A RANDOMIZED, DOUBLE-BLIND, MULTI-CENTER, PLACEBO-CONTROLLED, EFFICACY AND SAFETY STUDY OF GLENZOCIMAB USED AS AN ADD-ON THERAPY ON TOP OF MECHANICAL THROMBECTOMY FOR ACUTE ISCHEMIC STROKE

CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE

Glenzocimab for REperfusion in the setting of Endovascular therapy for brain infarctioN: GREEN Study

Version N°4.0 du 24/04/2024
Project Code: APHP 201028 / ACT-CS-004
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SIGNATURE page for a research PROTOCOL

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Version N°4.0 dated 24/04/2024

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

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1 LIST OF ABBREVIATIONS

ADA	Anti-glenzocimab Drug Antibodies
ANSM	Agence Nationale de Sécurité des Médicaments et des Produits de santé
CPP	Comité de Protection des Personnes
EVT	Endovascular therapy
IVT	Intravenous thrombolysis
MCA	Middle Cerebral Artery
mRS	modified Rankin Scale
MT	mechanical thrombectomy
MRI	magnetic resonance imaging
MRA	magnetic resonance angiography
AIS	acute ischemic stroke
LVO	large vessel occlusion
ICA	intracranial internal carotid artery
CTA	CT angiography
CTP	Perfusion CT-scan
DAPT	dual anti-platelet therapy
ICH	IntraCranial Hemorrhages
CCTAE	common toxicity criteria
AE	adverse effect
SAE	serious adverse event
SUSAR	Suspected Unexpected Serious Adverse Reaction
BRE	Bleeding-Related Event
TEAE	Treatment Emergent Adverse Event
tPA	tissue plasminogen activator

2 SUMMARY

Full Title	**A RANDOMIZED, DOUBLE-BLIND, MULTI-CENTER, PLACEBO-CONTROLLED, EFFICACY AND SAFETY STUDY OF GLENZOCIMAB USED AS AN ADD-ON THERAPY ON TOP OF MECHANICAL THROMBECTOMY FOR ACUTE ISCHEMIC STROKE**
Short Title	**G**lenzocimab for **RE**perfusion in the setting of **E**ndovascular therapy for brain infarctio**N**
Study Acronym	**GREEN** Study
Clinical Trial Code	APHP201028 / ACT-CS-004
EudraCT Number	2020-000889-16.
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Scientific justification	Emergent reperfusion is the main goal for acute ischemic stroke therapy (AIS). Endovascular therapy (EVT) is recommended within 6 hrs of stroke onset, and up to 24 hrs following perfusion imaging criteria. Despite the major benefit associated with MT, more than 50% of the patients remain disabled at 3 months. Reperfusion rates after MT are critical to determine functional outcome. However, complete reperfusion is obtained in only 50 % of the patients, due to, at least in part, erratic emboli and/or no-reflow processes. Thrombus composition analysis has shown that platelet rich clots are more resistant to alteplase, suggesting that platelets inhibition represent a relevant target to improve reperfusion. Nevertheless, the currently available molecules are not recommended at the acute phase due to the associated sICH risk. Therefrom, there is still a need for a safe and efficient antithrombotic agent administrable at the acute phase without inducing a bleeding risk in order to reduce the size of the clot, to favour cerebral reperfusion. The results obtained during the escalating dose phase of the ACTIMIS study showed very promising safety data. After the completion of the five cohorts where a dose progression has been carried out, the study DSMB members recommended to use the highest dose, 1000 mg, for the consolidation phase.

	Of 60 AIS patients recruited, 12 were treated with the highest dose, they experienced no symptomatic ICHs, a lowest rate of asymptomatic ICH and a similar incidence of SAEs/SUSARs in comparison to patients treated with each lower dose, 125, 250, 500 mg and placebo. The consolidation phase was conducted in additional 106 AIS patients with a parallel-group design glenzocimab 1 000 mg versus placebo, both in add-on of the reperfusion standard of care. The global safety results combining both phases (n=166) concern the incidence of symptomatic ICHs observed in all-dose (1 event/102 patients - 1%) and 1 000 mg (no event/66 patients - 0%) glenzocimab groups was lower than that one shown in placebo group (5 events/64 patients - 8%), The incidence of non-symptomatic ICHs observed in all-dose (30 events/102 patients - 30%) and 1 000 mg (20 events/66 patients - 30%) glenzocimab groups was lower when compared to the placebo group (30 events/64 patients - 48%), The Kaplan-Meier curve showed a reduced mortality in all-dose and 1 000 mg glenzocimab groups when compared to placebo group, with a p value of 0.03 and 0.04 respectively. Twenty deaths occurred, 5 in phase Ib and 15 in phase 2a, and 12 of them were a stroke-related outcome. Glenzocimab 1000 mg showed a favorable safety profile, in terms of hemorrhagic events, as well as more generally, including in patients aged above 80 years (40% of the population), and despite concomitant medical conditions. Though not powered for a showing of efficacy, in this study Glenzocimab 1000 mg showed a real benefit in terms of death rate, and was shown to decrease the proportion of patients with the most severe level of handicap. These encouraging results have to be confirmed in ongoing and future studies. Platelet glycoprotein VI (GPVI) belongs to the immunoglobulin superfamily and its expression is restricted to the megakaryocyte/platelet lineage. GPVI is a key receptor for collagen and plays a major role in platelet activation, platelet recruitment and thrombus growth. Studies have also demonstrated that GPVI is a platelet receptor of polymerized fibrin and this interaction contributes to the thrombus growth and to its reformation. Furthermore, inhibition of the GPVI does not impair hemostasis and subjects with a genetic or acquired GPVI deficiency are not prone to excessively bleed. GPVI is therefore a major target in the growth and stabilization of the thrombus, offering a new therapeutic approach with a high safety profile. This study aims to evaluate the efficacy of GPVI inhibitor, glenzocimab, in addition to EVT. The current protocol allows any Standard of Care to be used for thrombolysis, depending on routine practice in each study site. In particular, the simpler mode of administration of tenecteplase with its single bolus injection, led many sites to

	adopt tenecteplase as an alternative to alteplase for all AIS patients.
Study Objectives	**Primary Objective:** To evaluate the efficacy of glenzocimab in addition to EVT and compared to EVT plus placebo, whether or not associated with IVT, on functional outcome at day 90. **Secondary Objectives** • To evaluate the impact of glenzocimab in addition to EVT compared to EVT, whether or not associated with IVT, plus placebo on overall survival at day 90 and 1 year • To evaluate the impact of glenzocimab in addition to EVT compared to EVT, whether or not associated with IVT, plus placebo on: 1. reperfusion at the end of EVT 2. early clinical improvement at 24 hrs 3. symptomatic intracranial haemorrhage at 24 hrs 4. overall intracranial haemorrhage at 24 hrs 5. serious adverse events (SAEs) 6. suspected unexpected serious adverse reactions (SUSARs) at 24 hrs and at day 90 7. bleeding-related events (BREs) at 24 hrs and at day 90 8. quality of life at day 90 and 1 year • To evaluate the cost effectiveness of glenzocimab in addition to EVT compared to EVT plus placebo
Study Endpoints	**Primary Efficacy Endpoint:** The primary efficacy endpoint is the functional outcome at day 90 assessed by the modified mRS at day 90 +/- 15 days. **Secondary Endpoints:** *Efficacy :* • Favourable functional outcome defined by a mRS score ≤ 2 at day 90 • Proportion of patient with severe handicap (mRS 4-6) at Day 90 • Overall Survival at day-90 and 1 year • Early reperfusion outcomes: o Stroke volume by brain imaging at 24 hrs o Reperfusion at the end of MT procedure assessed by eTICI score o Early neurological improvement by NIHSS at 24 hrs • EQ-5D-5L at day 90 and 1 year

	Safety: • Incidence of symptomatic or non-symptomatic IntraCranial Hemorrhages (ICH) at 24 hrs • Incidence of symptomatic IntraCranial Hemorrhages (ICH) at 24 hrs • Incidence of non-symptomatic IntraCranial Hemorrhages (ICH) at 24 hrs • Incidence, nature and severity of Adverse Events, SAEs, SUSARs, Bleeding-Related Events (BREs) and Treatment-Emergent Adverse Events (TEAEs), at 24 hrs, at D7/discharge, 30 days and 90 days • Incidence of bleeding-related events at 90 days • Anti-glenzocimab antibodies (ADA) at baseline (pre-dose) and at 3 months for at least 50 patients. *Cost -effectiveness* • Cost per QALY (Quality adjusted Life Year) gained with the use of glenzocimab in addition to EVT • Cost per patient with a mRS score ≤ 2 gained with the use of glenzocimab in addition to EVT
Design / phase / category	This is a national, multicenter, prospective, randomized (1:1 ratio), parallel group, double-blinded, placebo controlled, phase II/III study.- Category 2
Population of study participants	Patients over 18 with a clinical diagnosis of AIS from a large cerebral vessel occlusion (LVO) between 0 and 24 hrs of symptom onset or when a patient has been seen the last time well and eligible for EVT based on perfusion imaging for the time window 6-24 hours.
Inclusion criteria	1. Age 18 years or older (Age≥18 years) 2. No significant pre-stroke disability (pre-stroke mRS must be equal to 0 or 1); 3. Indication of EVT within the time-window of 0 to 24 hrs in participants, treated with or without intravenous thrombolysis, and presenting with a clinico-radiological mismatch (defined by a NIHSS≥10 and an ASPECT score≥ 6) 4. Occlusion of the cervical or intracranial internal carotid artery (ICA) or the proximal middle cerebral

	artery (MCA - M1 and/or M2), on magnetic resonance angiography (MRA) or, when this is not possible, on CT angiography (CTA); 5. Informed consent signed: • By the patient, • Or informed consent signed by a family members/trustworthy person if his condition does not allow him to express his consent by written as per L. 1111-6, • In a situation urgently and in the absence of family members/trustworthy person, the patient can be enrolled. The consent to participate to the research will be requested as soon as the condition of the patient will allow him to consent. 6. Post-menopausal women defined as not having menses for 12 months without an alternative medical cause. For WOCBP, a highly effective birth control method should be in place that can achieve a failure rate of less than 1% per year that should last for at least 2 months after IMP administration. Birth control methods which may be considered as highly effective in WOCBP include: - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (intravaginal, transdermal), - progestogen-only hormonal contraception associated with inhibition of ovulation (injectable, implantable) - intrauterine device (IUD), - intrauterine hormone-releasing system (IUS), - bilateral tubal occlusion, - vasectomized partner, Birth control methods which may be considered as highly effective for men and that should last for 4 months after IMP administration include: - vasectomy, - use of condom combined with a highly effective birth control method for their WOCB partner. Please note that hormonal contraception is a risk factor for thromboembolic events and attention should be called to reconsider it passed the acute stroke phase. 7. Women of child-bearing potential (WOCBP) must have a negative serum/urine pregnancy test at baseline. Women of childbearing potential, i.e., fertile, are defined as women following menarche and until becoming post-

	menopausal unless permanently sterile, i.e., having undergone hysterectomy, bilateral salpingectomy and bilateral oophorectomy. 8. Affiliation to social security or any health insurance
Non Inclusion criteria	1. Contraindications to EVT; 2. Contraindication to contrast agents 3. Pre-existing neurologic and psychiatric disease with mRS ≥ 2; 4. Unknown symptom's onset or last seem well > 24 hours; 5. Patients under or needing immediate DAPT administration; 6. Significant mass effect with midline shift as confirmed on CT/MRI; 7. Gastrointestinal or urinary tract hemorrhage in previous 21 days; 8. Patient with intracranial haemorrhage 9. Known Platelet count <100 000 mm3; 10. Pregnant or breastfeeding woman; 11. Known hypersensitivity to glenzocimab or to any of the excipients; 12. Known Severe renal insufficiency (Grades 4-5) with a glomerular filtration rate < 30mL/Min/1.73m2; 13. Participation in another interventional clinical trial within 30 days prior to the inclusion. 14. Persons deprived of their liberty by a judicial or administrative decision, persons subject to psychiatric care under sections L.3212-1 et L.3213-1 and persons admitted to a health or social institution for purposes other than research (L.1121-6) 15. Adults subject to a legal protection measure (L.1121-8) 16. The patient or his/her family (if the patient is unable to give his/her opinion) expresses an inability to return for protocol visits 17. patients receiving anticoagulants (i.e. heparin within 48 hours and an elevated aPTT -greater than upper limit of normal for laboratory-; (current use of oral anticoagulants (ex: warfarin) and INR >1.7; Current use of direct thrombin inhibitors or direct factor Xa inhibitors, as already mentioned in the non-authorized concomitant treatments 18. patients who have already received another humanized fragment of monoclonal antibody with a suspicion of hypersensitivity

