A large observational study of patients with primary immune thrombocytopenia receiving romiplostim in European clinical practice

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Abstract

Objective: Romiplostim has maintained long-term platelet counts in patients with immune thrombocytopaenia (ITP) for up to 5 yr in clinical studies. This prospective observational study aimed to describe romiplostim utilisation and outcomes in European clinical practice. Methods: Adults with primary ITP who received romiplostim in routine care were eligible. Results: Three-hundred and forty patients were eligible for analysis, of whom 299 (88%) completed the 2-yr observation period. The median age was 62 yr, with 43% of patients aged ≥65 yr, and two-thirds of patients initiated romiplostim before splenectomy. The median average weekly dose of romiplostim was 2.8 lµg/kg. The median baseline platelet count was 20 × 10⁹/L, which increased after 2 wk of romiplostim treatment and remained >50 × 10⁹/L thereafter. After romiplostim initiation, there was a decrease in rates of grade ≥3 bleeding events (from 12 to 2 per 100 patient-years) and ITP-related hospitalisations (from 87 to 33 per 100 patient-years). The rate of thrombotic events was 2 per 100 patient-years, and bone marrow fibrosis occurred in two patients. Conclusions: Romiplostim dosing, effectiveness and safety in an unselected real-world ITP population seemed comparable with that observed in clinical studies.

Key words primary immune thrombocytopaenia; romiplostim; observational research; platelet disorders; platelet count; splenectomy

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splenectomised and non-splenectomised patients in two phase 3 studies, allowing many to reduce or discontinue other ITP medications (7). In another phase 3 study in non-splenectomised patients, romiplostim significantly reduced the incidence of treatment failure, splenectomy and use of other treatments compared with the standard of care (8). Romiplostim was well tolerated and has not been associated with clinically significant adverse events in patients with ITP (7, 8). Furthermore, romiplostim efficacy and safety were maintained up to 5 yr (9).

Romiplostim has been approved in ITP for several years now, and information on its utilisation in the European clinical practice setting is currently lacking. The objectives of this large multicentre observational study were to describe the population of patients with ITP treated with romiplostim, as well as romiplostim utilisation, in European routine clinical practice.

Patients and methods

Patients

Eligible patients were at least 18 yr of age with a diagnosis of ITP and had received at least one dose of romiplostim. All patients provided informed consent according to local regulations. Those who had received (or in whom receipt was planned) platelet-related products (e.g., recombinant human thrombopoietin, thrombopoietin receptor agonists, PEG-rHuMGDF) were participating in any interventional clinical study, or who had initiated romiplostim use prior to commercial availability of the product were excluded from the study.

Study design

This was a prospective multicentre, single-arm, observational study conducted in seven countries (Austria, Belgium, Czech Republic, France, Greece, Portugal and Sweden) with centres selected to represent a wide geographical distribution within each country and a mix of academic and non-academic practices. Consecutive patients were to be enrolled, up to a maximum of 25 per centre. Patients were treated according to local practice. Data were collected every 3 months for up to 2 yr after the first dose of romiplostim. Retrospective data were collected for bleeding events (up to 6 months before the first dose of romiplostim) and ITP-related hospitalisations (up to 2 yr before the first dose of romiplostim). Data collected included demographics and patient characteristics, romiplostim dose and administration, use of other therapies for ITP, adverse drug reactions (ADRs) to romiplostim (defined as any undesirable experience that the investigator considered associated with the use of romiplostim) and related resource utilisation, bleeding events and related resource utilisation, and discontinuation of romiplostim. Bleeding events were classified according to the WHO scale (10).

Statistical analyses

Baseline was defined as the time of initiation of romiplostim treatment. The analysis included all patients who met the study eligibility criteria (full analysis set; FAS) and was descriptive in nature. Continuous data were summarised using summary statistics. Categorical data were summarised by the number and percentage of patients in each category. Number of hospitalisations and number of bleeding events were summarised using event rates per 100 patient-years. For patients with a period of withheld doses/missing dosing data between initiation and the final dose of romiplostim, doses were imputed based on the reason: for the reason ‘self-administration’, the last known dose was carried forward, and for the reasons ‘high platelet count/ADR/other’, doses of zero were imputed.

