CTC North

Investigator-initiated, placebo-controlled, randomized trial to assess the efficacy and safety of platelet inhibition and/or lipid lowering in non-ACS-patients with elevated high-sensitivity troponin values

Acronym: GRAY-ZONE

Short Title: Acetylsalicylic acid and statin in subclinical myocardial ischemia

Clinical Study Report

EudraCT-No.	2019-002833-12
Protocol-No.	Sponsor: GRAY-ZONE / CRO: CTC151085
Version / Date	1.0 / 05-APR-2023
Investigational product	Acetylsalicylic acid (ASA) and/or Statin on top of standard of care.
Indication studied	Myocardial Ischemia
Study Phase	Phase III
Study Start and Completion Date	First patient in to last patient out (months): 30 Duration of the entire trial (months): 30 Recruitment period (months): 18 First patient first visit (FPFV): 21-FEB-2020 Last patient last visit (LPLV): 07-APR-2022
Sponsor	University Medical Centre Hamburg-Eppendorf Martinistraße 52 20246 Hamburg Germany
Coordinating Principal Investigator	Mahir Karakas, MD University Medical Center Hamburg-Eppendorf Department of Intensive Care Medicine Email: m.karakas@uke.de Phone: +49 (0) 152 22817493

SYNOPSIS

Name of Sponsor/Company: University Medical Centre Hamburg-Eppendorf	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Acetylsalicylic acid (ASA) and/or Statin	**Volume:**	
Name of Active Ingredient: ASA / Statin	**Page:**	
Study Title	Investigator-initiated, placebo-controlled, randomized trial to assess the efficacy and safety of platelet inhibition and/or lipid lowering in non-acute coronary syndrome (ACS)-patients with elevated high-sensitivity troponin values	
Principal Investigator	Mahir Karakas, MD University Medical Center Hamburg-Eppendorf Department of Intensive Care Medicine Email: m.karakas@uke.de Phone: +49 (0) 152 22817493	
Substantial Amendments to study protocol	No substantial amendments were made, therefore not applicable	
Study Centres	Seven Cardiology departments in Germany participated in this study. The coordinating centre was the University Heart Centre Hamburg; Department of General and Interventional Cardiology. Further centres were located in Stuttgart, Leipzig, Ulm, Berlin, Heidelberg, and Goslar (site closed prematurely).	
Publication (Reference)	n/a	
Protocol No.	GRAY-ZONE (Sponsor), CTC151085 (CRO)	
EudraCT-No.	2019-002833-12	
Study Period	Date of FPFV: Q1/2020 (21-FEB-2020) LPLV: Q3/2022 (07-APR-2022); this study was terminated early on 20th December 2021 due to poor recruitment and limited resources during the Covid-19 pandemic.	
Phase of Development	Phase III	
Primary Objective	To evaluate if platelet inhibition with Aspirin 100 mg (ASA) and/or lowering of low density lipoprotein (LDL)-cholesterol with Atorvastatin 20 mg (Statin) is superior to placebo in reduction of death, myocardial infarction (MI) and coronary revascularization in patients with symptoms suggestive for Acute Coronary Syndrome (ACS) and elevated high-sensitivity troponin (hsTn) values, not classified as having ACS.	

Methodology	Prospective, randomized, assessor-blinded, multi-centre, controlled, biomarker-guided, personalized, interventional, 2*2 factorial-design phase III trial After a screening period (14 days) eligible patients were randomized (1:1:1:1) to: • ASA 100 mg and Placebo • Statin 20 mg and Placebo • ASA 100 mg and Statin 20 mg • Placebo and Placebo on top of standard of care. **Experimental intervention / index test:** ASA and/or Statin once daily in patients with acute chest pain. **Control intervention / reference product:** Placebo in patients with acute chest pain. Randomization was performed as 1:1:1:1 randomization with respect to the four comparison groups, resulting in a 1:1 randomization for two-group comparisons. Randomization was carried out centrally using SecuTrial. A block randomization procedure was applied with stratification by age (above versus below 65 years), and sex (male versus female). 3000 patients were planned to receive daily ASA and/or Statin and/or Placebo up to 30 months and were to be followed up until 290 events had been observed. **Efficacy Assessments:** The following assessments were planned to be performed at month 3, 9, 15, 21, 27 and 30 (±60 days) to assess efficacy of treatment: • Bleeding events: Location of bleeding, hemoglobin level prior to bleeding, and lowest hemoglobin level recorded at the time of the event had to be classified. Bleeding events were classified as minor, major, extensive bleeding, life-threatening or fatal bleeding. • Disability-free survival: Defined as survival free from dementia or persistent physical disability. The diagnosis of dementia was adjudicated according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, and persistent physical disability was considered to have occurred when a participant reported having an inability to perform or severe difficulty in performing at least one of the six basic activities of daily living that had persisted for at least 6 months. • Bio-Chemistry / translational research for secondary endpoints: The following parameters were planned to be assessed by the core lab: o B-type natriuretic peptide (NTproBNP) o Mid-regional proadrenomedullin (MR-proADM) o Dipeptidyl-Peptidase (DPP3)

