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Romiplostim

James E. Frampton and *Katherine A. Lyseng-Williamson*

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Conshohocken, Pennsylvania, USA

Contents

Abstract

▲ Romiplostim is an Fc-peptide fusion protein (or 'peptibody') that stimulates megakaryopoiesis and thrombopoiesis by binding to, and activating, the thrombopoietin receptor.

▲ Because it has no sequence homology to thrombopoietin, romiplostim theoretically avoids the risk of eliciting cross-reacting, neutralizing antibodies to thrombopoietin.

▲ In well designed, 24-week, phase III trials, subcutaneous romiplostim was significantly more effective than placebo in achieving the primary endpoint of a protocol-defined durable platelet response in nonsplenectomized (61% vs 5%) or splenectomized (38% vs 0%) adults with chronic immune (idiopathic) thrombocytopenic purpura (ITP).

▲ Romiplostim was also significantly more effective than placebo with regard to a number of secondary endpoints, including the proportions of patients with an overall (durable plus transient) platelet response or who required ITP rescue medications. The majority of romiplostim-treated patients receiving concurrent ITP drugs were able to reduce or discontinue these therapies.

▲ Platelet response was maintained by most patients during longer-term treatment with romiplostim for up to 3 or 4 years in an open-label extension study.

▲ Romiplostim was generally well tolerated. Almost all adverse events in the phase III studies were of mild-to-moderate intensity; most were unrelated to treatment. Longer-term treatment with romiplostim had an adverse event profile consistent with that observed in the phase III studies.

Features and properties of romiplostim (AMG-531; Nplate™)	
Indication	
Adult chronic immune (idiopathic) thrombocytopenic purpura (ITP)	
Mechanism of action	
Thrombopoietin receptor agonist ('peptibody') that stimulates megakaryopoiesis and thrombopoiesis	
Dosage and administration	
Dose	1–10 μg/kg (adjustable, depending on platelet count)
Route of administration	Subcutaneous
Frequency of administration	Once weekly
Pharmacokinetic profile (following subcutaneous administration of romiplostim 3–15 μg/kg/week in patients with chronic ITP)	
Time to peak serum concentration	7–50 (median 14) hours
Serum half-life	1–34 (median 3.5) days
Most frequent treatment-related adverse events (≥5% incidence) in phase III clinical trials	
Headache, myalgia, fatigue, arthralgia, injection-site bruising, injection-site pain and dizziness	

Immune (idiopathic) thrombocytopenic purpura (ITP) is a relatively common acquired haemorrhagic disorder in adults, with an incidence of ≈2 per 100 000 adults.[1] It is characterized by a low platelet count (typically $<20 \times 10^9$/L at presentation[2]) due to antibody-mediated destruction and impaired production of platelets, and a varying propensity for bleeding.[3,4] Many adults develop chronic ITP that requires long-term therapy.[2,3]

The main goal in the management of ITP is to prevent major bleeding episodes (e.g. intracranial haemorrhage) by increasing the platelet count, while minimizing treatment-related toxicity.[3] Adult ITP patients with a platelet count $<30 \times 10^9$/L or bleeding usually require treatment; their management should also take into account other factors (e.g. age, lifestyle and concomitant medical conditions) that may increase the risk of serious bleeding.[5] Currently available treatments are primarily aimed at decreasing platelet destruction; they include traditional first-line therapies (corticosteroids and immunoglobulins), removal of the spleen (splenectomy) and various agents that have been used in patients with ITP refractory to these initial interventions (e.g. danazol, dapsone, cyclophosphamide, immunosuppressants and rituximab).[3,5] As these treatments may be ineffective, poorly tolerated or unsuitable,[6-9] alternatives are desirable.

Despite the reduced platelet count, ITP is often associated with normal or less-than-expected increases in plasma levels of thrombopoietin,[3,5,10] the principal cytokine regulator of platelet production, which stimulates megakaryopoiesis and thrombopoiesis through binding to its receptor (c-Mpl).[11,12] Another approach to the treatment of ITP, therefore, is to enhance platelet production through stimulation of thrombopoiesis.[11,13] Clinical development of first-generation thrombopoietic agents (recombinant thrombopoietins) was halted due to immunogenicity.[11,13] However, that of nonimmunogenic second-generation c-Mpl agonists has continued; examples include the thrombopoietin peptide mimetic romiplostim (AMG-531; Nplate™) and the thrombopoietin nonpeptide mimetic eltrombopag.[8,11,13,14]

Romiplostim has been investigated for the treatment of ITP and is currently being investigated in chemotherapy-induced thrombocytopenia and thrombocytopenia in myelodysplastic syndrome.[9] This profile briefly discusses the pharmacological properties of romiplostim and focuses on its clinical efficacy and tolerability in the treatment of thrombocytopenia in adults with chronic ITP.

