Eltrombopag treatment during induction chemotherapy for acute myeloid leukaemia: a randomised, double-blind, phase 2 study

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Summary

Background Patients with acute myeloid leukaemia frequently have thrombocytopenia during induction chemotherapy. Eltrombopag, an oral thrombopoietin receptor agonist, stimulates platelet production by a similar mechanism to endogenous thrombopoietin. This study investigated safety and efficacy of eltrombopag versus placebo during anthracycline-based induction treatment of patients with acute myeloid leukaemia.

Methods In this randomised, double-blind, phase 2 study, treatment-naive patients were recruited from clinical centres across 10 countries (Australia, Belgium, Canada, Greece, Hungary, Israel, South Korea, Poland, Russia, and the USA). Patients with acute myeloid leukaemia of any subtype except M3 and M7 were stratified by antecedent malignant haematological disorder (yes or no) and age (18–60 years or >60 years) and were then randomly assigned (1:1) using an automated interactive voice–response system randomisation schedule. Investigators and patients were blinded to study treatment. Starting on day 4, patients received standard induction chemotherapy (daunorubicin bolus intravenous infusion on days 1–3 [90 mg/m^2 for patients aged 18–60 years or 60 mg/m^2 for patients aged >60 years], plus cytarabine continuous intravenous infusion on days 1–7 [100 mg/m^2]), with eltrombopag 200 mg (100 mg for east Asians) or placebo once daily, until platelet counts were 200×10^9/L or higher, until remission, or after 42 days from the start of induction chemotherapy. The primary objective of the study was safety and tolerability assessed by adverse events, changes in left ventricular ejection fraction (LVEF), and clinical laboratory parameters in all treated patients. This study has been completed and is registered with ClinicalTrials.gov, number NCT01890746.

Findings Between Sept 7, 2013, and Jan 30, 2015, 149 patients were assessed for eligibility and 148 were then randomly assigned to receive eltrombopag (n=74) and placebo (n=74). Groups were matched in mean (SD) age (56·7 years [12·3] in the eltrombopag group *vs* 56·6 years [11·6] in the placebo group), mean (SD) initial platelet count (59·5×10^9/L [43·3] *vs* 63·7×10^9/L [48·0]), and poor-risk karyotype (16 [22%] of 74 patients in both groups). The most common grade 3–4 adverse events (≥10% in either group) were febrile neutropenia (31 [42%] *vs* 28 [39%]), decreased white blood cell count (8 [11%] *vs* 5 [7%]), and hypophosphataemia (3 [4%] *vs* 9 [13%]). Serious adverse events occurred in 24 (32%) patients in the eltrombopag group compared with 14 (20%) patients in the placebo group. 39 (53%) patients in the eltrombopag group died versus 29 (41%) patients in the placebo group. Thromboembolic events (5 [7%] *vs* 4 [6%]) and mean (SD) change in LVEF (–2·5% [7·8] *vs* –4·3% [8·5]) were similar.

Interpretation Data from this trial do not support combining eltrombopag with induction chemotherapy in patients with acute myeloid leukaemia.

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Introduction

Acute myeloid leukaemia is a heterogeneous haematological malignancy characterised by clonal expansion of myeloid blasts, primarily in the peripheral blood and bone marrow. Patients often present with symptoms or complications from bone marrow failure.[1] Induction chemotherapy with cytarabine and an anthracycline, such as daunorubicin, is the standard of care for first-line treatment of adult patients with acute myeloid leukaemia and has remained essentially unaltered over the past four decades.[2] Patients often have disease-related thrombocytopenia, which is exacerbated by induction chemotherapy and is a considerable cause of morbidity for many patients with acute myeloid leukaemia.[3] Almost all patients with acute myeloid leukaemia experience grade 4 thrombocytopenia, secondary to the underlying disease and induction chemotherapy, resulting in frequent platelet transfusions, either prophylactically or to treat bleeding complications. Platelet transfusions have a short-lived therapeutic effect (1–5 days) and can cause mild-to-severe transfusion reactions, such as transfusion-related acute lung injury.[4] Patients can also become refractory to platelet transfusions, thereby reducing the therapeutic

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Research in context

Evidence before this study

In March, 2013, during the development of the study protocol, we did a review of the literature using PubMed (no date restrictions; search terms "eltrombopag" and "leukaemia"), which indicated that eltrombopag had antileukaemic activity that led to disease response and platelet count improvements in myeloid malignancies, making eltrombopag a suitable candidate to be studied after induction therapy for acute myeloid leukaemia. Furthermore, available data from randomised phase 1 and phase 2 studies at that time showed that eltrombopag monotherapy in adult patients with advanced myelodysplastic syndromes or acute myeloid leukaemia resulted in improvements in thrombocytopenia and had an acceptable safety profile compared with placebo. Induction chemotherapy with cytarabine and daunorubicin is the standard of care for the first-line treatment of adult patients with acute myeloid leukaemia. However, patients often have disease-related thrombocytopenia, which is exacerbated by induction chemotherapy and is a considerable cause of morbidity. Almost all patients who receive induction chemotherapy require frequent platelet transfusions. Eltrombopag, an orally available, small-molecule thrombopoietin receptor agonist, stimulates platelet production by a similar, but not identical, mechanism to that of endogenous thrombopoietin, thereby increasing platelet counts and reducing thrombocytopenic sequelae.

Added value of this study

This study provides insight into the use of eltrombopag specifically in patients with acute myeloid leukaemia receiving induction chemotherapy. The results of this randomised, phase 2 study did not indicate any clinical benefit of eltrombopag over placebo. Patients receiving eltrombopag had a higher incidence of serious adverse events and deaths due to haemorrhage within 30 days after the last dose. The pharmacokinetic parameters analysed gave no indication that eltrombopag interfered with exposure to induction chemotherapy.

Implications of all the available evidence

These data do not support a favourable benefit–risk profile for eltrombopag in combination with induction chemotherapy in patients with acute myeloid leukaemia. The reasons for these findings remain unclear. As such, data from this trial do not support combining eltrombopag with induction chemotherapy in patients with acute myeloid leukaemia.

potential.[4] As such, minimising the need for platelet transfusions is desirable.