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Name of Active Ingredient: ASA / Statin	**Page:**	
	o Adrenomedullin (ADM) o Troponin o C-reative Protein (CRP) o Proencephaline (PenKit) o Mid-regional pro-atrial natriuretic peptide (MR-proANP) o Creatinine o Micro-RNAs (miRNAs) o Further cardio-metabolic biomarkers **Safety** Safety was evaluated by collecting reported adverse events (AEs) at regular intervals throughout the study and by the assessment of physical examination findings, vital signs, clinical laboratory parameters, electrocardiograms (ECGs), and AEs.	
Number of Patients	Planned: 3000 Screened: 70 Screen failure: 2 Randomized: 68 Dosed: 68 Drop out: 3 Completed: 0 Early terminated:65 Discontinued: 0	
Indication	Myocardial Ischemia	
Main Criteria for In- and Exclusion	**Key inclusion criteria:** • Patients presenting in the emergency department (ER)/ Chest Pain Unit (CPU), and expected to be discharged within 24 hours • Patients at risk for cardiovascular events as defined by at least one elevated high-sensitive troponin level during clinical work-up (> 90th percentile) • Clinical exclusion of ACS, despite elevated hsTn (e.g., because of missing troponin dynamics) • At least 50 years of age **Key exclusion criteria:** • Indication for antiplatelet therapy (e.g., transient ischemic attack, or stable coronary artery diseases -CAD) or anticoagulation therapy (such as atrial fibrillation)	

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Name of Active Ingredient: ASA / Statin	**Page:**	
	• Indication for anti-lipid therapy at the discretion of the treating physician (no routine measurement of LDL-cholesterol) • Any known evidence of an acute myocardial necrosis (e.g., imaging evidence of new regional wall motion abnormality, or significant ST-segment–T wave (ST–T) changes in ECG) • Untreated, known clinically significant CAD requiring revascularization • Hemoglobin value below 8 mg/d, and/or creatinine kinase ≥3 times upper limit of normal (ULN), and/or aspartate transaminase (AST) or alanine aminotransferase (ALT) ≥3 times ULN • Active malignancy of any organ system, treated or untreated. Subjects have to be in remission for at least 36 months to be eligible.	

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Name of Active Ingredient: ASA / Statin	**Page:**	
Test Product, Dose and Mode of Administration, Batch No. **Reference Product, Dose and Mode of Administration, Batch No.**	**Test product:** Acetylsalicylic acid (ASA) and/or Statin on top of standard of care. Dosage form: Conventional pill Strength: 100 mg (ASA) and 20 mg (Statin) Dose: One pill per day (ASA, Statin groups) [+one placebo pill each], or 2 pills per day (group with combined intake of ASA and Statin) Route: Oral intake **Reference product:** Placebo on top of standard of care Route of administration corresponding to test product. The sites were provided with the test product and the reference product. All products were labelled in accordance with local study site regulations for investigational medicinal products. Batch no: ASS : V18059A Atorvastatin: 13964; from 23rd March 2021: 16315, from 09th Nov. 2021: 17856 Placebo: 190127; from 27th Apr. 2021:191908 and 201046	
Duration of Treatment	Up to 30 months	

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Name of Active Ingredient: ASA / Statin	**Page:**	
Criteria for Evaluation Efficacy and Safety	***Primary endpoint*** Primary efficacy endpoint: Time to MI, coronary revascularization, or death, whatever came first ***Secondary endpoints*** The secondary efficacy objectives were to compare the active treatment and placebo groups with respect to: 1.) The risk of the composite endpoint of first occurrence of death and MI 2.) The risk of the composite endpoint of first occurrence of death, MI, stroke, transitory ischemic attack (TIA), coronary revascularization or rehospitalization for unstable angina pectoris 3.) The risk of the composite endpoint of first occurrence of death, MI, or stroke 4.) Mortality 5) Bleeding events 6.) Change (fold induction) in cardio-renal biomarkers from baseline to end of study visit (biomarkers will be measured in Principal Investigators core lab at end of study). 7.) Cancer 8.) Disability-free survival ***Safety*** Safety endpoints for tolerability included all AEs, and serious adverse events (SAEs) (including deaths and hospitalisations with date-change).	