Results

Patients and disposition

A total of 356 patients were enrolled from 73 centres in seven countries. Sixteen patients failed the eligibility criteria and were excluded from the FAS. The FAS thus contained 340 patients, of whom 299 (88%) completed the 2-yr observation period. The main reasons for discontinuation in the observation period were death (n = 25; 7%) and loss to follow-up (n = 9; 3%) (Fig. 1). The median (range) duration of observation was 24 (2.5, 33) months. Just over half of the patients were female (n = 183, 54%), and median age was 62 yr (Table 1). Overall, approximately one-third of patients (34%) were splenectomised before baseline; the rate of prior splenectomy varied by country from a low of 8% in Austria to a high of 73% in Portugal (Table S1). Median age at ITP diagnosis was 55 yr. Median (Q1, Q3) time from ITP diagnosis to first dose of romiplostim (duration of ITP) was 3.3 (0.4, 10.4) yr. In about one-third of patients, romiplostim was initiated within the first year after ITP diagnosis. Compared to all patients, those ≥65 yr of age (43% of the population), had a lower proportion of women (44%), a shorter duration of ITP [median (Q1, Q3) 2.8 (0.3, 8.2) yr], a higher median age at time of ITP diagnosis (71 yr), and a lower proportion of splenectomised patients (25%).

Romiplostim utilisation

The median average weekly dose was 2.8 μg/kg (Table 2) (2.9 μg/kg in patients with prior splenectomy and 2.8 μg/kg in non-splenectomised patients). Most patients (n = 236, 69%) received 1 μg/kg/wk as the starting dose of
romiplostim; the remainder received a starting dose >1 µg/kg/wk. Patients received a median of 64 romiplostim doses during the 2 yr of the study. The average weekly dose of romiplostim remained relatively stable throughout the observation period (Fig. 2A). Median (Q1, Q3) romiplostim exposure was 102 (39, 105) wk. Around one-third of patients (37%) self-injected at least one dose of romiplostim (Table 2). The median (Q1–Q3) baseline platelet count was 20 × 10^9/L (9–35), which rose sharply after 2 wk of romiplostim treatment and remained >50 × 10^9/L thereafter (Fig. 2B).

A total of 142 (42%) patients discontinued romiplostim before the end of the 2-yr observation period. The reasons for romiplostim discontinuation included the requirement for another therapy in 44 (13%) patients; ADR in 16 (5%) patients; death in 9 (3%) patients (reasons included three

Table 1 Demographics and baseline characteristics

| Splenectomised (n = 116) | Non-splenectomised (n = 224) | Age $\geq$65 yr at baseline (n = 147) | FAS (n = 340) |
|--------------------------|-----------------------------|-------------------------------------|--------------|
| Age, yr – median (Q1, Q3) | 56 (40, 69) | 64 (47, 75) | 75 (70, 80) | 62 (46, 72) |
| Weight, kg – mean (SD) | 77 (18) | 76 (16) | 74 (14) | 76 (17) |
| Female, n (%) | 68 (59) | 115 (51) | 65 (44) | 183 (54) |
| ITP duration, yr – median (Q1, Q3) | 9.1 (4.1, 21.6) | 1.3 (0.2, 5.3) | 2.8 (0.3, 8.2) | 3.3 (0.4, 10.4) |
| Age at time of ITP diagnosis, yr – median (Q1, Q3) | 44 (25, 59) | 60 (43, 73) | 71 (65, 78) | 55 (37, 68) |
| Splenectomised before baseline, n (%) | 116 (100) | 0 (0) | 37 (25) | 116 (34) |
| Baseline platelet count ×10^9/L – median (Q1, Q3) | 19 (9, 39) | 20 (9, 34) | 20 (8, 35) | 20 (9, 35) |
| Most common (≥10% frequency) prior ITP medications, n (%) |
| Corticosteroids | 109 (94) | 201 (90) | – | 310 (91) |
| Intravenous immunoglobulin | 87 (75) | 156 (70) | – | 243 (72) |
| Rituximab | 47 (41) | 86 (38) | – | 133 (39) |
| Platelet transfusion | 18 (16) | 41 (18) | – | 59 (17) |
| Cyclosporin | 18 (16) | 19 (9) | – | 37 (11) |
| Danazol | 24 (21) | 11 (5) | – | 35 (10) |
| Azathioprine | 15 (13) | 17 (8) | – | 32 (9) |
| Vinca alkaloids | 13 (11) | 12 (5) | – | 25 (7) |
| Other | 14 (12) | 19 (9) | – | 33 (10) |
| Number of prior ITP medications, n (%) |
| 0 | 3 (3) | 0 (0) | – | 3 (1) |
| 1 | 14 (12) | 44 (20) | – | 58 (17) |
| 2 | 27 (23) | 66 (30) | – | 93 (27) |
| ≥3 | 72 (62) | 114 (51) | – | 186 (55) |

