Randomized, double blind, mutlicenter, multinational, placebo controlled, single parallel escalating dose safety and efficacy study of ACT017 used as an add-on therapy on top of standard of care of acute ischemic stroke

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The study primary objective will consist of assessing the safety and tolerability of single IV (bolus + infusion) doses of glenzocimab in patients with an acute ischemic stroke administered on top of the best emergency standard of care (including...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Vascular disorders NEC
Study type	Interventional

Summary

ID

NL-OMON49177

Source
ToetsingOnline

Brief title
ACT-CS-002

Condition

- Vascular disorders NEC

Synonym
Acute Ischemic Stroke, stroke

Research involving

Human

Sponsors and support

Primary sponsor: ACTICOR BIOTECH
Source(s) of monetary or material Support: ACTICOR BIOTECH

Intervention

Keyword: Acute Ischemic Stroke, Anitplatelet agent, Pharmacokinetics

Outcome measures

Primary outcome

Primary Endpoint:

Safety:

Incidence of intra-cranial hemorrhages (ICH, symptomatic, total, fatal):

symptomatic hemorrhages being those defined by a secondary increase

in the NIHSS (National Institute of Health Stroke Scale) score of 4 points or

more, or death, in the absence of any other causative factor. Non-symptomatic

hemorrhages are those seen on the 24-hr CT scan and not present at the initial

assessment, once other diagnoses have been excluded. ICH detected by brain

imaging should be classified according to the Heidelberg classification.

Incidence, nature and severity of Adverse Events (AEs), SAEs, bleeding-related

adverse events, including mortality, and TreatmentEmergent Adverse Events

(TEAEs).

Safety results will be displayed by treatment group. For glenzocimab, results

by dose levels will also be summarized.

SAE and TEAE will be graded using CTCAE version 5.0.

Pre-defined bleeding-related events will be compared across groups and

dose-levels.

Secondary outcome

Secondary Endpoints:

Safety:

* Changes to vital signs over the study course duration versus screening;

* Changes to clinical laboratory assessments (hematology, biochemistry, urinalysis) over the study duration versus screening;

* ECG over the study duration versus screening;

Efficacy:

* Neurological recovery as assessed by:

- NIHSS score at 24 hrs versus that measured at screening (pre-thrombolysis) in each group.

- Dramatic improvements (defined by a reduction in the NIHSS score of > 8 points) or recovery (NIHSS = 0) will be assessed in each group.

- Patients with a favorable outcome as defined by a Day 90 mRS score of 0-2.

* Impact on brain lesions as measured by diffusion T2 weighted MRI and recanalization assessed by angiogram in,eligible patients to determine the infarct size (volume).

Other Biological parameters:

* PK: glenzocimab plasma concentration will be assayed.

* Immunogenicity: search for anti-ACT017 antibodies (ADA)

Study description

Background summary

Thrombolysis with alteplase is the only approved pharmacological therapy for acute ischemic stroke (AIS). Nevertheless, the benefit of this therapy, (a) extremely time sensitive and the eligibility criteria are limited to a very short time window not exceeding 4.5 hrs after symptom onset, (b) limited in its effects with an overall recanalization rate of 46% overall. Altogether, only 7 to 15% of patients are deemed eligible for thrombolysis treatment with alteplase and 14 to 34% of them will suffer from a secondary re-occlusion after initial recanalization, associated with clinical deterioration and poor outcome. Re-occlusion has been attributed to increased platelet aggregation caused by local thrombus, endothelial injury and probably the thrombolytic treatment itself.
Combining alteplase with a treatment that has a potential to inhibit secondary platelet aggregation seems to be therefore obvious. Nevertheless, as previously stated the currently available molecules are not recommended at the acute phase (0 to 12 hrs) due to an associated over-risk of hemorrhagic conversion in tPA-treated patients.
Due to its specific mechanism of action showing no evidence of any additional bleeding risk both in animals or in healthy subjects, glenzocimab candidate drug seems to be a promising agent administrable at the acute phase of the stroke in addition to the best standard of care with the following medical management objectives:
1) Reduce the size of the clot,
2) Favor cerebral reperfusion, thus decreasing the infarct volume
3) Decrease the occurrence of ischemia-reperfusion injury, thereby increasing the percentage of salvageable brain tissue and improving neurological recovery

Study objective

The study primary objective will consist of assessing the safety and tolerability of single IV (bolus + infusion) doses of glenzocimab in patients with an acute ischemic stroke administered on top of the best emergency standard of care (including fibrinolysis by recombinant tissue plasminogen (tPA), administered within 4h30, with or without added mechanical thrombectomy). This entails with a specific focus on Intra-Cranial Hemorrhage (ICH), whether clinically symptomatic, or seen only on 24-hr CT scan (after exclusion of other diagnoses), serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs), and medically important events, bleeding-related events and other safety parameters including biological and immunological tolerability.

