

# Avatrombopag, an oral thrombopoietin receptor agonist: results of two double-blind, dose-rising, placebo-controlled Phase 1 studies

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## Summary

Avatrombopag is an oral thrombopoietin receptor agonist that has been recently approved for treating thrombocytopenia in chronic liver disease patients needing invasive procedures. Clinical trials supporting this new treatment were guided by two double-blind, dose-rising, placebo-controlled Phase 1 studies in healthy adults reported here that assessed safety, tolerability and pharmacokinetic profile of avatrombopag, and its effect on platelet counts. Subjects were randomised (2:1) in the single-dose study ( $N = 63$ ) to avatrombopag (1, 3, 10, 20, 50, 75 and 100 mg) or placebo, and in the multiple-dose study ( $N = 29$ ) to avatrombopag (3, 10 and 20 mg) or placebo daily for 14 days. There were no serious adverse events (AEs), dose-limiting toxicities, deaths, AEs causing withdrawal, thromboses or liver function abnormalities. In both studies, avatrombopag peak concentration and exposure increased proportionally relative to dose; half-life was 18–21 h and independent of dose, supporting once-daily dosing. Effects on platelet counts depended on dose, concentration and treatment duration. Platelet count increases began 3–5 days post-administration, with maximum changes of  $>370 \times 10^9/l$  over baseline with 20 mg daily after 13–16 days. These data support continued development of avatrombopag for treatment of other thrombocytopenic conditions and provide important guidance for the haematologist in the use of this new thrombopoietin receptor agonist.

**Keywords:** avatrombopag, thrombopoietin, pharmacokinetics, pharmacodynamics, platelets.

Avatrombopag (E5501, previously known as AKR-501 and YM477; see Figure S1 for chemical structure) is an orally administered, small molecule, thrombopoietin (TPO) receptor agonist that mimics the biological effects of TPO *in vitro* and *in vivo* (Desjardins, 2007; Fukushima-Shintani *et al*, 2008, 2009). Avatrombopag binds to a distinct transmembrane site on the TPO receptor and does not block the binding of native TPO (Fukushima-Shintani *et al*, 2008). *In vitro* studies have shown that avatrombopag stimulates the proliferation of human c-Mpl-Ba/F3 cells [half maximal effective concentration ( $EC_{50}$ )  $3.3 \pm 0.2$  nmol/l] and promotes megakaryocyte colony formation from human CD34<sup>+</sup> cells ( $EC_{50}$   $24.8 \pm 7.8$  nmol/l) (Fukushima-Shintani *et al*, 2009). The effects of avatrombopag and TPO on megakaryocytopoiesis have been shown to be additive (Fukushima-

Shintani *et al*, 2008). Furthermore, oral avatrombopag increased human platelet counts in non-obese diabetic/severe combined immunodeficiency mice transplanted with human haematopoietic stem cells in a dose-responsive manner (Abe *et al*, 2011). Together, these preclinical data predicted that avatrombopag would have therapeutic potential for the treatment of thrombocytopenia of various aetiologies, including that associated with immune thrombocytopenia (ITP), chronic liver disease (CLD) and chemotherapy-induced thrombocytopenia (CIT).

Avatrombopag was approved by the United States Food and Drug Administration (FDA) in 2018 for the treatment of thrombocytopenia in adults with CLD who are scheduled to undergo a medical or dental procedure (<https://dova.com/pdf/doptelet-fda-prescribing-information.pdf>); the first drug

approved by the FDA for this indication (Food and Drug Administration, 2018). In two Phase 3 randomised trials, avatrombopag was superior to placebo in reducing the need for platelet transfusions or rescue procedures for bleeding in patients with thrombocytopenia and CLD undergoing a scheduled procedure (Terrault *et al*, 2018). In addition, in a 28-day Phase 2 study, once-daily oral avatrombopag was shown to increase platelet counts above baseline in patients with chronic ITP (Bussel *et al*, 2014). These effects were also mirrored in a randomised Phase 3 study (NCT01438840), in which avatrombopag was superior to placebo in increasing the cumulative number of weeks of platelet response and durable platelet response in patients with chronic ITP (Jurczak *et al*, 2017). Avatrombopag was generally well tolerated in all of these clinical studies (Bussel *et al*, 2014; Jurczak *et al*, 2017; Terrault *et al*, 2018). There has been no evidence for increased thromboembolic events, hepatotoxicity (Terrault *et al*, 2018) or significant food interactions with avatrombopag (Nomoto *et al*, 2018) reported in these studies.

Dosing in all of these studies with avatrombopag was based on two Phase 1 dose-finding studies in healthy human subjects (reported here). These two Phase 1 studies provide extensive pharmacokinetic (PK) and pharmacodynamic (PD) data not reported in the clinical trials mentioned above, as well as a detailed assessment of adverse effects of this drug in subjects without major medical conditions. These data serve to inform future clinical trials in other thrombocytopenic disorders, and to provide the haematologist with a clear overview of the attributes of this newly available treatment option.

## Materials and methods

### Study design

Both single- and multiple-dose studies were of a double-blind, dose-rising design and were conducted at a single study site (Phase 1 Unit, Quintiles, Inc., Lenexa, Kansas) over a 28-day period. The studies were conducted under the principles of the Declaration of Helsinki, and study protocols were reviewed and approved by the Heartland Institutional Review Board. Written informed consent or oral witnessed informed consent was obtained from all subjects prior to screening.

### Subjects

Subjects eligible for inclusion were healthy men and women aged 18–65 years, with a body weight of 50–100 kg, body mass index of 18–30 kg/m<sup>2</sup> and platelet count between 150 and 300 × 10<sup>9</sup>/l. Key exclusion criteria included abnormal laboratory test results for renal function, known platelet disorders, recreational drug use or history of thromboembolism, bleeding diathesis, cardiovascular disease, malignancy, inflammatory/autoimmune disease or splenectomy.