Eltrombopag is an orally available, small-molecule thrombopoietin receptor agonist approved for the treatment of patients with chronic immune thrombocytopenia, hepatitis C virus-related thrombocytopenia, and refractory severe aplastic anaemia.[5–9] Eltrombopag stimulates platelet production by a similar, but not identical, mechanism to that of endogenous thrombopoietin, thereby increasing platelet counts and reducing thrombocytopenic sequelae.[10] Findings from a phase 1/2 study[11] of patients with acute myeloid leukaemia or advanced myelodysplastic syndromes suggested a potential benefit of eltrombopag monotherapy that warranted further investigation. Furthermore, preclinical and early studies[12–16] indicated that eltrombopag could inhibit haematological malignant growth and might, therefore, have additional antileukaemic effects. These results contrast with clinical findings with the thrombopoietin receptor agonist romiplostim, which increased leukaemic blasts upon treatment of patients with low or intermediate-1-risk myelodysplastic syndromes.[17] As such, further study of the role of eltrombopag during induction therapy for acute myeloid leukaemia was of interest, particularly further understanding of a potential drug–drug interaction between eltrombopag and daunorubicin. Inhibition of breast cancer resistance protein (BCRP) by eltrombopag might result in increased plasma and tissue exposure of daunorubicin (a BCRP substrate),[6,18,19] which, in turn, might lead to decreased left ventricular ejection fraction (LVEF).

In this study, we assessed the safety and efficacy of eltrombopag versus placebo in patients receiving standard anthracycline-based induction therapy for acute myeloid leukaemia, and the effects of eltrombopag on daunorubicin pharmacokinetics.

Methods

Study design and participants

In this randomised, double-blind, placebo-controlled, phase 2 study we enrolled patients from clinical sites across 10 countries (Australia, Belgium, Canada, Greece, Hungary, Israel, South Korea, Poland, Russia, and the USA). Patients were 18 years or older and were diagnosed with acute myeloid leukaemia (according to the WHO 2008 classification) of any subtype, except acute promyelocytic (M3) or acute megakaryocytic (M7) leukaemia. Patients had not previously been treated for acute myeloid leukaemia, had adequate cardiac function with LVEF of 50% of more, adequate baseline renal and liver function (total bilirubin concentration ≤1·5×upper limit of normal [ULN], alanine aminotransferase concentration ≤3×ULN, and serum creatinine concentration ≤2·5×ULN), and no history of thrombosis. The study was done in accordance with the Declaration of Helsinki. An independent ethics committee or institutional review board for each study site approved the study protocol. All patients provided written informed consent to participate in the study.

Randomisation and masking

Eligible patients were entered into the randomisation system by the investigator or by authorised staff. The

randomisation schedule was done using an in-house validated computerised system (RANDALL NG). Patients were randomly assigned (1:1) to receive either eltrombopag or matching placebo via RAMOS (Registration and Medication Ordering System), a telephone-based, randomisation schedule. Once a randomisation number was assigned, it could not be reassigned. The investigator or treating physician could only unmask the patient's treatment assignment when knowledge of the study treatment was essential for the appropriate clinical management or welfare of the patient.

Procedures

Eligible patients received induction chemotherapy with a standard anthracycline-based regimen consisting of daunorubicin bolus intravenous infusion on days 1–3 (90 mg/m² for patients aged 18–60 years or 60 mg/m² for patients aged >60 years), plus cytarabine continuous intravenous infusion on days 1–7 (100 mg/m²). Reagents were sourced locally from commercial stock. Patients were stratified by antecedent malignant haematological disorder (yes or no) and age (18–60 years or >60 years) and then randomly assigned to receive either oral eltrombopag (200 mg once daily; 100 mg once daily for patients of east Asian heritage) or matching placebo using an interactive voice-response system. Eltrombopag or placebo (provided by Novartis Pharmaceuticals) was administered starting on day 4 of initial induction chemotherapy, at least 20 h after the end of the day 3 daunorubicin infusion. If the platelet count was less than 100×10^9/L after 7 days, the dose was escalated to a maximum of 300 mg (150 mg for patients of east Asian heritage). Patients who were not aplastic after the first cycle of induction chemotherapy received a second induction chemotherapy cycle (re-induction) with a modified daunorubicin dose (45 mg/m²) on days 1–3 plus cytarabine on days 1–7 (100 mg/m²); eltrombopag was withheld from days 1–3, then resumed at the same dose on day 4. Treatment continued until remission (platelet count $>200\times10^9$/L), which was assessed by bone marrow biopsy, or until a maximum of 42 days from the start of the most recent chemotherapy induction cycle had been reached. Treatment was discontinued if the patient became pregnant or had a grade 4 adverse event (judged to be study drug-related by the investigator or of unacceptable risk). Other discontinuation criteria included an LVEF event (an absolute decrease ≥15% from baseline if the follow-up measurement was ≥50% or an absolute decrease of ≥10% from baseline if the follow-up measurement was <50%) and QT interval criteria (QTc >500 ms, uncorrected QT >600 ms, or a change from baseline of >60 ms for QTc).