Medical literature on the use of romiplostim in the treatment of chronic ITP was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

- Romiplostim is an Fc-peptide fusion protein (or 'peptibody').[9] It consists of four peptide-containing domains that bind to and activate c-Mpl, and a carrier Fc domain that, by binding to the FcRn salvage receptor and undergoing endothelial recirculation, extends the half-life of the compound in the circulation.[9,11,15]
- Romiplostim effectively mimics thrombopoietin in binding to human c-Mpl,[16] and reportedly uses a random peptide sequence to activate the receptor.[9,15] Like thrombopoietin, binding of romiplostim to murine c-Mpl activates a number of signalling pathways, including tyrosine phosphorylation of c-Mpl, Janus kinase 2 and signal transducer and activator of transcription 5 (STAT5).[16]
- The biological effects of romiplostim on murine megakaryopoiesis *in vitro* are similar to those of endogenous thrombopoietin.[16] It promotes megakaryocytic colony growth (alone and synergistically with other cytokines [erythropoietin, stem cell factor, interleukin-3 and -6]), and increases megakaryocyte ploidy and maturation.[16]
- Because it shares no sequence homology with endogenous human thrombopoietin, romiplostim theoretically avoids the risk of eliciting cross-reacting neutralizing antibodies to thrombopoietin;[5,17] no such antibodies have been observed in clinical trials of romiplostim to date (section 4).

- Romiplostim is associated with dose-dependent increases in platelet counts.[7,15,18,19] In randomized, double-blind, placebo-controlled studies in 48 healthy adult volunteers[15] or 30 healthy adult Japanese volunteers,[18] subcutaneous administration of a single dose of romiplostim 0.1–2.0 μg/kg increased mean platelet counts in a dose-dependent fashion 4–9 days after administration and reached a peak after 12–16 days. Platelet counts were elevated to a similar extent after subcutaneous or intravenous administration of romiplostim 1 μg/kg.[15,18]
- Multiple doses of subcutaneous romiplostim also increased platelet counts in a dose-dependent manner in adult patients with ITP (baseline platelet count $<30 \times 10^9$/L [$<50 \times 10^9$/L if receiving corticosteroids]) in phase I–II multicentre studies.[7,19] Platelet responses (defined as a platelet count of $50–450 \times 10^9$/L and double the baseline level) were shown in patients receiving romiplostim equivalent to ≥1 μg/kg in an open-label dose-finding study (n = 16),[7] and those receiving romiplostim 3, 6 and 10 μg/kg in the open-label phase of a two-phase study (n = 24).[19] Lower doses of romiplostim (i.e. equivalent to <1 μg/kg[7] or 0.2–1 μg/kg[19]) were generally not associated with a targeted platelet response.[7,19]
- In the double-blind, placebo-controlled phase of the two-phase study (n = 21),[19] the targeted platelet range was reached in seven of eight patients receiving romiplostim 1 μg/kg. In the eight patients receiving romiplostim 3 μg/kg, three achieved the targeted platelet response and two exceeded the targeted range. Of the four patients receiving placebo, one (who had undergone a splenectomy 3.5 months prior to the study) had a spontaneous remission. Mean peak platelet counts with romiplostim 1 μg/kg, romiplostim 3 μg/kg and placebo were 135, 241 and 81×10^9/L, respectively. The highest-dose cohort (romiplostim 6 μg/kg; n = 1) was closed early due to concern about the possibility of excessive platelet counts.
- Durable platelet responses were achieved in nonsplenectomized and splenectomized adult patients with chronic ITP who received subcutaneous romiplostim for 24 weeks in two well designed phase III studies[6] (see section 3 for further details).

2. Pharmacokinetic Profile

The pharmacokinetics of romiplostim following subcutaneous[15,18,20] or intravenous[15] administration have been evaluated in studies in healthy adult volunteers[15,18] or adult patients with ITP; results from the latter (which include a long-term open-label extension trial[21] [see section 3 for further details]), have been reported in the US prescribing information.[20] Values presented are means unless otherwise stated.

The pharmacokinetic properties of romiplostim in patients with hepatic or renal impairment, children and the elderly have not been reported.