### Interventions

For both 28-day studies, subjects were randomised (2:1) to receive either avatrombopag or placebo (microcrystalline cellulose). All subjects fasted for 8 h prior to dosing until 4 h post-dose. Fluids were withheld from 2 h pre-dose to 2 h post-dose. The subjects, investigator and study staff were blinded to the identity of the administered substance. The starting dose for the single-ascending dose study was 1 mg, and successive groups received a single dose of 3, 10, 20, 50, 75 or 100 mg. For the multiple-ascending-dose study, the starting dose was 3 mg, and successive cohorts were scheduled to receive 10, 20, 50 or 100 mg avatrombopag daily for 14 days. In the single-ascending-dose study, avatrombopag or matched placebo was administered as a single 60 ml aqueous oral suspension [30 ml dose suspension and 30 ml wash (Ora-Plus<sup>®</sup>, Perrigo, Allegan, MI, USA suspending vehicle/water solution)] for the 1, 3, 10, 50 and 75 mg dose cohorts, and as a 120 ml suspension (2 × 30 ml dose suspension and 2 × 30 ml wash) for the 20 and 100 mg cohorts. For the multiple-dose study, avatrombopag or placebo was administered once-daily as a 60 ml aqueous oral suspension (30 ml dose suspension and 30 ml wash) for the 3, 10 and 50 mg cohorts, and a 120 ml suspension (2 × 30 ml dose suspension and 2 × 30 ml wash) for the 20 and 100 mg cohorts. Treatments were administered over 14 consecutive days for the multiple-ascending-dose study. Dosing for the multiple-dose study was based on safety and tolerability data from the single-dose study. Dose escalation for all dose cohorts did not proceed until all safety and PD parameters from the previous dose cohort had been reviewed by the investigator and sponsor. Dose escalation and enrolment in a dosing cohort stopped if a dose-limiting toxicity (DLT) was experienced by at least one subject in a dose cohort. A DLT was defined as the occurrence of a drug-related Grade 3 laboratory abnormality in any one or more subjects at a given dose level, or the same Grade 2 laboratory abnormality in two or more subjects at a given dose level. In the event of a DLT, the previous dose was to be considered the maximum tolerated dose. Subjects with a platelet count  $\geq 500 \times 10^9/l$  (PD limit) at any platelet assessment were discontinued from further treatment. If five out of six actively treated subjects in any dose cohort reached the PD limit, no further dose escalation was to occur in the study.

### Safety assessments

In both studies, adverse event (AE) data were obtained by questioning the subjects at regular time intervals throughout the 28-day study period. The Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup>; www.meddra.org) was used for coding AEs. Details included a description of the event, date and time of onset; date; and time of end, severity; and whether the event was ongoing. The intensity of the event was recorded as mild, moderate or severe, and the

relationship to drug noted as probable, possible or unlikely. Any further action taken or treatment required for management of an AE was recorded. Outcome was recorded as recovered, not yet recovered, recovered with sequelae, fatal or unknown.

Blood and urine samples for haematology (complete blood count with differential, mean platelet volume), serum chemistry and urinalysis were prepared using standard procedures. Blood samples (15 ml) for routine clinical laboratory tests and urine (~30 ml) were collected at screening, baseline and during treatment in both studies, and on days 21 and 28 in the multiple-dose study.

Vital-sign measurements (systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature) were performed at screening, baseline, during treatment and at follow-up (or early termination visit) in both studies. During treatment, vital signs were measured prior to study drug administration, at 4 and 8 h after dosing, then every 8 h post-dose until discharge from the clinic (or as clinically indicated). A standard 12-lead electrocardiogram (ECG; 25 mm/s) was performed at screening, pre-dose and at 4–6 h and 24 h post-dose in both studies.

#### *PK assessments*

The PK analyses were conducted utilising a validated bioanalytical method that employed a liquid-liquid extraction and high-performance, reversed-phase liquid chromatography with tandem mass spectrometric detection. In the single-dose study, blood was collected for analysis at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 h. For the 100 mg dose cohort, additional blood samples were collected at 72, 96 and 120 h. For each dose level in the multiple-dose study, blood samples were collected for PK analysis at pre-dose (0 h) on days 1 and 14, then at 5, 15, 30, 45, 60, 90, 120, 150 and 180 min, plus 6, 12, 16, 24, 36 and 48 h after the first dose of study drug was administered on day 1 and after the last dose was administered on day 14. The following PK parameters were assessed: area under the concentration-time curve from time 0 to infinity ( $AUC_{0-\infty}$ ), area under the concentration-time curve from time 0 to time of last quantifiable concentration ( $AUC_{0-\text{last}}$ ), observed peak analyte concentration ( $C_{\text{max}}$ ), observed peak analyte concentration at steady-state ( $C_{\text{max,ss}}$ ), first observed time to reach peak concentration ( $T_{\text{max}}$ ), first observed time to reach peak concentration at steady-state ( $T_{\text{max,ss}}$ ) and terminal phase half-life ( $t_{1/2}$ ).

#### *PD assessments*

PD assessments included the change in peripheral blood platelet counts and mean platelet volume. Platelet counts were assessed at screening; baseline; during the treatment period on days 1, 2, 3, 7, 10 and 14; and at follow-up on day 21. These assessments were also done on day 28 if the Day 21

platelet count was more than 20% above baseline. Peak observed platelet count change from baseline ( $C_{\text{pmax}}$ ), observed time to  $C_{\text{pmax}}$  ( $T_{\text{pmax}}$ ), and area under the platelet count; and change from baseline over time curve from day 1 to last measured platelet counts ( $AUC_{\text{p}}$ ) were also assessed.

#### *Determination of sample size*

The single-dose, dose-rising study planned to recruit a total of 63 healthy volunteers in seven dose cohorts of nine subjects each. Within each cohort, six subjects were to receive avatrombopag and three subjects were to receive placebo. The starting avatrombopag dose was 1 mg, and successive cohorts were to receive a single dose of 3, 10, 20, 50, 75 or 100 mg.

Forty-five healthy volunteers in five groups of nine subjects each were planned to enter the multiple-dose, dose-rising study. During each study period, six subjects were to receive a dose of 3, 10, 20, 50 and 100 mg avatrombopag and three subjects were to receive placebo.

No formal statistical sample size calculations were performed for either study.

#### *Statistical analysis*

No formal statistical testing was planned to be performed on the safety and tolerability data. A one-way analysis of variance (ANOVA) was performed to test for differences among the study cohorts with respect to  $C_{\text{pmax}}$  and  $AUC_{\text{p}}$ . All  $C_{\text{pmax}}$  and  $AUC_{\text{p}}$  parameters were assumed to be log-normal in distribution and, thus, were log-transformed for the ANOVA analyses. The safety population included all subjects who received at least one dose of study drug (including placebo). The PD analysis population included all eligible subjects who received avatrombopag treatment and provided evaluable platelet counts, and the PK analysis population included all eligible subjects who provided evaluable concentrations of avatrombopag over the planned collection period. In the multiple-dose study, PK samples for the 20 mg dose group were only drawn on day 1. However, simulated profiles and corresponding parameters are included as part of this analysis for comparative purposes.

