Eltrombopag versus placebo for low-risk myelodysplastic syndromes with thrombocytopenia (EQoL-MDS): phase 1 results of a single-blind, randomised, controlled, phase 2 superiority trial

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Summary

Background In myelodysplastic syndromes, thrombocytopenia is associated with mortality, but treatments in this setting are scarce. We tested whether eltrombopag, a thrombopoietin receptor agonist, might be effective in improving thrombocytopenia in lower-risk myelodysplastic syndromes and severe thrombocytopenia.

Methods EQoL-MDS was a single-blind, randomised, controlled, phase 2 superiority trial of adult patients with low-risk or International Prognostic Scoring System intermediate-1-risk myelodysplastic syndromes and severe thrombocytopenia. Patients with a stable platelet count of lower than 30×10^9 platelets per L, aged at least 18 years, with refractoriness, ineligibility to receive treatment with alternative medications, or relapse while receiving treatment with alternative medications were included in this trial. Patients were randomly assigned (2:1) to receive eltrombopag (50 mg to 300 mg) or placebo for at least 24 weeks and until disease progression and were masked to treatment allocation. Here, we report the results in the intention-to-treat population of the first phase of the trial, for which the primary endpoints were the proportion of patients achieving a platelet response within 24 weeks and safety. The interim analysis presented here was protocol-specified and used a two-sided significance level of 0·001 and a p value at or below this limit for both primary endpoints to indicate the need for early trial termination. Duration of platelet transfusion independence, duration of response, overall survival, leukaemia-free survival, and pharmacokinetics will be reported at the end of the phase 2 portion of the trial. This trial is registered with EudraCT, number 2010-022890-33.

Findings Between June 13, 2011, and June 17, 2016, we enrolled 90 participants for the first phase of the trial. The median follow-up time to assess platelet responses was 11 weeks (IQR 4–24). Platelet responses occurred in 28 (47%) of 59 patients in the eltrombopag group versus one (3%) of 31 patients in the placebo group (odds ratio 27·1 [95% CI 3·5–211·9], p=0·0017). During the follow-up, 21 patients had at least one severe bleeding event (WHO bleeding score ≥2). There were a higher number of bleeders in the placebo (13 [42%] of 31 patients) than in the eltrombopag arm (eight [14%] of 59 patients; p=0·0025). 52 grade 3–4 adverse events occurred in 27 (46%) of 59 patients in the eltrombopag group versus nine events in five (16%) of 31 patients in the placebo group (χ^2=7·8, p=0·0053, stopping rule not reached). The outcome acute myeloid leukaemia evolution or disease progression occurred in seven (12%) of 59 patients in the eltrombopag group versus five (16%) of 31 patients in the placebo group (χ^2=0·06, p=0·81).

Interpretation Eltrombopag is well-tolerated in patients with lower-risk myelodysplastic syndromes and severe thrombocytopenia and is clinically effective in raising platelet counts and reducing bleeding events. The assessment of long-term safety and efficacy of eltrombopag and its effect on survival (phase 2 part of study) is still ongoing.

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Introduction

Myelodysplastic syndromes are clonal myeloid neoplasms characterised by ineffective haemopoiesis, dysplastic haemopoiesis, cytopenias, and a substantial risk of progression to acute myeloid leukaemia.[1] Anaemia is prevalent in individuals with myelodysplastic syndromes, but about 10% of individuals with low-risk myelodysplastic syndromes (low-risk and intermediate-1-risk, according to the International Prognostic Scoring System [IPSS]) have thrombocytopenia with platelet counts lower than 30×10^9 platelets per L.[2,3] In such patients, both low platelet counts and platelet function abnormalities contribute to the risk of bleeding.[3] New prognostic scoring systems, such as the revised IPSS, take into account the effect of thrombocytopenia severity on survival.[4–6]

Patients with low-risk myelodysplastic syndromes and thrombocytopenia receive platelet transfusions, mainly in the presence of either bleeding or severe thrombocytopenia (<10×10^9 platelets per L).[7] Short therapeutic effect and refractoriness to platelet transfusions provide an impetus

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See Online for appendix

Research in context

Evidence before this study

In 2009, we did a literature search using the PubMed database to identify published studies of the effect and treatment of thrombocytopenia in myelodysplastic syndromes, with no date restrictions. We used the search terms "thrombocytopenia" and "myelodysplastic syndromes". The search returned a number of reviews describing the negative effect of thrombocytopenia on patients with myelodysplastic syndromes. In low-risk and International Prognostic Scoring System (IPSS) intermediate-1-risk myelodysplastic syndromes with severe thrombocytopenia, the only globally accepted treatment was platelet transfusions; the hypomethylating and disease-modifying drug azacitidine was approved by the US Food and Drug Administration, but not specifically for the treatment of thrombocytopenia. No report had yet been published of a randomised clinical trial assessing a thrombopoietin-receptor agonist in this indication. Phase 1/2 trials with romiplostim had yielded some positive safety and efficacy data, but no assessment of eltrombopag in myelodysplastic syndromes had yet been published or registered on the ClinicalTrials.gov website.

Added value of this study

To our knowledge, this is the first randomised, placebo-controlled clinical trial to assess eltrombopag in the treatment of patients with low-risk and IPSS intermediate-1-risk myelodysplastic syndromes and thrombocytopenia. The results obtained showed that treatment with eltrombopag induces platelet responses and improvements in patient-reported outcomes (quality of life). Progression of myelodysplastic syndromes and acute myeloid leukaemia evolution did not differ in patients receiving eltrombopag versus those allocated to placebo. Treatment-related adverse events, particularly nausea and vomiting, were problematic in a few patients, and led to five premature discontinuations in the eltrombopag group; however, the treatment was well tolerated overall. Our findings confirm eltrombopag as an important new therapeutic option for thrombocytopenia in patients with low-risk and IPSS intermediate-1-risk myelodysplastic syndromes, and the first oral drug to be proven beneficial in this setting.

