DATA AND SAFETY MONITORING BOARD REPORT

PROTOCOL TITLE: Ticagrelor and preconditioning in patients with stable coronary artery disease (TAPER-S)

PROTOCOL NUMBER: POR-TAP-16-007

EudraCT No. 2016-004746-28

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Executive Summary

Report Overview	This report reviews enrollment, safety, and efficacy data available in the study database as of September 12, 2020.
Enrollment Status	• N=60 subjects have been pre-specified for the primary endpoint analysis. • N=40 subjects have been enrolled and evaluated in the interim analysis.
Subject Status	• N=40 subjects have been randomized to receive either clopidogrel or ticagrelor as per protocol.
Stopping Rules	• There are no safety alerts in the present DSMB review.
Safety Summary	• N=1 adverse event occurred in Group 1. • No adverse events occurred in Group 2. • N=8 patients reported dyspnea in Group 1, of whom 6 cases were defined as mild. • N=11 patients reported dyspnea in Group 2, of whom 8 cases were defined as mild.
Efficacy Summary	• The mean difference in the delta of ST-segment deviation was higher than the pre-specified futility boundary of 2 mm, with a substantial difference between groups favoring Group 2 (approximating to 4 mm).
End of Study Information	• N=6 and N=7 patients in Group 1 and Group 2 prematurely terminated the study, respectively, and were excluded from the primary endpoint analysis.

1.0 Report Overview

The purpose of this report is to independently review the safety and efficacy data of the subjects enrolled in the Ticagrelor and preconditioning in patients with stable coronary artery disease (TAPER-S) study (EudraCT No. 2016-004746-28). This report reflects blinded data from the study dataset and statistical analysis as of September 12, 2020. As the study group assignment was concealed to the DSMB (i.d., blinded data monitoring), in the present report, the two study groups are referred as Group 1 and Group 2. Within the body of the report are summary tables of enrollment, demographic characteristics, safety and efficacy analyses, and adverse events. There have been five DSMB meetings for this study, and the last meeting was on October 02, 2020. At that time, the DSMB concluded that the available safety and efficacy data supported the continuation of the trial. Readers of this report are asked to maintain the confidentiality of the information provided in this report.

2.0 Enrollment Status

The study enrolled 40 patients overall (N=20 in Group 1, and N=20 in Group 2). As pre-specified in the protocol (version 4.0, April 10, 2019), the present interim analysis has been conducted after the accrual of two-third of the total number of patients evaluable for the primary endpoint (N=60).

3.0 Subject Status

A total of N=53 patients have been randomized in the study. The primary endpoint analysis included N=20 patients in Group 1 and N=20 patients in Group 2. All patients evaluated for the primary endpoint completed the baseline visit (i.e., screening visit), Visit 1 (i.e., the day of the index procedure), and Visit 2 (i.e., follow-up, one day after the index procedure).

In Group 1, a total of 6 out of 26 randomized patients prematurely terminated the study, of whom N=1 patient for adverse events and “Other” reasons, and N=5 patients for “Other” reasons only.

In Group 2, a total of 7 out of 27 randomized patients prematurely terminated the study, of whom N=1 patient for consent withdrawal, and N=6 patients for “Other” reasons.

No patient was lost to follow-up.

4.0 Baseline Characteristics

Baseline characteristics, including demographics, clinical, and procedural characteristics (i.e., age, sex, and ethnicity) were well balanced between the two study groups. Data collected at baseline also included symptomatic status (i.e., New York Heart Association [NYHA] class), laboratory

values (i.e., hemoglobin, white-blood-cells count), chest X-ray, electrocardiographic measurements, and cardiac ultrasound data – that were similar in the two study groups.

Table D.2 Summary of Demographic and Screening/Baseline Characteristics by group
Population: Per Protocol

		Group 1	Group 2
		N=20	N=20
Age at the time of IC Signature Date (years)	N	20	20
	Missing	0	0
	Mean	65.6	61.2
	Std. deviation	7.2	8.6
	Median	66.0	59.0
	Q1-Q3	63.0 - 70.5	54.5 - 67.0
Gender at birth	Male	15 (75.0%)	17 (85.0%)
	Female	5 (25.0%)	3 (15.0%)
Race	Caucasian	19 (95.0%)	20 (100.0%)
	Oriental	0	0
	Hispanic	0	0
	Afro-American	0	0
	Other	1 (5.0%)	0
Hospedalized?	Yes	19 (95.0%)	19 (95.0%)
	No	0	0
	N.A.	1 (5.0%)	1 (5.0%)