- In one study,[18] two of eight Japanese volunteers receiving subcutaneous romiplostim 2 μg/kg had detectable serum romiplostim concentrations: 20.8 pg/mL at 24 hours post-dose decreasing to 18.9 pg/mL at 30 hours post-dose; and 47.6 pg/mL at 24 hours post-dose, declining to 24.0 pg/mL at 48 hours post-dose.
- Systemic absorption of romiplostim appears to be slow; the peak serum romiplostim concentration is observed 24–36 hours after subcutaneous administration.[15]
- In patients with chronic ITP, peak serum romiplostim concentrations were seen ≈7–50 (median 14) hours after subcutaneous administration of romiplostim 3–15 μg/kg/week.[20] Interpatient variability was observed, with no apparent correlation between administered romiplostim dosages and serum romiplostim concentrations.[20]
- Serum romiplostim concentrations did not show accumulation following subcutaneous administration of six doses of romiplostim 3 μg/kg/week in patients with ITP.[20] The accumulation at romiplostim dosages >3 μg/kg/week is not known.[20]
- Values for the central volume of distribution of romiplostim were 122, 78.8 and 48.2 mL/kg following single intravenous doses of romiplostim 0.3, 1.0 and 10 μg/kg, respectively.[15] Although the reason for the dose-dependency of the central volume of distribution is unknown, it is postulated that the binding kinetics of romiplostim to c-Mpl receptors on platelets and megakaryocytes could be nonlinear at low drug concentrations.[15]

- The serum half-life of romiplostim ranged from 1 to 34 (median 3.5) days following subcutaneous administration of romiplostim 3–15 μg/kg/week.[20]
- The elimination of serum romiplostim is partly dependent on the c-Mpl receptor on platelets.[20] For a given dose of the drug, therefore, patients with high and low platelet counts are associated with low and high serum romiplostim concentrations, respectively.[20]

3. Therapeutic Efficacy

The efficacy of subcutaneous romiplostim in the treatment of chronic ITP in adult patients was evaluated in two randomized, double-blind, placebo-controlled, multicentre, phase III studies of 24 weeks' duration.[6] These trials were of identical design, with the exception that one enrolled patients who were nonsplenectomized (n = 62), while the other enrolled patients who had undergone splenectomy ≥4 weeks prior to study entry (n = 63).[6] Results from both studies have been reported in a single fully published paper.[6] Additional data are available from a preliminary report of these trials[22] and a US FDA briefing document.[23]

The longer-term efficacy of romiplostim is being assessed in an ongoing, open-label, multicentre extension in patients with chronic ITP who have participated in a previous clinical trial of the drug. A 3-year update from this trial has been published in full;[21] a 4-year update is available as an abstract/poster.[24]

Phase III Studies

With the exception of splenectomy status, eligibility criteria in the two 24-week phase III studies were the same, and included: age ≥18 years; ITP according to American Society of Hematology guidelines; and a baseline platelet count $\leq 30 \times 10^9$/L (mean value of three counts). Patients were not permitted to receive concurrent ITP therapy other than stable dosages of corticosteroids, azathioprine and/or danazol. Intervals of 2–14 weeks were required since the last administration of other ITP therapies.[6]

Patients were randomized to subcutaneous romiplostim (nonsplenectomized n = 41; splenectomized n = 42) or placebo (n = 21 in both trials) administered once weekly for 24 weeks. Thereafter, study treatment was discontinued and patients were followed up for a further 12 weeks or until platelet counts were $<50 \times 10^9$/L.[6]

The initial weekly dose of romiplostim (1 μg/kg) was adjusted (maximum 15 μg/kg) as necessary to achieve and maintain a target platelet count of $50–200 \times 10^9$/L; the median weekly dose of romiplostim was 2 and ≈3 μg/kg in nonsplenectomized and splenectomized patients. During weeks 1–12 only, reductions in concurrent ITP therapies were permitted when platelet counts were $>100 \times 10^9$/L. Throughout the study, increases in concurrent ITP therapies or the use of rescue drugs were allowed at the discretion of the investigator.[6]

Patient demographics and baseline characteristics in the romiplostim and placebo arms within each trial were well matched.[6] In nonsplenectomized patients randomized to romiplostim and placebo, the median age was 52 and 46 years, the median ITP duration was 2.2 and 1.6 years, the proportion of patients receiving at least three previous treatments was 37% and 24%, the median platelet count was 19×10^9/L (both arms), the median plasma thrombopoietin level was 94 and 81 pg/mL, and the proportion of patients receiving concurrent ITP therapies was 27% and 48%. The corresponding values in splenectomized patients randomized to romiplostim and placebo, were 51 and 56 years, 7.75 and 8.5 years, 93% and 95%, 14 and 15×10^9/L, 113 and 124 pg/mL, and 29% (both arms).