## **Results**

### *Single-dose study population*

Of 137 subjects screened, 63 met eligibility criteria and were enrolled in the single-dose study (subject disposition is shown in Fig 1A). A summary of patient demographics and baseline characteristics is presented in Table I. Nine subjects were assigned to each avatrombopag dose cohort (1, 3, 10, 20, 50, 75 and 100 mg). Within each cohort, six subjects received avatrombopag and three subjects received placebo. All 63 subjects received study drug on day 1 and were,

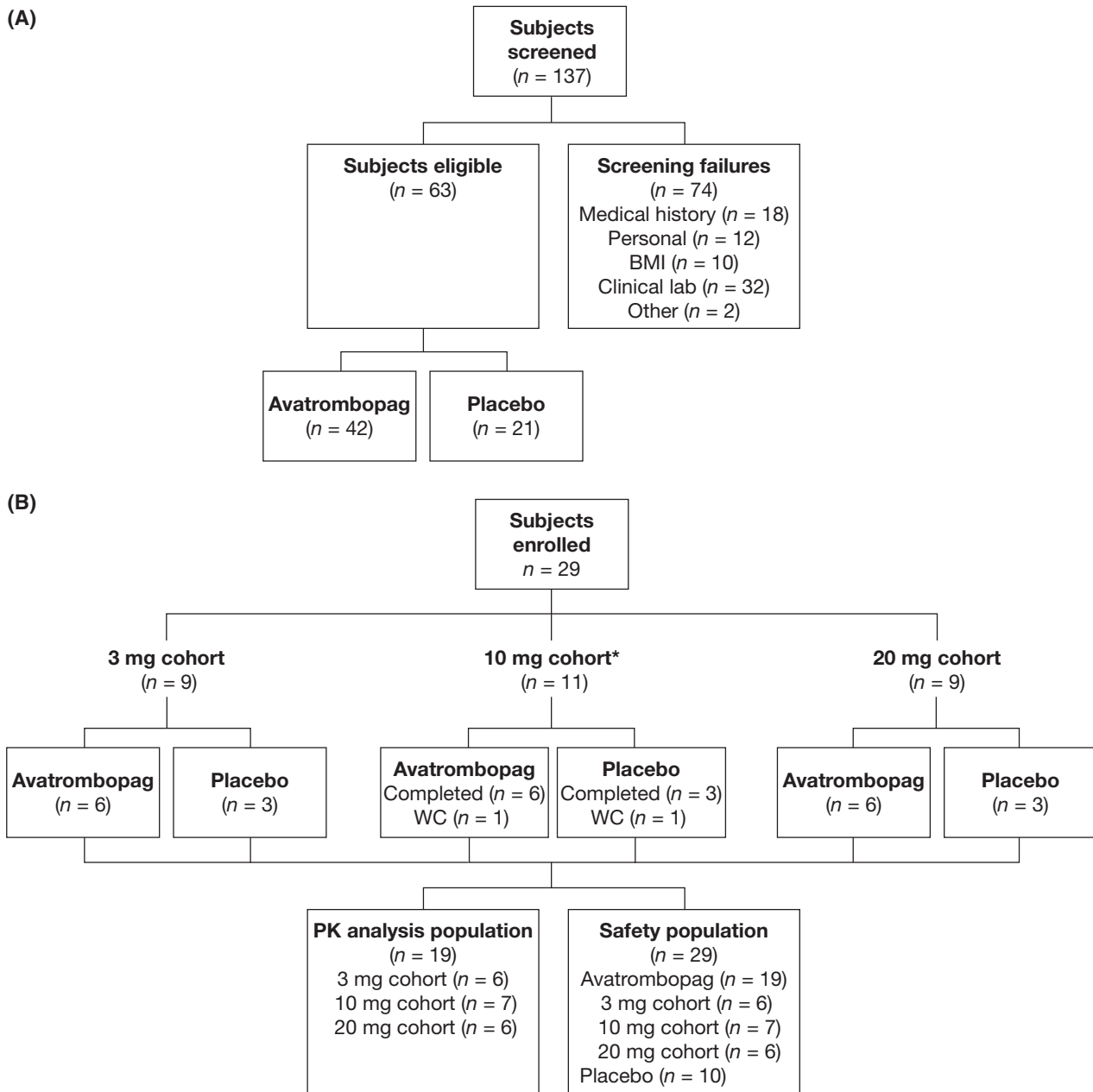


Fig 1. Disposition of subjects. (A) Single-dose study. (B) Multiple-dose study. \*Two subjects enrolled in the 10 mg cohort withdrew from the study and were replaced (1 was randomised to receive avatrombopag, and 1 was randomised to receive placebo). BMI, body mass index; PK, pharmacokinetic; WC, withdrew consent.

therefore, included in the full PD analysis set and safety analysis set. Forty-two subjects received avatrombopag at day 1 and were included in the PK data set. All subjects completed the 28-day study protocol.

#### Multiple-dose study population

Subject disposition for the multiple-dose study is summarized in Fig 1B. In total, 29 subjects were recruited, of whom nine were enrolled into the 3 mg cohort, 11 were enrolled

into the 10 mg cohort and nine were enrolled into the 20 mg cohort. The study was discontinued after dose escalation to the 20 mg cohort, as all subjects reached the pre-specified PD limit of platelet counts  $\geq 500 \times 10^9/l$  after either 10 or 11 days of daily dosing; therefore, no subjects were enrolled into the planned 50 or 100 mg dose cohorts. Within each cohort, six subjects received avatrombopag at the assigned dose; the remaining three subjects received placebo. Two subjects enrolled in the 10 mg cohort withdrew from the study and were replaced: one subject was randomised to

Table I. Patient demographics (single-dose administration).

Characteristic	Treatment									
	Placebo (n = 21)	1 mg (n = 6)	3 mg (n = 6)	10 mg (n = 6)	20 mg (n = 6)	50 mg (n = 6)	75 mg (n = 6)	100 mg (n = 6)	All subjects (n = 63)	
Sex (female)	8 (38.1)	2 (33.3)	2 (33.3)	2 (33.3)	3 (50.0)	2 (33.3)	2 (33.3)	2 (33.3)	23 (36.5)	
Race (Caucasian)	18 (85.7)	3 (50.0)	5 (83.3)	4 (66.7)	6 (100.0)	6 (100.0)	5 (83.3)	5 (83.3)	52 (82.5)	
Age (years)	Mean (SD) 27.4 (10.2)	36.3 (12.3)	34.0 (15.2)	32.2 (6.8)	34.0 (17.2)	33.2 (15.9)	29.8 (15.7)	25.5 (9.3)	30.6 (12.3)	
Height (inches)	Mean (SD) 67.93 (3.52)	66.17 (4.17)	67.66 (3.45)	68.39 (3.66)	68.86 (4.42)	67.86 (4.05)	69.39 (3.64)	69.26 (3.34)	68.13 (3.61)	
Weight (pounds)	Mean (SD) 164.10 (23.32)	162.72 (31.57)	152.80 (18.40)	177.22 (37.19)	154.53 (38.49)	171.05 (27.78)	150.23 (26.76)	168.17 (18.79)	162.96 (26.91)	
BMI (kg/m <sup>2</sup> )	Mean (SD) 25.09 (3.50)	26.07 (2.95)	23.73 (4.17)	26.45 (3.54)	23.77 (4.24)	26.00 (1.26)	21.90 (2.92)	24.70 (1.91)	24.80 (3.35)	

BMI, body mass index; SD, standard deviation.

receive avatrombopag 10 mg, and one was randomised to receive placebo. Twenty-nine subjects (six active and three placebo for each of the 3 and 20 mg dose cohorts; seven active and four placebo for the 10 mg dose cohort) received study drug on day 1 for each dose cohort and were included in the safety analysis. Therefore, the full PK analysis set included 19 subjects, each of whom had at least one measurable plasma concentration of avatrombopag. Baseline subject demographics and characteristics are shown in Table II and are similar to baseline demographics of subjects in the single-dose study (Table I).

