 6, and 10 micrograms/kg Phase 2: 8 with 1 micrograms/kg, 8 with 3 micrograms/kg and 1 with 6 micrograms/kg</td>
<td>Phase 1: Individual doses Phase 2: Placebo</td>
<td>Phase 1: dose dependent results with 1/3 of patients with min of 2x baseline platelet levels Phase 2: target platelet range met in 10/16 patients</td>
<td>RCT</td>
<td>5/5</td>
</tr>
<tr>
<td>Adrian Newland et al./ An open-label, unit dose-finding study of AMG 531, a novel thrombopoiesis-stimulating peptibody, in patients with immune thrombocytopenic purpura/ British Journal of Haematology</td>
<td>2006</td>
<td>16 total patients with 4 groups of 4 patients receiving 30, 100, 300 and 500 micrograms of AMG 531</td>
<td>30, 100, 300 and 500 micrograms of AMG 531</td>
<td>To different dosage levels</td>
<td>All patients achieved the target goal of 2x baseline value and between 50 and 450 thousand platelets per micro liter of blood</td>
<td>RCT</td>
<td>5/5</td>
</tr>
<tr>
<td>David J. Kuter et al./ Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial/ The Lancet</td>
<td>2008</td>
<td>63 Splenectomised and 62 non-splenectomised patients with Chronic ITP 42 placebo patients</td>
<td>Romiplostim 1micro-g/kg up to 2micro-g/kg subcutaneously weekly x 24 weeks</td>
<td>placebo</td>
<td>NNT= 1.27 and 1.36 for splenectomized and non-splenectomized patients</td>
<td>RCT</td>
<td>5/5</td>
</tr>
<tr>
<td>Yukari Shirasugi et al./ A phase II, open-labeled, sequential-cohort, dose-escalation study of romiplostim in Japanese patients with chronic immune thrombocytopenic purpura/ Int J Hematol</td>
<td>2009</td>
<td>12 original study patients 5 in the continuation study</td>
<td>Romiplostim 1.3, and 6 µg/kg</td>
<td>To different dosage levels</td>
<td>Starting dose for phase III should be 3 µg/kg</td>
<td>Cohort Study</td>
<td>5/5</td>
</tr>
</tbody>
</table>
**TABLE 2: STUDY A.** Adverse Events occurring in patients at least 10% of the time

<table>
<thead>
<tr>
<th></th>
<th>Phase I</th>
<th>Phase II</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Romiplostim, 0.2–1 µg/kg (N=12)</td>
<td>Romiplostim, 3–10 µg/kg (N=12)</td>
<td>Romiplostim, 1–6 µg/kg (N=17)</td>
</tr>
<tr>
<td><strong>Contusions, ecchymosis, or both</strong></td>
<td>6 (50)</td>
<td>10 (83)</td>
<td>10 (59)</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>6 (50)</td>
<td>5 (42)</td>
<td>5 (29)</td>
</tr>
<tr>
<td><strong>Petichiae</strong></td>
<td>3 (25)</td>
<td>5 (42)</td>
<td>4 (24)</td>
</tr>
<tr>
<td><strong>Epistaxis</strong></td>
<td>1 (8)</td>
<td>2 (17)</td>
<td>7 (41)</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>5 (42)</td>
<td>3 (25)</td>
<td>1 (6)</td>
</tr>
<tr>
<td><strong>Oral mucosal blistering</strong></td>
<td>1 (8)</td>
<td>2 (17)</td>
<td>5 (29)</td>
</tr>
<tr>
<td><strong>Gingival bleeding</strong></td>
<td>1 (8)</td>
<td>2 (17)</td>
<td>4 (24)</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td>1 (8)</td>
<td>3 (25)</td>
<td>2 (12)</td>
</tr>
<tr>
<td><strong>URI</strong></td>
<td>4 (33)</td>
<td>2 (17)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Excoriation</strong></td>
<td>1 (8)</td>
<td>1 (8)</td>
<td>3 (18)</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>3 (25)</td>
<td>0</td>
<td>2 (12)</td>
</tr>
<tr>
<td><strong>Arthralgia</strong></td>
<td>3 (25)</td>
<td>1 (8)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Peripheral Edema</strong></td>
<td>1 (8)</td>
<td>2 (17)</td>
<td>1 (6)</td>
</tr>
<tr>
<td><strong>Rash (NOS)</strong></td>
<td>3 (25)</td>
<td>1 (8)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Worsening of thrombocytopenia</strong></td>
<td>0</td>
<td>1 (8)</td>
<td>3 (18)</td>
</tr>
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**TABLE 3: Study B.** Adverse Events occurring in patients at least 10% of the time

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=41)</th>
<th>Romiplostim (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>13 (32%)</td>
<td>29 (35%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (29%)</td>
<td>28 (33%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>10 (24%)</td>
<td>27 (32%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8 (20%)</td>
<td>22 (26%)</td>
</tr>
<tr>
<td>Contusion</td>
<td>10 (24%)</td>
<td>21 (25%)</td>
</tr>
<tr>
<td>Petichiae</td>
<td>9 (22%)</td>
<td>14 (17%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (15%)</td>
<td>14 (17%)</td>
</tr>
<tr>
<td>Upper resp. infection</td>
<td>5 (12%)</td>
<td>14 (17%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>14 (17%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (7%)</td>
<td>13 (16%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (2%)</td>
<td>12 (14%)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>4 (10%)</td>
<td>11 (13%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (10%)</td>
<td>11 (13%)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>2 (5%)</td>
<td>11 (13%)</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (17%)</td>
<td>10 (12%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5 (12%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Gingival Bleeding</td>
<td>5 (12%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>7 (17%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>6 (15%)</td>
<td>6 (7%)</td>
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### TABLE 4: Study C: Most Common Adverse Events

<table>
<thead>
<tr>
<th>AEs</th>
<th>Percentage (n=16)</th>
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</thead>
<tbody>
<tr>
<td>Headache</td>
<td>50%</td>
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<tr>
<td>Arthralgia</td>
<td>31%</td>
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<tr>
<td>Fatigue</td>
<td>25%</td>
</tr>
<tr>
<td>Contusion</td>
<td>25%</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>25%</td>
</tr>
<tr>
<td>Petichiae</td>
<td>25%</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>19%</td>
</tr>
<tr>
<td>Injection site hemorrhage</td>
<td>19%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>19%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>19%</td>
</tr>
</tbody>
</table>

### TABLE 5: Study D: Most Common Adverse Events

<table>
<thead>
<tr>
<th>AEs</th>
<th>Percentage (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>25%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8.30%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>8.30%</td>
</tr>
<tr>
<td>Muscle tightness</td>
<td>8.30%</td>
</tr>
<tr>
<td>Flushing</td>
<td>8.30%</td>
</tr>
</tbody>
</table>
FIGURES

**Mean Platelet Maximum Response for Study A in Phase 1**

Figure 1: Comparison of 3 different cohort maximum responses

**Overall Platelet Response for Study B**

Figure 2: Overall platelet response
Figure 3: Number of weeks with platelet responses over 24 week period

Figure 4: Patients receiving rescue therapies