Efficacy analyses were performed on the full analysis set, which consisted of all randomized patients.[25] The primary endpoint was a durable platelet response (defined as a weekly platelet response [platelet count of $\geq 50 \times 10^9$/L at a weekly study visit] for ≥6 of the final 8 weeks of treatment). Patients could not be counted as having a durable platelet response if they used rescue medication (defined as an increased dosage of concurrent ITP therapy or the use of any new medication to increase platelet counts) at any time during the study. The rate of overall platelet

response (defined as either a durable platelet response or a transient platelet response [≥4 weekly platelet responses, without a durable platelet response, during weeks 2–25]) and the number of weeks with a platelet response were secondary endpoints. Weekly platelet responses that occurred within 8 weeks of using rescue medication were not counted towards these other platelet outcomes.[6]

Additional secondary endpoints included the proportion of patients discontinuing or reducing concurrent ITP therapy (during weeks 1–12) and the proportion of patients using rescue medications.[6]

Health-related quality of life (HR-QOL) was also examined in both trials using the ITP-patient assessment questionnaire (ITP-PAQ), a disease-specific patient-reported outcomes instrument developed for use in adults with chronic ITP.[26] Although baseline ITP-PAQ scale scores were similar in the romiplostim and placebo arms in each trial, splenectomized patients (n = 58) had significantly ($p \leq 0.04$) lower baseline scores than nonsplenectomized patients (n = 61) for 7 (symptoms, bother, fear, psychological health, work, social activity and overall quality of life [QOL]) of the 10 (symptoms, bother, fatigue, activity, fear, psychological health, work, social activity, women's reproductive health and overall QOL) ITP-PAQ scales, indicating poorer HR-QOL.[26]

- The durable platelet response rate was significantly ($p \leq 0.0013$) higher in romiplostim recipients than in placebo recipients, both in nonsplenectomized and splenectomized patients[6] (figure 1).
- This corresponds to differences between romiplostim and placebo in the proportions of nonsplenectomized and splenectomized patients achieving the primary endpoint of 56% (95% CI 38.7, 73.7) and 38% (95% CI 23.4, 52.8).[6]
- Among nonsplenectomized patients, 21 (51%) of 41 romiplostim recipients compared with 0 of 21 placebo recipients had a durable platelet response while taking a stable dosage of romiplostim (±1 μg/kg) during the final 8 weeks of treatment ($p = 0.0001$).[6,23] The corrresponding results for splenectomized patients were 13 (31%) of 42 romiplostim recipients versus 0 of 21 placebo recipients ($p = 0.0046$).[6,23]
- The overall (durable plus transient) platelet response rate was significantly ($p < 0.0001$) higher in romiplostim recipients than in placebo recipients, both in the trial in nonsplenectomized patients (87.8% vs 14.3%) and the trial in splenectomized patients (78.6% vs 0%). Eleven (27%) of 41 nonsplenectomized and 17 (40%) of 42 splenectomized patients receiving romiplostim had a transient platelet response.[6]
- The mean number of weeks with a platelet response was significantly ($p < 0.0001$) higher in romiplostim recipients than in placebo recipients, both in the trial in nonsplenectomized patients (15.2 vs 1.3 weeks) and the trial in splenectomized patients (12.3 vs 0.2 weeks).[6]
- One-quarter of both nonsplenectomized and splenectomized romiplostim recipients had a platelet response after 1 week, increasing to one-half after 2–3 weeks.[6]
- Seven (8.4%) of the 83 romiplostim recipients (five nonsplenectomized and two splenectomized

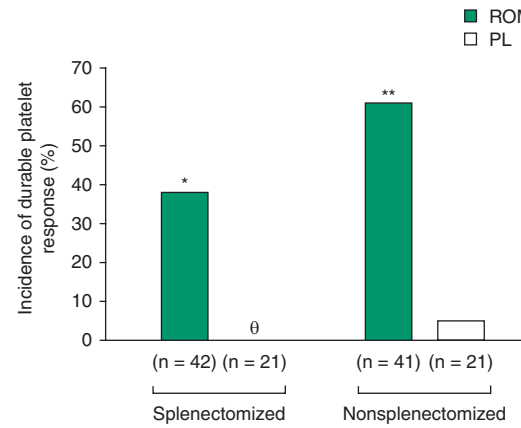

Fig. 1. Efficacy of romiplostim (ROM) in the treatment of chronic immune thrombocytopenic purpura (ITP). Incidence of durable platelet response (primary endpoint; defined as a weekly platelet response [platelet count of $\geq 50 \times 10^9$/L at a weekly study visit] for ≥6 of the final 8 weeks of treatment, with no rescue medication used at any time during the study) in nonsplenectomized and splenectomized chronic ITP patients who received subcutaneous ROM (starting dose 1 μg/kg [maximum dose 15 μg/kg]) or placebo (PL) once weekly for 24 weeks. Data are from two parallel, randomized, double-blind, multicentre, phase III studies of identical design, with the exception that one exclusively enrolled nonsplenectomized patients and the other only splenectomized patients. θ = incidence of 0%; * $p = 0.0013$, ** $p < 0.0001$ vs PL.[6]

patients) had a platelet count $\geq 50 \times 10^9$/L 12 weeks after discontinuing the drug.[6]