#### Safety and tolerability of single-dose avatrombopag

In the single-dose study, treatment-emergent AEs (TEAEs) were reported by 26/42 (61.9%) subjects who received avatrombopag and by 12/21 (57.1%) subjects who received placebo (Table SI). The most commonly reported TEAEs in subjects who received avatrombopag were blood-draw/catheter-site pain (14.3%), dysgeusia (14.3%) and blood-draw/catheter-site bruise (11.9%). In subjects who received placebo, the most common TEAE was headache (19%). Of placebo-treated subjects, blood-draw/catheter-site pain, dysgeusia or flatulence were reported by two (9.5%) subjects each.

Treatment-related TEAEs in the single-dose study were reported by 11/42 (26.2%) subjects who received avatrombopag and by 7/21 (33.3%) subjects who received placebo (Table III). For the subjects who received avatrombopag, the most common treatment-related TEAE was dysgeusia (14.3%), and two subjects (4.8%) each had treatment-related flatulence, dizziness, headache or somnolence. For subjects receiving placebo, the most common treatment-related TEAE was headache (14.3%), and two subjects (9.5%) each reported dysgeusia or flatulence.

All of the TEAEs were considered to be mild in severity with the exception of one TEAE for diarrhoea in one subject who received a 3 mg dose of avatrombopag. This event was classified as moderate, began on day 5, resolved on day 6 and was judged not to be related to study treatment by the investigator. There was no relationship between the TEAEs and the dose of avatrombopag received. No serious AEs occurred, and there were no deaths or study withdrawals due to AEs. There were no clinically significant changes in laboratory values that assessed renal and hepatic function, electrolytes and serum lipids. There were also no clinically significant changes in vital signs, ECG parameters or urinalysis results. No thrombotic events occurred and no DLTs were observed.

#### Safety and tolerability of multiple-dose avatrombopag

In the multiple-dose study, 17/19 (89.5%) subjects who received avatrombopag and 6/10 (60%) subjects who received placebo reported at least one TEAE (Table SII). The most commonly reported TEAEs in subjects who received



**Table II.** Patient demographics (multiple-dose administration).

Characteristic	Statistic	Treatment				All subjects (n = 29)
		Placebo (n = 10)	3 mg (n = 6)	10 mg (n = 6)	20 mg (n = 6)	
Sex (female)	n (%)	2 (20.0)	2 (33.3)	1 (14.3)	3 (50.0)	8 (27.6)
Race (Caucasian)	n (%)	8 (80.0)	4 (66.7)	6 (85.7)	6 (100.0)	24 (82.8)
Age (years)	Mean (SD)	36.7 (16.0)	25.3 (4.5)	28.6 (13.6)	53.0 (16.9)	35.8 (16.6)
Height (inches)	Mean (SD)	67.69 (2.09)	67.21 (4.20)	69.17 (4.49)	66.66 (4.55)	67.73 (3.66)
Weight (pounds)	Mean (SD)	162.95 (20.72)	166.05 (36.64)	170.08 (20.72)	172.17 (31.68)	167.22 (25.75)
BMI (kg/m <sup>2</sup> )	Mean (SD)	25.14 (3.52)	25.65 (3.41)	25.20 (2.56)	27.18 (3.13)	25.68 (3.14)

BMI, body mass index; SD, standard deviation.

**Table III.** Treatment-related TEAEs\* following single-dose administration of avatrombopag or placebo.

	Number (%) of subjects								
	Placebo (n = 21)	1 mg (n = 6)	3 mg (n = 6)	10 mg (n = 6)	20 mg (n = 6)	50 mg (n = 6)	75 mg (n = 6)	100 mg (n = 6)	All active treated subjects (n = 42)
Number of subjects with TEAEs	7 (33.3)	2 (33.3)	1 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	11 (26.2)
Dysgeusia	2 (9.5)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	0 (0.0)	1 (16.7)	1 (16.7)	6 (14.3)
Flatulence	2 (9.5)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	2 (4.8)
Dizziness	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	2 (4.8)
Headache	3 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	2 (4.8)
Somnolence	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	2 (4.8)
Diarrhoea	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (2.4)
Nausea	1 (4.8)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Lethargy	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Muscle contractions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (2.4)

AE, adverse event; TEAE, treatment-emergent adverse event.

\*TEAEs are preferred term from the Medical Dictionary for Drug Regulatory Activities (MedDRA), version, 8.1 (www.meddra.org). The numbers of subjects in each column cannot be added because a subject may have had more than 1 AE. A subject experiencing multiple occurrences of an AE was counted, at most, once per preferred term. Treatment-related TEAEs are defined as TEAEs assessed as possibly or probably related to study medication, or those for which the relationship is unknown or missing.

avatrombopag were headache (31.6%), catheter-site pain (21.1%) and diarrhoea (21.1%). In the subjects that received placebo, the most commonly reported TEAE was headache (20%).

Treatment-related TEAEs in the multiple-dose study were reported by 8/19 (42.1%) subjects who received avatrombopag and none of the subjects who received placebo (Table IV). The most common treatment-related TEAE in subjects who received avatrombopag was constipation (15.8%), with photophobia, diarrhoea, flatulence or fatigue occurring in two (10.5%) subjects each.

All TEAEs were either of mild or moderate intensity. No serious AEs occurred, and there were no deaths or study withdrawals due to AEs. One subject in the 20 mg cohort had moderate hyperkalaemia (5.6 mmol/l) at screening and intermittently during the study, with a maximum of 6.5 mmol/l reported. This event was assessed as clinically significant by the investigator, although there were no ECG or other laboratory abnormalities identified. Review of all safety

data for this subject led to the conclusion that these potassium elevations were probably due to *in vitro* red-blood-cell haemolysis and/or pseudohyperkalaemia from thrombocytosis. Other than this subject, there were no other clinically significant changes in any measured laboratory parameters, including liver function tests. There were no clinically relevant changes from baseline levels in vital signs or ECG parameters in any subjects. No thrombotic events were reported and no DLTs were observed.

#### PK

Following single-dose administration, avatrombopag was measurable in plasma 0.5–1 h after dosing, and maximum concentrations were observed approximately 4–6 h following drug administration. Concentration–time profiles of avatrombopag and a summary of the PK parameters in the single-dose study are presented in Fig 2A and Table V, respectively. Mean  $C_{max}$  increased in a dose-proportional manner to

Table IV. Treatment-related TEAEs\* following multiple-dose administration of avatrombopag or placebo.

	Number (%) of subjects				
	Placebo (n = 10)	3 mg (n = 6)	10 mg (n = 7)	20 mg (n = 6)	All active treated subjects (n = 19)
Number of subjects with TEAEs	0 (0.0)	2 (33.3)	1 (14.3)	5 (83.3)	8 (42.1)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	3 (15.8)
Photophobia	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	2 (10.5)
Diarrhoea	0 (0.0)	0 (0.0)	1 (14.3)	1 (16.7)	2 (10.5)
Flatulence	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	2 (10.5)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	2 (10.5)
Abdominal pain lower	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.3)
Chest wall pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.3)
Dysgeusia	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.3)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.3)
Hyperkalaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.3)
Migraine	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.3)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.3)

AE, adverse event; TEAE, treatment-emergent adverse event.