Outcomes

The primary objective of the study was to assess safety and tolerability as measured by the incidence of adverse events and clinical laboratory parameters (including haematological and hepatobiliary), assessed on a weekly basis, and changes in LVEF. LVEF was assessed within 14 days of the final disease response assessment and at any time during the 2-year follow-up, if performed, by either echocardiogram or multigated acquisition scan. An LVEF event was defined as a decline from baseline of 15% or more if the follow-up LVEF was 50% or more, or a decline of 10% or more if the follow-up LVEF was less than 50%. Additional safety endpoints included incidence and severity of bleeding adverse events determined by the WHO Bleeding Scale.[20] Secondary endpoints included assessment of the effect of eltrombopag on platelet counts (summary of platelet counts by visit, time to platelet counts $\geq20\times10^9$/L and $\geq100\times10^9$/L, proportion of patients achieving platelet count recovery [$\geq20\times10^9$/L] on or before day 21, duration of platelet transfusion independence, and number of platelet transfusions required per week), absolute neutrophil recovery (summary by visit and time to recovery [$\geq0{\cdot}5\times10^9$/L sustained for 3 days]), haemoglobin recovery (summary by visit), disease response (proportion of patients and type of response), and overall survival. Plasma concentrations and pharmacokinetic parameters (half-life [$t_{1/2}$], dose-normalised plasma area under the concentration–time curve [AUC]$_{0-\infty}$, AUC$_{0-24}$, and AUC$_{24-\infty}$, and maximum concentration [C_{max}]) were assessed for daunorubicin and daunorubicinol (metabolite of daunorubicin) on days 3–9 of induction cycle 1. AUC$_{0-24}$ and C_{max} were also assessed on days 1–2 of the re-induction cycle, where relevant.

Statistical analysis

With 120 evaluable patients (60 patients per group), we expected the half-width of the 90% CI around the difference in proportion of patients with a cardiac event measured by a drop in LVEF to be between 4·7% and 7·6% (assuming a proportion of patients with a cardiac event of 2·5% to 5·0% in the placebo group and a difference in proportions between the two groups of 0% to 4%). We estimated the precision around the point estimate for pharmacokinetic comparisons at cycle 1 to be 15·3% on a log scale; as such, if the point estimate was 1, the 90% CI would be 0·87 to 1·15. The intention-to-treat (ITT) population comprised all randomly assigned patients, regardless of whether study treatment was administered. The safety population consisted of all patients who received at least one dose of eltrombopag or placebo. We did the primary analysis after all patients had completed induction cycles. At this point, the study was unmasked. We updated analyses of overall survival, duration of response, LVEF assessment, and follow-up medications once patients had completed a 2-year follow-up (end of study). We summarised safety data descriptively; we tested occurrence of LVEF events using a Cochran-Mantel-Haenszel (CMH) χ^2 test. We compared time to platelet recovery using a log-rank test, analysed disease response using a CMH χ^2 test, and compared

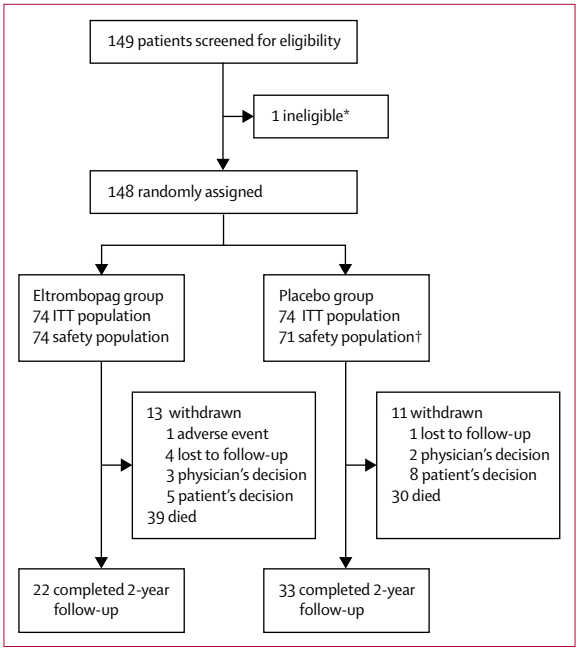

Figure 1: **Trial profile**
ITT=intention-to-treat. *Reason not recorded. †Three patients were excluded from the safety population because they discontinued the study during the induction phase, before receiving the investigational product.

overall survival curves using a stratified log-rank test. We analysed plasma daunorubicin and daunorubicinol concentration-time data by non-compartmental methods with WinNonlin version 5.3 or higher. SAS software version 9·3 was used for statistical analyses. This study is registered with ClinicalTrials.gov, number NCT01890746.

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. All authors had full access to all the trial data in the study and were responsible for interpreting the data, writing the manuscript, and the decision to submit for publication.

Results

Between Sept 7, 2013, and Jan 30, 2015, 148 patients were randomly assigned to receive either eltrombopag (N=74) or placebo (N=74; figure 1). Three patients assigned to the placebo group, who were included in the ITT population, were excluded from the safety population because they did not receive study treatment. The primary analysis was done in June, 2015, and the final analyses represent results through January, 2017. Baseline demographics were generally well balanced between treatment groups, although the eltrombopag group had a higher proportion of Asian patients (26 [35%]) than the placebo group (19 [26%]), and more female patients (38 [51%] *vs* 31 [42%]). The eltrombopag group also had more patients with acute myeloid leukaemia with recurrent cytogenetic abnormalities (table 1). Ten (14%) patients in the eltrombopag group and 12 (16%) patients in the placebo group received a re-induction cycle. A total of 22 (30%) patients in the eltrombopag group and 33 (45%) patients in the placebo

	Eltrombopag group (N=74)	Placebo group (N=74)
Age, years [range]	56·7 (12·3 [23–77])	56·6 (11·6 [21–75])
Sex		
Female	38 (51%)	31 (42%)
Male	36 (49%)	43 (58%)
Race or ethnic origin		
African American or African heritage	1 (1%)	2 (3%)
Asian	26 (35%)	19 (26%)
White	47 (64%)	53 (72%)
Strata		
Antecedent malignant haematological disorder	10 (14%)	11 (15%)
No antecedent malignant disorder	64 (86%)	63 (85%)
Age 18–60 years	38 (51%)	38 (51%)
Age >60 years	36 (49%)	36 (49%)
WHO acute myeloid leukaemia classification*		
Acute myeloid leukaemia with recurrent cytogenetic abnormalities	11 (15%)	4 (5%)
Acute myeloid leukaemia with multilineage dysplasia	13 (18%)	11 (15%)
Acute myeloid leukaemia and myelodysplastic syndromes, therapy related	3 (4%)	3 (4%)
Acute myeloid leukaemia, not otherwise categorised	47 (64%)	56 (76%)
Blast count		
Bone marrow	55·6% (25·8)	53·9% (25·3)
Blood smear	32·1% (30·1)	26·4% (28·7)
Karyotype risk factor		
Good or better	11 (15%)	9 (12%)
Intermediate	46 (62%)	43 (58%)
Poor	16 (22%)	16 (22%)
No result	1 (1%)	4 (5%)
Missing	0	2 (3%)
Platelet count, × 10^9/L	59·5 (43·3)	63·7 (48·0)
Platelet transfusion dependent†	12 (16%)	16 (22%)
Haemoglobin concentration, g/L	89·7 (13·0)	87·8 (12·6)
LVEF‡	64·4% (6·0)	65·1% (6·4)

