Original Research

Safety and Tolerability, Pharmacokinetics, and Pharmacodynamics of ACT017, an Antiplatelet GPVI (Glycoprotein VI) Fab

First-in-Human Healthy Volunteer Trial

Christine Voors-Pette,* Kristell Lebozec,* Peter Dogterom, Laurie Jullien, Philippe Billiald, Pauline Ferlan, Lionel Renaud, Olivier Favre-Bulle, Gilles Avenard, Matthias Machacek, Yannick Plétan, Martine Jandrot-Perrus

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Highlights

- Inhibiting platelet GPVI (glycoprotein VI) interaction with its ligands is a promising strategy to develop new antiplatelet agents with a reduced bleeding risk.
- ACT017 is a first in class, humanized antibody fragment, selective and reversible GPVI antagonist.
- Administration of ACT017 in healthy subjects results in the inhibition of collagen-induced platelet aggregation the intensity and duration of which increases with the dose.
- Administration of ACT017 is well tolerated and does not impact the bleeding time.
- Our results suggest that GPVI antagonism with ACT017 is a new opportunity as a novel antiplatelet strategy.

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Abstract

Objective—

ACT017 is a novel, first in class, therapeutic antibody to platelet GPVI (glycoprotein VI) with potent and selective antiplatelet effects. This first-in-human, randomized, placebo-controlled phase 1 study was conducted to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ACT017 in healthy subjects.

Approach and Results—

Six cohorts of 8 healthy male and female subjects each received ascending single doses of ACT017 (n=6) or placebo (n=2) as a 6-hour intravenous infusion, with ¼ of the total dose administered within 15 minutes and the rest of the dose (¾ of the total dose) administered within 5 hours and 45 minutes. The 6 investigated doses ranged from 62.5 to 2000 mg. All doses of ACT017 were well tolerated, and no serious adverse events occurred during the study. None of the subjects reported an infusion site reaction. Template bleeding time was not affected in a clinically significant manner by any of the ACT017 doses. Plasma concentrations, determined by liquid chromatography-tandem mass spectrometry, increased linearly with the dose received as were the established pharmacokinetics values. There was no change in the platelet count, platelet GPVI expression assessed by flow cytometry, or plasma levels of soluble GPVI assessed by ELISA. In contrast, administration of ACT017 inhibited collagen-induced platelet aggregation measured by light transmission aggregometry on platelet-rich plasma, and the extent and duration of the effect were dose-dependent.

Conclusions—

The novel antiplatelet agent ACT017 has consistent pharmacokinetic/pharmacodynamic properties and favorable safety and tolerability profiles warranting further clinical development.

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First-in-human randomized placebo controlled phase 1 trial

Single ascending dose
62.5; 125; 250; 500; 1000, 2000 mg (n=48)
IV administration
¼ of the dose in 15 min (loading dose)
¾ of the dose in 5hrs 45 min (maintenance dose)

No serious adverse effect
No effect on bleeding time
No effect on platelet count
No effect on GPVI expression
Reversible inhibition of collagen-induced platelet aggregation
Consistent PK and PD properties

