Safety, tolerability and pharmacodynamic results of a first in human study with the new antiplatelet agent ACT017 for the treatment of the acute phase of ischemic stroke

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INTRODUCTION

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

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

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.

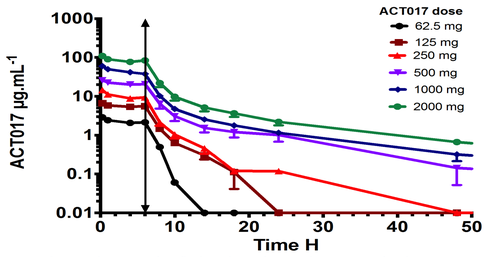
Subjects were hospitalized from Day -1 until the morning of Day 3.
All study related documents were approved by the local IRB/competent authorities. Subjects signed the approved Informed Consent Form prior to any study-related activity.

RESULTS: SAFETY/TOLERABILITY

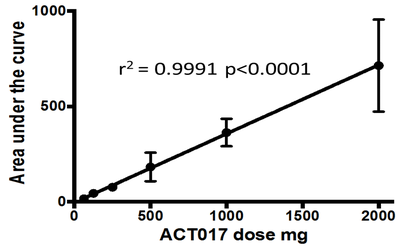
All subjects completed the study as per protocol. There were no SAEs. All treatment related AEs were of a mild intensity. None of the TEAEs considered as related to the study drug were identified as bleeding related. Most frequently reported AEs were headache and head discomfort. There were no time and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

RESULTS: PHARMACOKINETICS

Plasma concentration of ACT017



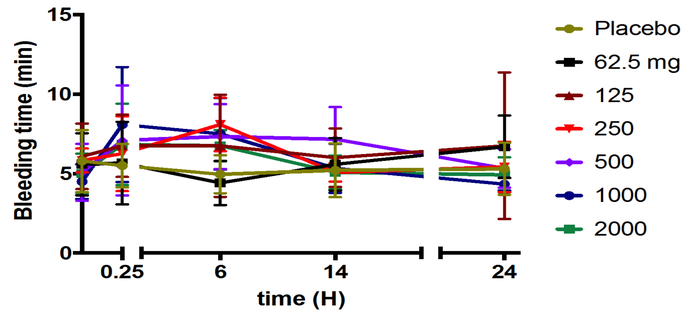
Peak at the end of the loading dose and plateau until the end of the infusion



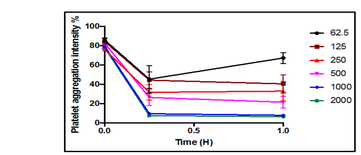
Linear relation between plasma concentration of ACT017 and the administered dose

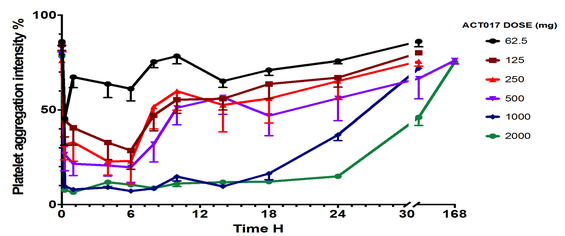
Recovery of ACT017 in urine is only significant (> 1%) at the two highest doses, which might indicate a saturation of the breakdown of ACT017.

RESULTS: PHARMACODYNAMICS



No prolongation of bleeding time at any dose





Increasing doses of ACT017 impacts both the extent of the aggregation and the duration of the effect

CONCLUSIONS

The novel antiplatelet agent ACT017, at doses between 62.5 to 2000 mg, has consistent pharmacokinetic/pharmacodynamic properties and favorable safety and tolerability profiles in healthy volunteers.
This first in human study paves the way for the subsequent assessment of ACT017 safety and efficacy in patients with thrombosis. A phase 1b/2a with ACT017 is on going as an add-on treatment in acute ischemic stroke