Baseline is defined as immediately prior to romiplostim initiation.
FAS, full analysis set; ITP, immune thrombocytopenia.
patients with cardiac failure and one patient each with acute respiratory failure and renal failure, respiratory failure, pneumonia, multiple organ dysfunction, infection due to cirrhosis and unknown cause); and other unspecified reasons in 33 (10%) patients. The median (Q1, Q3) average weekly romiplostim dose in patients who discontinued early was 3.0 µg/kg (2.0, 5.1) with a median of 38.5 wk exposure to romiplostim; in patients who discontinued due to requirement for alternative therapy, the median average weekly dose was 3.9 (0.8, 10.0) and the median exposure was 41.2 wk. All patients who ended romiplostim early achieved at least one platelet count ≥50 × 10^9/L during romiplostim treatment.

A further 34 (10%) patients discontinued because they had achieved a haemostatic platelet count range with no further treatment needed. The median platelet (Q1, Q3) count at the time of stopping romiplostim in these 34 patients was 188 × 10^9/L (97, 279), and counts were >100 × 10^9/L from week 3 onwards (Figure S1). There were no obvious differences between the characteristics of these patients and those of the overall population: median (Q1, Q3) age was 61 yr (44, 70) and median (Q1, Q3) duration of ITP was 3.4 (0.3, 12.0) yr, with most [20 (59%)] having chronic ITP (>12 months’ disease duration). These patients had received a similar number of prior medications compared with the overall population (59% had received three or more prior medications) and included both splenectomised (41%) and non-splenectomised (59%) patients. The median (Q1, Q3) duration of romiplostim treatment in these patients was 30 (12, 66) wk, considerably shorter than the overall population, and the median average weekly dose was 2.17 µg/kg (1.49, 3.60), somewhat lower than the overall population. During the observation period, one (3%) patient had a splenectomy and five (15%) received rituximab.

### Other ITP therapies
About half (55%) of all patients had received at least three different ITP medications before romiplostim administration (Table 1). The most common prior ITP treatments were

| Table 2 Romiplostim usage and dosing | FAS (n = 340) |
|--------------------------------------|--------------|
| Duration of romiplostim exposure, wks – median (Q1, Q3) | 102 (39, 105) |
| Number of doses – median (Q1, Q3) | 64 (23, 102) |
| Average weekly dose, µg/kg – median (Q1, Q3) | 2.8 (1.6, 4.5) |
| Number of patients with starting dose, µg/kg – n (%) | |
| 1 | 236 (69) |
| 2 | 40 (12) |
| ≥3 | 57 (17) |
| ≥4 | 14 (4) |
| Patients who received ≥1 dose by self-injection – n (%) | 125 (37) |
| Injected by patient under healthcare professional supervision | 98 (29) |
| Injected by family/friend | 27 (8) |

FAS, full analysis set.
corticosteroids (91%), intravenous immunoglobulin (IVIg) (72%) and rituximab (39%). Following initiation of romiplostim, additional ITP therapy was prescribed or continued for 218 (64%) patients at least once during the observation period. The most frequently administered of these medications were corticosteroids (52%) and IVIg (28%). The proportion of patients who used additional ITP therapy declined over time, and patients who were receiving other ITP medications that started before romiplostim initiation were largely able to discontinue within the first 6 months (Table S2).