Study design

For each given patient, whatever the study phase, the schedule will include:
* A screening assessment at admission including imaging

* A randomization procedure,
* A treatment phase,
* A post-treatment visit evaluation 24 hrs (+/- 3 hrs) after the initiation of treatment, including a CT-scan (and an MRI evaluation if possible).
* A 7-day (+/- 3 days) post-treatment infarct zone evaluation by MRI. This examination can be performed before Day 7 if the patient is discharged earlier than Day 4 from hospital, he/she needs to perform a MRI the day of discharge.
* A 30-day (+/- 3 days) post-treatment evaluation,
* Finally, a 90-day (+/- 3 days) post treatment evaluation corresponding to the EOS (End Of Study) visit,
* Additional follow-up visit or phone call may be required notably in the case of emerging adverse events

Intervention

Dose Escalation (Phase 1b):
During this phase, patients are unevenly randomized between groups, to obtain a total of 60 patients, 12 at each dose level, providing escalation is complete. This phase is complete.

Consolidation Phase with Final Dose (Phase 2a):
During this phase, randomization will be 1:1.
In addition, patients in each treatment arm will be stratified by type of Standard of Care (SOC) administered:
* Thrombolysis with tPA only;
* Thrombolysis with tPA AND mechanical thrombectomy.
A total of 100 new patients should be recruited, 50 under active treatment and 50 under placebo to complete up to 160 patients. Each treatment arm will contain 25 patients with one SOC, and 25 with the other SOC.
The active glenzocimab dose will be that recommended after the last safety analysis has been performed: 1000mg.

Study burden and risks

Glenzocimab is a humanized fragment of monoclonal antibody and therefore risks generally associated with protein-based medicinal including anaphylactic reactions and hypersensitivity also apply for glenzocimab. However, such reactions have not been observed in the non-clinical studies. Because glenzocimab is a humanized Fab, ADA assessment was not considered to be useful in the non-clinical studies. Nevertheless, immunogenicity of glenzocimab was assessed in silico using the EpiMatrix Protein Immunogenicity Scale from EpiVax. EpiMatrix predicted excess and shortfall in aggregate immunogenicity relative to a random protein standard. All scores are adjusted for the presence of Tregitopes. The submitted glenzocimab sequence scored on the low end of EpiMatrix scale. The regression analysis of licensed monoclonal antibodies predicted ADA response in ~2% of exposed patients.

Risks associated with the route-of-administration via IV infusion were assessed in the toxicology studies in cynomolgus monkeys. Results showed that glenzocimab infusion were well tolerated. However, the occurrence of local reactions related to the intended IV route-of-administration cannot be generally excluded in humans.

Antiplatelet drugs currently marketed present a higher risk of bleeding. Such effect is not expected with glenzocimab because of its unique mechanism of action. In non-clinical studies, no signs of bleeding were observed at doses up to 80 mg/kg in cynomolgus monkeys.

Glenzocimab represents a novel therapeutic approach for the emergency treatment of ischemic stroke. Based on its unique mechanism of action and non-clinical data demonstrating inhibition of collagen-induced platelet aggregation with no impact on bleeding time, glenzocimab displays promising efficacy and a high safety profile and is anticipated to have the potential to address the unmet medical need for this life-threatening condition.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1 Patients presenting with an acute disabling ischemic stroke in either the anterior or posterior circulation.The time of onset is known or if unknown, the last time the patient was seen well, was at most 4.5 hrs before confirmation of the diagnosis enabling the initiation of alteplase administration within this time-frame;
2. Patients presenting at least a NIHSS * 6 prior to thrombolysis with tPA;
3. Patients eligible for, or administered thrombolysis treatment with tPA;
4. Patients who can undergo mechanical thrombectomy if eligible;

Exclusion criteria

1.Coma, and/or NIHSS >25;
2.Prior ischemic stroke within the past 3 months with pre-stroke mRS known to be > 2;
3. Baseline CT-scan evaluation: more than 1/3 of the middle cerebral artery) regions of clear hypodensity on the baseline imaging;
4. Significant mass effect with midline shift;
5. Stroke of hemorrhagic origin;
6. Contra-indications to thrombolysis with tPA:
7. Patients receiving a dual antiplatelet treatment;
8. Cardiopulmonary resuscitation within the past 10 days;
9. Epileptic seizure at the onset of symptoms;
10. Known severe (grade 3 and above) renal impairment or Glomerular Filtration Rate < 30 ml/min/1.73 m2 or Serum Creatinine > 2X ULN (1.2 mg/dL for men and 1.0 mg/dL for women) at screening;

Study design

Design

Study phase:	2
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Glenzocimab
Generic name:	Glenzocimab

Ethics review

Approved WMO Date:	11-01-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-04-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-002855-13-NL
CCMO	NL76104.018.20