Data are n (%) or mean (SD). *Percentages do not add up to 100% because of rounding. †Defined as patients with ≥2 platelet transfusions in the 28-day period up to and including day 1. ‡Safety population: eltrombopag, n=74; placebo, n=71. LVEF=left ventricular ejection fraction.

Table 1: **Patient demographics and baseline characteristics**

	Eltrombopag group (N=74)				Placebo group (N=71)			
	Any grade	Grade 3	Grade 4	Grade 5	Any grade	Grade 3	Grade 4	Grade 5
Any event	72 (97%)	35 (47%)	17 (23%)	10 (14%)	66 (93%)	26 (37%)	15 (21%)	3 (4%)
Diarrhoea	42 (57%)	5 (7%)	0	0	42 (59%)	1 (1%)	0	0
Febrile neutropenia	40 (54%)	30 (41%)	1 (1%)	0	42 (59%)	28 (39%)	0	0
Nausea	37 (50%)	2 (3%)	0	0	46 (65%)	4 (6%)	0	0
Hypokalaemia	20 (27%)	2 (3%)	2 (3%)	0	27 (38%)	7 (10%)	0	0
Hypophosphataemia	10 (14%)	3 (4%)	0	0	14 (20%)	9 (13%)	0	0
Decreased white blood cell count	9 (12%)	2 (3%)	6 (8%)	0	5 (7%)	0	5 (7%)	0
Increased ALT concentration	8 (11%)	1 (1%)	0	0	15 (21%)	5 (7%)	0	0
Pneumonia	8 (11%)	4 (5%)	0	0	4 (6%)	0	0	1 (1%)
Hypocalcaemia	7 (9%)	1 (1%)	0	0	10 (14%)	5 (7%)	1 (1%)	0
Increased blood bilirubin concentration	7 (9%)	2 (3%)	0	0	8 (11%)	4 (6%)	0	0
Anaemia	7 (9%)	4 (5%)	0	0	7 (10%)	6 (8%)	1 (1%)	0
Decreased platelet count	7 (9%)	0	7 (9%)	0	4 (6%)	0	3 (4%)	0
Neutropenia	5 (7%)	0	5 (7%)	0	5 (7%)	0	4 (6%)	0
Sepsis	5 (7%)	3 (4%)	0	1 (1%)	5 (7%)	1 (1%)	0	2 (3%)
Acute kidney injury	5 (7%)	2 (3%)	0	1 (1%)	3 (4%)	1 (1%)	0	0
Thrombocytopenia	4 (5%)	0	4 (5%)	0	4 (6%)	0	4 (6%)	0
Septic shock	4 (5%)	0	1 (1%)	2 (3%)	2 (3%)	1 (1%)	1 (1%)	0
Decreased neutrophil count	4 (5%)	0	4 (5%)	0	1 (1%)	1 (1%)	0	0
Intracranial haemorrhage	2 (3%)	0	0	2 (3%)	0	0	0	0
Pulmonary haemorrhage	2 (3%)	0	0	1 (1%)	0	0	0	0
Cerebral haemorrhage	1 (1%)	0	0	1 (1%)	0	0	0	0
Cerebrovascular accident	1 (1%)	0	0	1 (1%)	0	0	0	0
Myocardial infarction	1 (1%)	0	0	1 (1%)	0	0	0	0
Pulmonary alveolar haemorrhage	1 (1%)	0	0	1 (1%)	0	0	0	0
Respiratory failure	1 (1%)	0	0	1 (1%)	0	0	0	0
Sudden death	0	0	0	0	1 (1%)	0	0	1 (1%)

Data are n (%). Any grade column includes events grade 1–5 or missing grade; only events for which grade 3, 4, or 5 events occurred are included in this table; all adverse events are listed in the appendix. ALT=alanine aminotransferase.

Table 2: **Most common adverse events by maximum grade (3–5), grade 3 and 4 events occurring in ≥5% of patients in either treatment group, and all grade 5 events**

group completed the 2-year follow-up (figure 1). In both groups, the main reason for not completing the study was death (39 [53%] patients in the eltrombopag group and 30 [41%] patients in the placebo group), and the most common reason for withdrawing from the study was patient decision (5 [7%] and 8 [11%]); most patients withdrew during the induction cycle.

The mean (SD) daily eltrombopag dose during the first induction cycle was 253·8 mg (21·3) for non-east Asian patients (planned starting dose 200 mg once daily) and 132·6 mg (9·1) for east Asian patients (planned starting dose 100 mg once daily) over a median of 21·5 days (IQR 13·0–24·0) on study drug. For patients receiving placebo, mean (SD) daily dose was 258·7 mg (23·0) for non-east Asian patients and 135·8 mg (6·6) for east Asian patients over a median of 23·0 days (IQR 18·0–27·0) on study drug.