Exclusion criteria	1. Withdrawal of consent 2. Patient's wish to withdraw from the trial 3. Persons deprived of their liberty by a judicial or administrative decision, persons subject to psychiatric care under sections .and persons admitted to a health or social institution for purposes other than research (L.1121-6)
Concomitant treatments	**Non-Authorized Concomitant Treatments**: Patients should not receive any other experimental therapies during the 90 days of the study participation. In addition to the aforementioned exclusion criteria, patients should not receive a dual anti-platelet therapy (DAPT) required after an intra- and/or extra-cranial stent, or a thrombolysis with Tenecteplase, during glenzocimab infusion. **Authorized Concomitant Treatments:** All other symptomatic treatments used routinely for disease-related symptoms will be allowed in all patients involved in this trial. Specific treatments for any adverse events will also be permitted. Thrombolysis with alteplase anti-platelet monotherapy are allowed. Glenzocimab should be started as soon as possible in addition with alteplase. Details of all treatments or procedures must be recorded in the eCRF.
Investigational medicinal product(s)	Glenzocimab (ACT-017, Acticor Biotech) is formulated for IV administration as a sterile product with 20 mM sodium citrate and 130 mM sodium chloride buffer at pH of 5.0. It is supplied for clinical trial use in vials containing 50 mL of the drug product at a concentration of 10 mg/mL. Each vial contains 500 mg of glenzocimab. Two vials (2x500 mg) of glenzocimab should be administered concomitantly for eligible patients for a total daily dose of 1g.
Comparator treatment	Placebo of glenzocimab is 0.9%NaCl (Acticor Biotech) for IV administration. It is supplied for clinical trial use in vials of 50 mL. Two vials of placebo of glenzocimab should be administered concomitantly for eligible patients.
Interventions added by the study	EVT + glenzocimab/placebo of glenzocimab,
Study intervention	The administered study treatment will be glenzocimab or placebo, as per central randomization allocation to the study group into which the patient is randomized. One arm will receive glenzocimab and the other arm the placebo in addition to EVT. EVT itself is not added by the research. Glenzocimab or the placebo is intended to be administered as an IV infusion over 6 hrs, with ¼ of the dose administered by a 15-minute bolus and ¾ of the dose administered by 5h45min-slow infusion. This is the proposed scheme to obtain a rapid

	effect during the emergency phase, and to cover a period of time long enough to avoid downstream complications.
Expected benefits for the participants and for society	The expected benefits are an improvement of the brain reperfusion and neurological functional outcome without increasing the intracranial bleeding rate. Expected benefits are the diffusion of an effective strategy with an acceptable cost for the society.
Risks and burdens added by the study	No predefined risks and/or burdens due to the administration of the study treatment have to be highlighted. One year follow-up phone call is scheduled. EVT is the standard of care for such a patient. EVT itself is not added by the research. Nevertheless, risk of adverse event linked to EVT will monitored as glenzocimab is given in association with EVT (thromboembolic event, bleeding and infection). The risks related to EVT are: thromboembolic event, bleeding (hemorrhagic transformations), infection and some other mechanical complications, like arterial perforation. Risk related to femoral arterial puncture and anaesthesia, include respectively groin hematoma with or without arterial hypotension for the first (i.e. femoral arterial puncture); and for the second (i.e. anaesthesia) arterial hypotension, anaphylactic shock to aesthetic drugs.
Practical implementation	Glenzocimab administration should start prior the EVT start
Number of participants included	260
Number of centres	13
Duration of the study	Specify: - inclusion period: 32 months - Participation period (treatment + follow-up): 1 year - total duration: 44 months - Interim analysis: after the Day-90 visit of the 78th patient - Final analysis: after the Day-90 visit of the 260th patient
Number of enrolments expected per site and per month	0.8 patients/site/month
Statistical analysis	An interim analysis will be performed when 30% of the patient enrolment will be achieved (78 patients). In the control group, we considered that the distribution of the mRS is “0“:0.10, “1“:0.17, “2“:0.19, “3“:0.17, “4“:0.16, “5“:0.06, “6“:0.15. We calculated that a sample of 258 patients would yield a power of 80% to detect a treatment effect associated with an OR of 1.85 considered a two-sided p value of 0.05. As we planned an interim analysis at 78 patients with an O“Brien and Fleming scheme, we increased the sample size to 260. The first interim analysis will be considered as statistically significant if the p value is below to 0.0054. The final analysis will be considered as statistically significant if

	the p value is below 0.0492. Interim analysis will also allowed a stop for futility. Futility bound has been calculated using O'Brien & Fleming type beta spending. After inclusion of 78 patients, if the statistic of the Wald test value associated with the OR is below -0.523 in favour of the placebo group, the trial will be terminated for futility.
Funding sources	ANR
DSMB : Data safety monitoring board	DSMB will be composed by four members: three neurologists, and one statistician.

3 SCIENTIFIC JUSTIFICATION FOR THE STUDY

In the setting of acute ischemic stroke (AIS) without large vessel occlusion (LVO) thrombolysis with intravenous (IV) alteplase is the only pharmacological approved therapy [1]. This therapy is of benefit up to 4.5 hrs after symptoms onset and is part of the standard of care [2,3]. Beyond 4.5 hrs, recent data support its use in wake-up strokes or up to nine hrs after stroke symptoms onset in patients selected with multimodal imaging [4,5].

Alteplase is also firmly contraindicated in patients at risk of hemorrhage. Symptomatic intracerebral hemorrhage (sICH) is the most feared complication after IV alteplase administration. All studies consistently showed an increased risk of IntraCranial Hemorrhages (ICH) after alteplase use compared with no alteplase. A meta-analysis including 6 RCTs comprising 1779 patients revealed that alteplase given within 3 hrs of stroke symptoms onset was associated with a nearly 5-fold risk of sICH[3]. Finally, given the risk of ICH and limited time window for alteplase administration, only 7 to 15% of patients can receive this treatment.

Beyond safety issues, thrombolysis with alteplase is also limited in terms of efficacy. In fact, the overall recanalization rate is only 33%[6]. In addition, re-occlusion rate after initial recanalization is 14-34% of patients and is 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 [7]. For these patients (i.e. AIS associated with LVO) the standard of care associates the intravenous thrombolysis (IVT) and the endovascular thrombectomy (EVT) [8]. Since 2015, EVT has been recognized in several clinical trials and has demonstrated efficacy in a clinical score at 90 days [9].

Several factors such as clot location and size, as well as, clot composition do influence recanalization rates. EVT in the setting of AIS consecutive to LVO has given the opportunity to study intracranial thrombi. Thrombus composition analysis has shown that platelet rich clots are more resistant to alteplase [10], suggesting that platelets inhibition represent a relevant target to improve reperfusion. In this perspective, a potent, IV, fast-acting, reversible antiplatelet agent may help to increase clot dissolution in this setting. Nevertheless, the currently available molecules are not recommended at the acute phase (0 to 12 hrs without and 0 to 24 hrs with a previous alteplase administration) due to the associated risk of ICH. Thus, early administration of IV aspirin in patients with AIS treated with alteplase is, associated with increased of ICH [7] [7]. Therefrom, there is still a need for a safe and efficient antithrombotic agent administrable at the acute phase without inducing a bleeding risk in order to reduce the size of the clot, to favor cerebral reperfusion and to prevent recurrences.

Platelet glycoprotein VI (GPVI) belongs to the immunoglobulin superfamily and its expression is restricted to the megakaryocyte/platelet lineage [11]. GPVI is a key receptor for collagen and plays a major role in platelet activation, platelet recruitment and thrombus growth [11-13].

Studies have also demonstrated that GPVI is a platelet receptor of polymerized fibrin and this interaction contributes to the thrombus growth and to its reformation [14]. Furthermore, inhibition of the GPVI does not impair hemostasis and subjects with a genetic or acquired GPVI deficiency are not prone to excessively bleed [15]. GPVI is therefore a major target in the growth and stabilization of the thrombus, offering a new therapeutic approach with a high safety profile.

Glenzocimab is a humanized fragment of monoclonal antibody (Fab) directed against the human platelet GP VI (hGPVI), being developed as an effective antiplatelet agent with minimal bleeding risk for treating the acute phase of documented ischemic stroke. It is intended to be an add-on treatment to the tissue plasminogen activator (tPA) and EVT or to EVT alone for patients who are not eligible for tPA.

The current protocol allows any Standard of Care to be used for thrombolysis, depending on routine practice in each study site. In particular, the simpler mode of administration of tenecteplase with its single bolus injection, led many sites to adopt tenecteplase as an alternative to alteplase for all AIS patients.
A meta-analysis of 5 randomized trials published in 2019, demonstrated that tenecteplase (a fibrinolytic agent) was non-inferior to alteplase for AIS with an mRS 0-1 at 3 months of 58% for tenecteplase and 55% for alteplase (25). Safety results were also consistent with non-inferiority of tenecteplase.
ACT trial, a multicenter, registry-linked, randomized trial, has confirmed the non-inferiority of tenecteplase (0,25mg/kg) versus alteplase with an mRS 0-1 at 90-120 days in 37% of patients in tenecteplase group and in 35% in alteplase group (26).
More recently, TRACE-2 study, a prospective interventional, randomized, placebo-controlled trial has also confirmed that tenecteplase was non inferior to alteplase with a 90-day mRS 0-1 observed in 62% of patients versus 58 respectively, with no increased bleeding
risk on tenecteplase (27).

In addition to the above, the co-administration of glenzocimab and tenecteplase was well tolerated in cynomolgus monkeys with no mutual pharmacokinetic interaction between the two molecules. Combined toxicity studies conducted in this species have shown no added risk to that of tenecteplase, as was previously demonstrated when glenzocimab was added to alteplase (28)
Hence, this amendment allows the use of glenzocimab as add on therapy to the intravenous thrombolysis based on standard of care. Glenzocimab administration time relative to IVT administration has also been adjusted to allow for a reasonable time interval to gain patient′s consent and prepare glenzocimab administration, irrespective of the lystic administrered as SOC. Therefore, glenzocimab administration should start no later than 2 hours after the initiation of IVT treatment, regardless of the type of thrombolytic agent used.″

3.1 Hypothesis for the study

We expect that the administration of a monoclonal antibody (glenzocimab) will increase favorable outcomes by reducing the rates of erratic emboli and increase the patency of the microcirculation with a favorable safety profile. Thus, we hope a better functional outcome for patients treated by the GPVI inhibitor. Moreover, the IV route for glenzocimab administration is adapted to the stroke population, who frequently has dysphagia, not allowing per os drug administration. The profile of glenzocimab suggests that this drug is quite adapted for this selected population of AIS patients.
Results from the ACTIMIS study showed a lower incidence of symptomatic and non-symptomatic intracranial hemorrhages (ICH), including hemorrhagic transformations. One of the most reliable hypothesis linked to this reduction is the mechanism of action of glenzocimab acting in the downstream circulation, more specifically on leukocyte-platelet micro-aggregates located beyond the culprit thrombus. This action might trigger a beneficial effect on no-flow of downstream circulation restoring the reperfusion of the infarcted zone and avoiding the blood extravasation and consequently an ICH.

The lower mortality rate seems directly related to a significant reduction of symptomatic ICHs because four of them occurred in placebo group were considered as a direct cause of death.

3.2 Description of knowledge relating to the condition in question

EVT in addition to best medical management (BMM), including intravenous IV alteplase, is the gold standard of care for AIS consecutive to anterior circulation (i.e. internal carotid artery -ICA- and middle cerebral artery -MCA-) LVO [16]. This gold standard refers to the publication of 6 randomized controlled trials proving the superiority of this combined approach versus BMM [1718] [1920] [21] [22]. The observed benefit resulted in an improved functional outcome with reduced disability (NNT of 2.6 [9], but without any effect on mortality except for one study) [21]. In addition, EVT may be proposed up to 24 hrs after stroke onset if perfusion imaging demonstrates the presence of a substantial ischemic penumbra. The effect on disability remains limited with less than 50% of AIS patients achieving functional autonomy [9].

3.3 Summary of relevant pre-clinical experiments and clinical trials

Glenzocimab is a humanized fragment of monoclonal antibody (Fab) directed against the human platelet glycoprotein VI (hGPVI), which is involved in the platelet aggregation. Glenzocimab is being developed as an effective antiplatelet agent with minimal bleeding risk for the treatment of the acute phase of ischemic stroke documented by imaging technique as an add-on treatment to alteplase and EVT or EVT alone for patients who are not eligible for alteplase. As glenzocimab belongs to the antiplatelet pharmaceutical class in which it is commonly expected a higher risk of bleeding. Nevertheless, such effect is not expected with glenzocimab because of its unique mechanism of action.

