2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Vastarel®, Adexor®, Flavedon®, Idaptan®, Preductal®, Vasorel®, Vastinan® Trizedon®, Tacirel®, Prenagor®, Trimetazidine MR. **Name of Active Ingredient:** Trimetazidine (S06790)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: The efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention. ATPCI study. An international, multicentre, randomised, double-blind, placebo-controlled study in patients treated for 2 to 4 years. Protocol No.: CL3-06790-010. EudraCT No.: 2010-022134-89.		
Chairman of the Executive Committee: [redacted]		
Study countries: 27 countries, 6059 included and randomised patients in 364 centres. Algeria (3 centres - 60 patients), Argentina (19 centres - 244 patients), Austria (6 centres - 28 patients), Belarus (5 centres - 114 patients), Bosnia-Herzegovina (4 centres - 120 patients), Brazil (18 centres - 280 patients), China (17 centres - 199 patients), Colombia (8 centres - 105 patients), Croatia (13 centres - 230 patients), Czech Republic (18 centres - 295 patients), France (8 centres - 60 patients), Georgia (9 centres - 300 patients), Greece (6 centres - 40 patients), Italy (23 centres - 260 patients), Korea (13 centres - 203 patients), Montenegro (2 centres - 74 patients), Peru (11 centres - 110 patients), Poland (37 centres - 771 patients), Portugal (8 centres - 80 patients), Romania (26 centres - 297 patients), Russia (33 centres - 809 patients), Serbia (16 centres - 322 patients), Slovakia (11 centres - 150 patients), Vietnam (5 centres - 69 patients), Spain (19 centres - 275 patients), Turkey (6 centres - 110 patients), Ukraine (20 centres - 454 patients).		
Publications (references): - Ferrari R, Ford I, Fox K, Marzilli M, Tendera M, Widimský P, *et al*. A randomized, double-blind, placebo-controlled trial to assess the efficAcy and safety of Trimetazidine in patients with angina pectoris having been treated by percutaneous coronary intervention (ATPCI study): Rationale, design, and baseline characteristics. American Heart Journal. 2019; 210:98-107. - Ferrari R, Ford I, Fox K, Challeton JP, Correges A, Tendera M *et al*. Efficacy and safety of trimetazidine after percutaneous coronary intervention (ATPCI): a randomised, double-blind, placebo-controlled trial. The Lancet. 2020; 396(10254):830-838.		
Studied period: Initiation date: 11 September 2014 Completion date: 13 December 2019	**Phase of development of the study:** Phase III	
Objectives: The purpose of this study was to demonstrate the long-term efficacy and safety of trimetazidine, when given in addition to other evidence-based cardiovascular therapies, in patients having had a recent Percutaneous Coronary Intervention (PCI). The primary objectives were to demonstrate the superiority of trimetazidine over placebo in preventing recurrence or exacerbation of angina pectoris and reducing cardiac events, and to document its safety by analysing the occurrence of serious adverse events (SAEs). The secondary objectives were to evaluate the effect of trimetazidine on the other efficacy endpoints, as well as the other safety, clinical and biological parameters.		

Methodology:
This study was a phase III, international, multicentre, double-blind, placebo-controlled event-driven study randomised in 2 parallel and balanced arms (trimetazidine MR 35 mg or placebo, twice daily *(b.i.d.)*). The study was conducted in adult patients with Coronary Artery Disease (CAD) treated by successful PCI, on top of post-PCI recommended treatment (both secondary prevention and regular antianginal therapies as per current guidelines). The randomisation was stratified at inclusion according to the country and the nature of the PCI procedure (whether elective or urgent).

Two adjudication committees were involved in the study: A Cardiovascular Endpoints Adjudication Committee (CVAC) adjudicated all efficacy Pre-Specified Events (PSEs) and a Safety Endpoints Adjudication Committee (SAC) adjudicated all Events of Interest (EIs) (occurring after randomisation and after the first Investigational Medicinal Product [IMP] intake until the end of the study).

Selection and Inclusion visits occurred within 30 days after PCI, followed by a treatment period of 2 to 4 years depending on the time of inclusion (extended, per protocol, by Executive Committee decision to 3 to 5 years) with a maximum of 12 visits (M001, M003, M006, M012, M018, M024, M030, M036, M042, M48, M54 and M60).
This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: 5800 included patients (2900 per group) and 1363 events required for the Primary Composite Endpoint (PCE) of efficacy.
Included and randomised: 6059 patients (3024 in the trimetazidine group and 3035 in the placebo group).

Diagnosis and main criteria for inclusion:
The target population was adult patients with single or multi-vessel CAD having undergone a recent successful PCI (maximum 30 days before randomisation) treating at least one stenosis of a native coronary artery or a coronary graft. The PCI before inclusion, called index PCI, had to be:

- Indicated because of angina pectoris, either stable angina (elective PCI) or acute presentation such as unstable angina / Non-ST segment Elevation Myocardial Infarction (NSTEMI), excluding ST segment Elevation Myocardial Infarction (STEMI).
- Achieved by stent implantation or by other acceptable interventional methods.
- Successful as planned by the operator and with no further revascularisation planned (either percutaneous or surgical).
- Uncomplicated, such that the patient's discharge was not delayed because of a cardiac or cerebrovascular problem.

Investigational Medicinal Products (IMPs):

Active: trimetazidine Modified Release (MR) 35 mg twice daily (*bis in die*, *b.i.d.*), one tablet in the morning and one tablet in the evening, at mealtimes.
Batches: L0050034, L0052402, L0052698, L0052703, L0052801, L0054030, L0054463, L0056798, L0059146 L0060257, L0061956, L0062635, L0065068, L0067975, L0068776, L0069494 and L0071108.