\*TEAEs are preferred term from the Medical Dictionary for Drug Regulatory Activities (MedDRA), version 8.1 (www.meddra.org). The numbers of subjects in each column cannot be added because a subject may have had more than 1 AE. A subject experiencing multiple occurrences of an AE was counted, at most, once per preferred term. Treatment-related TEAEs are defined as TEAEs assessed as possibly or probably related to study medication, or those for which the relationship is unknown or missing.

75 mg. Maximum concentrations of avatrombopag for the 100 mg dose group were slightly lower than expected and were, on average, approximately 20% less than the maximum concentrations observed for the 75 mg dose cohort.

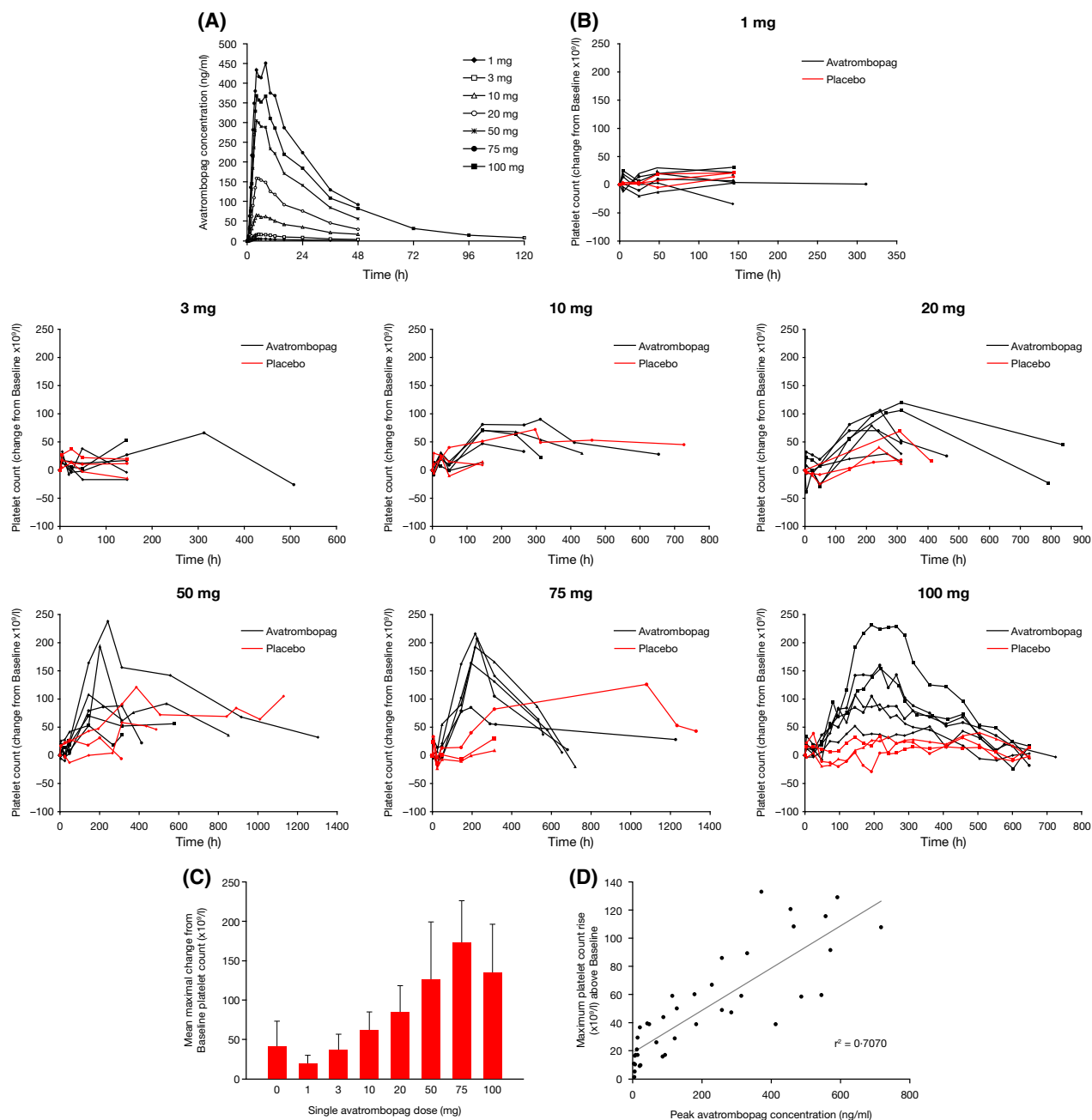
In the multiple-dose study, avatrombopag was detectable in plasma 0.25–1 h after initial- and repeat-dose administration; maximum concentrations were observed at approximately 4.5–6 h following initial (day 1) and final (day 14) dose administration (Fig 3A). The PK parameters for avatrombopag are summarised in Table VI. PK samples for the 20 mg dose group were only drawn on day 1; however, simulated profiles and corresponding parameters were included as part of this analysis for comparative purposes. The mean exposure estimates,  $C_{max}$  and AUC, increased in a dose-proportional manner following avatrombopag administration on days 1 and 14. Median  $T_{max}$  occurred at approximately 6 h across all treatment cohorts following administration on days 1 and 14. The range of  $T_{max}$  estimates indicated consistency across all treatment cohorts and did not suggest significant variability in the rate of drug absorption. The PK parameter variability was comparable in all treatment cohorts following avatrombopag administration on days 1 and 14 and ranged from approximately 11% to 38% (excluding simulated parameters) and 11% to 77% (including simulated parameters), respectively. Mean  $t_{1/2}$  ranged from 18 to 21 h and was found to be independent of dose.

#### PD

In the single-dose study, changes in platelet counts were not seen with avatrombopag doses lower than 10 mg (Fig 2B, C,

Table V). Increases in platelet counts were evident as early as 3–5 days post-administration (10–100 mg), with the highest observed changes in platelet counts observed by approximately 6–10 days. Increases in platelet counts were observed as the dose increased within the 10–100 mg dose range; however, the mean platelet count within the 100 mg dose cohort was slightly lower than that observed in the 75 mg dose cohort (Fig 2C). Graphical PK/PD analysis showed a linear relationship between  $C_{max}$  and  $C_{pmax}$  (Fig 2D).