Implications of all the available evidence

The development of treatments for cytopenias associated with myelodysplastic syndromes is a key therapeutic aim. Recent trials of eltrombopag in intermediate-2-risk and high-risk myelodysplastic syndromes showed no evidence of clinical benefits; however, the positive results that we report show the potential of eltrombopag in lower-risk myelodysplastic syndromes. Our findings might provide valuable evidence to support the approval of this new therapeutic option for the subset of patients with myelodysplastic syndromes and severe thrombocytopenia.

to research novel treatments.[8,9] Azacitidine is approved by the United States Food and Drug Administration for the treatment of patients with myelodysplastic syndromes, including low-risk patients with thrombocytopenia,[10] whereas the European Medicines Agency limits treatment with azacitidine to IPSS intermediate-2 and high-risk patients.[11] Therefore, the treatment of thrombocytopenia in low-risk patients remains a medical need that is unmet in most parts of the world.[12]

Thrombopoietin is the principal cytokine involved in the regulation of platelets by binding to its specific cellular receptor TPO-R.[13] Eltrombopag is an orally bioavailable, small molecule TPO-R agonist that is approved in Europe and the USA for the treatment of a subset of patients with immune thrombocytopenic purpura or idiopathic thrombocytopenic purpura in adult patients with chronic hepatitis C virus infection to facilitate interferon-based therapy, and adult patients with acquired severe aplastic anaemia who show an insufficient response to immunosuppressive therapy.[14,15] We designed this phase 2 clinical trial to assess eltrombopag in adult patients with low-risk or IPSS intermediate-1-risk myelodysplastic syndromes and severe, persistent thrombocytopenia (<30×10^9 platelets per L).

Methods

Study design and participants

EQoL-MDS was a randomised, single-blind, placebo-controlled, phase 2 superiority trial in patients with myelodysplastic syndromes from hospitals in Italy, France, Germany, and Slovenia. The trial was divided into two phases: the first (phase 1) was to determine the efficacy and safety of eltrombopag and the second was to assess the long-term response and safety (phase 2; appendix p 2). This trial reports phase 1 outcomes.

Patients had centrally and blinded confirmed morphological diagnosis of low-risk or IPSS intermediate-1 risk myelodysplastic syndromes with a stable platelet count of lower than 30×10^9 platelets per L. Cases with more than 5% blasts were not included in France. Patients aged at least 18 years, with refractoriness, ineligibility to receive treatment with alternative medications, or relapse while receiving treatment with alternative medications were included in this trial. Erythropoiesis-stimulating drugs or granulocyte colony-stimulating factor were permitted during the trial, as per accepted standards. Patients were excluded from the study if they had received previous chemoradiotherapy or TPO-R agonists; peripheral monocytosis of more than 1×10^9 cells per L or leukocytosis of at least 25×10^9 cells per L; marrow fibrosis with an inability to aspirate marrow; an Eastern Cooperative Oncology Group performance status[16] higher than 3; a creatinine concentration more than two times the upper limit of normal (110 µmol/L), a serum aspartate aminotransferase or alanine aminotransferase more than three times the upper limit of normal (6–34 IU/L in men; 8–40 IU/L in women), or a serum bilirubin more than

1·5 times the upper limit of normal (0–7 μmol/L); and pre-existing cardiovascular disease or arrhythmia associated with an increased thromboembolic event risk.

All trial personnel received good clinical practice training and certification, and all procedures were done in accordance with the tenets of the Declaration of Helsinki. The protocol conformed to the ethical guidelines of all institutions and received approval by Ethical Committees of participating centres and country regulatory authorities. Written informed consent was obtained by each participant at inclusion.

Randomisation and masking

Patients were centrally randomised (2:1 ratio) to receive either eltrombopag or placebo treatment for at least 24 weeks, and until progression. Randomisation was done by the statistician (Dielnet Srl, Reggio Calabria, Italy) using the simple randomisation method with the sequence being generated by means of the RAND function of the Excel software programme. The sequence was uploaded to a protected database, Secure Sockets Layer certificated on a server's web interface, guaranteeing allocation concealment. After the compilation of a specific electronic case report form, each enrolled patient was centrally assigned to the first available position on the randomisation list. The investigator was able to see, directly from the completed case report form, which group the patient was assigned to. The allocation sequence was transferred to Depo Pack snc, Saronno, Italy, where independent labels were applied with sequential code numbers on the appropriate bottles. Patients were masked to the allocation (single-blinded design). Trial medication was dispensed to patients by the supervising clinician at each of the participating centres. Tablets were packaged by Depo Pack snc in white, opaque, high-density polyethylene bottles containing 35 tablets each. Each bottle had child-resistant closures and was affixed with a blinded label with the study protocol number, patient randomisation number, and all additional required information. The contents of the label were in accordance with all applicable regulatory requirements.

Procedures

After baseline peripheral and bone marrow morphological assessment, accompanied by local cytogenetic analysis, subsequent assessments were done at 3 months and 6 months. Hepatitis B virus and hepatitis C virus testing and coagulation assays were done before randomisation. Complete blood count, liver, and renal chemistry were assessed at baseline, weekly for the first 4 weeks, every 2 weeks for the following 8 weeks, and monthly thereafter. Patients included in this analysis received oral eltrombopag or matching placebo at an initial dose of 50 mg once daily, titrated in 50 mg increments every 2 weeks up to a maximum of 300 mg to achieve the target platelet level of 100×10^9 platelets per L. Dose reductions were required for platelet concentrations greater than 200×10^9 platelets per L or adverse events, according to protocol specifications.