Placebo: *b.i.d.*, one tablet in the morning and one tablet in the evening, at mealtimes.
For patients with moderate renal failure, the treatment was every day (*omni die*, *o.d.)* with one tablet (active or placebo) in the morning at mealtime.
Batches: L0052356, L0052357, L0053018, L0053031, L0053033, L0053032, L0054029, L0055225, L0056910 L0059034, L0060336, L0061744, L0061961, L0061963, L0064057 L0064059, L0065072, L0065635, L0065637, L0065639, L0066151, L0066193, L0067496, L0068282, L0069311, L0069331, L0069333 L0069335, L0069394, L0070613, L0071116, L0071672 and L0071687.

Duration of treatment:
Run-in period: selection and inclusion visits within 30 days after the index PCI.
Treatment period: 3 to 5 years and the first dose of IMP was taken the day after the inclusion visit.
Follow-up period: 3 to 5 years, depending on the time of inclusion. Follow-up visit at 1 month (M001), 3 months (M003), 6 months (M006) and every 6 months until the final visit. If a definitive discontinuation of the IMP was decided, the patient was asked to attend the scheduled visits until the study end was declared.

Criteria for evaluation:
Efficacy measurements:

- PSEs data collection, including:
  - All deaths.
  - All hospitalisations for cardiovascular reason.
  - All coronary angiographies.
  - All coronary revascularisations.
  - All changes in antianginal therapy (addition, switch or increase of the dose of one of the antianginal therapies, excluding short-acting nitrates).
- Canadian Cardiovascular Society (CCS) classification of angina symptoms.
- Number of angina episodes per week.
- Number of doses of short-acting nitrates taken per week.
- Seattle Angina questionnaire (SAQ) - in countries where a validated translation was available – measured over the first twelve months of the study.
- Euro-QoL-5 Dimensions, 3 Levels questionnaire (EQ-5D) – measured over the first twelve months of the study.
- Cardiac troponin (before each repeat elective PCI and between 6 and 24 hours after).

Safety measurements:

- Adverse events (AEs) including Adverse Events of Interest (AEIs).
- Vital signs: Blood Pressure (BP) and Heart Rate (HR).
- Weight.
- Laboratory evaluation.
- Electrocardiograms (ECGs).

Statistical methods:

Analysis sets

- Randomised Set (RS): all included patients with a randomization number allocated.
- Efficacy Analysis Set (ES_{ana}): all patients of the RS excluding those possibly unblinded.
- Safety Set (SS): all patients having taken at least one dose of IMP.
- Safety Analysis Set (SS_{ana}): all patients of the Safety Set excluding those possibly unblinded.

Subgroups

Nature of the index PCI before selection: elective or urgent PCI, according to investigator's opinion.

Treatment groups

The treatment group considered for all analyses was the randomised treatment (*i.e.* allocated by the Interactive Response System [IRS; internet or voice]): trimetazidine MR 35 mg or placebo.

Efficacy analyses

The efficacy analyses (primary and secondary endpoints) were performed by treatment group in the ES_{ana} and its subgroups (elective and urgent index PCI).

Primary Composite Endpoint (PCE) of efficacy

The PCE was defined as the time to first event among (positively adjudicated and occurring during the efficacy time-window, *i.e.* between the randomisation date and the end of study date of the patient (or end of theoretical termination period [*i.e.* 30th November 2019] if before the end of study date).

- Cardiac death (cardiac death and death from unknown cause).
- Hospitalisation for a cardiac event (hospitalisation for acute myocardial infarction (MI), unstable angina, heart failure, sustained ventricular tachycardia, resuscitated cardiac arrest or angina and/or ischaemia leading to revascularisation).
- Recurrent or persistent angina leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies (angina alone or with documented ischaemia).
- Recurrent or persistent angina leading to performing a coronary angiography (angina alone or with documented ischaemia).

Major Secondary Composite Endpoint (MSCE) of efficacy
The MSCE was defined as the time to first event (positively adjudicated and occurring between the randomisation and the end of study) among components of the PCE and 2 additional components:

- Evidence of ischaemia (without angina; documented by stress imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies.
- Evidence of ischaemia (without angina; documented by stress imaging) leading to performing a coronary angiography.

Other secondary efficacy endpoints
Sixteen other secondary endpoints were defined (with an analytical approach of time to first occurrence):

- Cardiac death.
- Hospitalisation for a cardiac event.
- Recurrent or persistent angina leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies.
- Recurrent or persistent angina leading to performing a coronary angiography.
- Evidence of ischaemia (documented by stress imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies.
- Evidence of ischaemia (documented by stress imaging) leading to performing a coronary angiography.
- Cardiac death or hospitalisation for a cardiac event.
- Recurrent or persistent angina leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies, or leading to performing a coronary angiography.
- All-cause mortality.
- Hospitalisation for non-fatal MI.
- Hospitalisation for fatal or non-fatal MI.
- Hospitalisation for fatal or non-fatal MI or occurrence of cardiac death.
- Hospitalisation for ischaemic chest pain (*i.e.* hospitalisation for acute MI, hospitalisation for unstable angina, hospitalisation for angina (other than MI or unstable angina) leading to performing a coronary angiography or leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies).
- Hospitalisation for heart failure.
- Any coronary revascularisation.
- Repeat coronary revascularisation in response to angina.

Other efficacy endpoints (descriptive analysis only)

- CSS classification of angina severity.
- Number of angina episodes per week.
- Number of doses of short-acting nitrates per week.
- Number of antianginal drugs classes taken by the patient.
- SAQ.
- EQ-5D (3 levels).
- Cardiac troponin.