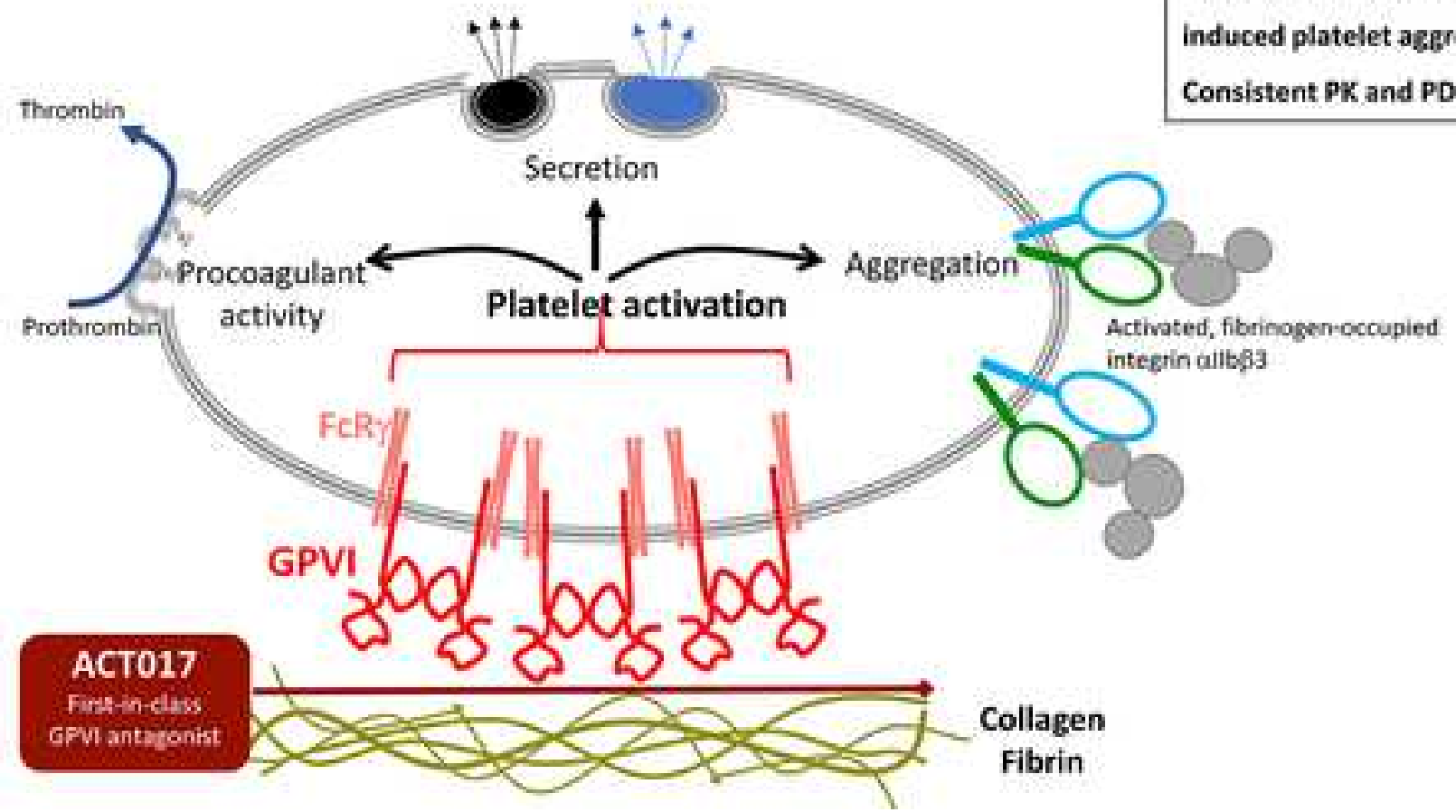

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Table 1. Summary (Means and SD) of Demographic and Baseline Characteristics

	Placebo (n=12)	62.5 mg (n=6)	125 mg (n=6)	250 mg (n=6)	500 mg (n=6)	1000 mg (n=6)	2000 mg (n=6)
Study completed (n)	12	6	6	6	6	6	6
Age, y							
Mean (SD)	51.0 (15.93)	39.7 (15.92)	58.5 (4.76)	54.8 (9.39)	48.8 (16.24)	47.8 (15.08)	56.5 (7.18)
Sex							
Female, n (%)	3 (25)	0 (0)	4 (66.7)	2 (33.3)	2 (33.3)	2 (33.3)	3 (50)
Male, n (%)	9 (75)	6 (100)	2 (33.3)	4 (66.7)	4 (66.7)	4 (66.7)	3 (50)
Weight, kg							
Mean (SD)	78.32 (14.372)	87.85 (6.913)	73.02 (10.033)	74.20 (15.367)	73.42 (12.723)	73.60 (6.887)	79.85 (21.027)
BMI, kg/m^2							
Mean (SD)	24.40 (3.389)	26.98 (2.090)	25.07 (3.539)	24.47 (2.604)	23.13 (3.322)	22.60 (0.800)	24.93 (2.946)
Bleeding time, min							
Mean (SD)	5.79 (1.959)	5.58 (1.960)	6.08 (2.060)	5.83 (0.753)	5.08 (1.800)	4.50 (1.095)	5.00 (1.265)
Collagen-induced platelet aggregation							
Mean (SD)	79.342 (9.2751)	76.158 (10.2289)	80.178 (3.7071)	80.373 (2.6121)	80.837 (6.6319)	79.763 (8.0922)	83.275 (6.0907)
Platelet count ($10^9/L$)							
Mean (SD)	217.5 (35.96)	232.0 (38.47)	262.7 (55.93)	217.5 (43.02)	228.7 (35.52)	224.7 (42.27)	225.2 (34.14)

BMI indicates body mass index.