Platelet response, defined according to International Working Group criteria,[17] was assessed at each visit. Titration for maintenance to intermediate doses was done to maintain platelet counts between at least 100×10^9 platelets per L and 200×10^9 platelets per L or less. Patients whose platelet count exceeded 200×10^9 platelets per L at any point during the treatment period had study drug decreased by 25 mg.

Temporary interruptions and titrations of trial medication were predetermined for platelet counts of more than 300×10^9 platelets per L, grade 3 to 4 toxicities (according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0), and blast increases that met the definition of progression of myelodysplastic syndromes.[17] At resolution, treatment was restarted at the next lower dose level. Response was considered long-lasting if maintained for more than 4 weeks.

Trial medication was withdrawn if patients had no response after 4 weeks at maximum tolerated dose, persistent grade 3 to 4 drug-related adverse events, irreversible progression of myelodysplastic syndromes, were pregnant, withdrew consent, did not comply with the protocol, or had a major protocol violation. A randomly assigned patient was considered to have completed the study if they died, withdrew consent, or were lost to follow-up.

Outcomes

The primary outcomes for phase 1 of this trial were the proportion of patients achieving a complete or partial response, and safety and tolerability parameters, including grade 3 to 4 non-haematological laboratory toxicities, changes in bone marrow blast counts from baseline, and adverse events. Complete platelet response was defined as a platelet count of at least 100×10^9 platelets per L without bleeding, with the following increases in platelet count from baseline levels: for patients with baseline platelets at least 20×10^9 platelets per L, an increase of at least 30×10^9 platelets per L from baseline; and for patients with baseline platelets less than 20×10^9 platelets per L, an increase of more than 20×10^9 platelets per L and an increase of at least 100%, not due to platelet transfusions. Partial platelet response was defined as absence of bleeding, and either an absolute increase in platelet count to at least 30 Gi/L for patients starting with more than 20×10^9 platelets per L or an increase from less than 20×10^9 platelets per L to at least 20×10^9 platelets per L and by at least 100%, not due to platelet transfusion.

Secondary endpoints included time to response, frequency of platelet transfusions, incidence and severity of bleeding, changes in quality-of-life score, measured at baseline and every 3 months by the EORTC QLQ-C30

questionnaire,[18] and the myelodysplastic syndromes-specific QOL-E questionnaire.[19] Phase 2 of the trial will comprise assessment of duration of platelet response and long-term safety and tolerability. The interim analysis presented in this study only focuses on phase 1 of the study.

Statistical analysis

The target sample size was calculated assuming that 15% and 55% of placebo and eltrombopag recipients, respectively, would achieve a platelet response. We further postulated that 10% of patients in the eltrombopag group versus 2% of patients in the placebo group would experience grade 3 to 4 hepatotoxicity; and that 10% of platelet responders and 80% of non-responders would experience grade 3 or worse adverse events not related to the trial medication. Given these assumptions, we expected 50% of patients in the eltrombopag group versus 72% of patients in the placebo group to experience at least one grade 3 or worse toxic event. With the use of a two-sided χ^2 test with $\alpha=0\cdot05$ for both endpoints, 63 patients would be required to detect a difference in platelet response rate (90% power), and 174 patients would be required to detect a difference in the proportion of patients with grade 3 or worse adverse events (80% power). Therefore, 174 patients (116 in the eltrombopag group and 58 assigned to placebo) needed to be enrolled to meet the requirements for both primary endpoints.

The final analysis will be done at the $0\cdot05$ significance level (two-sided test) according to the Haybittle-Peto method.[20] Efficacy and safety data analyses were done in the intention-to-treat population. Any patient who received a randomisation number was considered to have been randomly assigned and was included in the efficacy and safety analyses. Missing data were not imputed.

Time to response was calculated as the time from randomisation to the date of achievement of a complete or partial response and was compared between treatment groups by Kaplan-Meier analysis. Significant predictors of response were identified by logistic regression analysis, and data were expressed as odds ratios (ORs), 95% CIs, and p values. Between-treatment comparisons of safety data (adverse events, progression of myelodysplastic syndromes progression and evolution of acute myeloid leukaemia, and death) were done using a χ^2 test. The number needed to treat (for platelet response) and number needed to harm (for treatment-emergent adverse events) were also calculated as measures of the clinical impact of eltrombopag. The number needed to treat and number needed to harm were combined by calculating the likelihood of being helped or harmed[21] (a ratio of the two numbers that indicated how many times eltrombopag was more likely to help than to harm). This index was only calculated for harmful effects which were more frequent in the eltrombopag group than in the placebo group.

The effect of eltrombopag on platelet response over time and the effect of eltrombopag and platelet changes over time on each scale of each quality-of-life questionnaire were further investigated by linear mixed models.[22] In these models, data were expressed as regression coefficients, 95% CIs, and p values. The effect of a range of variables on platelet response to eltrombopag was investigated by introducing into the same models the treatment (0=placebo, 1=eltrombopag), potential effect modifier, and interaction term "treatment × effect modifier". The difference (eltrombopag – control) and 95% CI in platelet count throughout the trial period, according to predefined effect modifier categories, was then calculated by a linear combination method. Data analysis was done with SPSS for Windows, version 19, and Stata for Windows, version 13.1. An independent data and safety monitoring board oversaw the trial, confirmed data integrity, and approved the results and report for release. This trial was registered with EudraCT, number 2010-022890-33.