Primary analysis
Analysis of PCE: the superiority of trimetazidine over placebo was tested using a Cox proportional hazards model adjusted on treatment group and baseline covariates (country and nature of index PCI). The type I error of the statistical tests was set at 5% (2-sided test). Hazard ratio (trimetazidine *versus* placebo), associated standard error, two-sided 95% Confidence Interval (CI) and p-value were provided. The robustness of results was assessed by sensitivity analyses. Descriptive analyses and Kaplan-Meier curves by treatment group were also presented.

Analysis of secondary efficacy endpoints: the effect of trimetazidine compared with placebo was assessed using the same approach as for the primary analysis of the PCE except p-value was not provided.

The recurrence of other efficacy endpoints, except those including death was described.
Analysis of other efficacy endpoints was mainly descriptive.

Safety analyses
The safety analyses were performed by treatment group in the SS_{ana}.

Primary safety endpoint
Annual incidence rate of a first serious Treatment Emergent Adverse Events (serious TEAEs).

Emergent Adverse Events (EAEs; coded using MedDRA 21.0), including clinically significant abnormalities observed on ECG recordings and from laboratory parameters

- Emergent adverse events (EAEs), *i.e.* emergent during the study. They were defined as all adverse events which occurred from the first IMP intake date (included), or which occurred before the first IMP intake date and which worsened (in terms of intensity) or became serious according to the investigator's opinion from the first IMP intake date (included).
- TEAEs, *i.e.* emergent during the treatment period. They were defined as all adverse events which occurred between the first IMP intake date (included) and the last IMP intake date + 2 days (included), or which occurred before the first IMP intake date and which worsened (in terms of intensity) or became serious according to the investigator opinion between the first IMP intake date (included) and the last IMP intake date + 2 days (included).

Events of Interest (EIs) during the treatment period

All **EIs that were reported as AEs were** adjudicated by the SAC. The MedDRA codes were grouped into the following categories:

- Neurological symptoms (sub-categories for the adjudicator: Parkinson's syndrome, disorientation, hallucination and convulsion).
- Coagulation disorders and/or non-traumatic haemorrhages (sub-categories for the adjudicator: major bleeding (*i.e.* grade 2) and coagulation disorders).
- Thrombocytopenia.
- Agranulocytosis.
- Falls.
- Arterial hypotension (sub-categories for the adjudicator: supine hypotension, orthostatic hypotension).
- Serious skin disorders.
- Hepatic disorders.

EIs that were not reported as AEs, but detected by the Sponsor via the scrutiny of the post-baseline biological/clinical values were also adjudicated by the SAC and grouped into the following categories:

- Coagulation disorders (and/or non-traumatic haemorrhages).
- Thrombocytopenia.
- Agranulocytosis.
- Arterial hypotension (including hypotension in supine position and orthostatic hypotension).
- Hepatic disorders.

Clinical examination, vital signs, clinical laboratory evaluation:

- BP and HR.
- Haematology: haemoglobin, haematocrit, red blood cell, white blood cell (including absolute differential count) and platelet counts.
- Biochemistry (fasting condition): sodium, potassium, creatinine, ALT, AST, fasting blood level of glucose, total cholesterol, High-Density Lipoprotein (HDL) cholesterol, Low-Density Lipoprotein (LDL) cholesterol, triglycerides, International Normalized Ratio (INR) or alternatively prothrombin time / prothrombin ratio and activated Partial Thromboplastin Time (aPTT).

Analyses for the primary safety endpoint

The difference between treatment groups (trimetazidine *versus* placebo) was assessed on the annual incidence rate during the treatment period. A 2-sided 95% CI was calculated using a normal approximation. This analysis was provided for descriptive purposes. The number of serious TEAEs as well as the number, percentage and annual incidence rate of patients experiencing at least one serious TEAE were provided.

Analyses for EAEs

The number of events (presented by SOC and/or PT) as well as the number, percentage and annual incidence rate of patients experiencing at least one event were provided for EAEs and TEAEs. TEAEs were described according to the seriousness, the intensity, the relationship with the IMP, the action taken regarding the IMP, the requirement of added therapy and the outcome.

Analyses for AEIs and EIs non-AE

The difference between treatment groups was assessed on the annual incidence rate of AEIs and EIs non-AE according to adjudicator's opinion during the treatment period (as for the primary safety endpoint). The descriptive analysis of adjudication forms was provided. For AEI according to the investigator's opinion, description by System Organ Class [SOC] and Preferred Term [PT] were provided.

Analysis for clinical laboratory, vital signs and clinical examination parameters

Descriptive statistics were provided.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 6369 patients were screened and 6288 patients were selected. The number of patients retained in the Randomised Set (RS) was 6059 with a balance between the 2 treatment groups: 3024 patients (49.9%) allocated to trimetazidine and 3035 patients (50.1%) allocated to placebo.

Of the 6059 patients of the RS, 5498 completed the study with a similar frequency in both groups: 2751 patients (91.0%) in the trimetazidine group and 2747 patients (90.5%) in the placebo group. A total of 561 patients (9.3%) did not complete the study: 293 patients died before the end of study visit, 239 patients withdrew their consent, 27 patients were withdrawn due to other non-medical reason and 2 patients were lost to follow-up. Of the 293 deaths, 142 were in the trimetazidine group and 151 in the placebo group (RS).

The main analyses were conducted in the ES_{ana} and the SS_{ana} rather than in the RS and SS respectively (upon decision of the Executive Committee), because of the risk that a possible unblinding had occurred during the transfer of data for 52 patients at the beginning of the study. These 2 new sets were 99.1% (6007 patients) and 99.2% (5973 patients) of the RS and SS, respectively. The excluded patients were distributed evenly between the 2 treatment groups.