During the first induction cycle, mean (SD) daily dose of daunorubicin was 87·8 mg/m² (8·0) for patients in the eltrombopag group and 89·2 mg/m² (4·9) for those in the placebo group, in patients aged 18–60 years, and was 59·6 mg/m² (2·6) and 60·0 mg/m² (0·03) in patients aged 60 years and older, over 3 days. Mean cytarabine dose received during the induction cycle was 100 mg/m² over 7 consecutive days in both treatment groups. Two (3%) patients in the eltrombopag group and three (4%) patients in the placebo group had one dose

	Eltrombopag group (N=74)		Placebo group (N=71)	
	Baseline	Post-baseline	Baseline	Post-baseline
Haematological				
Thrombocytopenia	36/74 (49%)	74/74 (100%)	35/71 (49%)	71/71 (100%)
Neutropenia	38/69 (55%)	72/72 (100%)	44/69 (64%)	71/71 (100%)
Anaemia	15/74 (20%)	68/74 (92%)	20/71 (28%)	66/71 (93%)
Chemistry				
ALT or AST concentration ≥3×ULN	0	7/74 (9%)	0	11/71 (15%)
Bilirubin concentration ≥2×ULN	0	10/74 (14%)	0	7/71 (10%)
Creatinine concentration	0	3/74 (4%)	0	2/71 (3%)

Data are n/N (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase. ULN=upper limit of normal.

Table 3: **Incidence of grade 3–4 laboratory events at baseline and post-baseline**

	Eltrombopag group (N=74)	Placebo group (N=71)
Overall deaths	39 (53%)	29 (41%)
Alive at last contact, follow-up ended	35 (47%)	42 (59%)
Primary cause of death		
Myocardial infarction	1 (1%)	0
Haemorrhage	5 (7%)	3 (4%)
Intracranial or brain	2 (3%)	3 (4%)
Respiratory or lung	3 (4%)	0
Cancer	19 (26%)	11 (15%)
Disease under study (acute myeloid leukaemia)*	19 (26%)	10 (14%)
Other cancer†	0	1 (1%)
Sepsis	5 (7%)	6 (8%)
Pneumonia	0	2 (3%)
Respiratory arrest	1 (1%)	0
Missing	6 (8%)	2 (3%)
Time to death from last dose		
≤30 days after last dose of study treatment	11 (15%)	4 (6%)
>30 days after last dose of study treatment	28 (38%)	25 (35%)

Data are n (%). *Primary cause of death for one patient in the eltrombopag group was listed as disease under study, but the patient also had fatal cerebral haemorrhage. †Multiplex osseal metastasis (primary site unknown).

Table 4: **Summary of deaths during the study**

See Online for appendix

	Eltrombopag group (N=74)	Placebo group (N=74)	Estimate (95% CI)	p value
Patients achieving platelet recovery of ≥20 × 10^9/L for at least 3 consecutive days	6/70 (9%)	7/68 (10%)	0·84 (0·28–2·48)*	0·75†
Patients achieving platelet recovery of ≥100 × 10^9/L at any point	48/74 (65%)	51/73 (70%)	1·10 (0·74–1·63)*	0·62†
Overall response	52/74 (70%)	54/74 (73%)	0·87 (0·40–1·89)‡	0·71§
Any complete response	48/74 (65%)	52/74 (70%)	..	..
Partial remission	4/74 (5%)	2/74 (3%)	..	..
No overall response	22/74 (30%)	20/74 (27%)	..	..
Stable disease	3/74 (4%)	0	..	..
Progressive disease	7/74 (9%)	7/74 (9%)	..	..
Missing	12/74 (16%)	13/74 (18%)	..	..
Median duration of overall response, months¶	22·1	NR	..	..
Deaths, events¶	39/74 (53%)	30/74 (41%)	..	..
Median survival, months¶	15·4	25·7	1·54 (0·96, 2·47)*	0·069**

Data are n/N (%). Overall response: morphological leukaemia-free state, morphological complete response, cytogenetic complete response, molecular complete response, or partial remission. Any complete response: morphological leukaemia-free state, morphological complete response, cytogenetic complete response, or molecular complete response. NR=not reached. *Adjusted hazard ratio. †Log-rank test. ‡Odds ratio. §Cochrane-Mantel-Haenszel χ^2 test adjusted for stratification factors. ¶Based on final long-term follow-up. **Stratified log-rank test.

Table 5: **Platelet recovery, overall response, and overall survival**

reduction during the induction cycle and no patients had a dose reduction during the re-induction cycle.

Mean (SD) LVEF changed from 64·4% (6·0) at baseline to 62·2% (6·8) at the end of the study after 2 years of follow-up in the eltrombopag group (change from baseline –2·5% [7·8]) and from 65·1% (6·4) to 60·8% (7·7) in the placebo group (change from baseline –4·3% [8·5]). Overall, five (7%) patients in the eltrombopag group and seven (10%) patients in the placebo group had decreased LVEF (defined as either ≥15% with post-baseline LVEF ≥50% or ≥10% with post-baseline LVEF <50%) from baseline (p=0·65); all patients had completed 3 days of treatment with daunorubicin during the induction cycle. A decrease in LVEF of 10% or more from baseline with post-baseline LVEF of less than 50% was recorded in one (1%) patient in the eltrombopag group and in four (5%) patients in the placebo group, all of whom had completed 3 days of daunorubicin during the induction cycle.

On-treatment adverse events (including those within 30 days after the last dose of study treatment) occurred in 72 (97%) of 74 patients in the eltrombopag group and in 66 (93%) of 71 in the placebo group (table 2). The most common adverse events (incidence ≥30%) in the eltrombopag group compared with the placebo group were diarrhoea (42 [57%] *vs* 42 [59%]), febrile neutropenia (40 [54%] *vs* 42 [59%]), nausea (37 [50%] *vs* 46 [65%]), constipation (28 [38%] *vs* 22 [31%]), vomiting (27 [36%] *vs* 27 [38%]), pyrexia (26 [35%] *vs* 18 [25%]), decreased appetite (22 [30%] *vs* 27 [38%]), and rash (22 [30%] *vs* 13 [18%]; appendix). Adverse events considered by the investigator to be related to study treatment occurred in 61 (82%) patients in the eltrombopag group and 52 (73%) patients in the placebo group. The most common (≥20% incidence) adverse events considered related to eltrombopag were nausea (28 [38%] *vs* 35 [49%]), febrile neutropenia (17 [23%] *vs* 12 [17%]), and diarrhoea (16 [22%] *vs* 18 [25%]). Adverse events leading to treatment discontinuation occurred in 13 (18%) patients in the eltrombopag group versus nine (13%) patients in the placebo group, the most common reason in the eltrombopag group being increased blood bilirubin concentration (2 [3%] *vs* 1 [1%]). Serious adverse events were reported in 24 (32%) patients in the eltrombopag group and in 14 (20%) patients in the placebo group. Haematological grade 3–4 laboratory adverse events did not differ between the treatment groups (table 3). No patient met Hy's Law criteria.