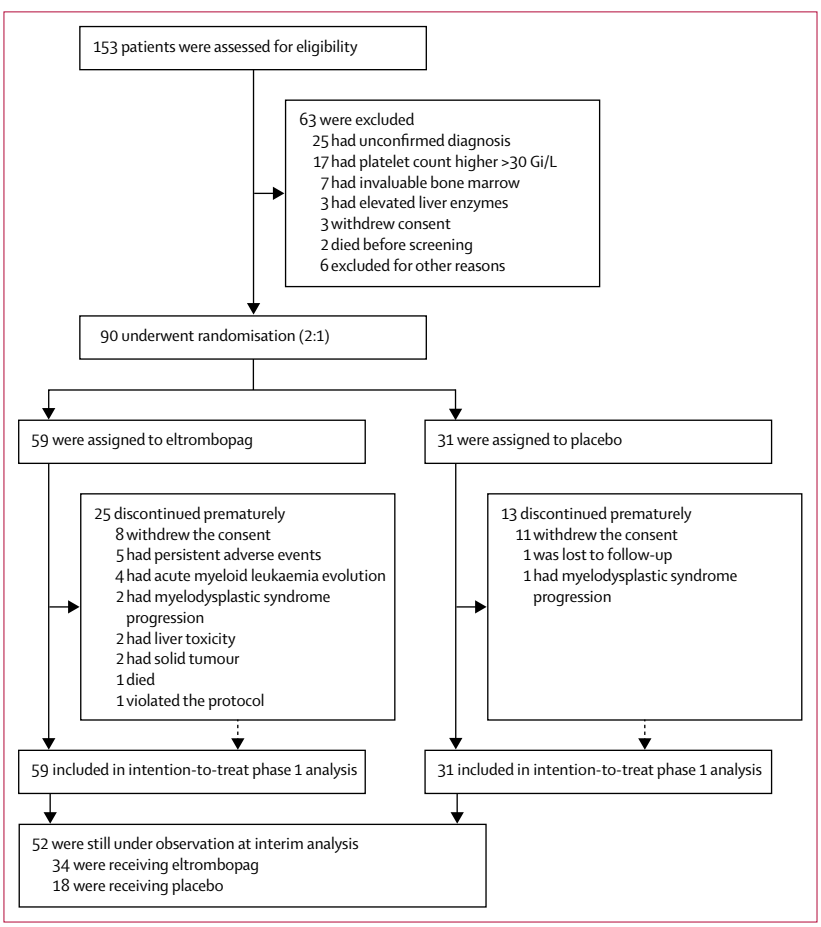

Figure 1: **Trial profile**
*25 patients in the eltrombopag group and 13 patients in the placebo group discontinued prematurely and were hence censored.

Role of the funding source

The funder of the study contributed to study design, data collection, data analysis, data interpretation, writing of

the report, and the decision to submit the report for publication. The funder also paid for the services of professional medical writers, who provided editorial assistance in refining the draft manuscript, and a statistician, who carried out the statistical data analyses. All authors had full access to all the trial data in the study and were responsible for the decision to submit for publication.

Results

Between June 13, 2011, and June 17, 2016, we enrolled 90 participants for the first phase of the trial, which coincided with the interim analysis of 50% of the total planned cohort. 153 patients were screened and 90 randomly assigned (figure 1). The treatment groups were similar with respect to baseline characteristics, except for a marginally higher prevalence of hypoplastic bone marrow in the eltrombopag group than in the placebo group (table 1). 90% of all patients were on corticosteroids, 2% were on deferasirox, and 12% were on erythropoiesis-stimulating drugs, with similar percentages in the individual treatment groups.

The median follow-up time to assess platelet responses was 11 weeks (IQR 4–24); median follow-up time was 7 weeks (IQR 2–21) in the eltrombopag group and 17 weeks (7–24) in the placebo group. Platelet responses were observed in 28 (47%) of the 59 eltrombopag recipients (11 partial responses and 17 complete responses) versus one (3%) partial response of the 31 placebo recipients ($p<0·0001$), giving an OR of 27·1 (95% CI 3·5–211·9, $p=0·0017$). A one-to-one exploratory comparison of eltrombopag-treated responders versus non-responders is given in the appendix (pp 4–7). In platelet transfusion-dependent patients in the eltrombopag group, seven (54%) of 13 had transfusion independence, five (71%) of whom had a platelet response; no patients in the placebo group had transfusion independence. 28 patients in the eltrombopag group were assessable for cytogenetic response at 24 weeks. One responder with del(20q) at baseline had a cytogenetic response (normal karyotype). By contrast, three cytogenetic progressions were observed in the placebo group.

In the eltrombopag group, 23 patients were anaemic, of whom 13 experienced haematological erythroid improvement. Four platelet responders and two platelet non-responders had a durable and significant haemoglobin rise, as defined by International Working Group 2006 criteria. Furthermore, nine red blood cell transfusion-dependent patients became transfusion-independent, so that the total number of cases with erythroid improvement was 13 (57%) of 23. Of the patients that became transfusion-independent, two also had a significant haemoglobin response, whereas only three had a concomitant platelet response. 16 patients had neutropenia. A durable neutrophil response was observed in one platelet responder and four platelet non-responders. Of note, one of the platelet non-responders had a bilineage (erythroid and neutrophil) response. Complete responses in terms of platelet response were observed in 17 (29%) of 59 patients, all in the eltrombopag group.