After discontinuation of romiplostim, 35 (10%) patients subsequently received eltrombopag. The median (Q1, Q3) duration of exposure to romiplostim before switching to eltrombopag was 50 (30, 67) wk, and the median (Q1, Q3) average weekly dose was 4.1 µg/kg (0.5, 9.1). The reasons for discontinuing romiplostim in these patients included the requirement for alternative therapy in 27 (77%) patients, ADR in 3 (9%) patients, haemostatic platelet range in one (3%) patient and ‘other’ in four (11%) patients. Patients who switched to eltrombopag remained in the study for a median (Q1, Q3) of 18 (6, 40) wk. Mean platelet counts in these patients remained above $5 \times 10^{9}$ /L through the end of the study. Thirty-one patients who received eltrombopag completed the observational period and four discontinued (three died and one was lost to follow up). Three patients received subsequent rituximab, and two of 21 non-splenectomised patients underwent splenectomy.

Forty-seven (14%) patients received aspirin and/or oral anticoagulants as additional therapy during romiplostim treatment. Twenty-one (45%) patients used these therapies during ≥75% of the observation period, 10 (21%) patients used them >25% to <75% of the time, and 16 (34%) used them ≤25% of the time.

### Clinical outcomes

Before romiplostim initiation, the rate of grade ≥3 bleeding was 12.1/100 patient-years overall (7.1/100 patient-years for splenectomised patients and 13.4/100 patient-years for non-splenectomised patients) (Table 3). The rate of ITP-related hospitalisation before romiplostim administration was 87.2/100 patient-years overall (57.5/100 patient-years for splenectomised patients and 104.4/100 patient-years for non-splenectomised patients). After romiplostim initiation, there was a decrease in grade ≥3 bleeding events to 2.2/100 patient-years (2.7/100 patient-years for splenectomised patients and 1.6/100 patient-years for non-splenectomised patients). The rate of ITP-related hospitalisations also decreased to 33.3 overall (27.8/100 patient-years for splenectomised patients and 26.0/100 patient-years for non-splenectomised patients). Prior to romiplostim, non-splenectomised patients had higher rates of grade ≥3 bleeding and hospitalisation than splenectomised patients; however, after romiplostim administration, these rates were similar between splenectomised and non-splenectomised patients.

In patients who switched to eltrombopag, there were two grade ≥3 bleeding events (2.9 per 100 patient-years) after initiating eltrombopag, from invasive sites, soft tissue or musculoskeletal bleeding.

In patients aged ≥65 yr ($n = 147$), the rate of grade ≥3 bleeding was 13.8/100 patient-years before romiplostim administration and 4.8/100 patient-years after romiplostim initiation; the rate of ITP-related hospitalisation was 86.1/100 patient-years before romiplostim administration and 53.6/100 patient-years after romiplostim administration (Table S3).

Of the 47 patients who received aspirin and/or oral anticoagulants as additional therapy, grade ≥3 bleeding occurred in

### Table 3 Clinical outcomes by splenectomy status and overall

|                         | Splenectomised (patient-years = 223) | Non-splenectomised | Total (patient-years = 645) |
|-------------------------|--------------------------------------|-------------------|-----------------------------|
|                         | ($n = 116$)                           | ($n = 369$)       | ($n = 340$)                 |
| Grade ≥3 bleeding       |                                      |                   |                             |
| Before romiplostim, $n$ (%) | 4 (3)                               | 9 (4)             | 13 (4)                      |
| Rate per 100 patient-years | 7.1                                 | 13.4              | 12.1                        |
| After romiplostim, $n$ (%) | 3 (3)                                | 4 (2)             | 9 (3)                       |
| Rate per 100 patient-years | 2.7                                 | 1.6               | 2.2                         |
| ITP-related hospitalisations |                                      |                   |                             |
| Before romiplostim, $n$ (%) | 55 (47)                             | 138 (62)          | 193 (57)                    |
| Rate per 100 patient-years | 57.5                                | 104.4             | 87.2                        |
| After romiplostim, $n$ (%) | 26 (22)                             | 47 (24)           | 99 (29)                     |
| Rate per 100 patient-years | 27.8                                | 26.0              | 33.3                        |

ITP, immune thrombocytopenia.

1Data for bleeding and hospitalisations after romiplostim administration exclude 28 patients who underwent splenectomy during the study. These patients are included in the data after romiplostim administration in the Total column; therefore, there are more events in the Total column than the splenectomised plus non-splenectomised columns combined.