- Four (36%) of 11 nonsplenectomized and 8 (67%) of 12 splenectomized romiplostim recipients receiving concurrent ITP therapies discontinued these treatments during weeks 1–12 (as allowed by the trial protocol). The corresponding placebo results were 3 (30%) of 10 nonsplenectomized and 0 of 6 splenectomized patients.[6]
- An additional 4 (36%) of 11 nonsplenectomized and 4 (33%) of 12 splenectomized romiplostim recipients receiving concurrent ITP therapies reduced the dosage of at least one of these treatments by >25% during weeks 1–12. The corresponding placebo results were 2 (20%) of 10 nonsplenectomized and 1 (17%) of 6 splenectomized patients.[6]
- Rescue medications were administered to significantly fewer romiplostim than placebo recipients, both in the trial in nonsplenectomized patients (17.1% vs 61.9%; $p = 0.0004$) and the trial in splenectomized patients (26.2% vs 57.1%; $p = 0.0175$).[6]
- The frequency of administration of immunoglobulin (as rescue medication) was significantly reduced in romiplostim relative to placebo recipients, according to an exploratory pooled analysis.[22] Fewer romiplostim than placebo recipients received immunoglobulin during each 4-week treatment interval (range 1–6% vs 19–37%; $p \leq 0.0173$ for each treatment interval). The cumulative probability of immunoglobulin use during the 24-week treatment period was 0.13 and 0.51 in romiplostim and placebo recipients (hazard ratio 5.31 [95% CI 2.55, 11.06]; $p < 0.001$).
- Pooled data for nonsplenectomized and splectomized patients confirmed the results of the individual studies with respect to the durable platelet response rate (romiplostim 49.4% vs placebo 2.4% [95% CI 35.3, 58.7]; $p < 0.0001$),[23] the durable platelet response rate while taking a stable dosage of romiplostim (41% vs 0%; $p < 0.0001$),[23] the overall platelet response rate (83.1% vs 7.1%; $p < 0.0001$),[6] the mean number of weeks with a platelet response (13.8 vs 0.8 weeks; $p < 0.0001$)[6] and the proportion of patients receiving rescue therapies (21.7% vs 59.5%; $p < 0.0001$).[6]
- Several ITP-PAQ scale scores were improved to a greater extent following treatment with romiplostim than with placebo.[26] Significant improvements with romiplostim relative to placebo were seen for one ITP-PAQ scale score in nonsplenectomized patients (activity; $p = 0.0458$) and four in splenectomized patients (symptoms, bother, social activity and women's reproductive health; all $p \leq 0.0337$).[26]

Open-Label Extension

Patients eligible for the open-label, multicentre extension had completed a prior study of romiplostim for the treatment of ITP (regardless of whether they had received romiplostim or placebo) and had a platelet count $\leq 50 \times 10^9$/L.[21]

Those who previously received romiplostim were initially given the same dosage of the drug as they received in the prior study or 1 μg/kg/week if >24 weeks had elapsed since their last dose or they had previously received placebo.[21] The romiplostim dosage was adjusted throughout the study, depending on platelet response; the target platelet count range was $50–250 \times 10^9$/L. Patients could continue to receive stable dosages of concurrent ITP medications (corticosteroids, azathioprine and danazol).

The 3-year update analysis[21] included 143 enrollees (median age 53 years, splenectomized 60% and baseline concurrent ITP therapy 22%) of whom 142 were treated with romiplostim (mean duration 69 weeks). The 4-year update[24] included 223 enrollees (mean age 50 years, splenectomized 44% and baseline concurrent ITP therapy 15%), of whom 215 were treated with romiplostim (including 11 who received the drug for >192 weeks).

The following results are derived from the 3-[21] or 4-year[24] analysis, as indicated.

- Most patients treated with romiplostim (87%[21] and 74%[24] in the 3-year[21] and 4-year[24] updates, respectively) had at least one platelet response (defined as a platelet count at a scheduled weekly visit that was $\geq 50 \times 10^9$/L and double the platelet count at baseline for the extension, in the absence of rescue medication in the preceeding 8 weeks).