Table D.11 Summary of NYHA Classification by group
Population: Per Protocol

		Group 1	Group 2
		N=20	N=20
NYHA Classification	Class I	1 (5.0%)	2 (10.0%)
	Class II	10 (50.0%)	3 (15.0%)
	Class III	2 (10.0%)	4 (20.0%)
	Class IV	0	0
	N.A.	7 (35.0%)	11 (55.0%)

Table D.5 Summary of Haematology at Baseline by group. (page 1 of 5)
Population: Per Protocol

		Group 1	Group 2
		N=20	N=20
Haemoglobin g/dL	N	20	20
	Missing	0	0
	Mean	13.7	13.5
	Std. deviation	1.2	1.4
	Median	13.8	13.7
	Q1-Q3	12.7 - 14.3	12.8 - 14.8
Haematocrit %	N	20	20
	Missing	0	0
	Mean	40.9	40.7
	Std. deviation	3.6	4.0
	Median	40.8	41.6
	Q1-Q3	38.4 - 41.8	38.0 - 43.3
Red Blood Cells x 10^12/L	N	20	20
	Missing	0	0
	Mean	4.7	4.6
	Std. deviation	0.4	0.5
	Median	4.7	4.6
	Q1-Q3	4.4 - 5.0	4.3 - 4.9
White Blood Cells gx 10^9/L	N	20	20
	Missing	0	0
	Mean	7.0	7.7
	Std. deviation	1.7	2.4
	Median	7.2	6.9
	Q1-Q3	5.9 - 7.8	5.9 - 9.4

Table D.9 Summary of ECG at Baseline by group
Population: Per Protocol

		Group 1 N=20	Group 2 N=20
ECG Performed?	Yes	20 (100.0%)	20 (100.0%)
	No	0	0
	N.A.	0	0
Are there any Abnormalities?	Yes	12 (60.0%)	14 (70.0%)
	No	8 (40.0%)	6 (30.0%)
	N.A.	0	0

Table D.10 Summary of Chest X-Ray at Baseline by group
Population: Per Protocol

		Group 1 N=20	Group 2 N=20
Pulmonary X-Ray Performed?	Yes	0	1 (5.0%)
	No	20 (100.0%)	19 (95.0%)
	N.A.	0	0
Are there any Abnormalities?	Yes	0	0
	No	0	2 (10.0%)
	N.A.	20 (100.0%)	18 (90.0%)

Table D.8 Summary of Echocardiogram at Baseline by group. (page 2 of 4)
Population: Per Protocol

		Group 1 N=20	Group 2 N=20
Ejaction fraction	N	17	18
	Missing	3	2
	Mean	59.7	61.4
	Std. deviation	4.2	5.3
	Median	60.0	62.0
	Q1-Q3	58.0 - 62.0	58.0 - 64.0
Left ventr. teledia. diameter	N	10	12
	Missing	10	8
	Mean	44.7	46.3
	Std. deviation	3.1	4.5
	Median	45.0	48.0
	Q1-Q3	44.0 - 47.0	42.0 - 49.5
Left ventr. telesys. diameter	N	10	13
	Missing	10	7
	Mean	29.7	32.4
	Std. deviation	3.4	8.7
	Median	30.0	31.0
	Q1-Q3	28.0 - 32.0	28.0 - 34.0
Thickness of the lower I.S.	N	11	13
	Missing	9	7
	Mean	10.7	10.9
	Std. deviation	1.6	2.1
	Median	11.0	11.0
	Q1-Q3	10.0 - 12.0	11.0 - 12.0

5.0 Safety Analysis

There are no safety alerts nor issues in the present DSMB review. Overall, N=1 patient experienced an adverse event in Group 1, while no adverse events occurred in Group 2.

In Group 1, patient n. 1002 experienced an adverse event during the index procedure. Specifically, the patient developed ventricular fibrillation and cardiac arrest following contrast injection in the right coronary artery. The patient was successfully defibrillated with the restoration of spontaneous circulation (ROSC). No further complications occurred.

No fatal event occurred at follow-up.