The predefined subgroups represented 58.1% of the population for patients with an elective index PCI and 41.9% for patients with an urgent index PCI. Both had balanced distributions of the 2 treatment groups.

Table 1 - Disposition of patients by status and by analysis set

Status and analysis sets		Trimetazidine	Placebo	All
Included and randomised	**n**	**3024**	**3035**	**6059**
Completed	**n (%)**	**2751 (91.0)**	**2747 (90.5)**	**5498 (90.7)**
Withdrawn due to	**n (%)**	**273 (9.0)**	**288 (9.5)**	**561 (9.3)**
Lost to follow-up	n (%)	-	2 (0.1)	2 (<0.1)
Death	n (%)	142 (4.7)	151 (5.0)	293 (4.8)
Patient consent withdrawal	n (%)	118 (3.9)	121 (4.0)	239 (3.9)
Other non-medical reason	n (%)	13 (0.4)	14 (0.5)	27 (0.5)
Randomised Set - RS	**n**	**3024**	**3035**	**6059**
Efficacy Analysis Set - ES_{ana}	n (%)	2998 (99.1)	3009 (99.1)	6007 (99.1)[(a)]
Efficacy Analysis Set - ES_{ana}	**n**	**2998**	**3009**	**6007**
Subgroup - Elective index PCI	n (%)	1742 (58.1)	1748 (58.1)	3490 (58.1)[(b)]
Subgroup - Urgent index PCI	n (%)	1256 (41.9)	1261 (41.9)	2517 (41.9)[(b)]
Safety Set - SS	**n**	**3008 (49.9)**	**3016 50.1)**	**6024 (100)**
Safety Analysis Set - SS_{ana}	n (%)	2983 (99.2)	2990 (99.1)	5973 (99.2)[(c)]

n number of patients. Percentages are based on n.
(a) % relative to RS; (b) % relative to ES_{ana}; (c) % relative to SS.

BASELINE CHARACTERISTICS

Demographic data and baseline characteristics revealed homogeneity between treatment groups, without clinically relevant differences.

Patients were mostly male (77.0%) of Caucasian ethnicity (85.3%) with a mean age (± SD) of 60.9 ± 9.7 years (36.2% were 65 years or older and 8.8% were 75 years or older). The majority were overweight or obese at baseline: the mean BMI was 28.6 ± 4.3 kg/m^2 and 33.6% of patients had a BMI over 30 kg/m^2. The mean (± SD) Systolic Blood Pressure / Diastolic Blood Pressure (SBP / DBP) was 127.9 ± 14.2 / 76.4 ± 9.0 mmHg and the mean supine HR was 66.4 ± 9.6 bpm. No Left Ventricular Ejection Fraction (LVEF) dysfunction was evidenced for the majority of patients (86.1%) and a small proportion of patients had an LVEF < 40% (2.3%).

Nearly half of the patients (48.5%) had a diagnosis of CAD for less than 3 months. The mean duration was 2.8 ± 5.1 years with a median duration of 3 months. The majority of patients (78.0%) had a CCS class II or III, considering the worst severity of angina symptoms during the 4-week period prior to the index PCI. The mean time between the index PCI and randomisation (± SD) was 12.5 ± 9.0 days (median: 11.0 days), with no difference between treatment groups.

The most frequently reported cardiovascular medical histories at baseline were stable angina pectoris (56.6%), MI (48.0%), unstable angina (37.8%) and heart failure (25.3%). Most patients had risk factors such as hypertension (82.8%), dyslipidaemia (65.1%) or diabetes mellitus (27.8%).

At inclusion, most patients (93.1%) were taking an antianginal therapy (beta-blockers (83.9%), CCBs (27.6%), short-acting nitrates (20.8%) and/or long-acting nitrates (11.4%). Antiplatelets agents were widely used (99.8%) as were statins (96.3%), inhibitors of the renin-angiotensin system: ACE inhibitors (60.5%) or angiotensin receptor blockers (21,5%).

The median treatment duration was 46.9 months with a large majority of patients treated at least 36 months (83.8%). The median follow-up duration was 47.5 months. The majority of patients (98.0%) had a treatment compliance between 70% and 130%.

Subgroups (elective versus urgent index PCI)

The differences in baseline characteristics between subgroups (elective *versus* urgent index PCI) were mainly those concerning ethnicity (the proportion of Asians was higher in the elective index PCI subgroup; 12.4% *versus* 2.1%, respectively), the medical history of CAD and other pathologies as well as concomitant treatments used.

The median duration of CAD was 0.4 years for patients enrolled following an elective index PCI and less than 0.1 year for patients enrolled following an urgent index PCI.

The CCS classes, considering the worst severity of angina symptoms during the 4-week period prior to the index PCI, were (subgroup elective *versus* subgroup urgent, respectively): 49.2% *versus* 26.8% in class II, 33.6% *versus* 44.6% in class III and 6.5% *versus* 26.3% in class IV. The severity of anginal symptoms prior to the index PCI was more marked in the urgent index PCI subgroup.

Medical history of stable angina was more frequently reported in patients in the elective index PCI subgroup (72.3% in subgroup elective *versus* 34.9% in subgroup urgent) while medical history of unstable angina and myocardial infarction were more frequently reported for patients in the urgent index PCI subgroup (28.8% *versus* 50.3% and 38.0% *versus* 61.8%, respectively).