- Between weeks 4 through 144, the platelet response rate ranged from 47% to 74%.[21] The proportion of patients responding was lower in splenectomized versus nonsplenectomized patients, as was the magnitude of the response.
- Platelet responses occurred, on average, for two-thirds of the time on treatment in responding patients.[21]
- Two-thirds of the patients treated with romiplostim had a platelet count $\geq 50 \times 10^9$/L for ≥25 consecutive weeks; 41% had a platelet count $\geq 50 \times 10^9$/L for ≥52 consecutive weeks.[24]
- The mean romiplostim weekly dose increased over the first 24 weeks, but remained relatively stable thereafter.[21,24] The mean average weekly dose was 5.9 μg/kg;[21] in three-quarters of the patients, the romiplostim weekly dose remained within 2 μg/kg of their most frequent dose for at least 90% of the time.
- One-half of the patients receiving concurrent ITP therapy at baseline discontinued this medication altogether.[21,24] An additional one-third[21] or one-quarter[24] reduced the dose of this medication by ≥25%.
- The proportion of patients who used rescue medication ranged between 12% and 24% in the 3-year analysis[21] and 5% and 21% in the 4-year analysis.[24] Rescue medication use was assessed over each 12-week period,[21] or the first and thereafter every fourth 12-week period,[24] between weeks 1 through 156. None of the 11 patients who received romiplostim for >192 weeks required rescue medication.[24]
- The mean platelet count was 108×10^9/L 8 weeks before initiation and 138×10^9/L 8 weeks after initiation in the subgroup of 135 patients who started self-injection of romiplostim (as permitted by the study protocol) [4-year analysis[24]]. The median average weekly romiplostim doses were 4 and 5 μg/kg before and after initiation, respectively. Three patients discontinued self-injection therapy and resumed study site injection.

4. Tolerability

This section primarily focuses on the tolerability of subcutaneous romiplostim in the phase III studies in nonsplenectomized or splenectomized adult patients with chronic ITP,[6] and their ongoing open-label extension[21,24] (see section 2 for study design details). Data from the romiplostim safety database (e.g. as reported in the US prescribing information[20]) are also discussed.

Phase III Studies

Romiplostim had a similar adverse event profile in nonsplenectomized and splenectomized patients; hence, pooled results from the phase III studies have been reported.[6,23,27,28] One nonsplenectomized patient randomized to placebo who mistakenly received romiplostim (three doses) was included as a romiplostim recipient in the safety analysis.[6]

- Romiplostim was generally well tolerated in the phase III studies. Almost all adverse events were mild to moderate in intensity; most were related to the underlying low platelet count.[6]
- All 84 (100%) romiplostim recipients reported an adverse event, 14 (17%) reported a serious adverse event, 34 (40%) reported a treatment-related adverse event and 2 (2%) reported a serious treatment-related adverse event. In comparison, 39 (95%) of 41 placebo recipients reported an adverse event, 8 (20%) reported a serious adverse event and 11 (27%) reported a treatment-related adverse event. No placebo recipient reported a treatment-related serious adverse event.[27]
- The most frequently reported (≥20% incidence in either treatment group) adverse events, regardless of causality, were: headache (35% of romiplostim recipients vs 32% of placebo recipients); fatigue (33% vs 29%); epistaxis (32% vs 24%); arthralgia (26% vs 20%); contusion (25% vs 24%); and petechiae (17% vs 22%).[6] Diarrhoea, upper respiratory tract infection, dizziness, insomnia, myalgia, back pain, nausea, pain in extremity, cough, anxiety, gingeval bleeding, abdominal pain, nasopharyngitis or ecchymosis were reported by 7–17% of romiplostim recipients and 0–17% of placebo recipients.[6]
- The most common adverse events related to romiplostim therapy were headache, myalgia, fatigue, arthralgia, injection-site bruising and pain, and dizziness (figure 2).[27]