Indeed, even at the highest dose of 2000 mg of glenzocimab given to healthy subjects in the first in human (FIH) study which ended in January 2018 no such side effects, including bleeding disorders, or effects on the central nervous system, respiratory system, or cardiovascular system were reported. These data were consistent with the results obtained in the animal studies, especially non-human primates. Thus, the highest dose of glenzocimab given to animals was 80 mg/kg (around 2.4 times higher than the highest dose given in the FIH study -2000 mg-) and this dose gave no side effects, including those reported above (i.e. bleeding disorders or effects on the central nervous system, respiratory system, or cardiovascular system). Moreover, glenzocimab is a humanized fragment of monoclonal antibody and therefore risks generally associated with protein based medicinal including anaphylactic reactions, fever, chills and headache and hypersensitivity also apply for glenzocimab; however, such reactions have not been observed in neither in the non-clinical studies nor in the first in human study.

Risks associated with the route-of-administration via IV infusion (including local pain or irritation) were assessed in the FIH study and results showed that escalating doses of glenzocimab infusions were well tolerated.

Preliminary FIH study conducted in healthy subjects from October 30th, 2017 (first healthy subject in) to January 2018 (Last healthy subject last visit). The study was designed as a single-center, randomized, double blind, placebo-controlled, single ascending-dose escalation trial.

Healthy subjects received glenzocimab or placebo as an IV infusion of 6 hrs, with a 15-min loading dose phase (bolus) of 1⁄4 of the total dose and a maintenance dose phase (slow infusion) of 3⁄4 of the total dose. Doses of 62.5, 125, 250, 500, 1000, 2000 mg, and a matching placebo were administered. Safety, clinical tolerability, biological safety as well as PK were the outcome parameters. Ex-vivo collagen-induced platelet inhibition was also tested at serial time points.

There were no serious adverse event (SAEs) reported at any of the doses tested, nor was there any dose-related trend in any non-serious adverse effect (AEs). None of the AEs were identified as bleeding related and no modifications of the hemostatic parameters nor hemoglobin concentration were observed. Bleeding time was not affected in a clinically significant manner by any of the glenzocimab doses. The detailed description of all adverse events reported can be found in the Investigator's Brochure.

Results showed that glenzocimab dose-dependently inhibited collagen-induced platelet aggregation. At the dose of 62.5 mg, collagen-induced platelet aggregation was observed in 3 out of 6 subjects, and results returned to baseline 1 hour after dosing. At the dose of 125 mg, platelet aggregation was rapidly inhibited in 4 out of 6 subjects and the effect lasted 6 hrs. At 250 mg, the inhibition was more homogeneous across the subjects (inhibition observed in 5 out of 6 subjects) with an effect lasting around 6 hrs. At the doses of 500 mg, 1000 mg and 2000 mg, the inhibition was observed in all subjects, with an effect lasting around 8 hrs, 18 hrs and 24 hrs, respectively. At 48 hrs, platelet aggregation returned to baseline levels at all dose levels, except for the 2000 mg, for which return to baseline levels was observed at follow-up (Day 7).

For all doses investigated, the applied dosing regimen indeed showed a fast increase in glenzocimab plasma concentrations within the first 15 min of administration. Thereafter, the speed of infusion was reduced, resulting in more or less stable plasma concentrations of glenzocimab for the remaining time of the infusion. Total clearance was constant for all doses. The primary PK parameters C_{max} and AUC, demonstrated dose proportionality across the investigated dose range. Recovery of glenzocimab in urine is only significant (> 1%) at the two highest doses.

These preliminary data concur with those observed in non-human primates.

The results obtained during the escalating dose phase of the ACTIMIS study showed very promising safety data. After the completion of the five cohorts where a dose progression has been carried out, the study DSMB members recommended to use the highest dose, 1000 mg, for the consolidation phase. Of 60 AIS patients recruited, 12 were treated with the highest dose, they experienced no symptomatic ICHs, a lowest rate of asymptomatic ICH and a similar incidence of SAEs/SUSARs in comparison to patients treated with each lower dose, 125, 250, 500 mg and placebo.
The consolidation phase was conducted in additional 106 AIS patients with a parallel-group design glenzocimab 1 000 mg versus placebo, both in add-on of the reperfusion standard of care. The global safety results combining both phases (n=166) were as follows:

- The incidence of symptomatic ICHs observed in all-dose (1 event/102 patients - 1%) and 1 000 mg (no event/66 patients - 0%) glenzocimab groups was lower than that one shown in placebo group (5 events/64 patients - 7.8%),

- The incidence of non-symptomatic ICHs observed in all-dose (30 events/102 patients - 30%) and 1 000 mg (20 events/66 patients - 30%) glenzocimab groups was lower than that one shown in placebo group (30 events/64 patients - 48%),
- The Kaplan-Meier curve showed a reduced mortality in all-dose and 1 000 mg glenzocimab groups when compared to placebo group, with a p value of 0.0360 and 0.0424 respectively. Twenty deaths occurred, 5 in phase Ib and 15 in phase 2a, and 12 of them were a stroke-related outcome.
- In terms of efficacy results, no difference was observed on NHISS at 24 hrs and mRS at Day-90 in the overall population, mostly due to the study small sample size. However, it was observed a favorable trend for patients with a more severe handicap and deceaded patients (mRS 4-6) and a favorable trend in some particular sub-groups, as patients over 65 years, including those ≥80 years (> 70% of the study population), patients treated by mechanical thrombectomy and patients having a baseline NIHSS score ≥ 10.

  Additionally, reperfusion rate after mechanical thrombectomy showed more favorable results in all-dose glenzocimab group (96%) than those observe in placebo group (85%), particularly due to the proportion of patients reaching grade 3 of mTICI score.

In conclusion, the ACTIMIS study results represent a key milestone and a proof-of-concept:

- The study primary endpoint was positively reached.
- Glenzocimab administered in add-on to the single or dual SOC showed no increase of the hemorrhagic risk in AIS patients.
- The pharmacologically targeted dose (non-clinical / phase 1) proves to be the optimal dose for clinical development, being safe and showing activity.

Glenzocimab 1000 mg showed a favorable safety profile, in terms of hemorrhagic events, as well as more generally, including in patients aged above 80 years (40% of the population), and despite concomitant medical conditions.
Though not powered for a showing of efficacy, in this study Glenzocimab 1000 mg showed a real benefit in terms of death rate, and was shown to decrease the proportion of patients with the most severe level of handicap.
These encouraging results have to be confirmed in ongoing and future studies.

3.4 Description of the population to be studied and justification for the choice of participants

The subject should be clinically evaluated in the same manner as any routine AIS patient. Clinical assessment documenting NIHSS and significant past medical history should be obtained. Imaging with CT-scan or MRI, performed as per the institutional standard of care, is required to exclude acute ICH. The studies must demonstrate an acute major vessel intracranial anterior circulation occlusion (ICA or MCA). All MRIs will be performed on MR scanners with echo-planar imaging capability to allow rapid acquisition of diffusion and perfusion scans. Following the AHA 2018 guidelines, patients with AIS up to 24 hrs of last known normal who have LVO in the anterior circulation, obtaining CTP, DW-MRI, or MRI perfusion are used for patient selection for EVT, using the DAWN [23] and DEFUSE 3 [24] studies.
Patients will undergo standard (not research added) stroke work-up including but not limited to: demographic confirmation, medical history, and focused physical examination. Baseline imaging may either be CT/CTA or MRI/MRA with or without perfusion prior to the pre-

procedure angiography. The baseline neurologic examination will be performed by a health care provider or study team member, certified to administer the exam and able to give an unbiased neurological and functional assessment (mRS and NIHSS).

3.5 Identification and description of the investigational medication or medications

Glenzocimab is a humanized fragment of monoclonal antibody (Fab) directed against the hGPVI, which is involved in the platelet aggregation.

Glenzocimab is being developed as an effective antiplatelet agent with minimal bleeding risk for the treatment of the acute phase of ischemic stroke documented by imaging technique as an add-on treatment to recombinant tissue plasminogen activator tPA and EVT or EVT alone for patients who are not eligible for tPA.

3.6 Description and justification of the dosage, route of administration, administration schedule and treatment duration

Glenzocimab (ACT-017, Acticor Biotech) is formulated for IV administration as a sterile product with 20 mM sodium citrate and 130 mM sodium chloride buffer at pH of 5.0.
It is supplied for clinical trial use in vials containing 50 mL of the drug product at a concentration of 10 mg/mL. Each vial contains 500 mg of glenzocimab.
Treatment will be administered as a single dose of 1000 mg (2x500 mg vials).

Placebo of glenzocimab (Acticor Biotech) is 0.9% NaCl for IV administration. It is supplied for clinical trial use in vials of 50 mL.
Two vials of placebo of glenzocimab should be administered concomitantly for eligible patients.

Glenzocimab and placebo is a solution for dilution, and the required amount of glenzocimab should be diluted in 0.9% Sodium Chloride.

Glenzocimab and placebo should be stored under appropriate storage conditions (2 -8°C) in accordance to the information available in the last applicable version of the IB.

See Section 7 for further information about the administration of the product and for further details regarding the physico-chemical and pharmaceutical properties and formulation of glenzocimab, please refer to the IB in its last applicable version.

3.7 Summary of the known and foreseeable benefits and risks for the research participants

Due to its complementary mechanism of action in comparison with that of the SoC, glenzocimab might be able to provide some foreseeable benefits. It should improve the brain reperfusion and at the same time the neurologic functional outcome, without increasing the ICH rate. The aim of the glenzocimab administration is to improve the reperfusion efficiency of the SoC.

EVT is the standard of care for such a patient. EVT itself is not added by the research. Nevertheless, risk of adverse event linked to EVT will monitored as glenzocimab is given in association with EVT (thromboembolic event, bleeding and infection).

4 OBJECTIVES

4.1 Primary objective

To evaluate the efficacy of glenzocimab in addition to EVT and compared to EVT plus placebo, whether or not associated with IVT, on functional outcome at day 90.

4.2 Secondary objectives

- To evaluate the impact of glenzocimab in addition to EVT compared to EVT, whether or not associated with IVT, plus placebo on overall survival at day 90 and 1 year
- To evaluate the impact of glenzocimab in addition to EVT compared to EVT plus placebo, whether or not associated with IVT, on:
  1. reperfusion at the end of EVT,
  2. early clinical improvement at 24 hrs
  3. sICH at the first 24 hrs
  4. overall ICH at the first 24 hrs
  5. serious adverse events (SAEs), within the first 24 hrs, at D7/discharge, 30 days, 90 days
  6. suspected unexpected serious adverse reactions (SUSARs), at 24 hrs, D7/discharge, 30 days, 90 days
  7. bleeding-related events (BREs) at 24 hrs and at day 90
  8. quality of life at 90 days and one year

To evaluate the cost-effectiveness or Efficiency of glenzocimab in addition to EVT compared to EVT plus placebo.

5 STUDY DESIGN

5.1 Study endpoints

5.1.1 Primary endpoint

The main efficacy endpoint assesses the functional outcome at 90 days, in patients with AIS eligible for EVT based on perfusion imaging between 0 and 24 hrs after symptom onset.

The primary efficacy endpoint is the functional outcome at day 90 assessed by the modified mRS at day 90 +/- 15 days.

5.1.2 Secondary endpoints

Efficacy :

- Favorable functional outcome defined by a mRS ≤ 2 at day 90 +/- 15 days
- Proportion of patients with a severe handicap: mRS 4-6
- Overall Survival at Day-90 and 1 year
- Early reperfusion outcomes:
    - Stroke volume by brain imaging at 24 hrs
    - Reperfusion at the end of procedure assessed by eTICI score
    - Early neurological improvement by NIHSS at 24 hrs
- EQ5D-5L at day 90 and at 1 year

Safety:

- Incidence of symptomatic or non-symptomatic IntraCranial Hemorrhages (ICH) at 24 hrs
- Incidence of symptomatic IntraCranial Hemorrhages (ICH) at 24 hrs
- Incidence of non-symptomatic IntraCranial Hemorrhages (ICH) at 24 hrs
- Incidence, nature and severity of Adverse Events, SAEs, SUSARs, Bleeding-Related Events (BREs) and Treatment-Emergent Adverse Events (TEAEs), at 24 hrs, at D7/discharge, 30 days and 90 days
- Incidence of bleeding-related events at 90 days
- Anti-glenzocimab antibodies (ADA) at baseline (pre-dose) at 3 months for at least 50 patients.