Thromboembolic events occurred in five (7%) patients in the eltrombopag group and four (6%) patients in the placebo group. Overall, 46 (62%) patients in the eltrombopag group had 94 bleeding events and 36 (51%) patients in the placebo group had 60 bleeding events reported as on-treatment adverse events. Most bleeding events were grade 1 or 2 and were consistent with the natural history of acute myeloid leukaemia. Grade 3–5 bleeding events were more common in the eltrombopag group (7 [9%]) than in the placebo group (1 [1%]). The most common bleeding events (≥5% in either group) were epistaxis (18 [24%] *vs* 14 [20%]), petechiae (12 [16%] *vs* 10 [14%]), gingival bleeding (6 [8%] *vs* 4 [6%]), haemoptysis (7 [9%] *vs* 2 [3%]), haematuria (1 [1%] *vs* 4 [6%]), catheter-site bleeding (4 [5%] *vs* 1 [1%]), and mouth bleeding (5 [7%] *vs* 0%).

In total, 39 (53%) patients in the eltrombopag group and 29 (41%) patients in the placebo group from the safety population died during the study, including the 2-year follow-up (table 4). One additional death occurred in the placebo group, but this patient was not part of the safety population. Most deaths were due to disease under study (acute myeloid leukaemia), occurring in 19 (26%) patients in the eltrombopag group and ten (14%) patients in the placebo group. 11 (15%) patients in the eltrombopag group and four (6%) patients in the placebo group (table 4) died within 30 days after the last dose of study treatment. Most other deaths were because of haemorrhage (5 [7%] *vs* 3 [4%]) or sepsis (5 [7%] *vs* 6 [8%]).

Use of follow-up medications (chemotherapy, immune, hormonal, or biological therapies) was balanced between the two groups: 26 (35%) patients in the eltrombopag group (16 [22%] at the primary data cutoff) and 27 (36%) in the placebo group (13 [18%] at the primary data cutoff).

Median platelet counts increased in both treatment groups between day 28 and day 42 for each treatment cycle, with higher levels in the eltrombopag group than in the placebo group. The average number of platelet transfusions per week within cycles was similar (post-baseline median of 1·3 [IQR 0·7–2·0] in the eltrombopag group and 1·1 [0·6–1·6] in the placebo group). The median duration of platelet transfusion independence was also similar (29·0 days [10·0–35·0] *vs* 29·5 days [19·0–36·0]; p=0·69). Time to platelet recovery was not significantly different between the two groups, with 20×10^9/L or higher for at least 3 consecutive days unaided by transfusions (hazard ratio [HR] 0·84 [95% CI 0·28–2·48]) and time to platelets 100×10^9/L or higher (1·10 [0·74–1·63]; table 5).

Median neutrophil counts increased in both treatment groups between day 28 and day 42 of each cycle, with similar levels in the two groups. Median time to neutrophil engraftment to $0·5\times10^9$/L or higher was similar (HR 2·46 [95% CI 0·95–6·38]) though more events occurred in patients in the eltrombopag group (12 [16%] *vs* 5 [7%]). Median haemoglobin and red blood cells counts were similar in both treatment groups throughout the study.