- One (of two) serious adverse events related to romiplostim therapy was an additional increase in bone marrow reticulin in a splenectomized patient who already had increased reticulin at baseline, which returned to baseline 3.5 months after discontinuing the drug. The other was a right popliteal artery thrombosis at a platelet count of 11×10^9/L in a splenectomized patient that was successfully treated with embolectomy and anticoagulation, enabling continued study participation.[6]
- Three (3.6%) romiplostim recipients compared with one (2.4%) placebo recipient discontinued treatment due to adverse events.[23]
- Fatal adverse events occurred in a single romiplostim recipient (intracranial haemorrhage 2 weeks after discontinuing the drug) compared with three placebo recipients (one each with cerebral haemorrhage, pulmonary embolism and atypical pneumonia after intracranial haemorrhage).[6]
- Neoplasm adverse events occurred in two (2.4%) romiplostim recipients compared with five (12.2%) placebo recipients.[23] Haematological malignancies occurred in one romiplostim recipient (1.2%; B-cell lymphoma) and one placebo recipient (2.4%; multiple myeloma).[23]
- Thrombotic/thromboembolic adverse events occurred in two romiplostim recipients (2.4%; one each with popliteal artery thrombosis and cerebrovascular accident) and one placebo recipient (2.4%; pulmonary embolus).[6]
- The incidences of grade ≥2 bleeding events were 15% with romiplostim versus 34% with placebo ($p = 0.018$; result reported in poster).[28] The corresponding incidences of grade ≥3 bleeding events were 7% versus 12%. No grade ≥2 bleeding events occurred in patients with platelet counts $>50 \times 10^9$/L; no grade ≥3 bleeding events occurred in patients with platelet counts $>20 \times 10^9$/L.[28]
- Neutralizing antibodies against romiplostim or thrombopoietin were not detected.[6]

Open-Label Extension

The following results are derived from the 3-[21] or 4-year[24] update analyses, as indicated.

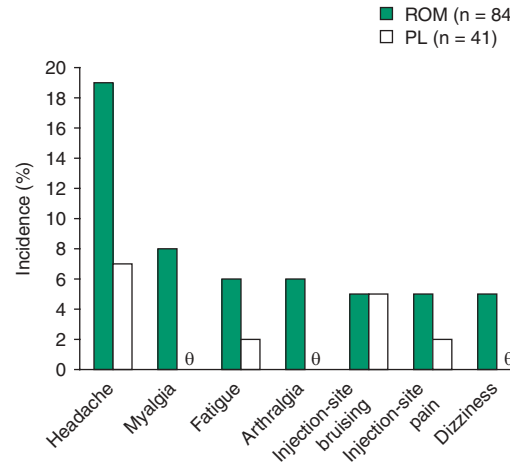

Fig. 2. Tolerability of romiplostim (ROM) in chronic immune thrombocytopenic purpura (ITP). Incidence of treatment-related adverse events occurring in ≥5% of chronic ITP patients receiving either subcutaneous ROM (starting dose 1 μg/kg [maximum dose 15 μg/kg]; n = 84) or placebo (PL; n = 41) once weekly for 24 weeks. Data are pooled from two parallel, randomized, double-blind, multicentre, phase III studies of identical design, with the exception that one exclusively enrolled nonsplenectomized patients and the other only splenectomized patients. θ = incidence of 0%.[27]

- The adverse event profile of romiplostim during treatment for up to 3[21] or 4[24] years was acceptable and generally similar to that in the 24-week phase III studies.
- Adverse events (most commonly headache, contusion, fatigue, epitaxis and nasopharyngitis) were reported by 95% (135 of 142)[21] and 86% (184 of 215)[24] of patients. In most patients, these events were rated as mild or moderate in severity.[21]
- Treatment-related serious adverse events were reported by 9% (13 of 142)[21] and 7% (14 of 215)[24] of patients. In the 3-year analysis,[21] these events included increased bone marrow reticulin (five), thrombotic episodes (five), ITP/bleeding events (two) and increased platelet count (two).
- Fatal adverse events occurred in three[21] and four[24] patients; however, none were related to romiplostim therapy.
- The presence of, or an increase in, bone marrow reticulin was spontaneously reported in eight patients;[21,24] one of these was a participant in the phase III studies (see section 3).

However, the true incidence of this adverse event cannot be determined from this study because bone marrow examinations were not performed routinely (i.e. they were done at the discretion of the investigator) and the exact number of biopsies performed is unknown.[21] The observed bone marrow reticulin increase was not associated with clinical symptoms.

- Thrombotic/thromboembolic complications occurred in seven patients, all of whom had pre-existing risk factors.[21,24]
- Based on the 3-year analysis,[21] a total of 14 severe bleeding events (none life-threatening or fatal) were reported by 12 (8.5%) patients, typically within the first 24 weeks of treatment. In a *post hoc* analysis, the proportion of patients experiencing bleeding events decreased numerically over time; this figure was 42%, 29%, 23% and 20% during weeks 0–24, 24–48, 48–72 and 72–96 of treatment, respectively.[21]
- One patient developed neutralizing antibodies to romiplostim (no clinical sequelae or cross reactivity to thrombopoietin) that were no longer detected 4 months after discontinuing the drug.[21,24]

Safety Database

The romiplostim safety database includes patients with chronic ITP (n = 271), myelodysplastic syndrome (MDS; n = 44) and chemotherapy-induced thrombocytopenia (n = 21) who have been exposed to the drug in clinical trials.[20,29] As indicated, some or all of the patients with chronic ITP were included in the analyses discussed in this section[20,23,29-31] (available as abstracts/posters only[30,31]).