	Total (n=90)	Eltrombopag group (n=59)	Placebo group (n=31)
Age (years)	69 (12)	70 (11)	67 (15)
Sex			
Male	52 (58%)	37 (63%)	15 (48%)
Female	38 (42%)	22 (37%)	16 (52%)
Duration of myelodysplastic syndromes (months)	17 (5–50)	21 (7–54)	14 (4–40)
Myelodysplastic syndromes WHO classification at baseline			
Refractory anaemia	6 (7%)	2 (3%)	4 (13%)
Refractory thrombocytopenia	25 (28%)	18 (31%)	7 (23%)
Refractory cytopenia with multilineage dysplasia	40 (44%)	25 (42%)	15 (49%)
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts	2 (2%)	0	2 (6%)
Refractory anaemia with excess blasts type 1	14 (16%)	12 (20%)	2 (6%)
Myelodysplastic syndrome unclassified	3 (3%)	2 (3%)	1 (3%)
International Prognostic Scoring System risk			
Low risk	30 (33%)	17 (29%)	13 (42%)
Intermediate-1 risk	60 (67%)	42 (71%)	18 (58%)
Revised International Prognostic Scoring System			
Very low risk	4 (4%)	1 (2%)	3 (10%)
Low risk	55 (61%)	34 (58%)	21 (68%)
Intermediate risk	24 (27%)	18 (31%)	6 (19%)
High risk	7 (8%)	6 (10%)	1 (3%)
Cytogenetics			
Normal	63 (70%)	45 (76%)	18 (58%)
Del(5q)	2 (2%)	1 (2%)	1 (3%)
Y chromosome missing	4 (4%)	1 (2%)	3 (10%)
Del(20q)	12 (13%)	7 (12%)	5 (16%)
Del(11q)	1 (1%)	1 (2%)	...
Trisomy 8	4 (4%)	2 (3%)	2 (6%)
Trisomy 15	1 (1%)	...	1 (3%)
Trisomy 14	1 (1%)	1 (2%)	...
Del(1q)	1 (1%)	1 (2%)	...
Del(9q)	1 (1%)	...	1 (3%)
WHO score ≥2	9 (10%)	6 (10%)	3 (10%)
Platelet transfusion			
Dependent	21 (23%)	13 (22%)	8 (26%)
Independent	69 (77%)	46 (78%)	23 (74%)
Hypoplasia	26 (29%)	21 (36%)	5 (16%)
Fibrosis grade			
0	42 (75%)	30 (79%)	12 (67%)
1	12 (21%)	6 (16%)	6 (33%)
2	2 (4%)	2 (5%)	0
Red blood cell transfusion			
Dependent	25 (28%)	17 (29%)	8 (26%)
Independent	65 (72%)	42 (71%)	23 (74%)
Haemoglobin (g/dL)	10·9 (2%)	10·8 (3%)	11·3 (2%)
Platelet count ($\times 10^3$)	18·0 (10·8–22·1)	17·4 (10·0–22·4)	18·0 (11·0–22·0)

Data are mean (SD), n (%), or median (IQR).

Table 1: **Baseline characteristics**

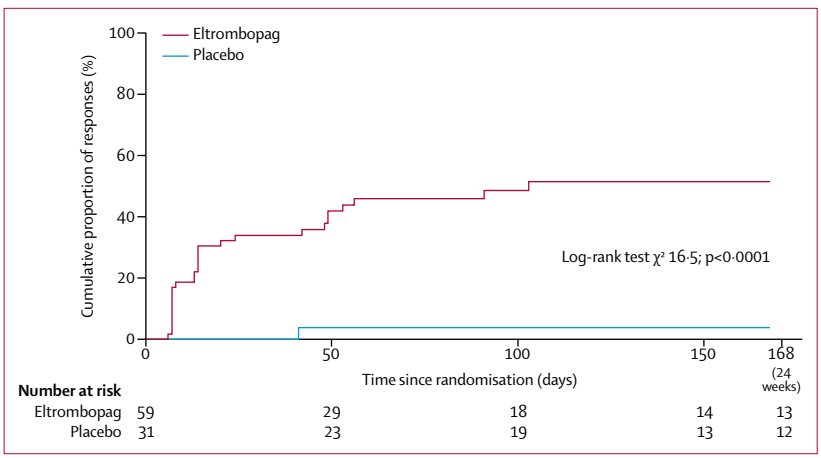

Figure 2: **Incidence of platelet response in both treatment groups**

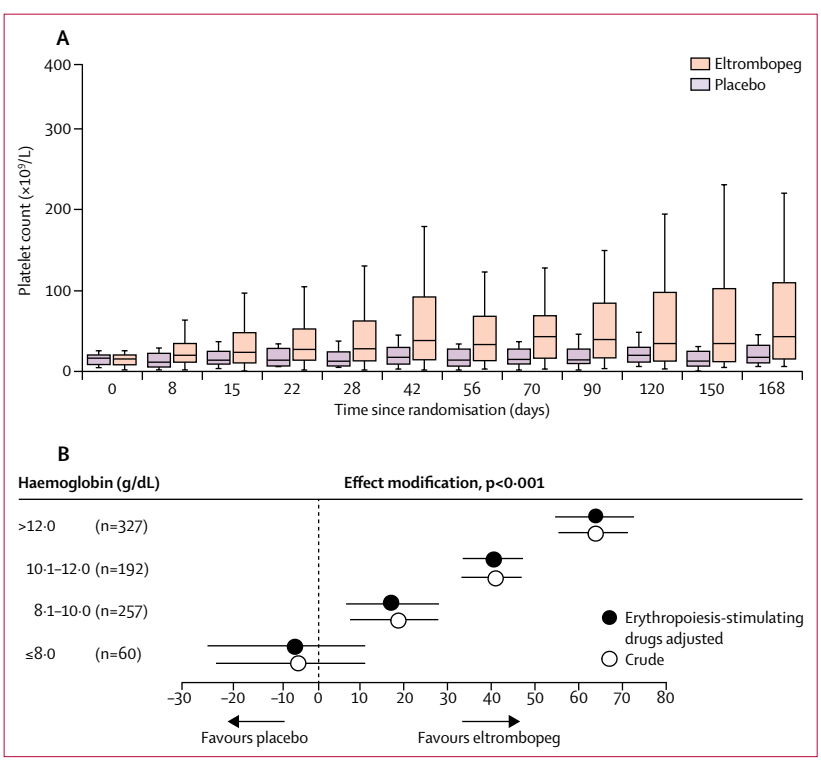

Figure 3: **Box and whisker plot of platelet count over time (A) and haemoglobin as an effect modifier of platelet response to eltrombopag (B)**

