| | Clinical Trial<br>Summary Attachment<br>(based on RRF) | SA |
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| 1 | **Sponsor:** CHU de Bordeaux | |
| 2 | **Naming of the experimental drug(s):**<br>- Brilique 90mg<br>- Plavix 300mg and 75mg<br>- Kardegic 75mg | |
| 3 | **Naming of the experimental active(s) substance(s):**<br>- Ticagrelor 90mg<br>- Clopidogrel 300mg and 75 mg<br>- Acétylsalicylate de D-Lysine 75 mg | |
| 4<br>4.1<br><br><br><br><br>4.2<br>4.3 | **Study identification**<br>**Official Title:**<br>Evaluation du profil de sécurité du TICagrelor utilisé seul en comparaison avec une association acétylsalicylate de lysine-clopidogrel dans le contexte de l'implantation de valve aortique percutanée (TAVI).<br>Safety Profile Evaluation of TICagrelor Alone Compared to a Combination of Lysine Acetylsalicylate-Clopidogrel in the Context of Transcatheter Aortic Valve Implantation<br><br>**Acronym:** TICTAVI<br>**Unique Protocol ID:** CHUBX 2014/24 | |
| 5.1<br>5.2 | **ID EudraCT:** 2015-004144-20<br>**ID NCT :** NCT02817789 | |
| 6 | **Investigator(s):** Dr Lionel Leroux (coordonnating investigator)<br>And : Eric VANBELLE, Pr ; Jean-Philippe COLLET, Pr ; Thomas CUISSET, Pr ; Guillaume CAYLA, Pr. | |
| 7 | **Location(s):**<br>CHU de Bordeaux : Dr Lionel Leroux<br>CHRU de Lille: Eric VANBELLE, Pr<br>APHP : Jean-Philippe COLLET, Pr<br>APHM : Thomas CUISSET, Pr<br>CHRU de Nîmes : Guillaume CAYLA, Pr | |
| 8 | **Paediatric regulatory details if necessary: ☐yes / ☒no** | |
| 9<br><br><br><br><br><br>9.1 | **Trial status / Results Analysis stage:**<br>☒prematurely ended - Terminated<br>☐withdrawn<br>☐no subjects recruited<br>☒only partial results are available<br>☐trial transitioned to CTIS and its results will be posted there<br><br>**Detailed reason:**<br>- End of the financial support by Astra Zeneca<br>- Target number of inclusion not reached (16%) | |
| 10<br>10.1<br><br>10.2 | **Notification of the end of the trial to the NCA : ☒yes / ☐no**<br>**ANSM:** May 12 2018<br><br>**RRF (Résumé du Rapport Final):** April 5 2022 | |
| 11<br>11.1<br>11.2<br>11.3 | **Study duration**<br>- First inclusion: May 9 2016<br>- Primary completion date: May 30 2018<br>- Study completion date May 30 2018 | 12. **Clinical Trial Phase / Type:** IV |

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| 13<br>13.1<br>13.2<br>13.3 | **Population of trial subjects / Enrollment**<br>- **Number of subjects expected:** 308<br>- **Actual Number of subjects included in the trial:** 50<br>- **Actual Number of subjects analysed in the trial:** 47 | |
| 14<br><br><br><br>14.1 | **Main objective:**<br>Estimate if the ticagrelor does not lead to a less good tolerance compared with the association clopidogrel - Lysine acetylsalicylate in a context of TAVI accoding ti the combined safety criteria in 30 days of VARC-2 (Valve Academic Research Consortium-2)<br><br>**Secondary objectives:**<br>- Estimate independently every event of the combined criteria of the main objective as well as the rhythm disorders and the TAVI according to the VARC-2<br>- Verify that the ticagrelor does not lead to an increase of the complication rate owed to any bleedings.<br>- Estimate the efficacy of the therapeutic by a sub-study named “TICTAVI Emboli” involving a maximum 100 patients and at least patients in Bordeaux who will have accepted. | |
| 15 | **Research strategy:**<br>TICTAVI is a 36-month prospective, multicenter (5 centers), randomized, open-label, safety study in the aim to compare the safety of two antiplatelet regimens (Ticagrelor alone versus combination of lysine acetylsalicylate - clopidogrel) during and 30 days after a transcatheter aortic valve implantation. | |
| 16<br><br><br>16.1<br><br><br><br><br>16.2 | **Medical condition or disease studied:**<br>Aortic valve stenosis<br><br>**Inclusion Criteria:**<br>• Provision of informed consent prior to any study specific procedures<br>• Female or male aged > 18 years<br>• Patient eligible for TAVI as recommended by HAS (French health care system authority)<br><br>**Exclusion Criteria:**<br>• Allergy, hypersensitivity, or contraindication to lysine acetylsalicylate, clopidogrel, ticagrelor, any anticoagulation or MRI or CT-scanner contrast agents<br>• Use of CYP3a inhibitor<br>• Need for chronic anticoagulation<br>• Previous percutaneous coronary intervention or acute coronary syndrome requiring dual antiplatelet therapy<br>• Previous cardiac surgery for valve replacement<br>• Prior stroke, TIA or known carotid stenosis > 70%<br>• Active pathological bleeding or gastric ulcer < 3month<br>• Known thrombocytopenia, anemia or any coagulopathy<br>• Severe kidney or hepatic impairment<br>• Hemodynamic instability<br>• Refusal of Transfusion<br>• Significant mental impairment<br>• Inability to give informed consent or comply with study related procedures or high likelihood of being unavailable for follow-up<br>• Pregnant or breastfeeding women<br>• Women of childbearing potential without effective contraception (oetroprogestatifs, intrauterine devices)<br>• Participant in another investigational drug or device study | |
| 17 | **Experimental drug(s) studied (name, dose, route of administration, lot number):**<br>**Ticagrelor (**Brilique 90mg, film-coated tablet, oral medication) **alone:**<br>180 mg loading dose before intervention and 90 mg twice daily during 30 days after the procedure | |
| 18 | **Treatment duration:**<br>31 days | |
| 19 | **Reference Experimental drug(s) (name, dose, route of administration, lot number):** | |