A summary of mean PD parameters in the multiple-dose study is presented in Table VI. Changes from baseline platelet counts with time are shown for multiple 3, 10 and 20 mg doses of avatrombopag in Fig 3B. Significant increases in platelet counts over baseline were observed for the 10 and 20 mg dose cohorts approximately 3–5 days after the start of dosing with avatrombopag. Maximum changes in platelet counts were observed by approximately 13–16 days for all treatment cohorts and appeared to be dependent on dose, concentration and duration of treatment. Platelet counts continued to increase following completion of dosing (Fig 3B). Mean maximum platelet count rise over baseline did not differ from placebo in the 3 mg dose group (Fig 3C). At 10 and 20 mg of avatrombopag, however, significant increases in platelet counts over baseline were evident compared with placebo (Fig 3C). The variability in the maximum increases in platelet counts over baseline for all avatrombopag treatment cohorts was <40%. Increases in platelet counts were dose-related, as the greatest increases were observed with the 20 mg dose group, and maximum increases in platelet counts from baseline were related to peak plasma concentrations of avatrombopag (Fig 3D).



**Fig 2.** Single-dose study. (A) Mean avatrombopag concentration–time profiles by single-dose cohort. (B) Individual change from baseline in platelet counts with single-dose avatrombopag dose by time. (C) Mean maximum change ( $\pm$ SD) from baseline platelet count with single doses of avatrombopag. (D) Maximum platelet count rise ( $\times 10^9/l$ ) above baseline ( $C_{pmax}$ ) compared with peak avatrombopag concentration ( $C_{max}$ ).  $C_{max}$ , observed peak analyte concentration;  $C_{pmax}$ , peak observed platelet count change from baseline;  $r^2$ , coefficient of determination; SD, standard deviation.

In both studies, there was no change in mean platelet volume.

## Discussion

These Phase 1 studies have demonstrated the safety, tolerability, PK and PD of oral avatrombopag in healthy subjects.

Avatrombopag was well tolerated, with no significant drug-related AEs or DLTs following a single dose of up to 100 mg or multiple doses of up to 20 mg for 10–14 days. There were no thrombotic events, liver function test abnormalities or musculoskeletal AEs. The incidence and severity of most AEs were supported by those observed in the two other clinical studies with avatrombopag in patients with



Table V. Summary of mean PK/PD parameters for change from baseline platelet counts following single-dose avatrombopag administration in the single-dose study.

PK parameter	Dose cohort						
	1 mg (n = 6)	3 mg (n = 6)	10 mg (n = 5)	20 mg (n = 6)	50 mg (n = 6)	75 mg (n = 5)	100 mg (n = 6)
$C_{max}$ (ng/ml)*	5.7 (28.8)	17.1 (25.3)	69.1 (50.9)	168.8 (53.5)	311.5 (38.8)	473.7 (37.3)	388.0 (47.0)
$T_{max}$ (h)†	6.5 (4.0–8.0)	5.0 (4.0–10.0)	5.0 (4.0–6.0)	4.5 (4.0–8.0)	4.0 (3.5–8.0)	6.0 (4.0–8.05)	6.5 (4.0–8.07)
$AUC_{0-last}$ (ng h/ml)*	130.2 (26.6)	400.5 (22.0)	1645.2 (62.2)	3597.7 (52.4)	6879.3 (39.9)	10824.7 (41.6)	10863.5 (59.7)
$AUC_{0-inf}$ (ng h/ml)*	183.2 (21.5)	534.4 (20.0)	2378.3 (92.1)	4439.9 (54.5)	8477.6 (42.1)	13457.2 (43.6)	11077.5 (61.0)
$t_{1/2}$ (h)*	21.5 (17.5)	23.6 (38.6)	21.8 (44.3)	18.9 (18.0)	19.0 (11.9)	18.8 (19.5)	18.0 (17.8)