2Up to 6 months before first dose of romiplostim.

3Duration between first dose of romiplostim and end of study.

4Up to 2 yr before first dose of romiplostim.

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four (9%) patients before romiplostim initiation (at a rate of 26/100 patient-years); there were no grade ≥3 bleeding events after romiplostim initiation.

**Adverse drug reactions**

Seventy-three (22%) patients experienced a total of 156 ADRs (32.3/100 patient-years). Thirteen (4%) patients experienced 18 serious ADRs (3.7/100 patient-years), including three events of loss of response (reported as platelet count decreased or no therapeutic response); two events each of deep vein thrombosis, pulmonary embolism and myelofibrosis; and one event each of thrombosed haemorrhoids, myocardial infarction, phlebitis, retinal vein thrombosis, transient ischaemic attack, thrombocytosis, acute myeloid leukaemia, chronic myeloid leukaemia and polycythaemia. One (<1%) patient had two simultaneous life-threatening ADRs (0.4/100 patient-years) of thrombocytosis and pulmonary embolism. No fatal ADRs were reported.

Thrombotic ADRs were identified in advance as events of interest. Seven (2%) patients experienced 10 thrombotic ADRs (1.9/100 patient-years) (Table 4). The rate per 100 patient-years was 0.4 for deep vein thrombosis, and 0.2 each for pulmonary embolism, embolism, myocardial infarction, retinal vein thrombosis, transient ischaemic attack and thrombosed haemorrhoids. These rates were similar between splenectomised and non-splenectomised patients, although as the number of events was very small, conclusions are limited. In general, patients who experienced a thrombotic event were elderly, had not previously undergone splenectomy, were not on a high dose of romiplostim and had experienced at least one high platelet count before the event (Table S4).

Five of the 47 patients (11%) who received aspirin and/or oral anticoagulants as additional therapy experienced thromboembolic events (10/100 patient-years).

Bone marrow fibrosis ADRs occurred in two patients: one after 160 d and one after 615 d on observation. Both patients initially responded to romiplostim, but platelet counts subsequently returned to baseline level despite increasing the romiplostim dose to 9 or 10 μg/kg. Both patients discontinued romiplostim after the bone marrow ADR, and follow-up biopsies were not available.

The rate of ADRs in the first 4 wk of romiplostim treatment was similar whether the starting dose was 1 or >1 μg/kg/wk (206 vs. 185/100 patient-years). Grade ≥3 bleeding events in the first 4 wk were experienced by one patient in the 1 μg/kg/wk starting dose group and no patients in the >1 μg/kg/wk group. No patients in the 1 μg/kg/wk starting dose group and four (4%) patients in the >1 μg/kg/wk group experienced an ADR of thrombocytosis, and there were no thrombotic events in the first 4 wk of treatment in either group.

In patients ≥65 yr of age, the rate of ADRs was 32.5/100 patient-years for any ADR, 5.2/100 patient-years for serious ADRs and 3.3/100 patient-years for thrombotic events (Table S3).

**Discussion**

The results of this prospective observational study showed that both splenectomised and non-splenectomised patients with ITP treated with romiplostim in routine clinical practice across Europe experienced fewer bleeding events and ITP-related hospitalisations than before treatment with romiplostim, with an acceptable safety profile. The study was conducted in a range of European countries; other similarly designed observational studies conducted in Germany and central/eastern Europe have reported similar findings, although these were smaller studies with preliminary data (n = 125 and 66, respectively) (11, 12).

**Table 4 Adverse drug reactions (ADRs)**

|                | Splenectomised (n = 172) | Non-splenectomised (n = 292) | Total (n = 483) |
|----------------|--------------------------|-----------------------------|-----------------|
| Patients with any ADR, n (%) | 30 (26)                  | 38 (19)                     | 73 (22)         |
| Exposure-adjusted rate per 100 patient-years | 41.9                     | 26.1                        | 32.3            |
| Patients with serious ADRs, n (%) | 4 (3)                    | 8 (4)                       | 13 (4)          |
| Exposure-adjusted rate per 100 patient-years | 2.9                      | 4.1                         | 3.7             |
| Patients with ADRs leading to romiplostim discontinuation, n (%) | 5 (4)                    | 8 (4)                       | 14 (4)          |
| Exposure-adjusted rate per 100 patient-years | 2.9                      | 3.4                         | 3.3             |
| Patients with thrombotic ADRs, n (%) | 2 (2)                    | 5 (2)                       | 7 (2)           |
| Exposure-adjusted rate per 100 patient-years | 1.2                      | 2.3                         | 1.9             |
| Patients with bone marrow fibrosis ADRs, n (%) | 1 (0.9)                  | 1 (0.4)                     | 2 (0.6)         |
| Exposure-adjusted rate per 100 patient-years | 0.6                      | 0.3                         | 0.4             |