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Name of Active Ingredient: ASA / Statin	**Page:**	

Planned Statistical Methods

The primary endpoint was planned to be analysed as intended to treat.

The statistical analysis of the primary endpoint should be based on a log-rank test in an event-driven factorial design, using a two-sided significance level of 5%.
The primary analysis was planned to be adjusted for the stratification factors of the randomization. Randomization was carried out centrally using a computerised system. A block randomization procedure was applied with stratification by age (above versus below 65 years), and sex (male versus female).

Secondary endpoints:
The analysis of the secondary endpoints should follow the same lines of analyses of the primary outcome assessment. The time to event outcomes should be analysed using the Cox proportional hazards model.

Safety:
Adverse event data were summarised by treatment group using standard procedures.

Efficacy Results

Since the study was stopped due to pandemic-related low recruitment numbers no statistical evaluation of efficacy was performed.

Patient Disposition

A total of 68 patients (2.2% of target population) was treated in 7 study sites in Germany, out of which 3 patients from the study site Goslar were excluded from the following presentation of results due to unresolved data issues. In the following table an overview about the distribution of patients according to the treating study centre and treatment group is given (Table 1):

Table 1: Distribution of patients according to the treating study centre and treatment group

Centre-ID	Aspirin/Placebo (N=15)	Aspirin/Statin (N=14)	Placebo/Placebo (N=17)	Statin/Placebo (N=19)
UK Eppendorf	11 (73%)	9 (64%)	12 (71%)	10 (53%)
Stuttgart	3 (20%)	3 (21%)	2 (12%)	6 (32%)
Leipzig	0 (0%)	1 (7.1%)	1 (5.9%)	0 (0%)
UK Ulm	1 (6.7%)	0 (0%=	0 (0%)	2 (11%)
Charite Berlin	0 (0%)	1 (7.1%)	0 (0%)	1 (5.3%)

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Name of Active Ingredient: ASA / Statin	**Page:**	

UK Heidelberg	0 (0%)	0 (0%)	2 (12%)	0 (0%)

N=Number of patients; UK=Universitätsklinikum (University hospital)

Source: Descriptive report Gray-Zone, dated 28-Mar-2023

Patient Demographics

In this study almost the same number of females (n=32) and males (n=33) participated). The majority of patients was older than 65 years (n=43 out compared to n=22). The median body weight was well balanced between the groups: It was 80 kg in the Aspirin/Placebo and in the Aspirin/Statin group, it was 81 kg in the Placebo/Placebo group, and it was 76 kg in the Statin/Placebo group. An overview of important demographic parameters is given in Table **2**.

Table 2: Overview of important demographic parameters

Parameter	**Aspirin/Placebo (N=15)**	**Aspirin/Statin (N=14)**	**Placebo/Placebo (N=17)**	**Statin/Placebo (N=19)**
Age *<65 years* *≥65 years*	 4 (27%) 11 (73%)	 4 (29%) 10 (71%)	 6 (35%) 11 (65%)	 8 (42%) 11 (58%)
Sex *Female* *Male*	 7 (47%) 8 (53%)	 6 (43%) 8 (57%)	 8 (47%) 9 (53%)	 11 (58%) 8 (42%)
Body weight in kg *Mean (SD)* *Median (QR)* *[Range]* *Unknown*	 75 (14) 80 (64; 86) [44; 95] 0	 76 (11) 80 (67; 84) [60; 93] 3	 82 (15) 81 (70; 87) [62; 112] 2	 84 (17) 76 (72; 96) [58; 115] 0
Body height in cm *Mean (SD)* *Median (QR)* *[Range]* *Unknown*	 171 (10) 173 (166; 179) [154; 183] 0	 173 (9) 175 (167; 179) [155; 184] 3	 177 (10) 178 (169; 183) [160; 194] 2	 174 (12) 173 (167; 183) [154; 197] 0
Systolic blood pressure *Mean (SD)*	 154 (35)	 172 (34)	 150 (29)	 149 (26)