Efficiency or cost-effectiveness

- estimation of the incremental cost-effectiveness ratio (ICER), expressed in cost per QALY (quality adjusted Life Year) gained with glenzocimab in addition to EVT (cost-utility analysis)
- estimation of the incremental cost-effectiveness ratio (ICER), expressed in Cost per patient with a mRS score ≤ 2 gained with the use of glenzocimab in addition to EVT (cost-effectiveness analysis)

5.2 Description of research methodology

5.2.1 Design of the study

This is a national, multicenter, randomized (1:1 ratio), double blind, parallel group, placebo controlled, phase II/III study. After eligibility is confirmed and informed consent obtained from patients or his/her proxy or following an emergency procedure, patients will be randomized as soon as possible in two parallel groups: one will receive IV glenzocimab with BMM (EVT +/- IVT), and the other one will receive BMM (EVT +/- IVT) plus placebo of IV glenzocimab. All patients will be further transferred to the cath lab to perform EVT in case of persistent occlusion and clinic-radiological mismatch defined by a NIHSS≥10 and an ASPECT score≥ 6. A

perfusion brain imaging will be conducted at baseline if necessary for symptoms onset>6h, as recommended by the international guidelines.
Follow-up of patients will subsequently be performed at 24 hrs, day 7 or discharge, 30 days, and at 90 days by trained research nurses unaware of the group assignments during face-to-face interviews or via telephone (detailed procedures). The study will have an independent data and safety monitoring committee.
Further to the Day-90 visit of the 78th patient enrolled, the database will be partially locked after data monitoring and the interim statistical analysis for futility on study primary endpoint will be performed.
Further to the Day-90 visit of the 260th patient enrolled, the complete database will be locked after the data monitoring and the final statistical analysis on the study primary and secondary endpoints will be performed
A quality-of-life survey will be conducted by phone call at 90 days and 1 year for medico-economic scope. This survey will use some specific scales, as EQ-5D-5L. However, the medical-economic analysis including 1-year follow-up data will be evaluated as post-hoc analysis.

5.2.2 Number of participating sites

Recruitment centres

This is a multicentre trial involving several participating centres in France: The participants will be recruited in French hospitals, at neurological services. In first time, 12 centers will participate to the trial.

5.2.3 Identification of participants

The participants in this clinical trial will be identified as follows:
Site number: 3 digits - Sequential enrolment number for the site: 4 digits – first letter of the name - first letter of the first name.
This reference number is unique and will be used for the entire duration of the study.

A randomization number will also be assigned when the participant is randomized. This number will have the following format: R00000

A treatment number (a numbered treatment unit contains 2 vials of 50 mL) will be also assigned when the participant is allocated to a treatment arm. This number will have the following format: T0000

5.2.4 Randomisation

To assure a centralized real time randomization procedure, a web-based randomization will be performed using the electronic case-report form (e-CRF) system. A varying block sizes unknown to the investigators will be applied. A stratified randomization procedure will be used

to achieve a balance of the following pre-specified factors: age (< 80 vs. ≥ 80 years old), IVT (yes or no), time-to-treatment (0-6 hrs vs 6-24 hrs) and centre. Patients will be enrolled and randomized by vascular neurologists and neuro-interventionalists.
To evaluate a possible selection bias of patients included in the trial, participating centres will have to register baseline characteristics, reason for non-inclusion and treatment of all patients satisfying eligibility criteria which are not randomized.

5.2.5 Blinding methods and measures put in place to protect blinding

The study will be performed in a double-blind fashion. The Investigator and study staff, the patient, the monitors and the Sponsor's staff will remain blinded to the treatment throughout the study. The study drug and its matching placebo are indistinguishable. Indeed, each centre will be provided with numbered treatment units of glenzocimab or matching placebo and all units will be packaged in the same way. No additional blinding material is required. Two vials of glenzocimab 500 mg/50 ml or placebo 50 ml each will be used in order to administer glenzocimab at the global dose of 1000 mg/100 ml or 100 ml of placebo.

5.2.6 Unblinding procedures

Unblinding will be requested by the investigator for any reason requiring:

- a modification of the patient's follow-up as defined in the protocol
- a medical action.

Non-emergency situation

The request must be sent to the Promotion Unit of the DRCI-APHP using the current form-
- by email **drc-levee-insu@aphp.fr**
- followed by with a phone call to 01 40 27 57 30

The investigator requesting a non-urgent unblinding must first have obtained the opinion of the coordinating investigator or of the scientific director

Emergency Situation

The request should be made to the poison center at Fernand Widal Hospital, Telephone: **+33 (0)1 40 05 48 48** followed by sending the current form:
- by email to **alertes.rtu.lrb@aphp.fr**

or
- by fax to 01 40 05 48 88.

A copy will be sent simultaneously to the sponsor's Safety Department
- by email to drc-levee-insu@aphp.fr

6 IMPLEMENTATION OF THE STUDY

Before any examination or intervention related to the study may be carried out, the investigator must obtain the *freely given, informed and written consent of the participant, or of his/her legal representative* where applicable.

Individuals liable to participate in studies benefit from a preliminary medical examination adapted to the study.

Whose consent must be obtained	Who informs the individuals and collects their consent	At what point the individuals are informed	At what point the consent is obtained
the individual participating in the study; the legal representative	the PI or collaborating physician declared and trained in the study ICU	At screening visit	At inclusion/ Baseline visit or randomisation visit

6.1 Screening visit

Screening period will start as soon as possible. The screening visit takes place between 0 and 24 hrs before the baseline and randomization visit.
Consecutive potential eligible patients will be first informed by the GP investigator about the study, as follows:

During this visit the following examination will be performed before randomization:

- Demographic data (age, gender…);
- Relevant Medical history (including previous history of stroke or condition for not meeting the criteria to receive alteplase or glenzocimab);
- Clinical evaluation / physical exam including height and weight (weight may be estimated by PI or delegate as patient's condition may prevent proper weighing at this time);
- Vital signs (BP, Pulse) NIHSS score (pre-EVT and pre-IVT value when applicable);
- CT scan and/or MRI (according to imaging protocol recommendations);
- Hematology: Hemoglobin and Platelet count;
- Coagulation: INR/aPTT;
- Biochemistry:
    - Renal function test: Serum creatinine or GFR;
    - Other: Serum glucose;
- Recording of concomitant medication;
- Pregnancy test by a serum or urine HCG level assessment for childbearing women;
- Inclusion and exclusion criteria should be verified.

6.2 Baseline visit or randomisation visit

Randomization will start as soon as the written informed consent form (ICF) is signed. The ICF has o be obtained following the below specific sequence as per the local requirement for emergency inclusion procedure:

Randomization will be performed as early as possible after onset of stroke symptoms, and in any case early enough to allow the initiation of the test treatment as soon as possible and not later than 24 hours from the AIS symptom onset.
Randomization will be performed automatically via the eCRF with the randomization module (Cleanweb). Detailed procedure will be described in the dedicated instruction manual.
Dosage of anti-glenzocimab antibodies (ADA) will be performed for at least 50 patients.

6.3 Treatment period

The EVT procedure should be started immediately after the patient has been randomized . The study treatment should be administered as soon as possible after dilution. Glenzocimab or the matching placebo is intended to be administered as a 6 hrs IV infusion (+/- 1 hour), with ¼ of the dose administered in 15 min and ¾ of the dose administered in 5 hrs 45 min. The study drug administration and performed during the time of infusion (6 hrs +/- 1 hour).

The following examination will be performed:

- eTICI score to be assessed at the end of the EVT to measure the recanalization rate (patients reaching the 2b-3 grades);
- Vital signs (BP, Pulse) will be assessed every 30 min during the first 6 hrs (infusion), then every 3 hrs up to 24 hrs;
- Recording of concomitant medication;
- Recording of adverse events according to NCI-CTCAE.

6.4 24-h Evaluation

24 hrs after the start of the glenzocimab/placebo infusion the following examination will be performed:

- Vital signs (BP, Pulse);
- NIHSS assessment compared to the baseline NIHSS score (pre-EVT and pre-IVT value when applicable). In case of drip & ship patients, it’s necessary to collect the NIHSS baseline value measured before any treatment administration in the original hospital;
- brain imaging (MRI or CT) at 24 hrs
- Recording of adverse events according to NCI-CTCAE.

6.5 Day-7 or discharge evaluation

The following examinations will be performed:

- mRS assessment;
- Recording of adverse events according to NCI-CTCAE (version 5.0).

For the day-7 evaluation, a window of ± 3 days is allowed. This assessment will be performed by certified research nurses, unaware of the group assignments.

6.6 Day-30 evaluation

The following examinations will be performed:

- mRS assessment;
- Recording of adverse events according to NCI-CTCAE (version 5.0).

For the 30-day evaluation, a window of ± 7 days is allowed. This assessment will be performed by certified research nurses, unaware of the group assignments, via telephone survey.

6.7 Day-90 : End of the Study Visit

The following examinations will be performed:

- mRS assessment;
- Recording of adverse events according to NCI-CTCAE (version 5.0).

For the 90-day evaluation, a window of ± 15 days is allowed. This assessment will be performed by certified research nurses, unaware of the group assignments, via telephone survey, except for patients participating in ADA assessment.

- Drugs prescription
- EQ-5D-5L
- Dosage on site of anti-glenzocimab antibodies (ADA) for at least 50 patients; The 90-day evaluation will be performed on site for these patients

6.8 1-year Evaluation

A 1-year ± 30 days medico-economic survey will be conducted using the following scales:

- EQ-5D-5L by phone contact
- Drugs prescription

- Vital status

Information will be obtained via a phone contact

6.9 Expected length of participation and description of the chronology and duration of the study

- Maximum period between screening and randomization: both visits will be conducted within 24 hrs.
- Duration of enrolment period: 32 months
- Duration of participation for each participant: 12 months
- Study treatment duration: 6 hrs
- Total study duration: 44 months
- Follow-up duration and procedures for the participant in the event of premature discontinuation : all patient will be follow up until 1 year.

6.10 Table or diagram summarising the chronology of the study

Actions	*D 0-24 H (Screening visit)*	*D0 -24hrs **(Baseline visit randomization)***	*24h hrs*	*D7 or discharge*	*D30*	*90 +/- 15 Days*	*M12 +-30 appel tel*
Information	*X*						
Informed consent	*X*						
Verification of inclusion (including brain imaging performed before inclusion) and exclusion criteria	*X*	*X*					
History	*X*						
*Clinical examination, NIHSS**	*X*	*X*	*X*				
CT or MRI/MRA	*X*		*X*				
Pregnancy test (urinary or blood)	*X*						
Tests (ADA.)*	*X*					*X*	
Dispensation of treatments		*X*					
Functional outcome				*X*	*X*	*X*	
Adverse events		*+/-X (consistent with the section on Vigilance)*	*X*	*X*	*X*	*X*	
Vital status phone contact				*X*	*X*	*X***	*X***
(EQ-5D-5L)						*X***	*X***

**When possible and legible, use one line per intervention.*

*X**: phone contact only*

For ADA, 50 patients will have an additional visit for blood sampling

6.11 Distinction between standard care and study

TABLE: "Standard care" vs. "additional interventions" required specifically for the study

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with <u>standard care</u>**	**Interventions, procedures and treatments added for <u>research purposes</u>**
Treatments	Thrombolysis	Glenzocimab + EVT, Placebo of glenzocimab + EVT
Visits	*Day 0, 24 hours, day 7 or discharge,*	*Phone contact 30 days, 3months* at 12 months*
Imaging	*Standard brain imaging (MRI or CT) at 24 hrs*	
Examinations (biological and clinical)	Vital signs (BP, Pulse), ECG Clinical and paraclinical examinations, NIHSS Pregnancy test	*ADA at baseline and 90 days For 50 patients*

	Tests* (biochemistry, haematology, etc.)	

* except patient participating in ADA samples, 3 months visit will be on site

7 ELIGIBILITY CRITERIA

7.1 Inclusion criteria

The target population is patients as follows:

1. Age 18 years or older (Age≥18 years);

2. No significant pre-stroke disability (pre-stroke mRS must be equal to 0 or 1);

3. Indication of EVT within the time window of 0 to 24 hrs in participants, treated with or without intravenous thrombolysis, and with a clinic-radiological mismatch (defined by a NIHSS≥10 and an ASPECT score≥ 6);
4. Occlusion of the cervical or intracranial internal carotid artery (ICA) or the proximal middle cerebral artery (MCA - M1 and/or M2), on magnetic resonance angiography (MRA) or, when this is not possible, on CT angiography (CTA);

5. Informed consent signed:
   - By the patient,
   - Or informed consent signed by a family members/trustworthy person if his condition does not allow him to express his consent by written as per L. 1111-6,
   - In a situation urgently and in the absence of family members/trustworthy person, the patient can be enrolled. The consent to participate to the research will be requested as soon as the condition of the patient will allow him to consent.

6. Post-menopausal women defined as not having menses for 12 months without an alternative medical cause. For WOCBP, a highly effective birth control method should be in place that can achieve a failure rate of less than 1% per year that should last for at least 2 months after IMP administration.

   Birth control methods which may be considered as highly effective in WOCBP include:

   - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (intravaginal, transdermal),

   - progestogen-only hormonal contraception associated with inhibition of ovulation (injectable, implantable)

   - intrauterine device (IUD),

   - intrauterine hormone-releasing system (IUS),

   - bilateral tubal occlusion,

   - vasectomized partner,

Birth control methods which may be considered as highly effective for men and that should last for 4 months after IMP administration include:

- vasectomy,
- use of condom combined with a highly effective birth control method for their WOCB partner.

Please note that hormonal contraception is a risk factor for thromboembolic events and attention should be called to reconsider it passed the acute stroke phase.