- The short-term tolerability profile of romiplostim in the phase III studies (see discussion earlier in this section) has been substantiated in a larger pooled analysis of 229 patients with chronic ITP, of whom 183 received romiplostim only, 10 received placebo only and 36 received both romiplostim and placebo.[31] According to this analysis,[31] the exposure-adjusted adverse event rates were 1789 and 2274 per 100 patient-years in the romiplostim and placebo recipients. The corresponding exposure-adjusted treatment-related adverse event rates were 197 and 202 per 100 patient-years.[31]
- Ten (3.7%) of 271 patients with chronic ITP had bone marrow reticulin deposition, including four who discontinued treatment because of this adverse event.[20] All patients affected received romiplostim doses ≥5 μg/kg/week; six received doses ≥10 μg/kg/week.[20] Reticulin deposition decreased in several patients following romiplostim discontinuation, with no evidence of chronic idiopathic myelofibrosis attributable to the drug.[31]
- The incidence of haematological malignancies with romiplostim was low and of a similar magnitude to that with placebo in clinical trials of patients with chronic ITP[20] (see discussion earlier in this section). In comparison, 25% of the romiplostim recipients in a noncomparative study of 44 patients with MDS had possible disease progression, including four (9%) who had confirmed acute myelogenous leukaemia.[20] These MDS data, although inconclusive, provide important evidence of a potential risk for haematological neoplasia among those at risk.[29]
- The incidence of thrombotic/thromboembolic complications with romiplostim was of a similar magnitude to that with placebo in clinical trials of patients with chronic ITP[20] (see discussion earlier in this section). According to one analysis,[23] 14 (6.9%) of 204 patients with chronic ITP experienced thrombotic events following exposure to romiplostim in (controlled and uncontrolled) clinical trials.
- Worsening thrombocytopenia (i.e. thrombocytopenia of greater severity than was present prior to romiplostim therapy) was observed in 4 (7%) of 57 patients with chronic ITP who discontinued the drug in clinical studies.[20] This worsened thrombocytopenia was observed in phase I/II studies only, resolved within 2 weeks of discontinuing romiplostim and was not associated with clinically significant bleeding.[20,29] However, worsened thrombocytopenia may increase the risk of bleeding, particularly if romiplostim is discontinued while the patient is receiving anticoagulants or antiplatelet agents.[20]
- Neutralizing antibodies to thrombopoietin were not detected in any of the 236 patients with chronic

ITP who were tested.[30] One patient developed neutralizing antibodies to romiplostim (see discussion earlier in this section), while 5% and 11% of the tested population developed 'binding antibodies' (of uncertain clinical significance) to thrombopoietin and romiplostim.[30]

5. Dosage and Administration

In the US, romiplostim is indicated for the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy.[20] The US label[20] recommends that romiplostim should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding. Additionally, romiplostim should not be used to normalize platelet counts (excessive dosages may increase platelet counts to a level that produces thrombotic/thromboembolic complications).

The recommended starting dosage of subcutaneous romiplostim is 1 μg/kg once weekly; this dosage should be adjusted in increments of 1 μg/kg/week (up to a maximum dosage of 10 μg/kg/week) to achieve and maintain a platelet count of $\geq 50 \times 10^9$/L, as necessary to reduce the risk for bleeding. Romiplostim should not be administered if the platelet count is $>400 \times 10^9$/L; it should be discontinued if the platelet count does not increase after 4 weeks at the maximum dosage.[20]

Local prescribing information should be consulted for full details of contraindications, warnings and precautions that relate to the use of romiplostim.

6. Romiplostim: Current Status

Romiplostim has been approved by regulatory authorities in the US and Australia for the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy.[20,24] In the EU, it has been approved for the treatment of adult chronic ITP splenectomized patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).[32] Additionally, romiplostim may be considered as second-line treatment for adult non-splenectomized patients where surgery is contraindicated.[32]

Subcutaneous romiplostim was significantly more effective than placebo in achieving maintained increases in platelet counts in adult patients with chronic ITP, regardless of splenectomy status, and was generally well tolerated. Romiplostim also resulted in less use of rescue therapies and permitted the majority of patients receiving concurrent ITP drugs to reduce or discontinue these therapies. Most patients experienced a platelet response for much of the time during long-term treatment with romiplostim, which was generally well tolerated.

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Correspondence: *James E. Frampton*, Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand.
E-mail: demail@adis.co.nz