Exposure-adjusted rate based on duration of exposure to romiplostim.

1Data after romiplostim administration exclude 28 patients who underwent splenectomy during the study. These patients are included in the data after romiplostim administration in the Total column; therefore, there are more events in the Total column than the splenectomised plus non-splenectomised columns combined. For non-splenectomised patients, the denominators are 224 patients and 311 patient-years.
During the observation period of the study, romiplostim was indicated in the post-splenectomy setting and could be considered for patients with contraindications to splenectomy (6). We found that only one-third of study participants had undergone splenectomy before receiving romiplostim, with the proportion of patients with prior splenectomy varying widely from country to country. It was not clear from the medical histories of patients who received romiplostim without a prior splenectomy whether or not medical contraindications were present. Furthermore, the low rates of prior splenectomy in some countries reflect the objections of patients (and physicians) concerning splenectomy (13). In addition, 34% of patients received romiplostim for the treatment of newly diagnosed or persistent ITP despite romiplostim being indicated for patients with chronic ITP. A deviation from the SmPC (6) was also seen in terms of the doses recommended, as 31% of patients were treated successfully and safely with a starting dose higher than the recommended 1 µg/kg. Although neither a dosing algorithm nor a target platelet count was predefined as this was an observational study, the median romiplostim dose applied (2.8 µg/kg/wk) and the median long-term platelet count achieved were comparable to those in controlled clinical trials (7, 14). This treatment pattern is remarkable as there is no accepted target platelet count for chronic ITP patients undergoing treatment in the literature.

Although not licensed for ITP treatment, rituximab had been prescribed before romiplostim administration in 39% of patients in this study and up to 20% of romiplostim-treated patients in clinical studies (9). These findings suggest that romiplostim may be an effective treatment option after failure of rituximab. In clinical studies, romiplostim-treated patients were able to reduce or discontinue other ITP medications (7–9), and sparing patients from the adverse effects of corticosteroids is a major goal of therapy. Accordingly, patients in this study who had previous and ongoing treatment with other ITP medications were largely able to discontinue these therapies, and there were substantial reductions in the use of immunosuppressive agents after the first 6 months of romiplostim treatment.

A particularly interesting finding from this real-world study was that 10% of patients were able to discontinue romiplostim due to a haemostatic platelet count. These patients had no apparent differences in baseline characteristics compared with the overall population, and they included patients with chronic ITP and those with and without prior splenectomy. These results support observations from other prospective and retrospective studies, indicating that remission is possible in a proportion of patients treated with romiplostim (5, 15, 16). We note that six of these patients also underwent splenectomy or received rituximab during observation, which may also have contributed to long-term responses. Although we do not know how long the patients from this study were able to continue to maintain platelet counts after withdrawal of romiplostim treatment, a single-arm clinical study that prospectively assessed remission in patients with ITP <6 months duration treated with romiplostim found rates as high as 32% (5), and observational studies with romiplostim or eltrombopag in patients with ITP of longer duration found rates in the range 10% to 15% (15, 16).

The rate of ADRs in this study was lower than the rate of treatment-related adverse events reported in clinical studies: all ADRs, 32 vs. 139/100 patient-years; serious ADRs, 3.7 vs. 8.5/100 patient-years; thrombotic events, 1.9 vs. 2.9/100 patient-years; and bone marrow events, 0.4 vs. 1.2/100 patient-years (17). The lower rate of ADRs collected in this observational study compared with the clinical studies likely reflects reporting bias. Bone marrow ADRs occurred in two patients, both of whom received high doses of romiplostim in the absence of a platelet response. Similar characteristics were observed in a small number of patients with increased reticulin in a prospective clinical study (18). Safety as evaluated by the rates of ADRs during romiplostim treatment was similar among splenectomised and non-splenectomised patients in this study.