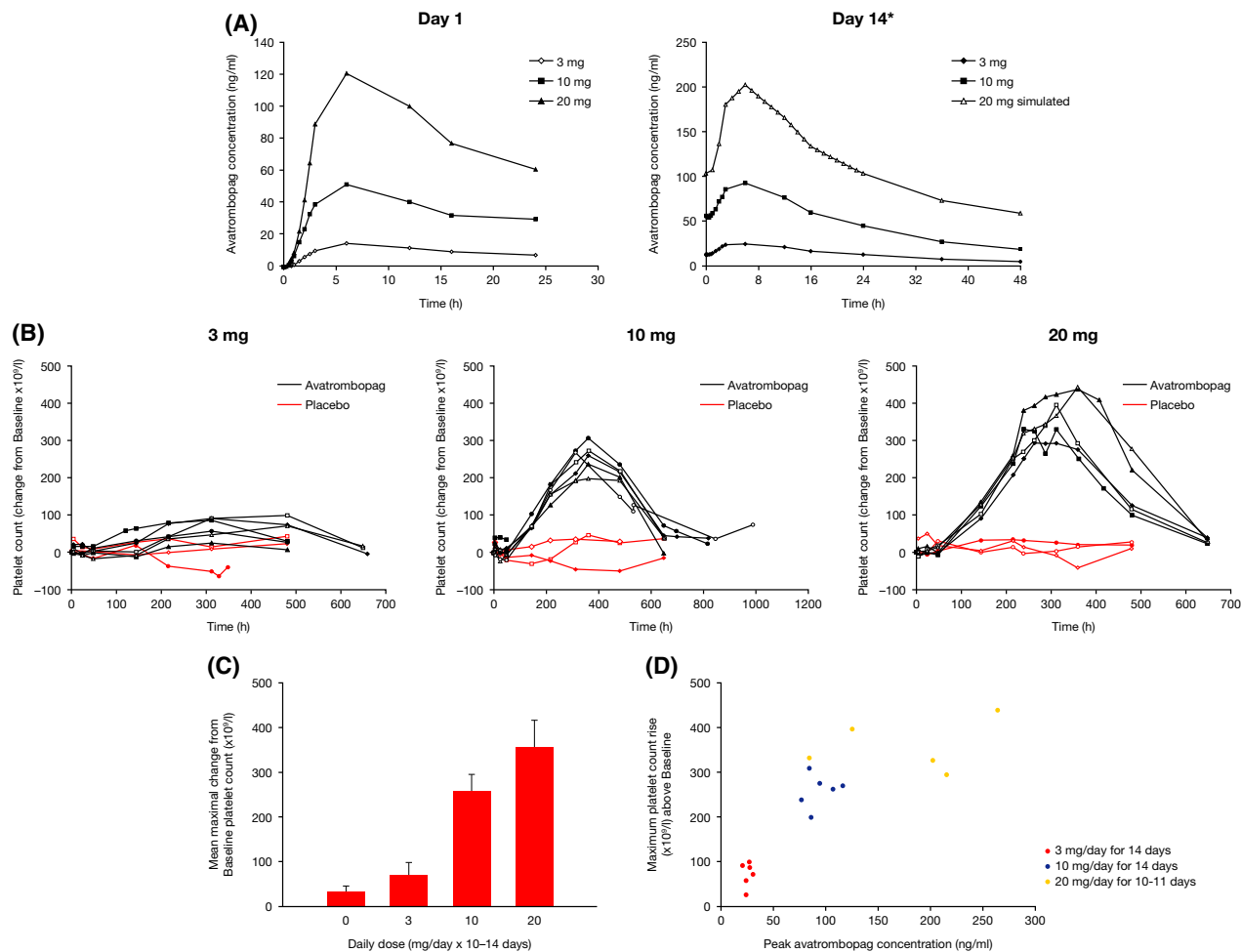
  

PD parameter (change from baseline platelet count)	Dose cohort							
	Placebo (n = 21)	1 mg (n = 6)	3 mg (n = 6)	10 mg (n = 6)	20 mg (n = 6)	50 mg (n = 6)	75 mg (n = 6)	100 mg (n = 6)
$C_{pmax}$ ( $10^9/l$ )*	41.3 (78)	18.8 (58)	37.2 (52)	60.5 (34)	85.0 (39)	125.2 (59)	158.3 (38)	134.8 (45)
$T_{max}$ (h)†	216 (4–1080)	48 (4–145)	96 (4–313)	145 (24–312)	255 (144–313)	174 (144–313)	207 (194–225)	193 (145–219)
$AUC_p$ ( $10^9 h/l$ )*	13874 (202)	1335 (126)	2779 (119)	14532 (80)	21583 (92)	46208 (100)	47735 (37)	38818 (50)

$AUC_{0-inf}$  area under the concentration–time curve from time 0 to infinity;  $AUC_{0-last}$  area under the concentration–time curve from time 0 to time of last quantifiable concentration;  $AUC_p$  change from baseline over time curve from day 1 to last measured platelet counts;  $C_{pmax}$  observed peak analyte concentration;  $C_{pmax}$  peak observed platelet count change from baseline; CV, coefficient of variation; PD, pharmacodynamic; PK, pharmacokinetic;  $T_{max}$ , first observed time to reach peak concentration;  $t_{1/2}$ , terminal phase half-life.

\*Value presented as mean (CV%).

†Value presented as median (min–max).



**Fig 3.** Multiple-dose study. (A) Mean avatrombopag concentration time profiles on days 1 and 14 by multiple-dose cohort. (B) Change from baseline platelet counts by time for 3, 10 and 20 mg avatrombopag cohorts. (C) Mean change ( $\pm$ SD) from baseline platelet counts by dose cohorts. (D) Maximum platelet count rise ( $\times 10^9/l$ ) above baseline ( $C_{pmax}$ ) compared with peak avatrombopag concentration ( $C_{max}$ ). \*Day 14 results are simulated for 20 mg daily dose.  $C_{max}$ , observed peak analyte concentration;  $C_{pmax}$ , peak observed platelet count change from baseline; SD, standard deviation.

ITP and CLD. Mild headache and diarrhoea were commonly reported AEs (Bussel *et al*, 2014; Jurczak *et al*, 2017; Terrault *et al*, 2018), but, as expected, the healthy subjects lacked the haemorrhagic complications and fatigue seen in patients with ITP (Bussel *et al*, 2014) or the pain, pyrexia and bleeding seen in patients with CLD (Terrault *et al*, 2018).

Avatrombopag  $C_{max}$  and AUC were shown to increase proportionally relative to dose following single and repeat administration.  $t_{1/2}$  was independent of dose and was estimated to be approximately 18–21 h, supporting once-daily dosing of avatrombopag.

Effects on platelet counts were shown to be dependent on dose and duration of treatment. Increases in platelet counts were first observed 3–5 days after administration, and maximum changes in platelet counts were seen after 13–16 days. In the avatrombopag studies in patients with ITP (Bussel *et al*, 2014) and CLD (Terrault *et al*, 2018),

increases in platelet counts were first noted after 4–7 days and peak platelet counts occurred around day 10–14.

Increases in platelet counts in healthy subjects were evident at  $\geq 10$  mg single doses of avatrombopag and seemed to peak after 75 mg single doses. At 100 mg, avatrombopag concentration and exposures (and associated platelet count rise) were slightly lower than expected and did not demonstrate dose proportionality. The reason for this lack of dose proportionality is unknown; however, it may be related to potential solubility issues with the suspension formulation used for this early development study, saturation of some physiological processes related to drug absorption or outlying data (lower exposure) obtained from one subject. However, there was a very clear association of the maximal rise in platelet count with the maximal avatrombopag concentration attained at all dose levels tested. Indeed, in the multiple-dose study, dosing needed to be stopped after 10 or 11 days, as all

**Table VI.** Summary of mean PK/PD parameters for change from baseline platelet counts for avatrombopag following initial and final dose administration in the multiple-dose study.

PK parameter	Dose cohort		
	3 mg ( <i>n</i> = 6)	10 mg ( <i>n</i> = 6)	20 mg* ( <i>n</i> = 5)
Study day 1			
$C_{\max}$ (ng/ml)†	14.8 (23.5)	53.2 (27.6)	121.4 (37.0)
$T_{\max}$ (h)‡	6 (3–6)	6 (6–6)	6 (3–6)
$AUC_{0-\text{last}}$ (ng h/ml)†	235.4 (21.4)	840.8 (25.7)	1956.7 (37.8)
Study day 14			
$C_{\max,ss}$ (ng/ml)†	25.6 (13.7)	94.1 (15.8)	204.8 (44.7)
$T_{\max,ss}$ (h)‡	6 (3–12)	4.5 (3–6)	6 (3–6)
$AUC_{0-\text{last}}$ (ng h/ml)†	659.4 (19.4)	2364.7 (18.5)	3610.0 (51.7)
$AUC_{0-\text{inf}}$ (ng h/ml)†	804.3 (24.5)	2868.0 (21.6)	7148.1 (76.9)
$t_{1/2}$ (h)†	18.2 (21.6)	18.1 (10.8)	20.8 (34.5)

PD parameter (change from baseline platelet count)	Dose cohort			
	Placebo ( <i>n</i> = 21)	3 mg ( <i>n</i> = 6)	10 mg ( <i>n</i> = 6)	20 mg* ( <i>n</i> = 5)
$C_{p\max}$ ( $10^9/l$ )†	33.6 (38)	71.5 (38)	227.1 (39)	371.5 (17)
$T_{\max}$ (h)‡	215 (5–480)	312 (312–480)	361 (24–363)	288 (239–360)
$AUC_{p0-\text{last}}$ ( $10^9$ h/l)†	5157 (98)	20904 (49)	78477 (48)	111427 (19)

$AUC_{0-\text{inf}}$ , area under the concentration–time curve from time 0 to infinity;  $AUC_{0-\text{last}}$ , area under the concentration–time curve from time 0 to time of last quantifiable concentration;  $AUC_{p0-\text{last}}$ , change from baseline over time curve from day 1 to last quantifiable platelet counts;  $C_{\max}$ , observed peak analyte concentration;  $C_{\max,ss}$ , observed peak analyte concentration at steady-state;  $C_{p\max}$ , peak observed platelet count change from baseline; CV, coefficient of variation; PD, pharmacodynamic; PK, pharmacokinetic;  $T_{\max}$ , first observed time to reach peak concentration;  $T_{\max,ss}$ , first observed time to reach peak concentration at steady-state;  $t_{1/2}$ , terminal phase half-life.