The intake of antianginal therapy was similar in each subgroup of index PCI (93.9% in subgroup elective *versus* 91.9% in subgroup urgent) and most patients were prescribed beta-blockers in either group (82.9% *versus* 85.2%, respectively). Regarding preventive treatments, ACE inhibitors were more frequently prescribed in urgent index PCI subgroup (55.4% *versus* 67.5%, respectively) while ARBs were more frequently prescribed in elective index PCI subgroup (24.6% *versus* 17.2%, respectively).

Table 2 - Demographics and baseline characteristics - ES_{ana} (N = 6007)

		Trimetazidine (N = 2998)	Placebo (N = 3009)	All (N = 6007)
Age (years)	Mean ± SD	61.1 ± 9.6	60.7 ± 9.8	60.9 ± 9.7
Male	n (%)	2311 (77.1)	2313 (76.9)	4624 (77.0)
Caucasian	n (%)	2546 (84.9)	2578 (85.7)	5124 (85.3)
BMI (kg/m²)	Mean ± SD	28.7 ± 4.3	28.5 ± 4.2	28.6 ± 4.3
Supine SBP (mmHg)	Mean ± SD	128.1 ± 14.4	127.7 ± 14.1	127.9 ± 14.2
Supine DBP (mmHg)	Mean ± SD	76.4 ± 9.0	76.5 ± 9.0	76.4 ± 9.0
Supine HR (beats/min)	Mean ± SD	66.3 ± 9.6	66.5 ± 9.5	66.4 ± 9.6
History of CAD				
CAD duration (years)	Mean ± SD	2.8 ± 5.2	2.8 ± 5.0	2.8 ± 5.1
	Median	0.25	0.25	0.25
Time between index PCI and randomisation (days)	Mean ± SD	12.5 ± 9.0	12.4 ± 9.0	12.5 ± 9.0
	Median	11.0	11.0	11.0
LVEF (%)	Mean ± SD	57.8 ± 8.6	57.8 ± 8.9	57.8 ± 8.8
Medical and surgical history				
Risk factors				
Hypertension	n (%)	2490 (83.1)	2482 (82.5)	4972 (82.8)
Dyslipidaemia	n (%)	1931 (64.4)	1978 (65.7)	3909 (65.1)
Diabetes	n (%)	831 (27.7)	839 (27.9)	1670 (27.8)
Diabetes treated by insulin	n (%)	249 (8.3)	221 (7.3)	470 (7.8)
Cardiovascular medical history				
Stable angina	n (%)	1701 (56.7)	1699 (56.5)	3400 (56.6)
Myocardial infarction	n (%)	1448 (48.3)	1433 (47.6)	2881 (48.0)
Unstable angina	n (%)	1128 (37.6)	1142 (38.0)	2270 (37.8)
Heart failure	n (%)	760 (25.4)	759 (25.2)	1519 (25.3)
Peripheral artery disease	n (%)	212 (7.1)	209 (7.0)	421 (7.0)
ACS	n (%)	152 (5.1)	153 (5.1)	305 (5.1)
Stroke	n (%)	121 (4.0)	118 (3.9)	239 (4.0)
TIA	n (%)	31 (1.0)	36 (1.2)	67 (1.1)
Surgical history				
Coronary revascularisation (except index PCI)	n (%)	1002 (33.4)	1025 (34.1)	2027 (33.7)
Concomitant treatments related to CAD				
All	**n (%)**	**2998 (100)**	**3008 (100)**	**6006 (100)**
Antianginal therapies	n (%)	2778 (92.7)	2812 (93.5)	5590 (93.1)
Beta-blockers	n (%)	2508 (83.7)	2530 (84.1)	5038 (83.9)
Short-acting nitrates	n (%)	608 (20.3)	640 (21.3)	1248 (20.8)
Long-acting nitrates	n (%)	339 (11.3)	344 (11.4)	683 (11.4)
CCBs	n (%)	828 (27.6)	827 (27.5)	1655 (27.6)
Antiplatelet agents	n (%)	2988 (99.7)	3004 (99.8)	5992 (99.8)
Anticoagulants	n (%)	139 (4.6)	122 (4.1)	261 (4.3)
Lipid-lowering agents	n (%)	2887 (96.3)	2917 (96.9)	5804 (96.6)
ACE inhibitors	n (%)	1826 (60.9)	1809 (60.1)	3635 (60.5)
ARBs	n (%)	636 (21.2)	655 (21.8)	1291 (21.5)
Diuretics (excl. aldosterone antagonists)	n (%)	714 (23.8)	751 (25.0)	1465 (24.4)
Aldosterone antagonists	n (%)	177 (5.9)	192 (6.4)	369 (6.1)

n Number of patients; Percentages are based on N and have been rounded to one decimal place.
For concomitant treatments number of patients having taken at least one concomitant treatment related to CAD.
Treatments were coded using WHO-DD 2018.1.
ACE Angiotensin Converting Enzyme; ACS Acute Coronary Syndrome; ARB Angiotensin II Receptor Blockers; CAD Coronary Artery Disease; CCB Calcium channel blocker; LVEF Left Ventricular Ejection Fraction; PCI Percutaneous Coronary Intervention; TIA Transient Ischaemic Attack; excl. excluding.

EFFICACY RESULTS

Primary Composite Endpoint: ES_{ana}

In the ES_{ana} (N = 6007), the PCE of efficacy (first event of cardiac death, hospitalisation for cardiac event, recurrent/persistent angina leading to adding, switching or increasing the dose of an antianginal therapy, or to performing a coronary angiography) was attained by 700 patients (23.3%; annual incidence rate of 7.0%py) in the trimetazidine group *versus* 714 patients (23.7%; 7.1%py) in the placebo group. The estimated hazard ratio was 0.98 (95% CI [0.88 ; 1.09], p = 0.727), using the Cox model adjusted on treatment, nature of index PCI and country.

