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

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PURPOSE

Glycoprotein VI (GPVI) is accepted as a target to develop effective antiplatelet agents without bleeding risk. Current treatments for acute ischemic stroke, thrombolytics and thrombectomy, are limited by narrow time window and the risk of bleeding that prohibit the use of currently available antiplatelet drugs. GPVI antagonists would therefore potentially be useful at the acute phase of stroke. ACT017 is a clinical-grade anti-GPVI fragment of monoclonal antibody. Preclinical studies of ACT017 in non-human primates have shown its ex vivo biological efficacy, specificity, excellent tolerability.

OBJECTIVE

This first-in-human study aimed to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single ascending intravenous doses of ACT017 in healthy volunteers

METHODS

This was a first-in-human, randomized, double blind, placebo-controlled, single ascending intravenous dose study in 6 cohorts of 8 subjects each. Per cohort, 6 subjects received ACT017 and 2 subjects received placebo. Doses were 62.5, 125, 250, 500, 1000 and 2000 mg ACT017. ¼ of the dose was administered in 15 min (loading dose) and ¾ of the dose was administered in 5h and 45 min (maintenance dose).
Safety/tolerability was assessed by AE reporting, local tolerability, safety lab, vital signs, ECG, coagulation parameters, platelet count, GPVI expression and immunogenicity.
ACT017 pharmacokinetics were determined in plasma and urine
ACT017 pharmacodynamics were assessed by (IVY) bleeding time and collagen-induced platelet aggregation.

Subjects were hospitalized from Day -1 until the morning of Day 3.
All study related documents were approved by the local IRB/competent authorities. Subjects signed the approved Informed Consent Form prior to any study-related activity.

RESULTS

A total of 48 healthy subjects (32 males and 16 females) were enrolled in this study and all subjects completed the study as per protocol. The mean age was 51 years and the mean BMI was 24.50 kg/m2.

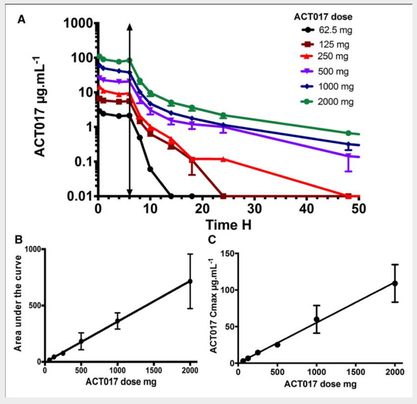
RESULTS

There were no SAEs. All treatment related AEs were of a mild intensity. None of the TEAEs considered as related to the study drug were identified as bleeding related. Most frequently reported AEs were headache and head discomfort. There were no time and dose related effects on vital signs, ECG, safety lab, coagulation, GPVI expression and immunogenicity. None of the subjects reported infusion site reactions

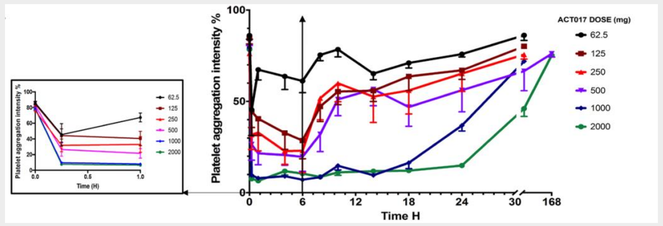
ACT017 plasma concentration-time curves are presented below. The PK evaluation shows that the area under the mean plasma concentration (AUC) as well as the maximal plasma concentrations (C_{max}) were proportional to the dose. The recovery of ACT017 in the urine was negligible for the 62.5, 125, and 250 mg doses and increased to 0.5 %, 6.5%, and 19.8%, respectively, for the 500, 1000, and 2000 mg doses.

	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/m²							
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)

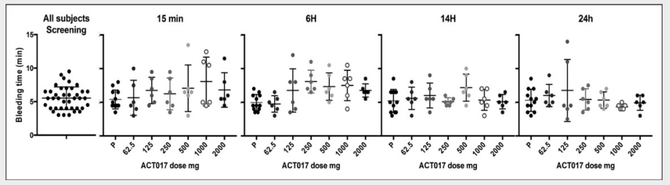
Summary of Demographic and Baseline Characteristics of Subjects



Plasma concentrations of ACT017 (A, with arrow indicating end of infusion) and $AUC_{0\text{-}t}$ (B) and C_{max} (C) plotted as function of the administered dose (C_{max}, $r^2 = 0.9994$; $P<0.0001$ and $AUC_{0\text{-}t}$, $r^2 = 0.9963$, $P<0.0001$)



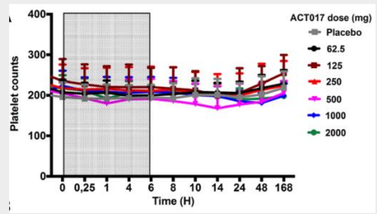
Inhibition of collagen-induced platelet aggregation. Collagen-induced platelet aggregation was measured before and at different time points during and after the administration of ACT017 at fixed doses. Black arrow: end of infusion.

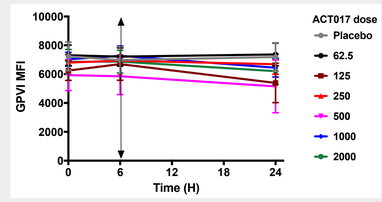


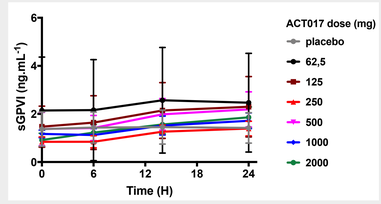
Bleeding time as measured at screening, end of loading (15 min) and infusion time (6h) and 14 and 24h after beginning of ACT017 administration

RESULTS

No change in platelet count (top), GPVI expression (middle) or elevation of sGPVI in plasma (bottom) was observed.







CONCLUSION

Single ascending, intravenous doses of the novel antiplatelet agent ACT017 (INN Glenzocimab), as a 6-hour i.v. infusion, are considered safe, well tolerated without clinically significant effects on bleeding time and has consistent pharmacokinetic and pharmacodynamics properties at doses between 62.5 and 2000 mg.

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