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| | **Combination lysine acetylsalicylate – clopidogrel :** 75 mg before and 75 mg daily after the procedure of lysine acetylsalicylate and 300mg loading dose before and 75 mg of clopidogrel daily after the procedure<br>- Plavix 300mg, film-coated tablet, oral medication<br>- Plavix 75mg, film-coated tablet, oral medication<br>- Kardegic 75mg, powder in single-dose pockets, oral medication |
| 20 | **Evaluation criteria**<br>*Efficacy :*<br>*Security :* |
| 20.1 | **Primary endpoint:**<br>The primary outcome will use the VARC2 early safety (at 30 days) composite endpoints which combines:<br>- All-cause mortality<br>- All stroke (disabling and non-disabling)<br>- Life-threatening or disabling bleeding<br>- Acute kidney injury—Stage 2 or 3 (including renal replacement therapy)<br>- Coronary artery obstruction requiring intervention<br>- Major vascular complication<br>- Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR) |
| 20.2 | **Secondary endpoints:**<br>• Individual analysis of each endpoint of the combined criteria, but also conduction disturbances, arrhythmias and other TAVI-related complications as defined in VARC2<br>• Analysis of all bleeding events<br>• Analysis of the biological efficiency and the silent cerebrovascular events in a sub study named «TICTAVI Emboli» involving a maximum of 100 patients and at least patients in Bordeaux who will have accepted. These patients will experience per-procedure Doppler, brain MRI, neurologic evaluation |
| 21 | **Statistical analysis of the data**<br>All statistical tests will be with a bilateral α risk of 5%. P-values are expressed with 3 digits only and a p-value less than 0.05 will be considered statistically significant. All confidence intervals will be bilateral and presented with a confidence level of 95%.<br>A intermediate analysis is planned after the inclusion of the first 75 patients. During this analysis, the description of all the data will be presented. This analysis is intended to check the safety profile of the treatment. Therefore this intermediate analysis only include an analysis of tolerance (AEs / SAEs) per group. Because the aim of this analysis is to produce information for the IDMC, no decision rule leading to the stop for efficacy or futility will be implemented and therefore it will not be necessary to correct the risk of the first species on the multiplicity.<br>Missing data will not be replaced.<br>Statistical analysis of data will be carried out by the company after Capionis freezing the base using the SAS software v9.4 (or later). |
| 22 | **Trial Summary – Results** |
| 22.1 | - **Outcomes / Efficacy evaluation:**<br>No efficacy evaluation done. |
| 22.2 | - **Adverses events / Security evaluation:**<br>No formal analysis was conducted by the Center for Methodology and Management.<br>A total of 53 adverse events (29 in the “ticagrelor” arm and 24 in the “standard” arm) involving 27 patients were reported by the investigators to the sponsor.<br><br>In an analysis conducted by the sponsor’s safety and vigilance unit on 47 of the 50 randomized patients, the incidence of “Conduction disturbances and/or arrhythmia lasting more than 72 hours within 30 days following the procedure” was 56.5% (13 of 23 randomized patients) in the “ticagrelor” arm versus 29.2% (7 of 24 randomized patients) in the “standard” arm. The analysis showed an increase in risk that was borderline statistically significant (Relative Risk: 1.94; CI: [0.94–3.98]; p = 0.07).<br>Given the small number of patients included in the study, the benefit-risk ratio of the study could not be fully determined. |
| 23 | **Conclusion** |

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| | The target of 308 patients to be included in the study was not met.<br>Only 50 participants were included<br><br>Due to the small number of patients eligible for analysis, no analysis was performed. Nevertheless, an increased risk of bradyarrhythmia-type arrhythmias cannot be ruled out when ticagrelor is used in patients undergoing percutaneous aortic valve implantation. |
| 24 | **More Information**:<br>*Global Substantial Amendments:*<br>*Global Interruptions and re-starts:*<br>*Limitations & Caveats:* |
| 25 | **Publication(s):** |
| 26 | **Establishment date:** July 16 2026 |