In (A), the horizontal line in the middle of each box represents the median, while the top and bottom of each box mark the 75th and 25th percentiles, respectively. The whiskers above and below the box plot mark the 97·5th and 2·5th percentiles, respectively. In B, the horizontal axis shows platelet count difference (eltrombopag *vs* placebo; $\times 10^9$ platelets per L $\times 10^3$) with 95% CIs across the study period.

The median daily dose at response was 50 mg (IQR 50–175). The eltrombopag daily dose at response was 25 mg in one patient, 50 mg in 17 patients, 100 mg in three patients, 150 mg in one patient, 200 mg in three patients, 250 mg in two patients, and 300 mg in one patient (median daily dose at response was 50 mg). Median time to response was 2 weeks (range 1–15) in the eltrombopag group (figure 2) and 6 weeks in the one responder who received placebo (figure 2). All responsive patients required dose titration increases or decreases during the first 6 months. Platelet count change at best response within the first 6 months was 71 Gi/L in the placebo group; median change in the eltrombopag group was 124×10^9 platelets per L (IQR 50–217×10^9 platelets per L). Median platelet counts at each visit within the first 6 months are shown in figure 3.

During the 24 week follow-up, among the 21 patients who had at least one bleeding event with a WHO bleeding score of at least 2, there were a higher number of bleeders in the placebo group (13 [42%] of 31 patients) for a total of 57 events compared with the eltrombopag group (8 [14%] of 59 patients) for a total of 42 events (treatment *vs* control group, p=0·0025).

In the whole group of patients (n=90), with the exception of haemoglobin concentration (1 g/dL; OR 1·38; 95% CI 1·12–1·70, p=0·0024) and, consequently, red blood cell transfusion dependence, none of the baseline characteristics listed in table 1 or any of the concomitant treatments were associated with platelet response (appendix). This was also confirmed when the analysis was restricted to the eltrombopag treatment group. In a linear mixed models analysis (n=836 observations), haemoglobin concentration was also found to modify the platelet response to eltrombopag, with the between-treatment difference in platelet count over the trial period being closely related to haemoglobin concentrations over time (figure 3, appendix p 3). The effect modification by haemoglobin on platelet response in the eltrombopag group link also exists (p<0·001) by considering haemoglobin as a continuous variable. The cutoff values in the figure were chosen on pragmatic grounds—ie, by moving from severe anaemia (<8 g/dL), to moderate anaemia (from 8·1–10 g/dL to 10·1–12·0 g/dL) up to acceptable haemoglobin concentrations (>12 g/dL). The effect of eltrombopag became apparent at a haemoglobin concentration of 8·1 g/dL and increased linearly.

No treatment-related deaths were reported. Incidences of grade 3 to 4 non-haematological adverse events were: 52 in 27 (46%) of 59 eltrombopag recipients versus nine in five (16%) of 31 placebo recipients table 2). This difference was statistically significant (χ^2=7·8, p=0·0053; stopping rule not reached). Eight patients required permanent treatment discontinuation due to persistent drug-related toxicity in the eltrombopag group. Overall, no significant between-treatment difference was observed in the incidence of grade 1–2 non-haematological adverse events (χ^2=0·30, p=0·87, appendix pp 8–10). Grade 1 and 2 adverse events occurring in more than 10% of patients did not differ between the treatments groups (χ^2=1·85, p=0·17; table 2). Four patients in the eltrombopag-treated group had leucocytosis associated with myelodysplastic syndromes progression or acute myeloid leukaemia. No transient increases in circulating peripheral myeloblasts were observed otherwise. Three patients in the placebo

group had karyotype evolution without bone marrow blast increase compared with one platelet-responsive patient in the eltrombopag arm with cytogenetic remission.

Acute myeloid leukaemia evolved in four (7%) of the 59 eltrombopag patients (in weeks 21, 30, 114, and 183, respectively) versus one (3%) of the 31 placebo patients (week 58; χ^2=0·05, p=0·83). The same analysis done by the Kaplan-Meier method (ie, by a time-to-event analysis) provided similar results (active *vs* control, p=0·54). The three early acute myeloid leukaemia evolutions in the eltrombopag group were observed in patients with refractory anaemia with excess blasts-1, whereas the fourth case occurred in a patient with refractory cytopenia with multilineage dysplasia and a 3·4-year history of myelodysplastic syndromes. Three (5%) of the 59 eltrombopag recipients (weeks 37, 62, and 374) versus four (13%) of the 31 placebo recipients (three cases at week 12 and 1 case at week 33) had disease progression (χ^2=0·81, p=0·37). Among the patients who had disease progression, three had cytogenetic progression without blast count increase. The progressions in the eltrombopag group occurred in one patient with refractory anaemia with excess blasts-1 and in two patients with unilineage dysplasia, with an overall time from diagnosis to progression of 5·3 years, 3·6 years, and 14·1 years, respectively. Overall, the combined outcome acute myeloid leukaemia evolution or disease progression occurred in seven (12%) of 59 eltrombopag patients versus five (16%) of 31 placebo patients (χ^2=0·06, p=0·81). Unrelated death occurred in four (7%) of the 59 eltrombopag patients (one death from pneumonia, two deaths from heart failure, and one death from massive rectal haemorrhage) versus two (6%) of the 31 placebo patients (one death from heart failure and one death from pneumonia; χ^2=0·0, p=1·00). Of note, patients with progression or evolution had normal karyotype at baseline.