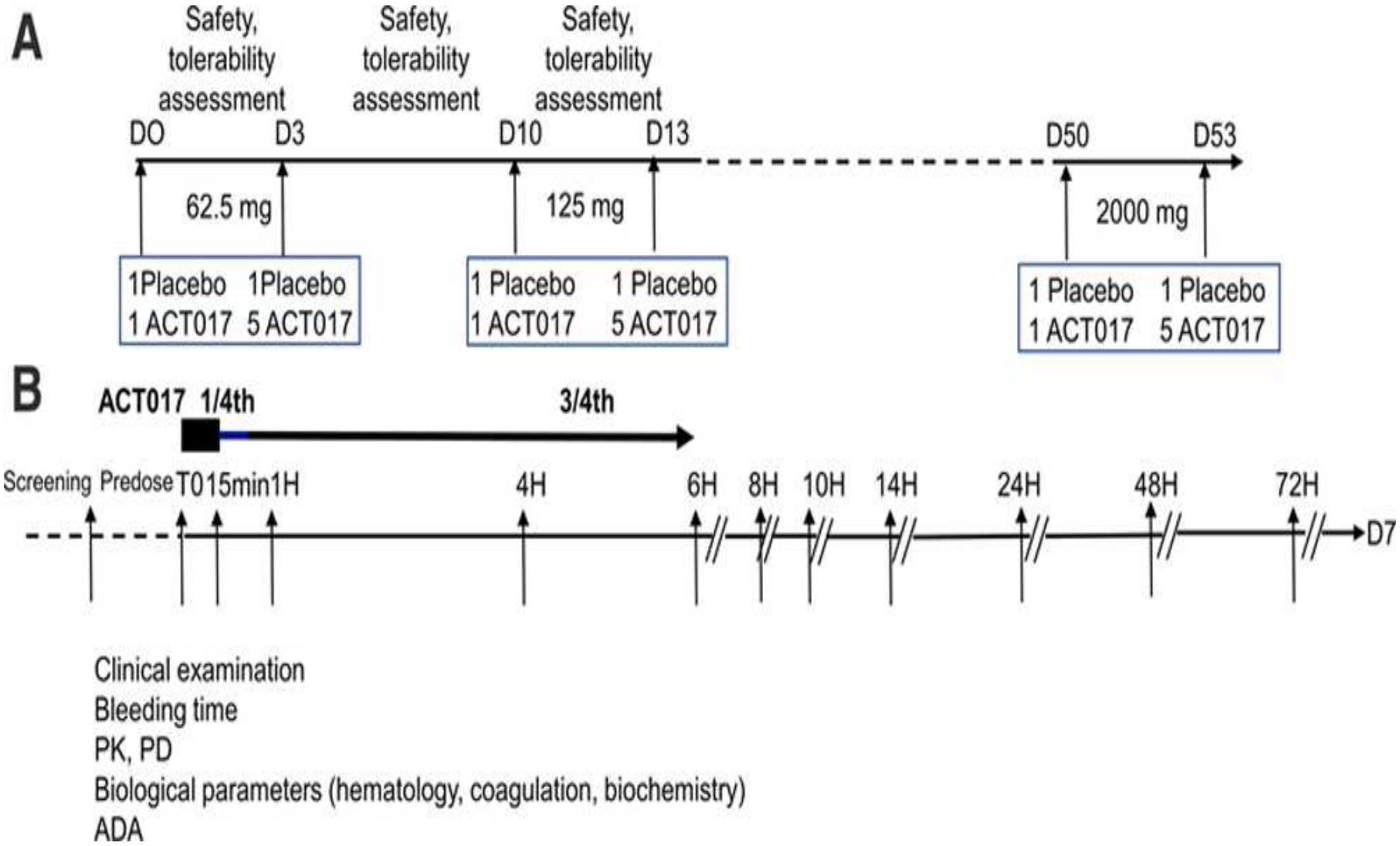

Figure 1. Study design. Flow chart A describes the mode of ACT017 administration. Flow chart B describes the time course of infusion and scheduled examinations. ADA indicates antidrug antibody; PD, pharmacodynamics; and PK, pharmacokinetics.