Thus, there was no statistically significant difference in the risk of occurrence of an event of the PCE between the 2 treatment groups. The PCE was driven mainly by hospitalisation for cardiac events (314 events in the trimetazidine group *versus* 320 events in the placebo group), followed by angina that led to a change in antianginal therapy (245 *versus* 235, respectively) and angina that led to a coronary angiography (108 *versus* 112, respectively). Cardiac death was the least frequent event within the composite endpoint (33 *versus* 47, respectively).

The sensitivity analyses as well as the analysis in the RS provided similar results.

Major secondary composite endpoint (MSCE): ES_{ana}

The MSCE of efficacy was the first event between the 4 components of PCE with 2 additional components: evidence of ischaemia leading to adding, switching or increasing the dose of an antianginal therapy and evidence of ischaemia leading to performing a coronary angiography.

The additional components in the MSCE were relatively rare, thus in the ES_{ana} the overall event rate did not vary much from the PCE, with 706 patients (23.6%, 7.1%py) in the trimetazidine group *versus* 723 patients (24.0%; 7.3%py) in the placebo group. The estimated hazard ratio using the adjusted Cox model was 0.98 (95% CI [0.88 ; 1.08]), indicating no treatment effect.

Table 3 - Incidence of efficacy endpoints - Primary composite endpoint and major secondary composite endpoint including their components - ES_{ana} (N = 6007)

	Trimetazidine (N = 2998)				Placebo (N = 3009)			
	NPY	n	%	%py	NPY	n	%	%py
Primary Composite Endpoint (PCE) of efficacy	**10010**	**700**	**23.3**	**7.0**	**9995**	**714**	**23.7**	**7.1**
Cardiac death		33	1.1	0.3		47	1.6	0.5
Hospitalisation for cardiac event		314	10.5	3.1		320	10.6	3.2
Angina leading to coronary angiography		108	3.6	1.1		112	3.7	1.1
Angina leading to change in anti-anginal therapies		245	8.2	2.4		235	7.8	2.4
Major Secondary Composite Endpoint (MSCE) of efficacy	**9994**	**706**	**23.5**	**7.1**	**9977**	**723**	**24.0**	**7.2**
Cardiac death		33	1.1	0.3		47	1.6	0.5
Hospitalisation for cardiac event		309	10.3	3.1		319	10.6	3.2
Angina leading to coronary angiography		108	3.6	1.1		112	3.7	1.1
Angina leading to change in anti-anginal therapies		245	8.2	2.5		234	7.8	2.3
Ischaemia (without angina) leading to coronary angiography		9	0.3	0.1		8	0.3	0.1
Ischaemia (without angina) leading to treatment change		2	0.1	< 0.1		3	0.1	< 0.1

N number of patients at risk
NPY number of patient-years (i.e. time to first event or, if no event, time to censor)
n number of patients having experienced the endpoint
% crude incidence rate 100 x (n/N)
%py annual incidence rate (i.e. number of patients having experienced the endpoint for 100 patient-years at risk, %py=100(n/NPY)).*

Other secondary endpoints: ES_{ana}

Each other secondary endpoint was analysed in terms of time to first event and showed no relevant effect of treatment (also the case for the analysis of recurrent secondary endpoints).

Following the index PCI, the severity of anginal symptoms occurring since the previous visit was considered at each visit starting from M001. At M001, 18.0% of patients had a CCS class II or more in the trimetazidine group *versus* 18.2% in the placebo group. These proportions decreased over the study to 9.8% *versus* 10.0% at last post-baseline visit, respectively. The percentage of patients having at least 1 angina episode within the 4 weeks preceding the visit was 16.8% *versus* 17.9% at M001 and decreased regularly to 7.9% *versus* 8.1% at last post-baseline visit. There was no relevant change in the mean number of antianginal drugs taken at any visit. The percentage of patients taking short-acting nitrates at M001 was low (5.6% *versus* 6.5%) and decreased to the last post baseline visit (3.0% *versus* 3.4%).

Results of the SAQ scores showed a good quality of life in both treatment arms from the first assessment at M001. No clear changes over twelve months were observed and no between group differences evolved, in any of the 5 dimensions (angina frequency, angina stability, physical limitation, treatment satisfaction and disease perception).

Similarly, the EQ-5D index score confirmed the sustained and good quality of life of patients with high QoL scores from baseline to the M012 assessment in both treatment groups.

Subgroups analysis
The effect of treatment on the PCE, MSCE and other secondary efficacy endpoints in the subgroups (elective/urgent index PCI) showed results that were consistent with the overall analysis.

SAFETY RESULTS
The main focus of the analyses was TEAEs (defined as AEs that occurred, worsened or became serious between the first IMP intake and the last IMP intake + 2 days). The patient having received the study treatment without randomisation, was counted in the corresponding treatment group. Unless specified, the following results are presented in the SS_{ana}.

The primary safety endpoint was the annual overall incidence rate of a first serious TEAE according to the investigator or sponsor opinion occurring during the treatment period. A total of 3077 serious TEAEs were reported in 1219 patients (40.9%, 11.3%py) in the trimetazidine group *versus* 2944 in 1230 patients (41.1%, 11.4%py) in the placebo group. The difference between the groups (trimetazidine *minus* placebo) in annual incidence rate and its associated confidence interval were estimated at -0.09 (95% CI [-0.99;0.81]), using a normal approximation. Thus, there was no difference in the risk of primary safety endpoint between the 2 treatment groups.