Overall, the incidence of thrombotic complications observed in this real-world patient population was comparable to that observed in clinical trials in which patients bearing a high thrombotic risk (e.g. history of previous thrombotic events) were often excluded (19). Among the 14% of patients who received concomitant treatment with aspirin and/or oral anticoagulants, the risk of bleeding did not appear to be increased compared with the rest of the study population.

This study has shown that bleeding and hospitalisation rates were similar in splenectomised and non-splenectomised patients after romiplostim treatment, indicating romiplostim efficacy in both groups. Furthermore, 37% of patients administered romiplostim by self-injection and this subgroup also showed similar safety and efficacy compared with the rest of the cohort, demonstrating that self-administration of romiplostim is feasible in routine clinical practice.

Older patients are not well represented in clinical studies but – consistent with ITP epidemiology (20) – comprised a substantial proportion (43%) of the study population, thereby increasing external validity of data captured in this observational study. Use of romiplostim was associated with strong reductions in grade ≥3 bleeding and hospitalisation in the subset of older patients in this study, although the extent of reductions was somewhat less pronounced than in the overall population. The rate of ADRs overall was similar for both older and overall populations, although older patients experienced numerically higher rates of serious ADRs and thrombotic events. These findings are similar to those of older and younger patients treated with romiplostim in the clinical trial setting (19, 21). Thus, romiplostim may be a safe and effective treatment option for elderly ITP patients.
in whom a splenectomy is considered contraindicated due to increased peri-operative risk.

The inherent limitations of observational studies include potential biases in site and patient selection, and missing or underreported data. To limit the potential for over-representation of treatment practices by one physician or site, the maximum number of patients enrolled by each investigator was restricted to 25. Given potential differences between investigator expertise and characteristics of patients referred to academic vs. non-academic centres, we ensured that both types of centres contributed to the study. It is recognised that data collected retrospectively – such as those for ADRs, hospitalisations and bleeding events – may be less complete than those collected prospectively and that data collected in observational studies may be less complete than those from clinical studies. The reduction in bleeding and hospitalisation reported in our study thus represent a conservative estimate of the true reduction, given potentially incomplete data on historical bleeding and hospitalisation events. The WHO scale (10) was widely used at the time the study started, but is not tailored for ITP. An ITP-specific bleeding assessment tool was developed in 2013 (22), which provides grades and definitions of bleeding manifestations that are more specific to ITP, and this tool should be adopted in future studies.

Due to our efforts to limit bias in this study, we believe that our study population was a representative sample of ITP patients, unlike clinical studies in which the patient population is often not representative due to strict inclusion and exclusion criteria. This study therefore gives us important insights into real-world romiplostim treatment patterns.

In conclusion, this study provided a broad view of ITP patients treated with romiplostim in Europe and confirmed the results of clinical trials, showing that patients experience fewer bleeding events and hospitalisation once treated with romiplostim. This cohort reflects a much broader ITP population representative of clinical practice, supporting the safety and effectiveness of romiplostim in a wide spectrum of patients with ITP, including elderly patients and those with increased thrombotic risk.

Conflict of interest and sources of funding

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Author contributions

M. Steurer performed the research, wrote the manuscript, critically revised the manuscript for important intellectual content and approved the final manuscript. P. Quittet, H. Papadaki, D. Selleslag, F. Viallard, A. Janssens, T. Kozak, G. Kaiäfa and H. Wadenvik performed the research, critically revised the manuscript for important intellectual content and approved the final manuscript. M. Schoonen and G. Kreuzbauer designed the study, critically revised the manuscript for important intellectual content and approved the final manuscript. L. Belton analysed the data, critically revised the manuscript for important intellectual content and approved the final manuscript.

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**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Median (Q1, Q3) platelet counts over time in patients who discontinued romiplostim due to a haematostatic platelet range.

**Table S1.** Baseline splenectomy status by country.

**Table S2.** ITP medications by time interval.

**Table S3.** Clinical outcomes in older patients (≥65 yr).

**Table S4.** Characteristics of patients who experienced thrombotic events.