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Table 2. Pharmacokinetic Noncompartmental Analysis: Summary (Mean and SD) of ACT017 Plasma Pharmacokinetic Parameters Following a 6-Hour Intravenous Infusion of 62.5, 125, 250, 500, 1000, and 2000 mg of ACT017 to Healthy Adult Subjects

Group	A			B			C			D			E			F
Dose, mg	62.5			125			250			500			1000			2000
Parameters	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean±SD
C_{max}, µg/mL	6	2.89	0.485	6	6.62	1.40	6	14.5	3.31	6	26.1	3.70	6	59.9	18.9	6	109±25.7
T_{max}, h*	6	0.25 (0.25–1.00)		6	0.25 (0.25–0.30)		6	0.27 (0.25–0.28)		6	0.25 (0.25–6.00)		6	0.25 (0.25–0.35)		6	0.25 (0.12–0.25)
AUC_{0-t}, h/(µg·mL)	6	15.3	3.44	6	43.5	8.89	6	75.8	20.2	6	182	74.7	6	363	72.2	6	714±242
AUC_{0-inf}, h/(µg·mL)	1†	22.5	NA	6	45.1	9.64	4†‡	75.0	19.3	6	189	76.6	6	373	72.1	6	726±245
λ_z, 1/h	1†	0.507	NA	6	0.289	0.181	4†‡	0.232	0.0258	6	0.107	0.0561	6	0.0620	0.0266	6	0.0550±0.00648
$t_{1/2}$, h	1†	1.37	NA	6	3.30	2.04	4†‡	3.01	0.373	6	8.43	4.75	6	12.8	4.76	6	12.7±1.40
CL, L/h	1†	2.78	NA	6	2.87	0.578	4†‡	3.48	0.787	6	3.03	1.17	6	2.77	0.553	6	3.06±1.09
Vz, L	1†	5.49	NA	6	12.5	5.72	4†‡	15.1	3.75	6	31.1	8.13	6	49.5	18.0	6	57.1±23.4

N=no. of subjects for each treatment group. AUC indicates area under the curve; CL, total body clearance; NA, not applicable; and Vz, apparent volume of distribution.

*Median (range).

†AUC_{0-inf}, λ_z, $t_{1/2}$, CL and Vz could not be estimated for 5 subjects and 1 subject in treatment group A and treatment group C, respectively.

‡AUC_{0-inf}, λ_z, $t_{1/2}$, CL and Vz were not reportable and were excluded from the statistical analysis for 1 subject in treatment group C since the subject did not meet the criteria (%AUC_{extrap} <20% and adjusted R^2≥0.80).