7. Women of child-bearing potential (WOCBP) must have a negative serum/urine pregnancy test at baseline. Women of childbearing potential, i.e., fertile, are defined as women following menarche and until becoming post-menopausal unless permanently sterile, i.e., having undergone hysterectomy, bilateral salpingectomy and bilateral oophorectomy Women of childbearing potential, i.e., fertile, are defined as women following menarche and until becoming post-menopausal unless permanently sterile, i.e., having undergone hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

8. Affiliation to social security or any health insurance.

7.2 Non-Inclusion criteria

1. Contraindications to EVT;
2. Contraindication to contrast agent
3. Pre-existing neurologic and psychiatric disease with mRS ≥ 2;
4. Unknown symptom's onset or last seen well >24 hours;
5. Patients under or needing immediate DAPT administration;
6. Significant mass effect with midline shift as confirmed on CT/MRI;
7. Gastrointestinal or urinary tract hemorrhage in previous 21 days;
8. Patient with intracranial haemorrhage
9. Known Platelet count <100 000 mm3;
10. Pregnant or breastfeeding woman;
11. Known hypersensitivity to glenzocimab or to any of the excipients;
12. Known Severe renal insufficiency (Grades 4-5) with a glomerular filtration rate < 30mL/Min/1.73m2;
13. Participation in another interventional clinical trial within 30 days prior to the inclusion;
14. Persons deprived of their liberty by a judicial or administrative decision, persons subject to psychiatric care under sections L.3212-1 et L.3213-1 .and persons admitted to a health or social institution for purposes other than research (L.1121-6)
15. Adults subject to a legal protection measure (L.1121-8).

16. Patients receiving anticoagulants (i.e. heparin within 48 hours and an elevated aPTT - greater than upper limit of normal for laboratory-; (current use of oral anticoagulants (ex: warfarin) and INR >1.7; Current use of direct thrombin inhibitors or direct factor Xa inhibitors), as already mentioned in the non-authorized concomitant treatments
17. The patient or his/her family (if the patient is unable to give his/her opinion) expresses an inability to return for protocol visits
18. patients who have already received another humanized fragment of monoclonal antibody with a suspicion of hypersensitivity

7.3 Exclusion criteria

1. Withdrawal of consent
2. Patient's wish to withdraw from the trial
3. Persons deprived of their liberty by a judicial or administrative decision, persons subject to psychiatric care under sections .and persons admitted to a health or social institution for purposes other than research (L.1121-6)

7.4 Recruitment procedure

This is a national, multicenter, study, Patients are enrolled by investigators in one of the 11 stroke units selected among the following hospitals:

	Number of participants
Total number of participants to be included	*260*
Number of centres	*13*
Enrolment period (months)	*32*
Number of participants/centre	*40*
Number of participants/centre/month	***0.8***

7.5 Termination rules

7.5.1 Criteria and procedures for prematurely terminating the study treatment

Several situations are possible

- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form (CRF)
- Premature discontinuation of treatment, but the participant remains enrolled in the study until the end of their participation
- Premature discontinuation of treatment and withdrawal from the study

The investigator must:

- Document the reason(s)
- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

In case of serious adverse events, the investigator must notify the sponsor and follow up the participant for 24 h following the premature discontinuation of treatment. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse event will be monitored until it is resolved. If a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

7.5.2 Criteria and procedure for premature withdrawal of a participant from the study

- Patients may exit the study at any time and for any reason.
- If, during the course of his/her participation in the study, the participant presents one of the following exclusion criteria, then the study product/procedure must be discontinued but the participant will continue to be monitored for the study (cf. exclusion criteria).
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

- If a participant exits the study prematurely, and if the participant agrees, state the procedure and schedule for collecting the data required by the protocol (primary endpoint, secondary endpoints, safety assessment) (NB: this must be stated in the information and consent form)
- State how premature exit from the study will affect the participant's ongoing care (state exactly what the participant will be offered).
- In case of serious adverse events, see the corresponding section on vigilance

The case report form must list the various reasons why the participant has discontinued the study:

☐ Lack of efficacy

- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

7.5.3 Follow-up of participants following premature withdrawal from the study

If a participant discontinues the study, this will in no way affect their usual care for their condition.
In the event of serious adverse events following premature discontinuation of treatment and participation of the patient in the study; see section 6.4.1
Patients unreachable after 3 attempts are considered lost of follow-up.

7.5.4 Procedures for replacing participants

In case of prematurely discontinuation, patient will be replaced if the study is still in the inclusion period.

7.5.5 Full or partial discontinuation of the study

It is necessary to differentiate between the following 3 decisions:

- Early and temporary discontinuation of the study with inclusions suspended
- Early definitive discontinuation of one arm of the study
- Early definitive discontinuation of the entire study

For each of these 3 decisions, it is necessary to differentiate between 2 possible treatment situations:

- Premature and immediate discontinuation of treatment in all participants, as soon as the decision is taken.
- Participants are permitted to complete their treatment.

AP-HP as sponsor or the Competent Authority can prematurely discontinue all or part of the study, temporarily or permanently, further to the recommendations of the Data Safety Monitoring Board in the following situations:

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the two treatment arms, requiring a reassessment of the benefit-risk ratio for the study.
- if the interim analysis confirms the efficacy of one of the treatment arm.
- if the interim analysis shows the futility of the trial

Similarly, AP-HP, as the sponsor, or the Competent Authority may decide to prematurely discontinue the study due to unforeseen issues or new information about the product, in light of which the objectives of the study or clinical program are unlikely to be achieved.

The AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority and to the Ethics Committee within a period of 15 days, along with recommendations from the Data Safety Monitoring Board in the case of substantial modification.

In all cases in which the study is discontinued, the participants included in the study must be monitored until the end of their participation, as set forth in the protocol.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority and to the Ethics Committee within a period of 15 days, along with recommendations from the Data Safety Monitoring Board in the case of substantial modification.

8 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

8.1 Description of the investigational medicinal products

8.1.1 Investigational medicinal product 1: glenzocimab

8.1.1.1 Description

The active substance, glenzocimab (also called ACT-017, Acticor Biotech), is a humanized fragment of monoclonal antibody (Fab) directed against the hGPVI, which is involved in the platelet aggregation.
Glenzocimab is being developed as an effective antiplatelet agent with minimal bleeding risk for the treatment of the acute phase of ischemic stroke documented by imaging technique as an add-on treatment to alteplase and EVT or EVT alone for patients who are not eligible for alteplase.

Glenzocimab is formulated for IV administration as a sterile product with 20 mM sodium citrate and 130 mM sodium chloride buffer at pH of 5.0. No preservative is used since the vial is designed for single use.

For further details regarding the physico-chemical and pharmaceutical properties and formulation of glenzocimab, please refer to the IB in its last applicable version

8.1.1.2 Presentation

The primary packaging is a type 1 glass vial with an inert bromobutyl rubber stopper and sealed with a plastic flip-off cap.

It is supplied for clinical trial use in vials containing 50 mL of the drug product at a concentration of 10 mg/mL. Each vial contains 500 mg of glenzocimab.

Each vial will be manufactured and labelled, by a pharmaceutical sub-contractor of Acticor Biotech, according to the Good Manufacturing Practices.

8.1.2 Investigational medicinal product 2: Glenzocimab Matching Placebo

8.1.2.1 Description

The matching placebo of glenzocimab is 0.9%NaCl (Acticor Biotech) for IV administration.

8.1.2.2 Presentation

It will be supplied for clinical trial use in vials containing 50 mL of a solution of a 0.9% sodium chloride.

Each vial will be manufactured and labelled, by a pharmaceutical sub-contractor of Acticor Biotech, according to the Good Manufacturing Practices.

8.1.2.3 Presentation

Each vial will be manufactured and labelled, by a pharmaceutical sub-contractor of Acticor Biotech, according to the Good Manufacturing Practices.

8.1.3 Presentation of treatment units

Treatments will be presented in numbered units, labelled for this study, by a pharmaceutical sub-contractor of Acticor Biotech, according to the Good Manufacturing Practices.

Each unit will contain all glenzocimab or placebo necessary for the full treatment for each patient (2 vials).

8.2 Posology / administration

Treatment will be administered as a single dose of 1000 mg (2 vials).

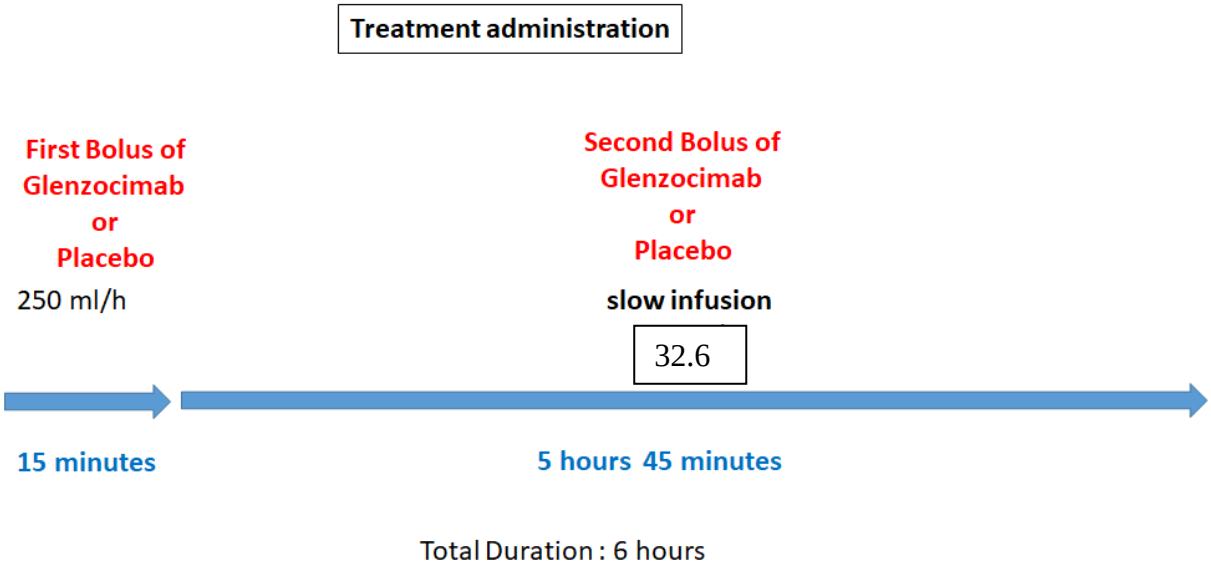
The infusion should be prepared according to the protocol described in the pharmaceutical documents.

For the administration, the infusion pump (supplied by Acticor Biotech) and the infusion kits (labelled by a pharmaceutical sub-contractor of Acticor Biotech) supplied to the centres for specific research needs should be used.

Glenzocimab or its matching placebo is a solution for dilution, and the required amount of glenzocimab or its matching placebo should be diluted in 0.9% Sodium Chloride.

Glenzocimab or the matching placebo is intended to be administered as an IV infusion over 6 hrs, with ¼ of the dose administered in 15 min (bolus with a rate of 250 ml/h) and ¾ of the dose administered in 5 hrs 45 min (slow infusion with a rate of 32.6 ml/h).

In exceptional cases, where thrombocytopenia<100,000/mm3 or severe renal insufficiency (GFR<30 ml/min) are not known to exist (during the biological work-up carried out systematically at the time of initial management, but after the start of administration of the investigational medicinal product), the infusion of the investigational medicinal product will be stopped immediately. Biological assays to assess platelets or renal function will be monitored at 24 hours in order to determine appropriate management.



8.3 Descript of Auxiliary medicinal product(s) (treatments required to conduct the study)

None

8.4 Description of traceability elements accompanying the investigational medicinal product(s)

The supplies of numbered units and infusion kits to investigational sites will be insured by the Clinical Trial Department of AGEPS.

- *Supply*

Numbered units and infusion sets will be sent after the opening visit (after ordering by CRA (Clinical Research Associate)).

- *Re-supply*:

Re-supplies of numbered units will be ordered via the eCRF : units will be automatically sentd to the centers' pharmacies according to their remaining stock.

Re-supplies of infusion kits will be ordered by Hospital Pharmacists according to their remaining stock.

Upon receipt, the Hospital Pharmacist or the appropriate person will inventory the supplies and send the acknowledgement of receipt to the sponsor or its
Representatives and maintain an accurate accounting of them.

Should any abnormality of the supplies be observed, the Hospital Pharmacist or the appropriate person must immediately inform the Sponsor and quarantine the supplies under appropriate storage conditions (2 -8°C for numbered units) until instructions received by sponsor to destroy, keep in quarantine or safe to use(Cf. pharmacy manual).

- *Storage*

Numbered units should be stored under appropriate storage conditions (2 -8°C) in accordance to the information available in the last applicable version of the IB of glenzocimab.

Infusion kits should be stored under appropriate storage conditions (15 -25°C)

- *Dispensing*

Pharmacies will dispense boxes to the care unit on the basis of a patient specific prescription edited by the investigator from the eCRF. The treatment number to dispense is write on the prescription. The traceability for numbered treatment unit will be insure with the peel-off label present on each and affixed on the prescription.