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Name of Active Ingredient: ASA / Statin	**Page:**	

Median (QR) [Range] Unknown	153 (136; 175) [90; 237] 0	175 (154; 184) [100; 238] 0	146 (130; 162) [112; 220] 1	140 (131; 160) [120; 219] 0
Diastolic blood pressure *Mean (SD) Median (QR) [Range] Unknown*	88 (15) 92 (81; 98) [60; 109] 0	93 (15) 92 (81; 106) [71; 120] 0	91 (14) 88 (83; 96) [73; 124] 1	90 (16) 90 (80; 98) [70; 139] 0
Pulse rate *Mean (SD) Median (QR) [Range] Unknown*	84 (15) 80 (76; 90) [62; 121] 0	74 (15) 72 (61; 82) [58; 104] 0	82 (20) 76 (69; 96) [56; 119] 1	80 (27) 75 (66; 83) [40; 153] 0
Rhythm *Sinus rhythm Atrial fibrillation Unknown*	14 (93%) 1 (6.7%) 0	14 (100%) 0 (0%) 0	13 (87%) 2 (13%) 2	17 (94%) 1 (5.6%) 1

N=Number of patients; SD=standard deviation; UK=Universitätsklinikum (University hospital)
Source: Descriptive report Gray-Zone, dated 28-Mar-2023

Related to the primary study endpoint 2 events could be observed:

- There was a myocardial infarction that happened in a 86 year old female (patient ID 01008) that was treated with Aspirin/Statin. The patient was hospitalized from 26-AUG-2021 to 30-AUG-2021.
- There was a coronary revascularization in a 88 year old male (patient ID 01025) that was treated with Aspirin/Placebo. The patient was hospitalized from 11-OCT-2020 to 21-OCT-2020 and he was in the intensive care unit from 16-OCT-2020 to 17-OCT 2020.

Safety Results	Overall, there were 18 SAEs that occurred in 12 patients out of 65 study patients. In addition, there were 69 AEs that occurred in 29 patients out of 65. Most SAEs as well as AEs were observed in the Placebo/Placebo group (n=7 and n=23, respectively) and there were 5 SAEs and 21 AEs observed in the group

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Name of Finished Product: Acetylsalicylic acid (ASA) and/or Statin	**Volume:**	
Name of Active Ingredient: ASA / Statin	**Page:**	

treated with Aspirin/Placebo. An overview of events per group is given in Table 3.

Table 3: Events per group

Characteristics	Aspirin/Placebo (N=15)	Aspirin/Statin (N=14)	Placebo/Placebo (N=17)	Statin/Placebo (N=19)
Number of SAEs	5	3	7	3
Number of AEs	21	9	23	16
Patients with SAE	4 (27%)	2 (14%)	4 (24%)	2 (11%)
Patients with AE	8 (53%)	5 (36%)	9 (53%)	7 (37%)

AE=Adverse Event; N=Number of events; SAE=Serious adverse event
Source: Descriptive report Gray-Zone, dated 28-Mar-2023

There was 1 SAE that was assessed as related to Aspirin (in the group treated with Aspirin/Placebo). This SAE occurred in the SOC 'gastrointestinal disorders', the term was upper gastrointestinal hemorrhage. All other SAEs were assessed as unrelated (no reasonable possibility) (Source: Descriptive report Gray-Zone, dated 28-Mar-2023).

SAE severity and outcome is depicted in the following table:

Table 4: Severity and Outcome of SAEs

Characteristics	Aspirin/Placebo (N=5)	Aspirin/Statin (N=3)	Placebo/Placebo (N=7)	Statin/Placebo (N=3)
Severity: mild	0 (0%)	1 (33%)	0 (0%)	0 (0%)
Severity: moderate	1 (20%)	0 (0%)	1 (14%)	0 (0%)
Severity: severe	4 (80%)	2 (67%)	6 (86%)	3 (100%)
Outcome: unknown	0 (0%)	0 (0%)	1 (14%)	0 (0%)
Outcome: recovered/ resolved	5 (100%)	3 (100%)	6 (86%)	2 (67%)
Outcome: recovering/ resolving	0 (0%)	0 (0%)	0 (0%)	1 (33%)

N=Number of events

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Name of Active Ingredient: ASA / Statin	**Page:**	

Source: Descriptive report Gray-Zone, dated 28-Mar-2023

There were 2 AEs that were assessed as related to Aspirin (in the group treated with Aspirin/Placebo), a total of 5 AEs were assessed as related to Statin (n=1 in the group treated with Aspirin/Statin and n=4 treated with Statin/Placebo), and 1 AE that was assessed as related to Placebo in the Statin/Placebo group. The remaining AEs were assessed as unrelated (no reasonable possibility) (Source: Descriptive report Gray-Zone, dated 28-Mar-2023).