Table S.1 Summary of End of Study Information (reasons for withdrawal) by group
Population: Safety

		Group 1	Group 2
		N=26	N=27
Adverse Event	N(%)	1 (3.9%)	0
Consent Withdrawal	N(%)	0	1 (3.7%)
Lost to Follow-up	N(%)	0	0
Other	N(%)	6 (23.1%)	6 (22.2%)

The occurrence of dyspnea was systematically collected at (i) baseline visit, (ii) Visit 1, and (iii) Visit 2. None of the study patients experienced severe or intolerable dyspnea, and most patients reported mild symptoms.

Table E.5 Summary of Dyspnoea Evaluation by group (page 1 of 2)
Population: Per Protocol

		Group 1	Group 2
		N=20	N=20
Screening	0 - Nessuna	4 (20.0%)	5 (25.0%)
	0.5 - Molto molto lieve	3 (15.0%)	4 (20.0%)
	1 - Molto lieve	3 (15.0%)	0
	2 - Lieve	4 (20.0%)	3 (15.0%)
	3 - Moderata	2 (10.0%)	3 (15.0%)
	4 - Piuttosto intensa	4 (20.0%)	3 (15.0%)
	5 - Intensa	0	0
	6 - Intensa	0	0
	7 - Molto intensa	0	2 (10.0%)
	8 - Molto intensa	0	0
	9 - Molto molto intensa	0	0
	10 - Insopportabile	0	0
Visit 1	0 - Nessuna	3 (15.0%)	4 (20.0%)
	0.5 - Molto molto lieve	0	2 (10.0%)
	1 - Molto lieve	4 (20.0%)	1 (5.0%)
	2 - Lieve	3 (15.0%)	4 (20.0%)
	3 - Moderata	2 (10.0%)	2 (10.0%)
	4 - Piuttosto intensa	4 (20.0%)	3 (15.0%)
	5 - Intensa	1 (5.0%)	0
	6 - Intensa	1 (5.0%)	0
	7 - Molto intensa	0	0
	8 - Molto intensa	1 (5.0%)	3 (15.0%)
	9 - Molto molto intensa	1 (5.0%)	0
	10 - Insopportabile	0	0

Table E.5 Summary of Dyspnoea Evaluation by group (page 2 of 2)
Population: Per Protocol

		Group 1	Group 2
		N=20	N=20
Follow-up	0 - Nessuna	11 (55.0%)	8 (40.0%)
	0.5 - Molto molto lieve	0	3 (15.0%)
	1 - Molto lieve	3 (15.0%)	2 (10.0%)
	2 - Lieve	3 (15.0%)	3 (15.0%)
	3 - Moderata	1 (5.0%)	1 (5.0%)
	4 - Piuttosto intensa	1 (5.0%)	1 (5.0%)
	5 - Intensa	0	1 (5.0%)
	6 - Intensa	0	0
	7 - Molto intensa	0	0
	8 - Molto intensa	0	0
	9 - Molto molto intensa	0	0
	10 - Insopportabile	0	0

6.0 Efficacy Analysis

In the study protocol (version 4.0, April 10, 2019), the investigators pre-specified an interim efficacy analysis to be conducted after the accrual of two-third of patients evaluable for the primary

endpoint and fixed a futility boundary at a delta level of 2 mm in ST-segment elevation by i.c. ECG between the two groups. Accordingly, the DSMB has evaluated the results of the primary endpoint analysis. The efficacy analysis was performed in N=20 patients in Group 1 versus N=20 patients in Group 2. The delta of ST-segment elevation by i.c. ECG was significantly higher in Group 2 versus Group 1 (4.26 mm [2.90 to 5.62] vs. 0.23 [-0.51 to 0.96]; p<0.0001) approximating to ≥4 mm difference. Therefore, with this respect, the DSMB concludes that there is a significant difference in terms of efficacy between groups favoring Group 2 and – according to the study protocol (version 4.0 10/04/2019) – leaves the final decision regarding the continuation of the study/enrolment to the Independent Statistician of the study. Additional efficacy analyses included the quantification of coronary microvascular resistance by means of different techniques, including fractional flow reserve (FFR), coronary flow reserve (CFR), and index of microcirculatory resistance (IMR).