In case of anomaly (broken vial), a new prescription will be edited via the eCRF, and another box may be dispensed.

- Accountability and destruction

These will be organized by the CRA through the study.
After completion of the study, all numbered boxes must be returned to AGEPS for a central destruction.

Immunogenicity Assessments

Potential presence of ADA will be determined at Central Laboratory in all patients enrolled and sampling times for blood collection can be found in the study flow chart (Baseline and Day 90).

At baseline, 50 patients randomized will receive a blood draw to assess the initial ADA level.

At day 90, these 50 patients will receive a blood draw to assess the final ADA level to be compared with the baseline level.

In case patient presents clinical symptoms suggesting the potential presence of ADA, a blood sample may be collected outside of the scheduled visits as unscheduled ADA assessment.

The study site team will be provided with sufficient ADA kits and the detail of the procedure will be described in a detailed central laboratory manual, as well as Sample handling, storage, and shipping conditions.
Specific measures and other blood assays must be necessary in case where an anaphylactic reaction is suspected, including samplings for histamine and tryptase assays at serial time-points.

8.5 Authorised and prohibited treatments (medicinal, additional medicinal, surgical), including rescue medications

8.5.1 Authorized Treatments

Symptomatic treatments routinely used for disease-related symptoms will be allowed to all patients on this trial. Specific treatments for any adverse events will be allowed too.
Details of any treatments or procedures must be recorded in the eCRF.
Heparin at sub-therapeutic doses (≤ 50 IU/kg) can be allowed during EVT procedure to avoid the microthrombi generation within the catheter.

8.5.2 Non-Authorized Treatments

Patients should not receive any other experimental therapies during the first 90 days of study participation.
As a risk for increased bleeding is associated with the use of tPA, in addition to the exclusion criteria (17 of Section 7.2.), it is mandatory that:

- Anticoagulants, whether oral or injectable, will not be authorized during the first 24 hrs post-ACT017 administration;
- Anti-platelet agents whether oral or injectable, will not be authorized during 24 hrs post-beginning of ACT017 and tPA co-administration.

8.6 Methods for monitoring compliance with the treatment

Treatment compliance is defined as the IV administration of the study drug at prescribed doses and volumes.
Prescribed doses and total volume administered will be recorded in the eCRF.

Study drug will be administered only under the direct supervision of a physician familiar with the requirements of the study protocol, therefore compliance should not be an issue.
Nevertheless, the reason for any non-compliance must be recorded in the eCRF.

Treatment must be recorded on the study treatment tracking form provided by the sponsor.
The investigator, or designee, must ensure the input of the correct information on the tracking form.

The tracking forms should be filed in the Investigator site file.
The Monitor will verify the drug tracking forms for completeness and accuracy at each site visit until the end of treatment period of the patients.

At the end of the study, it must be possible to reconcile delivery records with dispensing records and used/unused vials. Any discrepancy must be accounted for.

Used/unused vials of study drug should be kept in a secure place at the site until the tracking forms have been verified by the Monitor.

The Investigator or the Hospital Pharmacist or her/his representative is responsible for the traceability of study drug specifically used during the trial and must retain the documents for 15 years or per local requirements.

9 EFFICACY ASSESSMENT

9.1 Description of efficacy endpoints assessment parameters

Primary Efficacy Endpoint:
The primary efficacy endpoint is the functional outcome assessed by the mRS at day 90.

Secondary Endpoints:

Efficacy:
- Favorable functional outcome defined by a modified Rankin Scale (mRS) score ≤ 2 at day 90.
- Proportion of patients with a severe handicap: mRS 4-6
- Overall Survival at Day-90 and 1 year: Kaplan-Meier curve
- Early reperfusion outcomes:
    - Stroke volume assessed by brain imaging (Ct or MRI) at 24 hrs
    - Reperfusion at the end of EVT procedure assessed by eTICI score
    - early neurological improvement by NIHSS evolution at 24 hrs
- as EQ5D at 90 days and 1 year

9.2 Anticipated methods and timetable for measuring, collecting and analysing the efficacy data

	24 hrs	**D7 or discharge**	**D30**	**D90**	**M12**
The functional outcome assessed by the mRS.		A	A	A	
Favorable functional outcome defined by a modified Rankin Scale (mRS) score ≤ 2		A	A	A	
Proportion of patients with a severe handicap (mRS 4-6)		A	A	A	

Overall Survival		A	A	A	A
• Early reperfusion outcomes: o Stroke volume by brain imaging (CT or MRI) at 24 hrs o Reperfusion at the end of procedure assessed by eTICI score o Early neurological improvement by NIHSS evolution at 24 hrs	A				
EQ-5D-5L				A	A

10 SPECIFIC STUDY COMMITTEES

The possible committees are:

English name	French name	Description
(DSMB)	Comité de surveillance indépendant (CSI)	Dr Céline Guidoux, Pr Christian Denier, Pr Fernando Pico, Dr Silvy Laporte
Steering Committee	Comité de Pilotage JF Albucher, G Boulouis, JM Olivot, C Cognard, C Arquizan, G Turc, B Lapergue, T Cho, M Mazighi Representant of sponsor	Investigators, sponsor, etc.

N.B. Data Safety Monitoring Board (DSMB) is described in the Safety section.

10.1 Steering Committee

Composition: coordinating investigator, one or several other investigators, biostatistician, sponsor representatives appointed for this study.
Role:

- Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the study.

- Propose procedures to be followed during the study, acknowledging any recommendations from the Data Safety Monitoring Board (DSMB)), if applicable. The DRCI sponsor retains decision-making authority.

    - Committee members: JF Albucher, G Boulouis, JM Olivot, C Cognard, C Arquizan, G Turc, B Lapergue, T Cho, M Mazighi

11 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

11.1 Description of Safety endpoints assessment parameters

- Incidence of symptomatic or non-symptomatic at 24 hrs
- Incidence of sICH at 24 hrs
- Incidence of non-symptomatic ICH at 24 hrs
- Incidence, nature and severity of Adverse Events, SAEs, SUSARs, and Treatment-Emergent Adverse Events (TEAEs) at 24 hrs, at D7/discharge, 30 days, 90 days
- Incidence of bleeding-related events at 24 hrs and day 90
- ADA at baseline and 90 days for 50 patients

11.2 Recording and reporting adverse events

11.2.1 Definitions

• According to Article 2 of the Regulation (EU) No 536/2014:**Adverse event**
Any untoward medical occurrence in a subject, to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment

- **Serious adverse event**

Any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.

- **Unexpected serious adverse reaction**

A serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information.

According to Article 53 of the Regulation (EU) No 536/2014:

- **Unexpected event**

An unexpected event which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions as referred to in Article 42. That notification shall be made without undue delay but no later than 15 days from the date the sponsor became aware of this event.

According to Article 54 of the Regulation (EU) No 536/2014:

- **Urgent safety measure**

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects.
The sponsor shall notify the Member States concerned, through the EU portal, of the event and the measures taken.
That notification shall be made without undue delay but no later than seven days from the date the measures have been taken.

11.2.2 The role of the investigator

The investigator must **assess the seriousness of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF).
The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the severity** of the adverse events **and will grade serious adverse events according to the CTCAE classification Severity (NCI CTCAE classification version 5.0)** :

The investigator must **assess the causal relationship** between serious adverse events and the investigational medicinal product(s) or interventions/procedures added by the study.

The investigator used a binary method:

- Realated
- Not related

11.2.2.1 Serious adverse events that require the investigator to notify the sponsor without delay

The investigator notifies the sponsor without undue delay but not later than within 24 hours, on the day the investigator becomes aware of any serious adverse event which occurs during a study that meets the description in article 41 of Regulation (EU) N)536/2014, with the exception of any event which is listed in the protocol and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening to the participant enrolled in the study
3- requires hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

11.2.2.2 Specific features of the protocol

11.2.2.2.1 Other events that require the investigator to notify without delay the sponsor

- Adverse events deemed “medically significant”

- Incidence of sICH at day-90

  Incidence of systemic hemorrhages responsible hemodynamic failure/shock

The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

- ***In utero* exposure**

The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.
If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.

- Exposure **while breastfeeding**

Exposure while breastfeeding occurs if an infant or a child may have been exposed to a medicinal product *via* the breast milk of a mother being treated with an investigational medicinal product.
Even if it is not associated with an adverse event, the investigator must notify the sponsor without delay on the day the investigator becomes aware of the exposure while breastfeeding.

11.2.2.2.2 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are only recorded in the case report. A data retrieval of serious adverse events that do not require the investigator to notify the sponsor without delay will be implemented for serious adverse events every 12 months by Clinical Trial Unit and transmit to Safety Department at expertisecsi.drc@aphp.fr

- Non-symptomatic hemorrhages defined as “hemorrhagic transformation” with a localization in the same brain territory where the ischemic stroke occurred, will not be classified as important medical event excepted SAE leading to life threatning or death outcome. The classification of suspected adverse reactions as per Important Medical Event (IME) list is not justified as this kind of event is a frequent outcome of AIS cerebral infarcts upon reperfusion..
  - *Normal and natural course of the condition*:
    - *planned hospitalisation for monitoring the condition under investigation [no deterioration in the participant’s condition compared to baseline],*
    - *hospitalisation for routine treatment or for monitoring of the condition under investigation, not associated with a deterioration in the participant’s condition,*
    - *emergency hospitalisation at inclusion or prolongation of hospitalisation after inclusion for monitoring the condition under investigation*

worsening of the condition under investigation

- *Special circumstances*

- *Hospitalisation for a pre-existing illness or condition*
- *Hospitalisation for a medical or surgical treatment scheduled prior to the study*
- *Admission for social or administrative reasons*
- Diagnosis of severe pathology (i.e., cancer) jeopardizing the correct following of the study procedures.

- *Adverse events potentially related to treatments prescribed as part of the care provided during the study follow-up*

The investigator must report these adverse events to the relevant regional pharmacovigilance centre, Centre Régional de Pharmacovigilance (CRPV).

11.2.2.3 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:

- from the date on which the participant /begins treatment with the investigational medicinal product (Glenzocimab/placebo) and/or undergoes the first intervention specific to the study (EVT).
- throughout the whole follow-up period required for the trial
- until 4 weeks or more after the end of the participant's treatment with the investigational medicinal product.
- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities)

11.2.2.4 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be non-identifying. In addition, the documents must include the following: study acronym, number and participant’s initials.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

For studies which use e-CRFs

- the investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Safety Department can be contacted via email: vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the Notification and Follow-up form for a pregnancy occurring during participation in a study".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.
If it was the father who was exposed, the investigator must obtain the pregnant woman's permission before collecting information about the pregnancy.

11.2.3 Role of the sponsor

The sponsor, represented by its Safety Department, shall continuously, throughout the trial, assess the safety of each investigational medicinal product throughout the study.

11.2.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all the adverse events reported
- the **causal relationship** between these events and each investigational medicinal product and/or specific interventions/procedures added by the study and any other treatments,
  All serious adverse events which the investigator and/or the sponsor reasonably believe may have a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expected or unexpected nature** of the serious adverse reactions
  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected.

The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below.

❖ For serious adverse events likely to be related to the investigational medicinal products:
- refer to the SmPC of NaCl for placebo (section 4.8 “undesirable effects”) enclosed in CTIS platform and in the investigator study file
- refer to the Investigator's Brochure of glenzocimab (section safety) enclosed in CTIS platform and in the investigator study file

❖ For The serious adverse events potentially related to the added EVT that contains femoral arterial puncture ans medication anesthesics:

Expected adverse events related to EVT procedure are :
• Thromboembolic event, bleeding and infection.
• haemorrhage (hematoma at the arterial puncture site, retroperitoneal haemorrhage);
• lower limb ischemia
• infection at the puncture site.
• nausea, vomiting
• aspiration pneumonia
• kidney failure
• low blood pressure
• arrhythmia
• anaphylactic shock

All these adverse events will be considered as expected with ≤grade 3 (CTCAE)

Expected adverse events related to study procedures are : None other procedures added by the study

-

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), via Eudravigilance within the regulatory time frame, to the competent authority:
- In the case of fatal or life-threatening suspected unexpected serious adverse reaction, , as soon as possible and in any event not later than seven days after the sponsor became awre of the reaction;
- in the case of non-fatal or non-life-threatening suspected unexpected serious adverse reactions, not later than 15 days after the sponsor became aware of the reaction;
- in the case of a suspected unexpected serious adverse reaction which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening
- in the uncompleted case of fatal or life-threatening suspected unexpected serious adverse reactions, all additional information to complete this case have to be reported as soon as possible and in any event not later than eight days after the initial report
-
- All additional, relevant information must be declared by the sponsor in the form of follow-up reports within a period of 15 calendar days starting from when the sponsor had this information.

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the research participants.