TEAEs in the SS_{ana}, (serious or not) were reported in 2152 patients (72.1%, 20.0%py) in the trimetazidine group *versus* 2187 patients (73.1%, 20.3%py) in the placebo group (see summary table below). The percentage of patients with at least one TEAE tended to be similar and balanced between both treatment group in the SS_{ana}. The most frequently reported SOCs in both groups were cardiac disorders, vascular disorders, metabolism and nutrition disorders, infections and infestations. The PTs that were more frequently observed in either group were (in order of decreasing difference; trimetazidine *versus* placebo, respectively): hypertension (12.8%, 3.5%py *versus* 13.6%, 3.8%py), angina pectoris (11.2%, 3.1%py *versus* 10.8%, 3.0%py), angina unstable (9.1%, 2.5%py *versus* 8.7%, 2.4%py), type 2 diabetes mellitus (6.5%, 1.8%py *versus* 6.1%, 1.7%py) and acute MI (4.0%, 1.1%py *versus* 3.9%, 1.1%py).

Severe TEAEs: At least one severe TEAE was reported by 14.5% (4.0%py) of patients in the trimetazidine group *versus* 12.7% (3.5%py) of patients in the placebo group. The difference between the 2 groups in the most frequently reported events was mainly due to severe cardiac disorders (7.1, 2.0%py *versus* 5.9%, 1.6%py).

TEAEs considered as treatment-related were reported in 85 patients (2.8%, 0.8%py) in the trimetazidine group *versus* 98 patients (3.3%, 0.9%py) in the placebo group. The most frequently reported events were (trimetazidine *versus* placebo, respectively): tremor (0.3%, 0.1%py *versus* 0.1%, < 0.1%py), headache (0.1%, < 0.1%py *versus* 0.2%, 0.1%py), thrombocytopenia (0.1%, < 0.1%py *versus* 0.2%, 0.1%py), and vertigo (0.2%, 0.1%py *versus* 0.1%, < 0.1%py).

Adverse Events of Interest (AEIs) were reported without relevant differences between the 2 treatment groups over the treatment period as described below. A total of 9 patients (< 0.1%py) were reported with Parkinson's syndrome in the trimetazidine group (8 cases of Parkinson's disease and 1 of drug-induced parkinsonism) *versus* 5 patients (< 0.1%py) in the placebo group (all with Parkinson's disease).
The proportion of patients reporting coagulation disorders and non-traumatic haemorrhages was similar between treatment groups (198 patients [1.8%py] in both treatment groups). Hepatic disorders, arterial hypotension, falls, serious skins disorders, thrombocytopenia and agranulocytosis were each reported with fairly similar incidence rates in the 2 treatment groups (≤ 1.5%py with estimate of the difference < 0.2%py; given by decreasing order of incidence rates).

The table below summarises the main results of AEs in the SS_{ana}.

Table 4 - Overall summary of adverse events - SS_{ana} (N = 5973)

On-treatment events (unless stated)	Trimetazidine (N = 2983; NPY* = 10751)			Placebo (N = 2990; NPY* = 10763)		
	n	%	%py	n	%	%py
Patients having reported at least one:						
EAE (during the study)	2188	73.3	18.7	2219	74.2	19.0
TEAE	2152	72.1	20.0	2187	73.1	20.3
Treatment-related TEAE	85	2.8	0.8	98	3.3	0.9
Patients having experienced at least one:						
Serious EAE (including death)	1268	42.5	10.9	1285	43.0	11.0
Serious TEAE (including death)	1219	40.9	11.3	1230	41.1	11.4
Treatment-related serious TEAE	27	0.9	0.3	25	0.8	0.2
Severe TEAEs	432	14.5	4.0	381	12.7	3.5
TEAE leading to IMP withdrawal:	218	7.3	2.0	201	6.7	1.9
Serious TEAE leading to IMP withdrawal	157	5.3	1.5	131	4.4	1.2
Treatment-related TEAE leading to IMP withdrawal	52	1.7	0.5	51	1.7	0.5
Treatment-related serious TEAE leading to IMP withdrawal	21	0.7	0.2	14	0.5	0.1
Deaths:						
Patients who died on-treatment	108	3.6	1.0	120	4.0	1.1
Patients who died in the study*	142	4.7	1.2	149[a]	5.0	1.3
Patients having reported at least one on-treatment Adverse Event of Interest:**						
Neurological symptoms	230	7.7	2.1	209	7.0	1.9
Coagulation disorders et non-traumatic haemorrhages	198	6.6	1.8	198	6.6	1.8
Thrombocytopenia	68	2.3	0.6	67	2.2	0.6
Agranulocytosis	3	0.1	<0.1	3	0.1	<0.1
Falls	100	3.4	0.9	83	2.8	0.8
Arterial hypotension	107	3.6	1.0	116	3.9	1.1
Serious skin disorders	45	1.5	0.4	31	1.0	0.3
Hepatic disorders	152	5.1	1.4	164	5.5	1.5

AEI Adverse Event of Interest; EAE Emergent Adverse Event; TEAE Treatment Emergent Adverse Event
n number of patients having experienced at least one event
NPY number of patient-years (i.e. time to censor)
% crude incidence rate 100(n/N)*
%py annual incidence rate (i.e. number of patients having experienced at least one event for 100 patient-years %py = 100(n/NPY))*
** NPY were different from the column title for analyses of events during the study (NPY = 11679 in trimetazidine and 11674 in placebo.*
*** Adverse Events of Interest were all adjudicated*
[a] Additionally, 2 patients excluded from the SS and SS_{ana}, due to no IMP intake, died during the study (sudden death in both). These events were counted in the ES_{ana}.