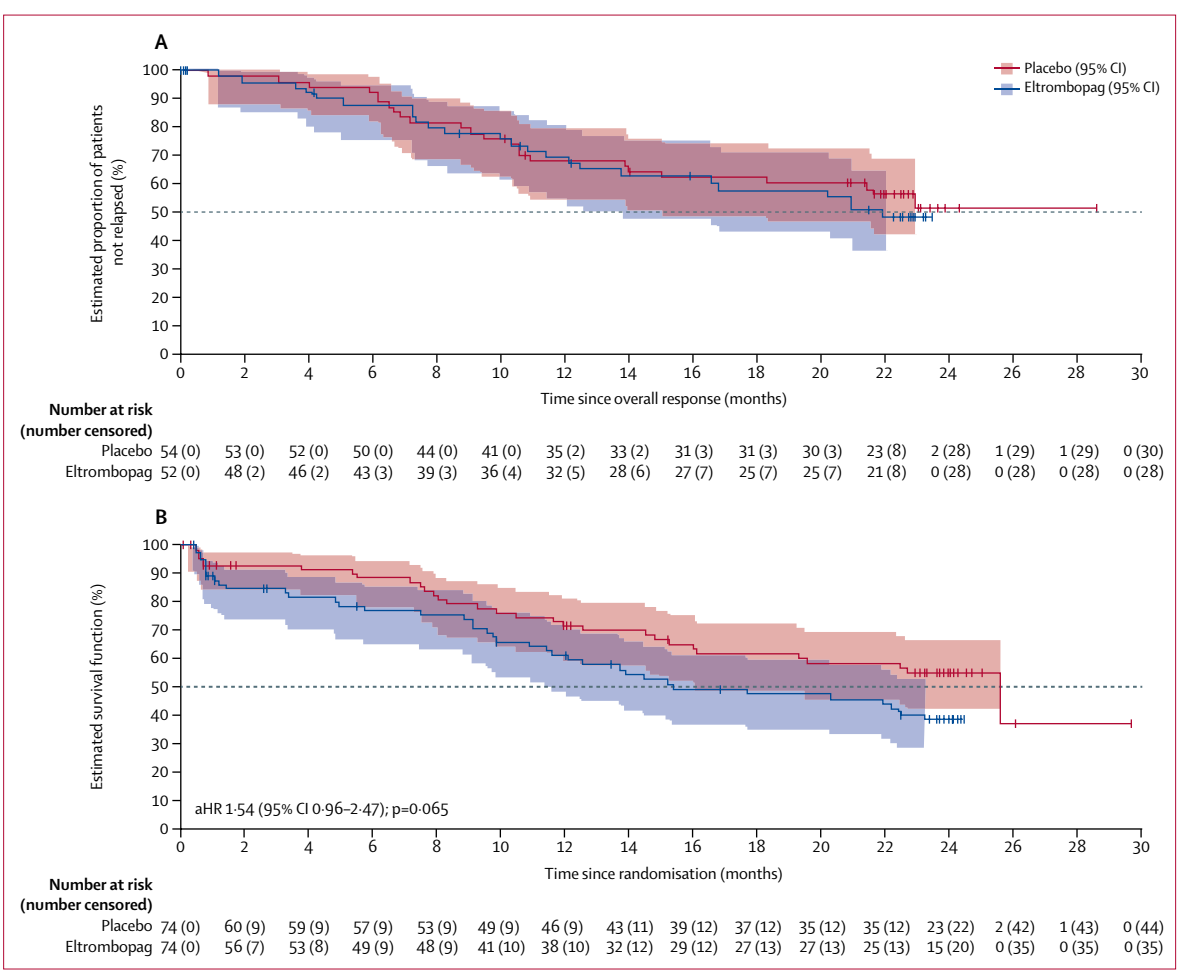

***Figure 2*: Kaplan–Meier plots of duration of response (A) and overall survival (B)**
A stratified log-rank test was not done for duration of response. Dashed lines indicate 50%. aHR=adjusted hazard ratio.

	Eltrombopag group (N=74)	Placebo group (N=74)	Ratio (90% CI)
Daunorubicin			
C_{max}, μg/mL/mg/m²	5·15 (n=73)	6·41 (n=70)	80·4% (57·2–113·0)
$AUC_{0-\infty}$, μg·h/mL/mg/m²	8·08 (n=73)	8·79 (n=69)	92·0% (76·8–110·2)
AUC_{0-24}, μg·h/mL/mg/m²	7·05 (n=73)	7·85 (n=69)	89·8% (74·4–108·3)
$AUC_{24-\infty}$, μg·h/mL/mg/m²	0·87 (n=73)	0·72 (n=69)	121·0% (102·5–142·8)
$t_{1/2}$, h	15·8 (n=73)	13·7 (n=69)	114·9% (99·5–132·7)
Daunorubicinol			
C_{max}, μg/mL/mg/m²	3·58 (n=73)	3·36 (n=70)	106·3% (87·6–129·0)
$AUC_{0-\infty}$, μg·h/mL/mg/m²	64·0 (n=73)	62·8 (n=69)	101·8% (92·9–111·7)
AUC_{0-24}, μg·h/mL/mg/m²	38·9 (n=73)	39·4 (n=69)	98·9% (90·7–107·9)
$AUC_{24-\infty}$, μg·h/mL/mg/m²	24·5 (n=73)	23·0 (n=69)	106·5% (95·0–119·4)
$t_{1/2}$, h	22·7 (n=73)	21·6 (n=69)	105·2% (97·1–114·0)

Data are geometric means. AUC=area under the concentration–time curve. C_{max}=maximum concentration. $t_{1/2}$=terminal-phase half-life.

Table 6: **Dose-normalised daunorubicin and daunorubicinol pharmacokinetic parameters in cycle 1**

The proportion of patients who achieved an overall disease response was similar between the eltrombopag and placebo groups (52 (70%) *vs* 54 (73%); odds ratio [OR] 0·87 [95% CI 0·40–1·89]; table 5). The proportion of patients who achieved a complete response and partial remission were also similar in both groups. For duration of response (figure 2A) and overall survival (figure 2B), patients were followed up to 2 years as per protocol. At the end of the study, the median duration of response was 22 months (IQR 10·5–not reached) in the eltrombopag group and was not reached (10·4–not reached) in the placebo group. Median overall survival was shorter in the eltrombopag group than in the placebo group (15·4 months *vs* 25·7 months; adjusted HR 1·54 [95% CI 0·96–2·47]; p=0·069), and more patients died in the eltrombopag group than the placebo group (39 [53%] *vs* 30 [41%]; table 5).

Eltrombopag administered on day 4 (approximately 24 h after the daunorubicin dose) resulted in a 21% increase in daunorubicin $AUC_{24-\infty}$ relative to placebo (table 6). However, because the mean proportion of $AUC_{24-\infty}$ relative to $AUC_{0-\infty}$ was approximately 10%, a 21% increase in daunorubicin AUC after 24 h could be expected to increase $AUC_{0-\infty}$ by approximately 2%, which is not clinically relevant. Daunorubicinol pharmacokinetic parameters were unaffected by eltrombopag.

Discussion

This randomised phase 2 study set out to assess the safety and tolerability of daily eltrombopag versus placebo in patients with acute myeloid leukaemia receiving anthracycline-based induction treatment. The incidence of LVEF events was similar in both groups and the frequency of adverse events was high but similar in both groups during daunorubicin and cytarabine induction therapy. However, there was a trend for more serious adverse events, including fatal adverse events, in the eltrombopag group than in the placebo group, most of which were related to acute myeloid leukaemia. Overall survival was also numerically longer in the placebo group compared with the eltrombopag group. It remains unclear why there were more deaths, particularly due to haemorrhage within 30 days after the last dose of treatment, in the eltrombopag group. Ongoing studies (eg, NCT02071901, NCT02446145, and NCT02912208) might help us to further understand the results of our study and to further assess eltrombopag in patients with acute myeloid leukaemia. Despite these unexpected findings regarding overall survival, no new safety signals were identified for eltrombopag that have not been reported in other studies.