Specific case of double-blind trials
After unblinding by the sponsor and if the patient is receiving the product under investigation: the case will be reported without delay as a suspected unexpected serious adverse reaction. If the patient is receiving the comparator product: the sponsor will reassess the unexpected nature of the adverse reaction based on the reference document for the comparator product identified in the protocol.
In exceptional situations, if the study involves a condition with a high mortality and/or morbidity rate, and if the Competent authority grants permission at the request of the sponsor as part of the clinical trial authorisation application, the methods for unblinding and for reporting suspected unexpected serious adverse reactions can be modified. These methods will then be defined thoroughly in the study protocol.

11.2.3.2 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials.

The sponsor will inform will report in CTIS platform without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

11.2.3.3 Annual safety report

Once a year for the duration of the clinical study, the sponsor must produce an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- a safety analysis for the research participants,
- a description of the patients included in the study (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- summary tables of all the serious adverse events that have occurred since the start of the study,

The sponsor produce one annual safety report (Development Safety Update Report - DSUR) for one clinical trial.

The report must be submitted in CTIS no later than 60 days after the anniversary of the date on which the competent authority authorised the trial.
The final annual safety report must be submitted in CTIS no later than 60 days after the end date of the clinical trial.
The end date of the clinical trial is defined as the date of the last visit of the last subject

11.2.4 Data Safety Monitoring Board (DSMB)

A DSMB will be established for this trial. The DSMB must hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the competent authority and the Ethics Committee. Its primary mission is to monitor safety data.
The DSMB will receive periodic reports of clinical study entry and accrual, adverse events and any other relevant data from the Promoter team. In addition, suspected unexpected serious adverse events (SUSARs), symptomatic and asymptomatic ICHs and bleeding-related events, number of deaths will be reported to the DSMB in a timely manner for consideration for their effect on study continuation. The DSMB will provide independent, competent, and timely review of the data quality and of safety of the clinical study.
DSMB will meet at least every 3 months during the first year, then at least every 6 months. For each DSMB meeting, safety data will be analysed and provided. Bleeding event within 24 hrs, within 7 days will be fully described globally and by groups as well as all Serious Adverse Events (SAE). Any imbalance between the occurrence of intracranial hemorrhages will be reported and tested between groups.
DSMB will be in charge of evaluating interim analysis and futility.

A DSMB will be established for this trial.

All missions as well as the specific operating procedures of the DSMB will be precised in the study's DSMB charter.

It will also monitor efficacy data for interim analyses. All other missions as well as the specific operating procedures of the DSMB are described in the study's DSMB charter.

The DSMB members are:
- Dr Céline Guidoux, Neurologie, CHU Bichat,Paris
- Pr Christian Denier, Neurologie, CHU Bicêtre, Le Kremlin Bicetre
- Pr Fernando Pico, Neurologie, CH Versailles
- Dr Silvy Laporte, Epidemio, Hôpital de Bellevue CHU Saint Etienne

The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.
The safety endpoints, with a special focus on symptomatic ICHs and mortality, will be evaluated by the DSMB members during some pre-defined and ad-hoc meetings.

12 DATA MANAGEMENT

12.1 Right to access data and source documents

12.1.1 Data access

In accordance with GCPs and appendix 1 of the European Regulation N°536-2014:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority

- the Sponsor declares that investigators and participating institution will ensure the persons in charge of monitoring, quality control and auditing or inspecting the clinical trial have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force

12.1.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

12.1.3 Data confidentiality

The persons responsible for the quality control of clinical studies will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy.
During and after the clinical trial, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown.
Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

12.2 Data processing and storage of research documents and data

12.2.1 Identification of the data processing manager and location(s)

The database will be handled by, and only by, Prof. Sylvie Chevret, who will be responsible for data storage, the statistical analysis, and the tables and figures for the study report. She will be in close contact with the Data Safety and Monitoring Board and with the statistical editors of the journal to which the study report will be submitted for publication

12.2.2 Data entry

Non-identifying data will be entered electronically via a web browser.

12.3 Data ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

13 STATISTICAL ASPECTS

13.1 Description of statistical methods to be used including the timetable for the planned interim analyses

The following analysis sets will be considered:

- **Intent-to-treat set:** Includes all randomized subjects in their randomized arm. This will refer to the primary analyses
- **Per protocol set:** Includes all subjects from the intent-to-treat set without any major violations which could affect the evaluation of the primary efficacy endpoint. Moreover, patients will be considered in the treatment group corresponding to the treatment actually received. This will be used as secondary analyses

Safety set: Includes all subjects who take any amount of the study drug.

As a general strategy, continuous efficacy and safety endpoints will be summarized using summary measures (median and interquartile range). Frequency distributions (counts and percentages) will be used to summarize categorical endpoints. Similarly, characteristics of patients will be presented using summary measures (median and interquartile range for quantitative characteristics and counts and percentages for categorical characteristics)

Analyses by treatment group will be presented according to the treatment to which subjects were randomized

Disposition of the Study Subjects
The disposition of subjects will be described with summaries by treatment group of the number of subjects enrolled, the number of subjects treated, and the number of subjects for whom study drug was permanently discontinued (including the reasons for discontinuation).

Demographic and Baseline Characteristics
Demographic and baseline characteristics will be summarized by treatment group.

Exposure to Study Treatment and Compliance
Frequency distributions of the number of received doses will be presented by treatment group. Treatment duration and treatment compliance for all randomized subjects will be described by treatment group.

Analysis of Primary Efficacy Endpoint
An interim analysis will be performed when 30% of the patient enrolment will be achieved (78 patients). This analysis will be performed following the rules of the others planned interim analyses (See sample size calculation)

Analysis of the primary endpoints (mRS) will be performed using a logistic model without any adjustment outside of the treatment arm (Odds proportional model). Treatment effect will be assess by estimating Odds Ratio (OR) with its 95% Confidence Interval (CI). OR will be tested using a Wald test with a alpha risks corresponding to an O'Brien and Fleming scheme for a global risk of 0.05 and a bilateral formulation (See sample size calculation). The first interim analysis will be considered as statistically significant if the p value is below to 0.0054. The final analysis will be considered as statistically significant if the p value is below 0.0492. Interim analysis will also allowed a stop for futility. Futility bound has been calculated using O'Brien

& Fleming type beta spending. If the statistic of the Wald test value associated with the OR is below -0.523 in favour of the placebo group, the trial will be stop for futility.

Sub group analyses
Subgroup analyses of the primary endpoints will be run within each group used for stratification of the randomization:

- Age : age < 80 and age ≥ 80 years old). Analyses will be run similarly to the main primary analysis. Qualitative interaction as well as quantitative interaction will be assesses using Gail and Simon tests.
- IVT : IVT yes and IVT no. Analyses will be run similarly to the main primary analysis. Qualitative interaction as well as quantitative interaction will be assesses using Gail and Simon tests.
- Time-to-treatment 0-6 hrs vs 6-24 hrs. Analyses will be run similarly to the main primary analysis. Qualitative interaction as well as quantitative interaction will be assesses using Gail and Simon tests.

Analyses of secondary Endpoints

- Rates of favourable functional outcome defined by a mRS score ≤ 2 at day 90 will be estimated within each arm with their 95% CI and compared between arms using fisher exact test.
- Overall Survival at Day-90 and at 1 year will be estimated within each arm by Kaplan Meier estimator and compared between arms using logrank test
- Early reperfusion outcomes:
    - Reperfusion at the end of procedure assessed by eTICI score will be estimated within each arm and compared between arms using Wilcoxon test
    - early neurological improvement by NIHSS evolution will be estimated within each arm and compared between arms using Wilcoxon test
- Quality of life at D90 and 1 year, estimated with the EQ5D5L score will be compared between arms using Wilcoxon test

Safety:

- Incidence of symptomatic or non-symptomatic ICH at 24 hrs, at day 7 or discharge, day 30, and day-90 will be estimated within each arm by Gray estimator and compared between arms using Gray test. Other events such as death without ICH will be considered as a competing event.
- Incidence of symptomatic ICH at 24 hrs, at day 7 or discharge, day 30, and day-90 will be estimated within each arm by Gray estimator and compared between arms using Gray test. Other events such as death without ICH will be considered as a competing event.
- Incidence of non-symptomatic ICH within 24 hrs, at day 7 or discharge, day 30, and day-90 will be estimated within each arm by Gray estimator and compared between

arms using Gray test. Other events such as death without ICH will be considered as a competing event.

- Incidence of Adverse Events within the first 24 hrs, at day 7 or discharge, day 30, and day-90 will be estimated within each arm and compared between arms using fisher exact test.
- Incidence of SUSARs within the first 24 hrs, at day 7 or discharge, day 30, and day-90 will be estimated within each arm and compared between arms using fisher exact test.
- Incidence of Bleeding-Related Events (BREs) at 24 hrs, and day-90 will be estimated within each arm and compared between arms using fisher exact test.
- Incidence of Treatment-Emergent Adverse Events (TEAEs) at 24 hrs, at day 7 or discharge, day 30, and day-90 will be estimated within each arm and compared between arms using fisher exact test.
- Nature and severity of Adverse Events, SAEs, SUSARs, BREs and Treatment-Emergent Adverse Events (TEAEs) will be described within each arm
- Incidence of bleeding-related events at 24 hrs, at day 7 or discharge, day 30, and day 90 will be estimated within each arm by Gray estimator and compared between arms using Gray test. Other events such as death without bleeding-related event will be considered as a competing event.
- Anti-glenzocimab antibodies (ADA) at baseline (pre-dose) and 3 months in 50 patients

The same efficacy endpoints will be analyzed during the interim analysis to be performed after having reached 30% (78 patients) of the global recruitment.
This analysis will be conducted with an O'Brien and Fleming scheme, the sample size has been increased to 260. The interim analysis will be considered as statistically significant if the p value is below to 0.0054. The final analysis will be considered as statistically significant if the p value is below 0.0492. Interim analysis will also allowed a stop for futility. Futility bound has been calculated using O'Brien & Fleming type beta spending. After inclusion of 78 patients, if the statistic of the Wald test value associated with the OR is below -0.523 in favour of the placebo group, the trial will be terminated for futility.

The safety endpoints, with a special focus on symptomatic ICHs and mortality, will be evaluated by the DSMB members during some pre-defined and ad-hoc meetings.

Cost-effectiveness analyses:

The efficiency of the glenzocimab in addition to EVT compared to EVT plus placebo will be assessed through cost-utility and cost-effectiveness analyses, as recommended by the French National Authority for Health. Incremental cost-effectiveness ratios (ICER) will be estimated for the two health economic endpoints,

expressed in i) cost per QALY gained and ii) Cost per patient with a mRS score ≤ 2 gained with the use of glenzocimab in addition to EVT

The analysis will be performed from a National Health Insurance point of view and with a time horizon corresponding to the study period: 12 months. Costs and consequences will then not be discounted, as recommended, since discounting is required only for several years long studies. QALY will be calculated using the answers to the EQ-5D-5L questionnaire, transformed into utilities (Van Hout B, Janssen MF, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 2012; 15:708–15). The EQ-5D-5L has been validated in French (Luo N, Li M, Chevalier J, Lloyd A, Herdman M. A comparison of the scaling properties of the English, Spanish, French, and Chinese EQ-5D descriptive systems. Qual Life Res 2013; 22:2237–43.), Life years will be measured with survival data.

Costs will be gathered from the study database and from the hospital Diagnosis Related Group information system (PMSI), The following resource items will be collected:
1. Direct health care costs : glenzocimab infusion, hospitalization, re-hospitalization (in-hospital data collected from the PMSI) , extra costs during hospitalisation du to : Intensive care units hospitalisation, extra costing medication, glenzocimab complications treatments. Will also be collected drug prescriptions at discharge, 90 days and 1 year of follow up

Each glenzocimab injection will be valued with its unit cost. For hospital costs, stays, extra in-hospital costs, they will be valued on the basis of the Social Health Insurance. Drugs prescription at discharge and follow up will be valued from market prices.

Costs will be expressed in euros. In each set of analysis, mean costs will be calculated for both strategies. ICER will be positioned within the cost-effectiveness plane. Statistical uncertainty will be taken into account using the non-parametric bootstrap method to construct a 95% CI and a confidence cloud. Sensitivity analysis will be performed for the costs and health care resources that seem non-robust. A peculiar attention will be provided for a sensitivity analysis around the Glenzocimab injection costs, as well as for the QALY estimation.

13.2 Calculation hypotheses for the number of participants required and the result

An interim analysis will be performed when 30% of the patient enrolment will be achieved (78 patients).

In the control group, we considered that the distribution of the mRS is "0":0.10, "1":0.17, "2":0.19, "3":0.17, "4":0.16, "5":0.06, "6":0.15. We calculated that a sample of 258 patients would yield a power of 80% to detect a treatment effect associated with an OR of 1.85 considering a two-sided p-value of 0.05 and using a using a Wald test. As we planned an interim analysis at 78 patients with an O'Brien and Fleming scheme, we increased the sample size to 260. The first interim analysis will be considered as statistically significant if the p value is below to 0.0054. The final analysis will be considered as statistically significant if the p value is below 0.0492. Interim analysis will also allowed a stop for futility. Futility bound has been calculated using O'Brien & Fleming type beta spending. After inclusion of 78 patients, if the statistic of the Wald test value associated with the OR is below -0.523 in favour of the placebo group, the trial will be stop for futility.