Table E.1 Primary Endpoint: Comparison of delta (difference) ST-segment elevation by intracoronary ECG by group
Population: Per Protocol

		Group 1 N=20	Group 2 N=20	p-value
Degree of ST-segment elevation by i.c. ECG inflation 1	Mean 95% IC	13.85 [9.70 , 17.99]	13.98 [10.21 , 17.74]	0.7300
Degree of ST-segment elevation by i.c. ECG inflation 2	Mean 95% IC	13.46 [9.32 , 17.60]	9.14 [5.06 , 13.21]	0.0398
Delta of ST-segment elevation by i.c. ECG	Mean 95% IC	0.23 [-0.51 , 0.96]	4.26 [2.90 , 5.62]	<0.0001

Table E.2b1 Quantification of coronary microvascular resistance (derived data) by group
Population: Per Protocol

		Group 1 N=20	Group 2 N=20	p-value
PRE - FFR (Pd Hyperemic/Pa Hyperemic)	Mean 95% IC	0.77 [0.76 , 0.79]	0.76 [0.68 , 0.83]	0.4691
PRE - CFR (Baseline Tmn/Hyperemic Tmn)	Mean 95% IC	2.19 [1.61 , 2.77]	2.37 [1.75 , 2.99]	0.5560
PRE - IMR (Hyperemic Pd * Hyperemic Tmn)	Mean 95% IC	37.76 [27.26 , 48.27]	38.29 [29.79 , 46.80]	0.5763
POST - FFR (Pd Hyperemic/Pa Hyperemic)	Mean 95% IC	0.90 [0.88 , 0.92]	0.88 [0.86 , 0.90]	0.3510
POST - CFR (Baseline Tmn/Hyperemic Tmn)	Mean 95% IC	2.09 [1.57 , 2.61]	1.85 [1.35 , 2.34]	0.6067
POST - IMR (Pd Hyperemic/Pa Hyperemic)	Mean 95% IC	26.90 [20.22 , 33.58]	42.14 [18.23 , 66.06]	0.1563

Table E.2b2 Summary of Quantification of coronary microvascular resistance (difference POST-PRE) by group
Population: Per Protocol

		Group 1 N=20	Group 2 N=20	p-value
(diff POST-PRE) - FFR	Mean 95% IC	0.12 [0.10 , 0.15]	0.12 [0.05 , 0.20]	0.7054
(diff POST-PRE) - CFR	Mean 95% IC	-0.10 [-0.83 , 0.63]	-0.52 [-1.36 , 0.31]	0.7280
(diff POST-PRE) - IMR	Mean 95% IC	-10.86 [-21.42 , -0.31]	3.85 [-21.50 , 29.19]	0.7280

7.0 End of Study Information

Overall, N=6 patients in Group 1 terminated the study and were not evaluated for the primary endpoint, of whom N=1 patient for the occurrence of an adverse event and “Other” reasons, and N=5 patients for “Other” reasons only. In Group 2, a total of N=7 patients terminated the study, of whom N=1 patient for consent withdrawal, and N=6 patients for “Other” reasons.

No patient was lost to follow-up.

Table S.1 Summary of End of Study Information (reasons for withdrawal) by group
Population: Safety

		Group 1	Group 2
		N=26	N=27
Adverse Event	N(%)	1 (3.9%)	0
Consent Withdrawal	N(%)	0	1 (3.7%)
Lost to Follow-up	N(%)	0	0
Other	N(%)	6 (23.1%)	6 (22.2%)

Patients prematurely terminated the study for the following reasons:

1. Sub. ID 1002: excluded for the occurrence of an adverse event during the index procedure (i.e., cardiac arrest), and for the presence of angiographically significant stenosis (>50%) of the left main (exclusion criterion n. 17);
2. Sub ID 1003: no significant coronary stenosis at FFR;
3. Sub ID 1010: no significant coronary stenosis at FFR;
4. Sub ID 1011: no significant coronary stenosis at FFR;
5. Sub ID 1012: critical coronary stenosis at index procedure;
6. Sub ID 1014: critical coronary stenosis at index procedure;
7. Sub ID 1018: angiographically significant stenosis (>50%) of the left main at index procedure;
8. Sub ID 1026: consent withdrawal;
9. Sub ID 1035: no significant coronary stenosis at FFR;
10. Sub ID 1037: patient on apixaban after randomization (exclusion criterion 2);
11. Sub ID 1039: no significant coronary stenosis at FFR;
12. Sub ID 1041: no significant coronary stenosis at FFR;
13. Sub ID 1045: patient underwent surgical coronary revascularization.