Supplementary Materials

The efficacy and safety of trimetazidine in patients having been treated by percutaneous coronary intervention (ATPCI): Results of a randomised double-blind placebo-controlled trial

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Supplementary Table S1: Main inclusion/exclusion criteria

Inclusion criteria
Men or women ≥21 years and <85 years
Evidence of single or multivessel coronary artery disease
Had undergone successful PCI as planned by the operator, and indicated because of angina pectoris in a context of stable angina (elective PCI) or acute presentation for unstable angina or NSTEMI (urgent PCI) with no further revascularization planned
Stable antianginal treatment (if applicable)
Informed consent obtained
Exclusion criteria
Index PCI carried out in the absence of prior chest pain
Index PCI carried out as part of the management of STEMI or within 4 weeks after a STEMI
Procedure-related Q-wave MI or procedural acute myocardial injury
Further revascularization planned during the study
Severe heart failure (NYHA class IV), severe valve disease, severe uncontrolled rhythm disturbance, uncontrolled arterial hypertension, or severe renal failure
Acute MI, repeat revascularization, or hospitalization/prolonged hospitalization due to a cardiovascular event between the index PCI and inclusion
Current or previous movement disorders such as Parkinsonian symptoms, restless leg syndrome, tremors, and gait instability of central origin
Ongoing treatment with trimetazidine, or known hypersensitivity to trimetazidine
Ongoing treatment with perhexiline or ranolazine

MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

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Supplementary Table S2: Definitions used by the Endpoint Adjudication Committees

A - Definitions used for adjudication of study efficacy endpoints (from the Cardiovascular Endpoints Adjudication Committee procedure)

1 All cause-mortality

This will consist of all deaths.

2 Cardiac Death

The cause of cardiac death will be classified as follows:
- Acute myocardial infarction
- Heart failure
- Coronary artery procedures
- Other cardiac procedures
- Arrhythmia
- Other cardiac death

3 Death From Acute Myocardial Infarction

Death occurring up to 28 days after a documented acute myocardial infarction unless there is an obvious other cause of death, or autopsy findings showing a recent myocardial infarction or an intracoronary thrombus.

4 Death From Heart Failure

Death occurring when at least one of the components of the heart failure definition is present even if the terminal event is arrhythmia, unless there is an obvious other cause of death.

5 Death Related To Coronary Artery Procedure

Death related to a coronary artery procedure (investigation/procedure/operation), unless there is an obvious other cause of death.

6 Death Related To Other Cardiac Procedure

Death related to a cardiac procedure (investigation/procedure/operation, other than coronary artery procedure), unless there is an obvious other cause of death.

7 Arrhythmic Death

Death related to a documented fatal arrhythmia.

8 Other Cardiac Death

Death caused by a cardiac cause, other than the ones mentioned before.

9 Other Cardiovascular Death

The pre-defined causes of other non-cardiac cardiovascular deaths are:
- Stroke
- Pulmonary embolism
- Acute aortic syndrome
- Peripheral arterial ischemia
- Other

10 Non-Cardiovascular Death

Death will be considered non-cardiovascular only if an unequivocal and documented cause can be established.

Predefined causes of non-cardiovascular death are:
- Cancer
- Gastrointestinal causes
- Infection
- Liver disease
- Renal failure
- Respiratory failure
- Suicide
- Trauma / violent death

- Other

11 Death Of Unknown Cause

Deaths of unknown cause will correspond to deaths for which it is not possible to specify whether they are cardiovascular or not. When there are multiple potential causes of death, the adjudicators should define the most probable cause. The mode of death (sudden, not sudden, non-classifiable) should be indicated for the deaths of unknown cause.

12 Sudden Death

Sudden death refers to a death that occurs unexpectedly and includes the following scenarios:
- death witnessed and occurring without new or worsening symptoms,
- death witnessed within 60 min of the onset of new or worsening symptoms,
- unwitnessed death in a subject seen alive and clinically stable ≤24 h before being found dead without any evidence supporting a specific cause of death.

13 Cardiac Event

In the context of this study cardiac event corresponds to one of these events:
- Acute myocardial infarction (STEMI/NSTEMI/Unknown)
- Unstable angina
- Heart Failure
- Sustained ventricular tachycardia
- Resuscitated cardiac arrest
- Coronary revascularization

14 Acute Myocardial Infarction

14.1. Criteria for acute myocardial infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

    • Symptoms of ischemia.
    • New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
    • Development of pathological Q waves in the ECG.
    • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
    • Identification of an intracoronary thrombus by angiography or autopsy.

- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

- Percutaneous Coronary Intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99^{th} percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.

- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

14.2. Universal classification of myocardial infarction

According to *Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. Eur Heart J, 2012; 33:2551-2567.*

15 Heart Failure

Heart failure is defined by the presence of symptoms such as dyspnea or fatigue either at rest or during exercise, and/or signs of fluid retention (e.g. peripheral edema, pulmonary edema, raised jugular venous pressure, ascites…), leading to hospitalization (or prolongation of hospitalization).

These symptoms should be associated with:
- The objective evidence of heart failure such as abnormal chest X-ray (congestion signs, pleural fluid…), or abnormal echocardiography (dysfunction, pericardial fluid…), or abnormal cardiac imaging, or BNP increase; AND
- The requirement or increase of dedicated treatment for heart failure such as intravenous/intramuscular or oral medications for heart failure (diuretics, vasodilators, positive inotropic agents…).

Patients with cardiogenic shock will fulfill the definition of heart failure.

16 Angina Pectoris

<table>
<tr><th colspan="3">Clinical classification of chest pain</th></tr>
<tr><td rowspan="2">Exertional angina</td><td>Definite exertional angina</td><td>Meets three of the following characteristics:
Chest discomfort of characteristic quality and duration
Provoked by exertion or emotional stress
Relieved by rest and/or short acting nitrates</td></tr>
<tr><td>Probable exertional angina</td><td>Chest discomfort of characteristic quality and duration
and one of the two other characteristics:
provoked by exertion or emotional stress,
OR, relieved by rest and/or short acting nitrates</td></tr>
<tr><td colspan="2">Resting angina</td><td>Chest discomfort of characteristic quality and duration, irrespective of the circumstances in which it occurs</td></tr>
</table>

17 Ischemia (Documented By Stress Imaging)

Confirmed ischemia documented by:

- Stress echography
- Scintigraphic stress test
- Stress cardiac magnetic resonance
- Stress myocardial CT perfusion

18 Evidence-Based Antianginal Therapy

Evidence-based antianginal therapy include drugs with a current antianginal indication as well as drugs that will obtain an antianginal indication during the study.

Currently evidence-based antianginal therapy includes drugs from the following therapeutic classes:
- Beta-blockers
- Calcium channel blockers (dihydropyridine and non-dihydropyridine)
- Long acting nitrates
- Nicorandil
- Ivabradine
- Molsidomine
- Ranolazine
- Perhexiline
- Trimetazidine

19 Change Antianginal Therapy

Defined as being either:
- an increase in the dose of an existing antianginal medication,
- or the addition of an antianginal medication,
- or a switching of one antianginal medication for another.

20 Hospitalisation For Coronary Revascularization

The coronary revascularizations in response to angina (ACS or not) and/or ischemia should be considered as hospitalization for coronary revascularization.
The following revascularizations should not fall within the definition of "hospitalization for coronary revascularization":
- the second planned revascularization (and the following) in case of staged procedure for cardiac event (including revascularization planned during the study but decided before inclusion, without respectingthe selection criteria),
- a revascularization following a planned angiography not performed in response to angina or ischemia.

21 Coronary Revascularization

Coronary revascularization includes:
- PCI
- CABG

22 Ischemic Chest Pain

Ischemic chest pain includes:
- Acute MI (NSTEMI, STEMI, Unknown)
- Unstable angina
- Angina leading to performing a coronary angiography or leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies.

23 Hospitalization / Prolongation Of Hospitalization

An admission to hospital is defined as any attendance at hospital requiring completion of the hospital admission procedures (hospitalization includes day care).

An event leading to the prolongation of an ongoing hospitalization decided for another reason, with or without the transfer of the patient to a specialized hospital department, will be considered as a hospitalization.

All coronary revascularizations will be considered as hospitalization.

24 Coronary Angiography

Invasive coronary angiography (with coronary catheterization). This excludes coronary CT angiography and coronary MR angiography.

25 Sustained Ventricular Tachycardia

A row of ventricular ectopic beats lasting more than 30 seconds.

26 Unstable Angina

Unstable angina is defined as recurrence or worsening of angina pectoris (or equivalent type of ischemic discomfort) sufficient to warrant hospitalization (or prolongation of hospitalization).

In addition, recurrence or worsening of angina should be confirmed by one or more of the following:
- ECG changes: new or worsening ST or T waves changes on ECG in the absence of LVH and permanent LBBB,
- Evidence of ischemia at low threshold on functional testing,
- Coronary revascularization performed as a consequence of ischemic symptoms".