AE severity and outcome is depicted in the following table (

Table **5**):

Table 5: Severity and Outcome of AEs

Characteristics	**Aspirin/Placebo (N=21)**	**Aspirin/Statin (N=9)**	**Placebo/Placebo (N=23)**	**Statin/Placebo (N=16)**
Severity: mild	12 (57%)	6 (67%)	6 (26%)	6 (38%)
Severity: moderate	7 (33%)	2 (22%)	15 (65%)	10 (62%)
Severity: severe	2 (9.5%)	1 (11%)	2 (8.7%)	0 (0%)
Outcome: unknown	0 (0%)	0 (0%)	1 (4.3%)	0 (0%)
Outcome: recovered/ resolved	17 (81%)	7 (78%)	19 (83%)	14 (88%)
Outcome: recovering/ resolving	4 (19%)	2 (22%)	3 (13%)	2 (12%)

N=Number of events
Source: Descriptive report Gray-Zone, dated 28-Mar-2023

Conclusion	The aim of this phase III, randomized, single-blind study was to evaluate if platelet inhibition with ASA and/or lowering of LDL-cholesterol with Statin is superior to placebo in reduction of death, MI and coronary revascularization in patients with symptoms suggestive for ACS and elevated hsTn values, not classified as having ACS. In November 2021 it became apparent that during the Covid-19-pandemic a successful completion of this large scale preventive study would not be achieved in a reasonable timeframe. Therefore, the sponsor decided in consultation with the funders the early termination of the study in December 2021. Due to the premature termination and enrolment of only 68 patients no efficacy analysis was performed. While all clinical studies faced recruitment issues during the pandemic, the situation was more difficult within this primary prevention study: it seems impossible to conduct a pure prevention study in formally healthy people in pandemic times, especially since in 2020 and 2021 an end of the pandemic was not foreseeable. Although we managed to keep the study running almost cost-neutrally (thanks to our own cross-funding), realistic planning has shown that under pandemic conditions the study would not be completed before 2027-2029. Only 2% of the planned patient number (n=3000) was achieved. Hence, the primary and secondary objectives of the trial were not achieved. Related to the primary study endpoint only 2 events could be observed. Overall, the safety evaluation showed that the study treatment (ASA and/or Statin and/or Placebo on top of standard of care) was well tolerated in all patients. There was only 1 SAE out of 18 SAEs that was assessed as being related to the study treatment (ASA). In addition, 69 AEs occurred that were mostly of mild severity. Out of these 69 AEs there were 8 AEs that were assessed as being related to study treatment. No safety concerns raised at any time during conduct of the clinical study. In conclusion, the primary objective of the study was not achieved due to pandemic-related poor recruitment resulting in an insufficient number of cases required for efficacy analysis. The study medication administered on top of standard of care was well tolerated. However, further investigations would be necessary to confirm this statement.
Date of Report	05-APR-2023

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LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
ADM	Adrenomedullin
AE	Adverse event
ALT	Alanine aminotransaminase
ASA	Acetylsalicylic acid
AST	Aspartate transaminase
CAD	Coronary artery disease
CPU	Chest pain unit
CRP	C reactive protein
DPP3	Dipeptidyl dipeptidase
ECG	Electrocardiogram
ER	Emergency department
FPFV	First patient first visit
hsTn	High sensitive troponine
LDL	Low density lipoprotein
LPLV	Last patient last visit
MI	Myocardial infarction
miRNAs	Micro RNAs
MR-proADM	Mid-regional proadrenomedullin
MR-proANP	Mid-regional pro-atrial natriuretic peptide
NT-proBNP	B-type natriuretic peptide
PenKit	For determination of Proencephaline
SAE	Serious adverse event
TIA	Transitory ischemic attack