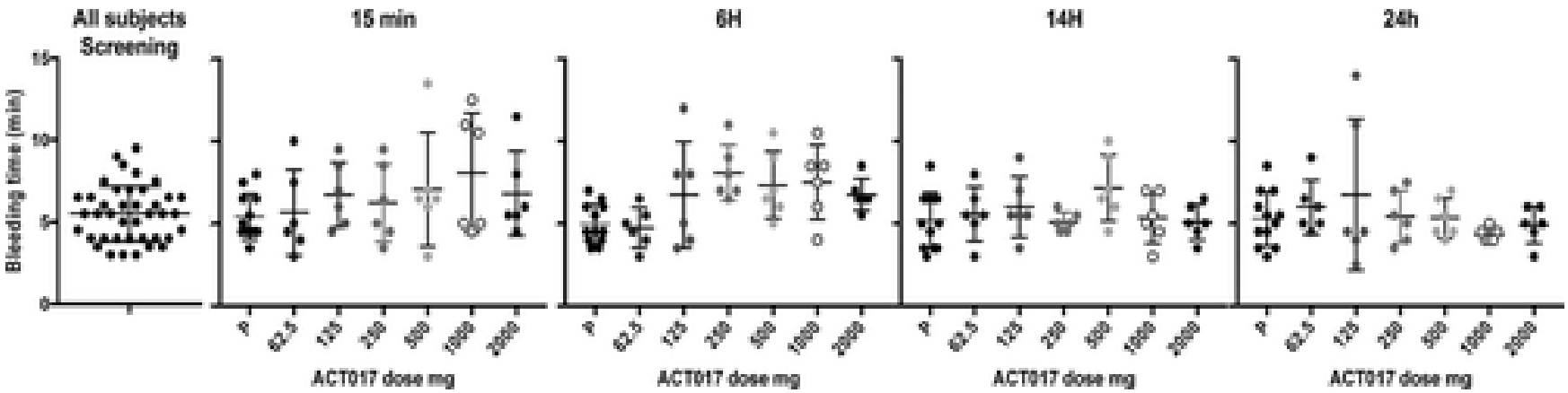

Figure 2. Bleeding time. The template bleeding time was measured at the screening, at the end of the loading and the infusion times and 14 and 24 h after the beginning of ACT017 administration. Individual values are shown for each dose and each time point with mean±SD.

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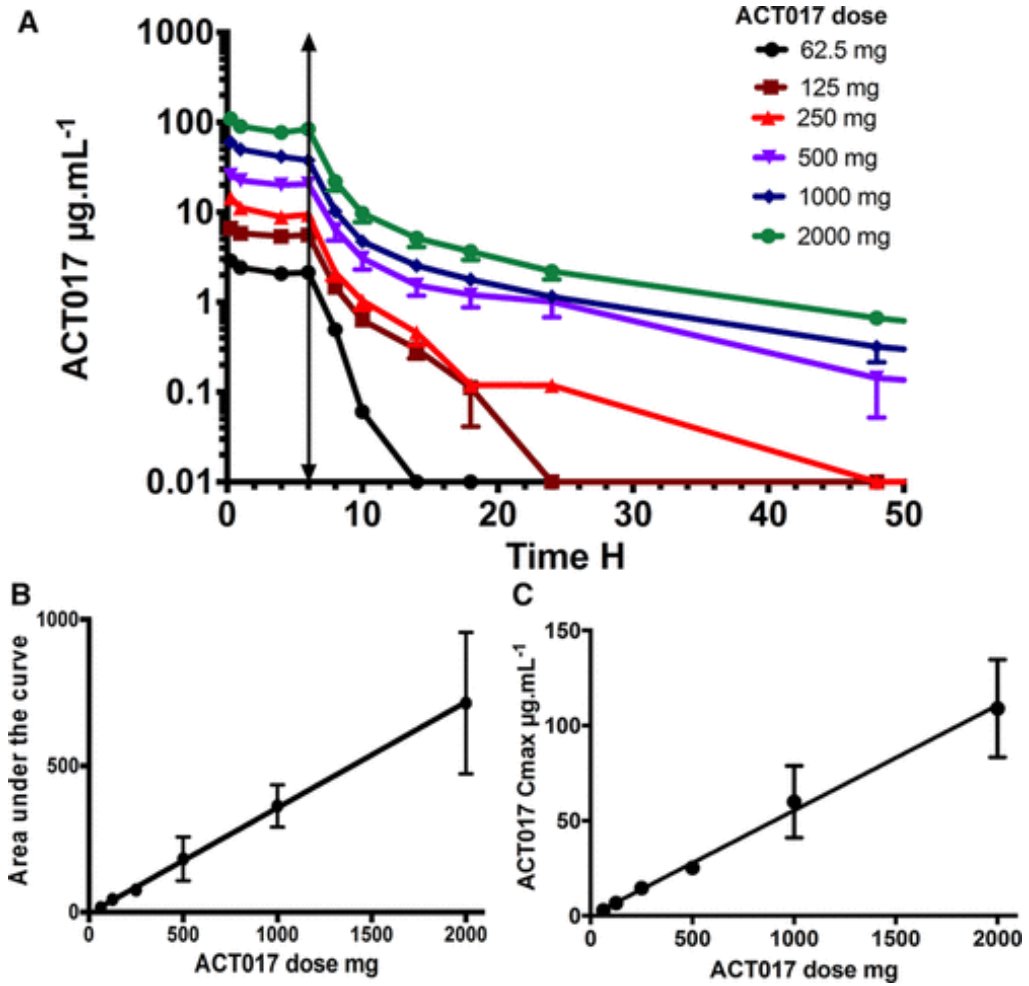