The number needed to treat for a platelet response of at least 4 weeks' duration was 2·3, and the number needed to harm for grade 3–4 adverse events was 3·4. The number needed to observe acute myeloid leukaemia evolution was 28. Thus, the likelihood of being helped or harmed, in terms of serious adverse events versus efficacy, was 1·5; acute myeloid leukaemia evolution versus efficacy was 12·2. Therefore, eltrombopag treatment was 1·5–12·2 times more likely to help (in terms of platelet response) than to harm.

QOL-E and EORTC QLQ-C30 global health status domains at baseline in the whole study sample and separately in eltrombopag treated and untreated patients are reported in the appendix (pp 11, 12). Although we did not find significant changes over time in QOL-E items neither within nor between the two study groups, QOL-E social, sexual, myelodysplastic syndromes-specific, treatment outcome index, general, and all scores improved with increasing platelet counts (appendix pp 13, 14).

	Grade 1–2 adverse events		Grade 3 adverse events		Grade 4 adverse events	
	Eltrombopag (n=59)	Placebo (n=31)	Eltrombopag (n=59)	Placebo (n=31)	Eltrombopag (n=59)	Placebo (n=31)
Nausea or vomiting	11	3	8	0	0	0
Lower respiratory tract infection	0	0	3	0	3	2
Heart failure	0	0	1	0	3	1
Hypertransaminasaemia	2	1	3	1	0	0
Sepsis	0	0	3	0	0	0
Ascites	0	0	2	0	0	0
Bone marrow fibrosis	0	0	2	0	0	0
Myalgia	0	0	2	0	0	0
Solid tumour	0	0	0	0	2	0
Urinary infection	1	1	2	0	0	0
Arrhythmia	0	2	1	1	0	0
Fever	5	4	0	1	1	0
Hyperbilirubinaemia	5	0	1	1	0	0
Skin lesions	6	0	1	1	0	0
Asthenia	6	11	1	0	0	0
Elevated creatinine	0	0	1	0	0	0
Gastric haemorrhage	0	0	1	0	0	0
Microembolism	0	0	1	0	0	0
Pain	11	4	1	0	1	0
Pancreatitis	0	0	1	0	0	0
Proctorrhagy	0	0	1	0	0	0
Pruritus	0	0	1	0	0	0
Rectal bleeding	0	0	0	0	2	0
Renal failure	0	0	1	0	0	0
Respiratory failure	2	1	1	0	0	0
Syncope	0	0	1	0	0	0
Gastric pain	0	0	0	1	0	0
Paraesthesia	2	1	0	0	0	0
Bronchopneumopathy	2	0	0	0	0	0
Herpes virus infection	2	0	0	0	0	0
Diarrhoea	1	1	0	0	0	0
Arthrosis	1	0	0	0	0	0
Bronze-coloured skin	1	0	0	0	0	0
Constipation	1	0	0	0	0	0
Cough	1	0	0	0	0	0
Cramps	1	0	0	0	0	0
Fainting	1	0	0	0	0	0
Headache	1	0	0	0	0	0
Scleral subicterus	1	0	0	0	0	0
Succulent lower limbs	1	0	0	0	0	0
Sweats	1	0	0	0	0	0
Vertigo	0	2	0	0	0	0
Drowsiness	0	1	0	0	0	0
Epithelioma	0	1	0	0	0	0
Gastric burning	0	1	0	0	0	0
Iron overload	0	1	0	0	0	0

All values represent number of events.

***Table 2*: All non-haematological adverse events**

Discussion

Eltrombopag is effective to increase platelet counts and is well tolerated in patients with lower-risk myelodysplastic syndromes and severe thrombocytopenia. Thus, both the efficacy and safety primary endpoints of this randomised trial were met in this first phase, thereby enabling commencement of the second phase of the trial (long-term follow-up). The stringent platelet cutoff and centralised morphology review led to the exclusion of patients with immune thrombocytopenia and subtle dysplasia. We observed clinically significant responses in nearly half of the eltrombopag recipients at a median of 2 weeks, and the 50 mg dose required to obtain a response was similar to that previously reported for patients with severe aplastic anaemia.[23,24] The platelet responses predominantly seen at the low dose of 50 mg might indicate that eltrombopag modulates aberrant immune pathways, and thereby acts as both a thrombomimetic and an immunomodulatory drug. We cannot exclude that some cases had concomitant immune thrombocytopenic purpura or idiopathic thrombocytopenic purpura, as suggested by spontaneous responders in the placebo group. Remarkably, we also found that the number of patients who had significant bleeding events (WHO bleeding score ≥2) across the follow-up was critically lower in the eltrombopag group than in the placebo group (14% *vs* 42%, p=0·0025).

In a phase 2, non-randomised clinical trial in severe aplastic anaemia,[24] trilineage responses were observed. In this trial, erythroid and neutrophil responses were evaluable in patients with anaemia and neutropenia patients, respectively. Since not all patients were pancytopenic, trilineage response was not assessable.

When taking into account patient and disease factors, the effect of eltrombopag was strongly correlated only with haemoglobin concentrations, possibly indicating an association with less severe myelodysplastic syndromes. In fact, low haemoglobin concentrations conferred a worse prognosis in myelodysplastic syndromes and identified patients with a higher risk of progression or evolution, thus suggesting more advanced disease. Thus, the interaction between haemoglobin and platelet response to eltrombopag needs further investigation. In any case, our finding underlines the potential benefits of eltrombopag in patients with low-risk myelodysplastic syndromes not requiring red blood cell transfusions. Increasing platelet counts were accompanied by improvements in many patient-reported outcomes, as captured by the quality-of-life questionnaires.