\*Simulated data was used for 20 mg at steady state.

†Value presented as mean (CV%).

‡Value presented as median (min–max).

subjects attained the pre-specified PD platelet count limit of  $500 \times 10^9/l$ . Upon drug cessation, there was no rebound thrombocytopenia.

In the multiple dosing study, the 3 mg/day dose of avatrombopag produced a small increase in platelet count, but a statistically significant increase in platelet count compared with placebo did not occur until doses of 10 and 20 mg. This is comparable to the study in patients with ITP, where avatrombopag doses of 2.5 mg/day produced a 13% response rate (compared with 0% for placebo), whereas doses of 20 mg/day resulted in a statistically greater proportion of responses (80%) compared with placebo (Bussel *et al*, 2014).

Another small molecule TPO receptor agonist, eltrombopag, completed multiple Phase 3 trials and was approved for the treatment of patients with ITP or thrombocytopenia associated with hepatitis C infection or severe aplastic anaemia in Europe and the US (Bussel *et al*, 2007) (<https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/promacta.pdf>). Eltrombopag activates the TPO receptor by binding in the same transmembrane region as avatrombopag (Yamane *et al*, 2008). A Phase 1 study of eltrombopag

showed that single doses up to 75 mg had no effect on platelet count, but daily doses of 75 mg for 10 days maximally increased the platelet count by  $119 \times 10^9/l$  above baseline (higher single or multiple doses were not explored in healthy subjects) (Jenkins *et al*, 2007). In contrast, single avatrombopag doses of  $\geq 10$  mg increased the platelet count, with a maximal rise above baseline of  $158 \times 10^9/l$  seen at the 75 mg dose, and once-daily avatrombopag at a dose of 20 mg over 10 days resulted in a mean maximum platelet count rise over baseline of  $372 \times 10^9/l$ . Higher avatrombopag doses were not investigated, as all subjects receiving 20 mg avatrombopag met the pre-specified PD limit. These data suggest that the maximum effect of avatrombopag on increasing platelet counts was not reached in this study and that avatrombopag may be more effective than eltrombopag at raising platelet counts in subjects with healthy bone marrow function.

As in the Phase 1 studies with eltrombopag (Jenkins *et al*, 2007), no patient in these Phase 1 studies with avatrombopag exhibited changes in laboratory parameters that were clinically significant or that could be reasonably attributed to the

study medication. Although subsequent studies with eltrombopag in patients with ITP (Wong *et al*, 2017) and hepatitis C (Afdhal *et al*, 2014) have reported hepatobiliary changes in 15% and hyperbilirubinaemia in 53–55% of patients, respectively, such hepatic events have been described in only 3% of patients with ITP treated with avatrombopag (Bussel *et al*, 2014). Moreover, there were no safety data to suggest hepatotoxicity in avatrombopag-treated patients with CLD (Terrault *et al*, 2018). The eltrombopag FDA prescribing information does specifically include a boxed warning for the risk of severe and potentially life-threatening hepatotoxicity (<https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/promacta.pdf>), whereas the recently approved FDA prescribing information for avatrombopag (albeit with a more acute dosing regimen) does not include any warnings regarding a risk of hepatotoxicity (<https://dova.com/pdf/dopte-let-fda-prescribing-information.pdf>).

As in the Phase 1 studies with eltrombopag (Jenkins *et al*, 2007), no patient in these Phase 1 studies with avatrombopag developed thrombosis, presumably related to the short time of drug exposure. Subsequent studies with eltrombopag in patients with ITP (Wong *et al*, 2017) and hepatitis C (Afdhal *et al*, 2014) have reported thromboembolic events in 6% and 3%, respectively, which are similar to such clinical events in Phase 2 studies with avatrombopag-treated patients with ITP (6%) (Bussel *et al*, 2014) and lower than Phase 3 studies in patients with CLD (<1%) (Terrault *et al*, 2018) receiving avatrombopag.

The reduced incidence of hepatic events and the lack of dietary interactions in healthy subjects from one study (Nomoto *et al*, 2018), may serve to distinguish avatrombopag from eltrombopag clinically. Such comparisons, however, clearly suffer from a lack of direct comparison of the two drugs in a single clinical trial in healthy subjects, or in patients with CLD or ITP.

The two Phase 1 studies in healthy subjects reported here provided the basis for the dose and schedule selected in the Phase 2 study in patients with thrombocytopenia secondary to cirrhosis (Terrault *et al*, 2014), which was then the basis for the subsequent Phase 3 studies in patients with thrombocytopenia and CLD (Terrault *et al*, 2018). These trials have led avatrombopag to be approved by the FDA in 2018 for the treatment of thrombocytopenia in adults with CLD who are scheduled to undergo a medical or dental procedure (Food and Drug Administration, 2018). The Phase 1 studies reported here also informed the dosing strategy used in studies in patients with ITP (Bussel *et al*, 2014; Jurczak *et al*, 2017), and demonstrated the apparent absence of significant AEs at higher doses of avatrombopag that would be used in clinical trials.

Future studies for avatrombopag are recruiting to evaluate the efficacy and safety of avatrombopag in patients with thrombocytopenia scheduled for surgical procedures

with a high risk of bleeding who would otherwise require a platelet count of  $\geq 100 \times 10^9/l$  to prevent bleeding (NCT03326843), and patients with ovarian, non-small cell lung or bladder cancer who develop CIT (NCT03471078). Importantly, in combination with the Phase 3 evidence, the data from the Phase 1 studies presented here support the continued investigation of avatrombopag in patients with other aetiologies of thrombocytopenia. Furthermore, they allow the practising haematologist to better understand the PD and PK of this new oral TPO receptor agonist.

## Disclosures

D.K. has received research support from Alnylam, Amgen, BMS, Rigel, Principia, Protalex and Syntimmune, and has consulted for Alnylam, Amgen, Argencx, BMS, Dova, Fujifilm, Genzyme, GSK, Novartis, Pfizer, Principia, Protalex, Rigel, Shire, Syntimmune, Zafgen and 3SBio. L.F.A. is an employee of Dova Pharmaceuticals.

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## Author contributions

D.K. participated in the design and development of the clinical protocol, helped oversee the study, actively participated in the data analysis and writing of the manuscript and gave final approval of the version to be submitted for publication. L.F.A. made substantial contributions to the analysis and interpretation of the data, and participated in drafting and revising the article's content.

## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Chemical structure of avatrombopag. Chemical name: 1-(3-Chloro-5-{{4-(4-chloro-2-thienyl)-5-(4-cyclohexylpiperazin-1-yl)thiazole-2-yl} carbamoyl}-2-pyridyl)piperidine-4-carboxylic acid.

**Table S1.** TEAEs\* following single-dose administration of avatrombopag or placebo.

**Table S2.** TEAEs\* following multiple-dose administration of avatrombopag or placebo.

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