***Deaths**:* In the during-the-study analysis, there were 142 deaths (4.8%, with 161 associated serious EAEs) *versus* 149 (5.0%, with 178 associated serious EAEs), respectively.

The during-the-treatment period analysis indicated 108 deaths (3.6%) in the trimetazidine group (with 118 associated serious TEAEs) *versus* 120 (4.0%) in the placebo group (with 142 associated serious TEAEs).
The most frequent causes of death in both groups were (trimetazidine *versus* placebo, respectively): fatal outcomes (High Level Group Term [HLGT]; mostly sudden unexplained deaths): 20 patients (0.7%) *versus* 26 patients (0.9%); respiratory and mediastinal neoplasms (HGLT): 14 patients (0.5%) *versus* 6 patients (0.2%); coronary artery disorders (HLGT): 12 patients (0.4%) *versus* 12 patients (0.4%); Gastrointestinal neoplasms (HGLT): 10 patients (0.3%) *versus* 15 patients (0.5%); central nervous system vascular disorders (HLGT): 9 patients (0.3%) *versus* 8 patients (0.3%); cardiac arrhythmias (HLGT): 8 patients (0.3%) *versus* 9 patients (0.3%); and heart failures (HGLT): 6 patients (0.2%) *versus* 12 patients (0.4%).

Serious TEAEs: The most frequently reported serious TEAEs by SOC in both groups were cardiac disorders (trimetazidine *versus* placebo, respectively): 22.5% (6.2%py) *versus* 22.8% (6.3%py); nervous disorders: 6.5% (1.8%py) *versus* 5.7% (1.6%py); and vascular disorders: 5.0% (1.4%py) *versus* 5.4% (1.5%py). The more frequently reported PTs (trimetazidine *versus* placebo, respectively) were: angina unstable: 8.6% (2.4%py) *versus* 8.3% (2.3%py); angina pectoris: 6.6% (1.8%py) *versus* 6.9% (1.9%py); acute MI: 4.0%, (1.1%py) *versus* 3.9%, (1.1%py); atrial fibrillation: 3.0% (0.8%py) *versus* 3.1% (0.9%py); and cardiac failure: 2.2% (0.6%py) *versus* 1.8% (0.5%py).

A serious TEAE led to IMP withdrawal in 5.3% (1.5%py) of patients in the trimetazidine group *versus* 4.4% (1.2%py) in the placebo group. The overall most frequently reported TEAEs of this type were (trimetazidine *versus* placebo, respectively): angina unstable (0.3%, 0.1%py *versus* 0.2%, < 0.1%py); acute MI (0.3%, 0.1%py *versus* 0.2%, < 0.1%py); tremor (0.3%, 0.1%py *versus* 0.1%, < 0.1%py); and ischaemic stroke (0.3%, 0.1%py *versus* 0.1%, < 0.1%py).

No relevant safety concerns and no clinically relevant differences were reported on treatment between groups regarding clinical laboratory parameters (biochemical, coagulation and haematological parameters).

No relevant safety concerns, nor clinically relevant changes over time were reported concerning vital signs (blood pressures and heart rate).

CONCLUSION

The ATPCI study (CL3-06790-010) was a phase III, international, multicentre, double-blind, placebo-controlled, event-driven study randomised in 2 parallel and balanced arms (trimetazidine MR 35 mg or placebo, twice daily) in patients with Coronary Artery Disease (CAD) having undergone a recent and successful Percutaneous Coronary Intervention (PCI) and receiving recommended post-PCI treatments (both secondary prevention and regular antianginal therapies as per current guidelines). Patients were treated for up to 5 years, while the median duration was 46.9 months.

The randomised groups were closely matched on demographic variables and disease characteristics (the randomisation was stratified on country and nature of index PCI [elective or urgent]). The population was well-medicated and the treatment was in accordance with current guidelines.

The Efficacy Analysis Set comprised 6007 patients (2998 in the trimetazidine group and 3009 in the placebo group). The incidence of the primary composite endpoint (PCE; 1414 events in total; defined as time to first event of cardiac death, hospitalisation for a cardiac event, persistent/recurrent angina leading to adding, switching or increasing the dose of an antianginal therapy or to performing a coronary angiography) was reached by 23.3% (7.0%py) of the patients in the trimetazidine group *versus* 23.7% (7.1%py) in the placebo group, with a hazard ratio of 0.98 ([0.88 ; 1.09]; p = 0.727). In this population of CAD patients with recent successful PCI, trimetazidine did not change the clinical outcome. Analyses of the major secondary efficacy endpoint and the other secondary efficacy endpoints similarly showed no evidence of benefit.

In the Safety Analysis Set (N = 5973), the annual incidence rate of the primary safety endpoint (all first events of serious TEAE during the treatment period) was 11.3%py (overall incidence: 40.9%) in the trimetazidine group *versus* 11.4%py (41.1%) in the placebo group with an estimated difference in annual incidence of -0.09 (95% CI [-0.99 ; 0.81]), evidencing no meaningful difference in the overall rate of serious TEAE between the treatment groups.

No relevant between-group differences were observed in the incidence of adverse events of interest, including Parkinson-like disorders or cases of arterial hypotension. None of the analyses of adverse events emergent during the treatment period, nor of laboratory parameters, nor vital signs showed relevant between-group differences.

The ATPCI study showed that, in this population of CAD patients with recent successful PCI treated with pharmacological therapies of the current highest standard of care, the addition of trimetazidine does not provide benefit on improvement of prognosis with reduction of cardiac events. The safety profile of the drug was good, with no safety issues evidenced.

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