13.3 Safety stopping rules

The only serious safety concern identified is symptomatic IntraCranial Hemorrhages (ICH). The expected number of symptomatic IntraCranial Hemorrhages (ICH) is low as we expect an incidence of 4%. However, a stopping rule for excess ICH in the active treatment arm of the study will be followed.

For this investigation, the stopping rules are based upon the 4% rate of ICH observed in randomized controlled trials[9]. Thus we will consider the expected rate of ICH for patients treated with Glenzocimab to be 4%. If the rate is significantly greater than 4%, the treatment arm of the GREEN Study will be put on voluntary hold pending DSMB review.

Using the binomial observed event rate, the associated lower 95% confidence interval was calculated for the observed event, as we were only interested in looking at that part of the distribution. The decision is based on when the assumed true event rate, 4%, falls below the lower 95% confidence interval for the observed rate which is dependent upon the number of subjects accrued. All ICHs will be monitored every 50 patients, by an unblinded study biostatistician.

In summary, the treatment arm of the study is placed on voluntary hold if there are :
4 symptomatic ICHs or more within the first 25 subjects treated with Glenzocimab
6 symptomatic ICHs within the first 50 subjects treated with Glenzocimab
8 symptomatic ICHs within the first 75 subjects treated with Glenzocimab
9 symptomatic ICHs within the first 100 subjects treated with Glenzocimab

13.4 Method for taking into account missing, unused or invalid data

In case of missing data, complete case analyses will be performed. Moreover sensitivity analyses will be performed after multiple imputation.

14 QUALITY CONTROL AND ASSURANCE

Every clinical trial sponsored by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored clinical trial

14.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centres.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits.
The purpose of monitoring the study, as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

14.1.1 Strategy for centre opening

The strategy for opening the centres established for this study is determined using the appropriate monitoring plan. It will be performed by the CRA from the URC-DRCI from Saint Louis hospital.

14.1.2 Scope of centre monitoring

In the case of this risk study **which is considered level C risk,** the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Thus, the sponsor and the coordinating investigator have agreed on the logistic score and impact, resulting in a research monitoring level to be implemented: level « intermediary ».

14.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent.
- compliance with the study protocol and with the procedures defined therein.
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.).
- management of the treatments used.

14.3 Case report forms

The case report forms should only contain the data needed to analyse the study and publish the results. All other data needed to monitor the participants during and outside of the study are recorded in the medical file.

Electronic CRF:
All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
The investigator must archive a copy of the authenticated document that was issued to the sponsor.

14.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsor's procedures.

The sponsor shall notify the Member States concerned about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

14.5 Audits/inspections

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.
An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

14.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (*Répertoire Partagé des Professionnels de Santé*, Collective Database of Health Professionals for France). The CV must include any previous involvement in clinical research and related training.
Any conditions, such as economic interests and institutional affiliations that might influence the impartiality of the investigators shall be presented.
Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki. Each investigator will give the sponsor's representative a GCP certificate dated fewer than three years ago.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

Suitability of the facilities
Before starting the study, each clinical trial sites will give the sponsor's representative a duly justified written statement on the suitability adapted to the nature and use of the investigational medicinal product and including a description of the suitability of facilities, equipment, human resources and description of expertise.

15 ETHICAL AND LEGAL CONSIDERATIONS

15.1 Methods for informing research participants and obtaining their consent

According to article 29 of European regulation N°536/2014, No clinical trials on medicinal products for human use can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in article 29.2 of the European Regulation.

- **Who is informed**? The participant, or if applicable: family members/trustworthy person
- **Who is providing consent**? The participant, or if applicable: family members/trustworthy person
- **When**? Before the person is enrolled in the study
- **How**? Information note given to the participant and oral explanation emergency situation, or if applicable: family members/trustworthy person
- **Who informs and obtains the consent**? The principal investigator or a physician representing the investigator before the person is enrolled in the study.

When the patient was enrolled in emergency situation and he stay not able to give his consent, family members/trustworthy person must sign pursuit consent as soon as possible after inclusion. In both cases, consent of the patient will be sought by the investigator as soon as the

patient will be able to consent. In case af death of patient enrolled in emergency context, Non opposition of his/her relatives to use data must be collected

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study

The person will be granted a reflection period between the time when the subject receives the information and the time when he or she signs the consent form at inclusion visit
In addition, the investigator will specify in the research participant's medical file the methods used for obtaining their consent [or the consent of any other person, in the cases described in Articles L.1122-1-1 to L.1122-2 CSP] as well as the methods used for providing information with a view to obtaining consent.
A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.
At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent *or consent from any other person in the cases set forth by article European regulation N°536/2014 (art. 29 and following)* as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

The investigator will retain one copy of the signed and dated consent form.
Special circumstances: If the person is unable to give his or her written consent, consent may be witnessed, in descending order of priority, from a trustworthy person, a family member or a close relative. These persons must be fully independent of the investigator and of the sponsor

Since this trial is performed in an emergency setting and may concern adult incapable of giving consent:

According to Article L.1122-1-2 of the Code de la Santé Publique (French Public Health Code) , If the person is unable to give his or her written consent, consent may be obtained, in descending order of priority, from a legal representative, family members or trustworthy person. These persons must have no connection whatsoever to the investigator or the sponsor

When the patient was enrolled in emergency situation, consent of family members or trustworthy person will be sign before inclusion. If a legal representative is not present, the deferred consent must be sign as soon as possible after inclusion.

In both cases, consent of the patient will be sought by the investigator as soon as the patient will be able to consent.

15.2 Prohibition from participating in another clinical study or exclusion period set after the study,

Patients should not receive any other experimental therapies during the first 12 months of study participation. The participant may not enrol in another interventional study for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.
There is no exclusion period of participation after the participant has finished this study.

15.3 Legal obligations

15.3.1 Role of the sponsor

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Direction of Clinical Research and Innovation) carries out the study's missions in accordance with regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and all national Laws. Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

15.3.2 Request for approval from the Research Committee

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants concerning a medicinal product for human use, approval from the appropriateResearch Ethics Committee, within the scope of its authority and in accordance with in force legislation and regulatory requirements.

15.3.3 Request for authorisation

Prior to starting the study, AP-HP, as sponsor, must obtain authorisation from the Competent Authority and the Research Committee for this clinical trial on a medicinal product for human use, within the scope of its authority and in accordance with in force legislation and regulatory requirements.

15.3.4 Start of the Clinical Trial

The sponsor shall notify each Member State concerned of the start of a clinical trial and the start of the recruitment through the EU portal. That notification shall be made within 15 days from the start of the clinical trial.

15.3.5 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

- Request for authorisation by the CNIL (French Data Protection Agency)

This research is not governed by the CNIL “Reference Method” (MR-001) because

As the processing of personal data for this study is not governed by the MR 001 Reference Method, the sponsor must obtain approval from the CNIL,
-because of emergency situation enrolment in accordance with Article L.1122-1-2 can be carried out in the case where the patient could not consent and family members/trustworthy person is not be present.
-because of centralization of personal identification of patients is necessary to perform the evaluation at 30-day and 90-day and 1 year by certified research nurse (name, first name, phone number of the patients will be collected for the follow up at 30days and 90 days and 1year)

The sponsor must obtain the authorisation of the CNIL (French Data Protection Agency) before implementing any data processing involving the data required to conduct the research.

15.3.6 Amendments to the clinical trial

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, approval from Ethics Committee and authorisation from the competent authority within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

15.3.7 End of the Clinical Trial

The end of the Clinical Trial corresponds to the end of the participation of the last person who participate to the Clinical Investigation [to be defined otherwise if this is not the case].
The end of the recruitment of subjects for the clinical trial and the end of the clinical trial should be notified in CTIS. That notification shall be made within 15 days from the end of the clinical trial in relation to that Member State.

15.3.8 Summary of the results of the clinical trial

According to article 37.4 of the European regulation n°536/2014, irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the CTIS a summary of the results of the clinical trial. This summary shall be accompanied by a summary written in a manner that is understandable to lay persons.

15.3.9 Archiving

Specific documents for a clinical trial on medicinal product for human use will be archived by the investigator and the sponsor for 25 years after the end of the research.
This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;

- A sealed envelope for the sponsor, containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list) :
  - the successive versions of the protocol (identified by the version number and its date), and any appendices
  - the competent authority authorisations and Research Ethics Committee decisions
  - any correspondence
  - the enrolment list or register
  - the appendices specific to the research
  - final study report
- The data collection documents

16 FUNDING AND INSURANCE

16.1 Funding sources

RHU 2018 BOOSTER-ANR

16.2 Insurance

Pursuant to Article L.1121-10 of the Code de la Santé Publique (French Public Health Code), insurance policies must guarantee the civil liability of the sponsor and that of any contributor and cover pecuniary consequences of damages arising from the study involving human participants.

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article 76(1) of regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and Article L.1121-10 of the Code de la Santé Publique (French Public Health Code).

17 PUBLICATION RULES

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant

- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
- The AP-HP institution must feature under the acronym "AP-HP" first in the address, specifically followed by: AP-HP, hospital, department, city, postcode, France

17.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

17.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

- The sponsor is Assistance Publique – Hôpitaux de Paris (Direction de la Recherche Clinique et de l'Innovation)"

17.3 Mention of the financial backer in the acknowledgements of the text

The study was funded by a grant from RHU 2018 BOOSTER-ANR

This study is registered on the website http://clinicaltrials.gov NTC05559398.

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List of addenda

18.1. Investigator's Brochure of glenzocimab

Specify here that the SmPC must have been obtained from the EMA website (http://www.ema.europa.eu/ema/), if absent from this site, the SmPC must have been obtained from the ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php) and if absent from the ANSM website, use the SmPC from the Vidal compendium.

Questionnaire EQ-5D-5L

Questionnaire sur la santé

Version française pour la France

(French version for France)

Pour chaque rubrique, veuillez cocher UNE case, celle qui décrit le mieux votre santé AUJOURD'HUI.

MOBILITÉ

Je n'ai aucun problème pour me déplacer à pied ❑

J'ai des problèmes légers pour me déplacer à pied ❑

J'ai des problèmes modérés pour me déplacer à pied ❑

J'ai des problèmes sévères pour me déplacer à pied ❑

Je suis incapable de me déplacer à pied ❑

AUTONOMIE DE LA PERSONNE

Je n'ai aucun problème pour me laver ou m'habiller tout(e) seul(e) ❑

J'ai des problèmes légers pour me laver ou m'habiller tout(e) seul(e) ❑

J'ai des problèmes modérés pour me laver ou m'habiller tout(e) seul(e) ❑

J'ai des problèmes sévères pour me laver ou m'habiller tout(e) seul(e) ❑

Je suis incapable de me laver ou de m'habiller tout(e) seul(e) ❑

ACTIVITES COURANTES *(exemples: travail, études, travaux domestiques, activités familiales ou loisirs)*

Je n'ai aucun problème pour accomplir mes activités courantes ❑

J'ai des problèmes légers pour accomplir mes activités courantes ❑

J'ai des problèmes modérés pour accomplir mes activités courantes ❑

J'ai des problèmes sévères pour accomplir mes activités courantes ❑

Je suis incapable d'accomplir mes activités courantes ❑

DOULEURS / GÊNE

Je n'ai ni douleur ni gêne ❑

J'ai des douleurs ou une gêne légère(s) ❑

J'ai des douleurs ou une gêne modérée(s) ❑

J'ai des douleurs ou une gêne sévère(s) ❑

J'ai des douleurs ou une gêne extrême(s) ❑

ANXIÉTÉ / DÉPRESSION

Je ne suis ni anxieux(se), ni déprimé(e) ❑

Je suis légèrement anxieux(se) ou déprimé(e) ❑

Je suis modérément anxieux(se) ou déprimé(e) ❑

Je suis sévèrement anxieux(se) ou déprimé(e) ❑

Je suis extrêmement anxieux(se) ou déprimé(e) ❑

- Nous aimerions savoir dans quelle mesure votre santé est bonne ou mauvaise AUJOURD'HUI.
- Cette échelle est numérotée de 0 à 100.
- 100 correspond à la <u>meilleure</u> santé que vous puissiez imaginer. 0 correspond à la <u>pire</u> santé que vous puissiez imaginer.
- Veuillez faire une croix (X) sur l'échelle afin d'indiquer votre état de santé AUJOURD'HUI.
- Maintenant, veuillez noter dans la case ci-dessous le chiffre que vous avez coché sur l'échelle.

VOTRE SANTÉ AUJOURD'HUI = ☐