This trial was possibly limited by its single-blind design; however, as it included dose-tailoring and intense safety assessments, a double-blind design might not have been optimum in an investigator-initiated setting. A key concern was the risk of progression to higher-risk myelodysplastic syndromes or acute myeloid leukaemia, as observed in the randomised trial of romiplostim in a similar cohort of patients with low-risk myelodysplastic syndromes, in which a more frequent increase in peripheral blast count was observed in the active treatment versus the placebo group.[25] Overall, phase 2 studies of romiplostim[26] as concomitant therapy with either hypomethylating (azacitidine, decitabine) or immunomodulatory drugs (lenalidomide) show romiplostim as having a similar efficacy profile to eltrombopag but with major safety concerns because of the systematic rise in blast counts and the potential for progression to acute myeloid leukaemia in all studies.[26] Furthermore, in the clinical trial in severe aplastic anaemia,[24] new cytogenetic abnormalities emerged in eight [19%] of 43 patients (with chromosome 7 aberrations in five of the eight cases) during eltrombopag treatment; the majority occurring in non-responders.[24] Of note, in-vitro preclinical studies in leukaemia and lymphoma cell lines indicate that eltrombopag does not stimulate leukaemic cell growth, but inhibits the proliferation of many acute myeloid leukaemia cell lines and primary cell cultures.[27–31] We observed that leukaemic evolution occurred more frequently in patients with refractory anaemia with excess blasts-1, with no evidence of an increased risk in eltrombopag recipients (confirmed by blinded, centralised morphological review); the time from diagnosis to myelodysplastic syndrome progression or acute myeloid leukaemia evolution was sufficient to explain the events. Although not investigated in this trial, discontinuation of eltrombopag could be contemplated in complete responders to shorten the duration of exposure. This approach is already established in idiopathic thrombocytopenic purpura and alopecia areata.

Efficacy and safety of eltrombopag in high-risk patients with myelodysplastic syndromes and in those with chronic myelomonocytic leukaemia were recently investigated.[32] The authors found that efficacy was more prevalent in patients with myelodysplastic syndromes than in patients with chronic myelomonocytic leukaemia (23% *vs* 14%), whereas adverse events were more frequent in patients with chronic myelomonocytic leukaemia (leucocytosis: 71% *vs* 3%; peripheral myeloblasts: 57% *vs* 42%).[32] In this study,[32] no difference in grade 3 fibrosis was observed between the two groups (chronic myelomonocytic leukaemia, 14% *vs* myelodysplastic syndromes, 12%). However, given the low number of patients with chronic myelomonocytic leukaemia enrolled in this study,[32] further investigation is needed to definitively assess the efficacy and safety of eltrombopag in this patient category.

The study protocol contemplates that a p value of 0·001 or less between the two study groups for both primary endpoints (increase in platelet count and grade 3 to 4 non-haematological adverse events) constitutes a stopping rule for early study termination. Although we found a p value for platelet response of less than 0·001 between the two study groups, this was not found when comparing the proportion of patients with grade 3 to 4 non-haematological adverse events (between groups comparison, p=0·005). Therefore, the stopping

rule was not reached for both primary endpoints, and, for this reason, the enrolment will continue to achieve the full accrual.

Overall, the findings reported in this study show that in patients with lower-risk myelodysplastic syndromes and thrombocytopenia, eltrombopag is effective in raising platelet counts and well tolerated. The increase in platelet count per se is associated with quality-of-life improvements. The ongoing phase 2 of the trial is designed to assess the long-term duration of response, safety, and tolerability of eltrombopag (appendix p 2).

Contributors

ENO, VS, AP, PN, FS, GS, EB, PS, PA, AC, AML, FB, MTV, SM, MB, PCu, and MAAS have participated sufficiently in the work to take public responsibility for the manuscript content. All other authors have participated sufficiently in the work to take public responsibility for partial content. ENO and PA were involved in the conception and design of the study. All authors were responsible for the acquisition of data. ENO, UG, PF, and AK were involved in the analysis and interpretation of data. ENO, SI, AK, PCu, and RL were involved in the drafting of the manuscript. All authors were involved in the critical revision of the manuscript for important intellectual content. ENO was involved in statistical analysis and obtaining funding. ENO, CA, VS, AP, FS, GS, UG, PS, MTV, SM, PCu, MAAS, and IB provided administrative, technical, or material support. ENO, VS, PF, AS, AML, and GZ were involved in supervision. AK contributed to the Data Monitoring Committee and there were no other contributions from any of the authors. All authors have provided final approval of the manuscript and agree to be accountable for all aspects of the work.

Declaration of interests

ENO has received consultancy fees from Novartis, Amgen, Celgene, and La Jolla; honoraria for lectures and speakers' bureau from Novartis, Janssen, Amgen, and Celgene; and honoraria for advisory boards from Novartis, Amgen, Celgene, and La Jolla. Valeria Santini (grants or personal fees from Celgene, Janssen, Amgen, Novartis, Astex, outside the submitted work). AS received personal fees from Celgene corporation, outside the submitted work. AK received personal fees or other fees from Alexion, Novartis, Celgene, Amgen, Ra Pharma, and Alnylam, outside the submitted work). RL received personal fees from Novartis, Bristol-Myers Squibb, Celgene, and Janssen. CA, AP, AM, PN, FS, GS, EB, UG, PF, GAP, PS, SI, PA, AC, AML, PC, FB, MTV, SM, FM, MB, PC, MAAS, IS, MGD'E, IB, and GZ declare no competing interests.

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