**Supplementary appendix**

**Evaluation of safety and efficacy of two ticagrelor-based de-escalation antiplatelet strategies in acute coronary syndrome - a randomized clinical trial
(ELECTRA-SIRIO 2)**

**Low-dose ticagrelor with or without aspirin in patients with acute coronary syndrome: rationale and design of the ELECTRA-SIRIO 2 trial**

This supplement contains the following items:

**1. Study registration data........................................................................................................2**

**2. Funding..................................................................................................................................2**

**3. Inclusion and exclusion criteria..........................................................................................2**

**4. Sample size calculation........................................................................................................4**

**5. Study conduct.......................................................................................................................5**

**6. The MEDMOTION project................................................................................................6**

**7. References....**............................................. .......................................................................**...6**

**1. Study registration data**

1. Study approval reference number KB 379/2020 issued by the Ethics Committee of Collegium Medicum of Nicolaus Copernicus, Bydgoszcz, Poland (Komisja Bioetyczna Uniwersytetu Mikołaja Kopernika w Toruniu przy Collegium Medicum im. Ludwika Rydygiera w Bydgoszczy, ul. M. Curie Skłodowskiej 9, 85-094 Bydgoszcz)
2. EudraCT number: 2020-005130-15
3. ClinicalTrials.gov Identifier: NCT04718025

**2. Funding**

The study is entirely and solely funded by the Medical Research Agency, Poland, through Project no. 2019/ABM/01/00009 (total amount of subsidy: 18,822,037.50 PLN).

**3. Inclusion and exclusion criteria**

The study population will include patients admitted to the study centers due to acute coronary syndrome, including ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA). The diagnosis of STEMI and NSTEMI will be made according to the Fourth Universal Definition of Myocardial Infarction [S1], and UA will be diagnosed according to the 2020 European Society of Cardiology (ESC) guidelines for the management of non-ST-segment elevation ACS (NSTE-ACS) [S2].

For patients with STEMI, the following three inclusion criteria will have to be met:

1) new ST-elevation at the J-point in two contiguous leads with the cut-point ≥1 mm in all leads other than leads V2–V3, where the following cut-points apply: ≥2mm in men ≥40 years; ≥2.5 mm in men <40 years, or ≥1.5 mm in women regardless of age; or a new left bundle-branch block;

2) the intention to perform primary PCI;

3) detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile upper reference limit.

For NSTE-ACS, at least two of the following three criteria will have to be met:

1) symptoms indicating myocardial ischaemia;

2) ST-segment changes on electrocardiography indicating myocardial ischaemia;

3) detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile upper reference limit;

in addition to at least one of the following:

1) ≥60 years of age;

2) previous MI or coronary artery by-pass grafting;

3) ≥50% stenosis in ≥2 coronary arteries;

4) previous ischaemic stroke or transient ischaemic attack;

5) ≥50% carotid stenosis or cerebral revascularization;

6) diabetes mellitus;

7) peripheral artery disease;

8) chronic kidney disease with glomerular filtration rate <60 mL/min.

The exclusion criteria include:

1) contraindications to ticagrelor or/and aspirin;

2) a need for oral anticoagulation therapy;

3) second or third grade atrio-ventricular block;

4) previous stent thrombosis on treatment with ticagrelor;

5) end stage kidney disease with glomerular filtration rate <15 mL/min or on dialysis;

6) administration of prasugrel during the index event;

7) pregnancy;

8) the patient is not able to provide informed consent.

**4. Sample size calculation**

 Sample size and power calculation were based on a superiority assumption for the primary safety endpoint for low-dose ticagrelor with placebo (LDTP) arm vs. standard-dose ticagrelor with aspirin (SDTA) arm. Assuming a bleeding incidence of 7.1% at 1 year with standard dose ticagrelor plus aspirin (rate reported in the TWILIGHT study [S3]), a sample size of 1178 patients per arm is required to provide 95% power to detect 40% lower incidence of the primary safety composite endpoint in LDTP vs. SDTA group (43.6% relative reduction observed in ticagrelor monotherapy arm of the TWILIGHT trial), with a type I error rate of 0.05. Enrolment of a total of 4500 patients (1500 in each arm) is planned to compensate the potential drop-out from the study up to 20%. This broad margin has been chosen as the time between randomization and actual onset of the investigated strategies is 1 and 3 months for experimental LDTA and LDTP strategies, respectively, which may increase the risk of drop-out before the beginning of the allocated regimen.

 The primary efficacy endpoint (composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke) will be evaluated with the use of a prespecified noninferiority hypothesis (LDTP vs. SDTA). Under the assumption of an incidence of 10.2% (occurrence rate reported for this endpoint in the PLATO study [S4] at 1 year in the SDTA, a sample size of 1204 patients per arm is needed to provide 90% power to rule out an absolute difference in risk of 1.6 percentage points, with a one-sided type I error rate of 0.025 (assumption made for the sample size calculations in the TWILIGHT study).

**5. Study conduct**

 The current project is planned as a multicentre study including up to 35 Polish regional cardiovascular centers. The trial was initially planned to be international and include sites from at least 6 European countries, however due to the funding body (Medical Research Agency, Poland) grant regulations only enrolment of patients in clinical sites located in Poland was allowed.

 The maintenance phase of the trial (enrolment and follow-up) is planned for 36 months, however due to potential difficulties with conduct of the study related to the SARS-CoV-2 pandemic, the prolongation of the study active phase might be considered.

 All study participants will be provided with blinded packages containing the antiplatelet medications (ticagrelor 60 mg or 90 mg, and aspirin 100 mg or placebo) according to the randomized allocation. The dispended medications will be free of charge and will be sufficient to cover the whole period (12 months) of each patient in the study.

**6. The MEDMOTION project**

 In the ELECTRA-SIRIO 2 a special care will be applied with regard to adherence to the study treatment (tablets counting at follow-up visits, and evaluation with use of the Adherence in Chronic Diseases Scale - ACDS) [S5]. To increase adherence to treatment all patients will undergo continuous multilevel educational and motivational interventions according to the Multilevel Educational and Motivational Intervention in Patients After Myocardial Infarction (MEDMOTION) project, including assessment with the Readiness for Hospital Discharge after Myocardial Infarction Scale (RHD-MIS) at the end of hospitalization, and with the Functioning in Chronic Illness Scale (FCIS) during follow-ups [S6].

**7. References**

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