The previous phase 1/2 study[11] examined the safety and tolerability of eltrombopag monotherapy (n=64) versus placebo (n=34) in the treatment of thrombocytopenia in patients with advanced myelodysplastic syndromes or acute myeloid leukaemia. Notably, the incidence of grade 3 or worse haemorrhage was lower in the eltrombopag group (10 [16%]) than in the placebo group (9 [26%]); the incidence of death was also lower in the eltrombopag group (21 [22%] *vs* 16 [47%]). Although the overall rate of adverse events was similar in both groups, some adverse events (eg, pyrexia, nausea, diarrhoea, fatigue, and decreased appetite) were more frequent in eltrombopag-treated patients. Similar findings were reported in a subsequent 12-week phase 2 study (ASPIRE)[21] in adults with advanced myelodysplastic syndromes or acute myeloid leukaemia who received either eltrombopag monotherapy (n=98) or placebo (n=47), whereby eltrombopag treatment reduced the number of clinically relevant thrombocytopenic events. Although a greater proportion of patients died in the eltrombopag group versus placebo in the ASPIRE study[21] (47 [48%] *vs* 18 [38%]), most of the deaths were due to the underlying disease (41 [87%] *vs* 17 [94%]; significance not reported).

In the present study, eltrombopag did not improve the time to platelet recovery or the incidences of grade 3–4 thrombocytopenia, neutropenia, or anaemia compared with placebo. Furthermore, the study did not reveal any differences in investigator-assessed response to treatment. These findings were unexpected given outcomes from previous studies of eltrombopag monotherapy in patients with myelodysplastic syndromes or acute myeloid leukaemia. In the previous phase 1/2 study,[11] platelet counts stabilised at about 20×10^9/L in the eltrombopag group and about 10×10^9/L in the placebo group, and more eltrombopag-treated patients were platelet transfusion-free for 56 or more consecutive days during treatment (38% *vs* 21%; OR 2·28 [95% CI 0·86–6·06]; p=0·10), although the two groups did not differ in protocol-defined platelet response. Patients in the eltrombopag group also had fewer haemorrhages of grade 3 or worse than in the placebo group. In the phase 2 ASPIRE study,[21] the proportion of patients who

had a clinically relevant thrombocytopenic event was significantly lower in the eltrombopag group (54% *vs* 69%; OR 0·20 [95% CI 0·05–0·87]; p=0·032). Additionally, in a preliminary report of an ongoing phase 2 study[22] of eltrombopag monotherapy in patients with lower-risk myelodysplastic syndromes, clinically significant platelet responses were observed in the eltrombopag group (28 [47%] *vs* 1 [3%]; OR 27·1 [95% CI 3·5–211·9]; p=0·0017), with a lower occurrence of bleeding events (8 [14%] *vs* 13 [42%]).

The reasons why eltrombopag appeared to have little clinical benefit in the present study is unclear. Data on the combination of eltrombopag with azacitidine in patients with intermediate-1-risk, intermediate-2-risk, or high-risk myelodysplastic syndromes (SUPPORT)[23] resulted in premature termination of the study because outcomes crossed the predefined futility threshold and also for safety reasons. Compared with placebo plus azacitidine, eltrombopag plus azacitidine worsened platelet recovery with a trend towards greater disease progression. Potential drug–drug interactions between eltrombopag and azacitidine are a plausible hypothesis to explain these findings.[24] The timing of eltrombopag administration during acute myeloid leukaemia induction chemotherapy could have conceivably affected outcomes, though the lower C_{max} in the first 24 h cannot explain the inferior survival in the experimental group as the two groups had a negligible difference in anthracycline C_{max}. In particular, the myelosuppressive effects of daunorubicin and cytarabine might have interfered with the proliferative effects of eltrombopag. Therefore, starting eltrombopag after completion of the induction chemotherapy cycle might permit better recovery of platelet counts and associated outcomes in patients with acute myeloid leukaemia. Further studies would be required to address this question. A notable limitation of this study is that the sample size was too small to detect meaningful differences in prognostic factors for survival, overall response, and platelet recovery. In particular, few patients in either group had daily blood counts once discharged from hospital, affecting the calculations of platelet recovery. A further limitation was that next-generation sequencing to try and identify an imbalance in prognostic disease-related mutations influencing outcomes between the two groups was not done.

In conclusion, the results of this phase 2 study of eltrombopag in combination with anthracycline-based induction therapy for acute myeloid leukaemia showed no clinical benefit over placebo. Furthermore, there was a trend that patients receiving eltrombopag had a higher incidence of serious adverse events, and deaths due to haemorrhage, within 30 days after the last dose. Although the reasons for our findings remain unclear, the data from this trial do not support a favourable benefit–risk profile for eltrombopag in combination with induction chemotherapy in patients with acute myeloid leukaemia. We found no statistically significant differences in LVEF events or the pharmacokinetics of daunorubicin and daunorubicinol between the two groups, suggesting that eltrombopag did not affect exposure to induction chemotherapy. This study provides some insight into the use of eltrombopag in patients with acute myeloid leukaemia receiving induction chemotherapy, although the reasons for our findings remain unclear.

Contributors

NF, SS, JS, AI, H-JK, RR, BHC, JMR, EB, JL, ESW, and JHJ served as investigators in this study, enrolling patients. AC, VA, and FG contributed to the analysis, interpretation, and reporting of the study data. All authors contributed to data interpretation, reviewed and provided their comments on this manuscript, and approved the final version.

Declaration of interests

NF reports non-financial support from Novartis during the conduct of the study and has received consultancy fees from Novartis outside of the submitted work. SS reports other support from Sunesis, Astellas, Pfizer, Novartis, Tolero, Boehringer-Ingelheim, and Baxalta outside of the submitted work. JS reports grants and personal fees from Alexion Pharmaceuticals, and personal fees from Pfizer, Shire Pharmaceuticals, and Amgen outside of the submitted work. BHC reports grants from Amgen during the conduct of the study and other support from Novartis outside of the submitted work. JL reports personal fees from AbbVie, Onconova, Novartis, and Seattle Genetics, outside of the submitted work. ESW reports personal fees from Shionogi Inc outside of the submitted work. AC and FG report personal fees from Novartis AG outside of the submitted work. All other authors have no competing interests.

Data sharing

Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymised to respect the privacy of patients who have participated in the trial, in line with applicable laws and regulations. This trial data availability is in accordance with the criteria and process described on www.clinicalstudydatarequest.com.

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