Figure 3. ACT017 pharmacokinetics in healthy subjects. A, The plasma concentration of ACT017 was measured at different time points during and after the administration of fixed doses of ACT017 as a 6 h infusion with one-fourth of the dose administered in the first 15 min. Results are the mean±SD of 6 subjects in each group. The black arrow indicates the end of the infusion. B, The area under the curve of the mean plasma concentration (AUC0-t) is plotted as a function of the dose administered (r2 = 0.9994; P<0.0001). C, The maximal ACT017 concentration (Cmax) is plotted as a function of the dose administered. (r2=0.9963; P<0.0001).

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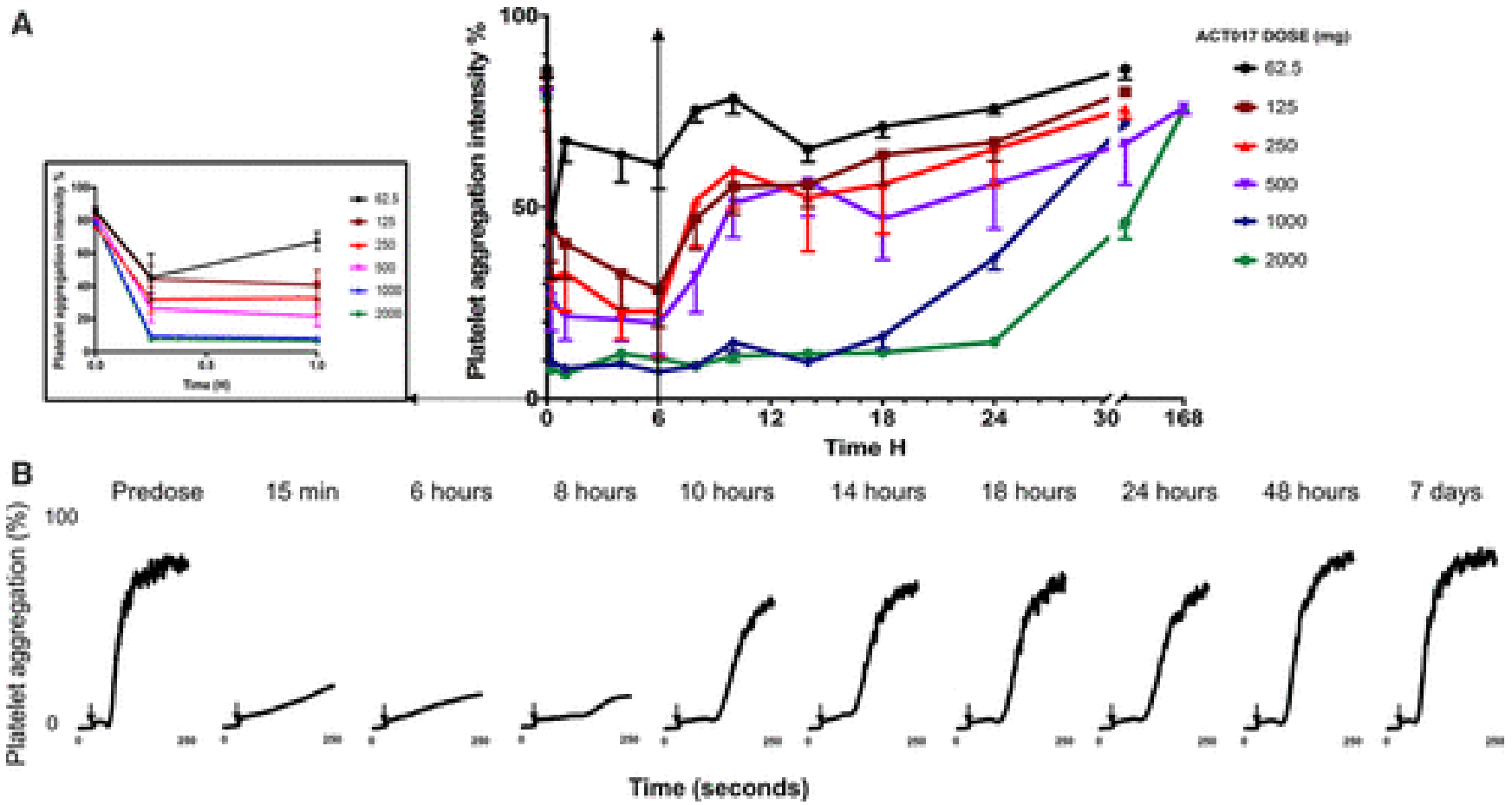

Figure 4. Inhibition of collagen-induced platelet aggregation. Collagen-induced platelet aggregation was measured before and at different time points during and after the administration of ACT017 at fixed doses. A, Aggregation intensity (mean±SD n=6 for each dose). The black arrow indicates the end of the infusion. An enlargement of the 0 to 1 h period is shown. B, Representative aggregation curves from 1 subject in the 1000 mg dose group. Arrows indicate the addition of collagen.

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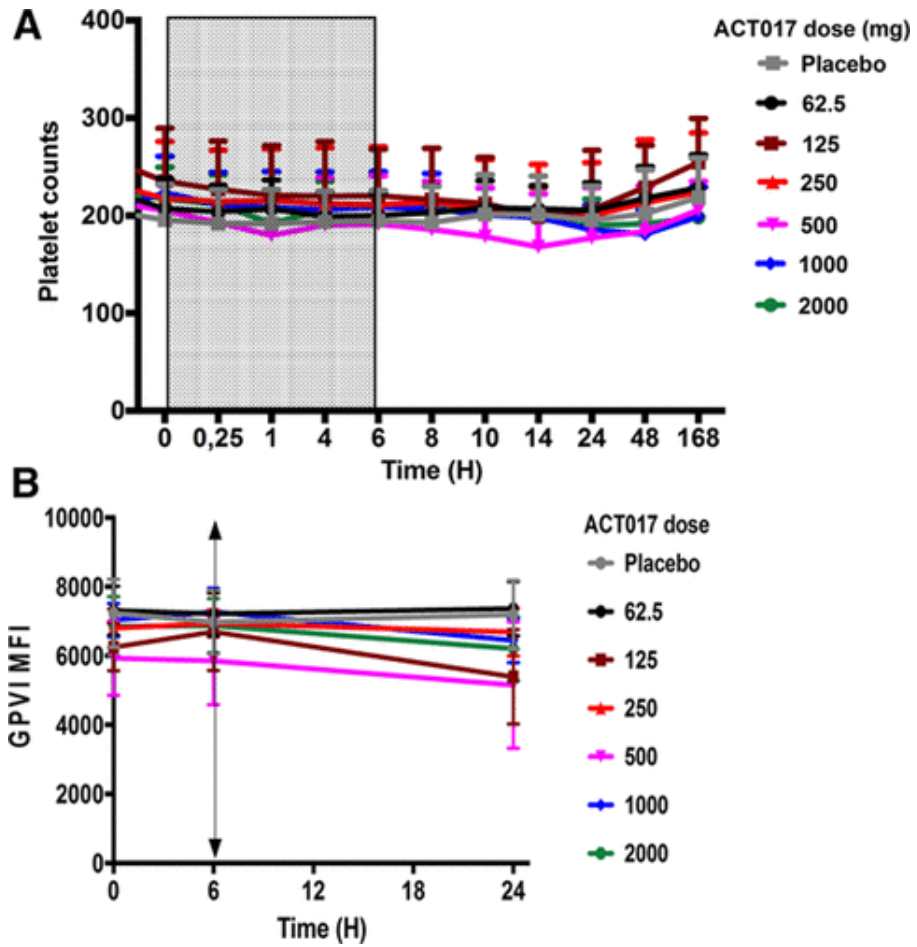

Figure 5. ACT017 administration does not impact the platelet count and GPVI (glycoprotein VI) expression. A, Platelet counts were determined at different time points before, during and after ACT017 administration. The period of ACT017 infusion is indicated by the shadowed area. Mean values±SD (n=6 for each ACT017 dose and 12 for the placebo). B, GPVI expression at the platelet surface was measured by flow cytometry before, at the end of the infusion and at 24 h. Results are expressed as mean platelet fluorescence (MFI) and are the mean values±SD (n=6 for each ACT017 dose and 12 for the placebo). The black arrow indicates the end of the infusion.

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