B - Definitions of adverse events of interest used for adjudication (from the Safety Endpoints Adjudication Committee procedure)

1. Neurological Events

Neurological symptoms

This will consist of clinically significant symptoms resulting from any disorder of the body central nervous system.

Parkinson' syndrome

A Parkinson's syndrome or parkinsonism is a set of symptoms including bradykinesia (or slowness with decrement and degradation of repetitive movements) and plastic rigidity, most often associated with resttremor and caused by a central dopaminergic deficiency. Parkinson's disease is the most common neurodegenerative cause of parkinsonism.

In addition to neurodegenerative causes, Parkinsonism can also be a symptom of drug-related (drug-induced Parkinsonism), vascular, infectious, toxic, structural causes.

Parkinson's disease

Parkinson's disease is a motor clinical syndrome, with levodopa-responsive parkinsonism, typical clinical characteristics (rest tremor, rigidity, bradykinesia, and gait impairment), and an absence of markers suggestive of other disease.

Probable: at least 2 out of rest tremor, bradykinesia, rigidity.
Possible: only 1 out of rest tremor, bradykinesia, rigidity.

Atypical parkinsonism

Parkinson's syndrome including other symptoms than those of Parkinson's disease (rest tremor, rigidity, bradykinesia, and gait impairment) and not responding to L-dopa.

Drug induced Parkinsonism

Patient with Parkinson's syndrome treated with drugs known to induce Parkinsonism.

Abnormal involuntary movements other than tremor

Movement disorders characterized by involuntary movements that may occur in isolation or in combination other than tremor.

Mild Cognitive impairment

Mild cognitive impairment is a syndrome defined as cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life. The criteria for Mild Cognitive Impairment include: memory problems, objective memory disorder, absence of other cognitive disorders or repercussions on daily life, normal general cognitive functioning and absence of dementia.

Severe Cognitive impairment

Dementia.

Somnolence

Somnolence is a subjective feeling of an imperious need of sleep in unusual time and environmental conditions.

Tremor

Tremor is an unintentional (involuntary), rhythmical alternating movement that may affect the muscles of any part of the body. Tremor is caused by the rapid alternating contraction and relaxation of muscles and is a common symptom of diseases of the nervous system.

Among them, essential tremor is the most common. It's an action tremor, postural (patients typically experience tremors when the arms are held up, such as while reading a newspaper) or kinetic (occur during voluntary movements like eating, drinking or writing). The tremors also may affect the head, voice, tongue and legs and worsen with stress, fatigue and stimulant medications.

Disorientation

A disorientation is defined as inadequate or incorrect perception of place, time, or identity. Disorientation is one of the symptoms of confusional syndrome and may be due to multiples causes as organic (dementia, brain tumor, metabolic, vascular, or infectious …), toxic (drug or alcohol intoxication), or psychiatric (less commonly after severe stress).

Hallucination

A hallucination is a profound distortion in a person's perception of reality. A hallucination is a « perception without object to perceive » with complete conviction that it exists in reality, this is a wrong perception. A hallucination may be a sensory experience in which a person can see, hear, smell, taste, or feel something. Hallucinations may also occur in confusional syndromes and have multiple etiologies.

Convulsion

A convulsion is an abnormal, involuntary contraction of muscles most typically seen with certain seizure disorders. These contractions may be tonic or clonic and they may be focal or generalized. Possible causes of convulsions include vascular, metabolic, toxic, hypoxic and traumatic (head injury) causes.

Restless legs syndrome

Restless legs syndrome (RLS) is a neurological disorder characterized by throbbing, pulling, or other unpleasant sensations in the legs with an uncontrollable urge to move them. Symptoms occur primarily at night when a person is relaxing or at rest and can increase in severity during the night. Moving the legs relieves the discomfort.

In most cases, the cause of RLS is unknown, but appears to be related to the following factors or conditions: low levels of iron, kidney failure, diabetes, and peripheral neuropathy. Certain medications, alcohol and sleep privation may aggravate symptoms.

Gait instability

Gait instability is any walking abnormality.

Only gait instability suspected of being of central origin will be adjudicated.

Stroke

Stroke is an acute episode ≥ 24h (according to AHA/ASA) of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

Transient ischemic attack

Transient ischemic attack is a transient episode < 24h (according to AHA/ASA) of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia without acute infarction.

2. Haematological Events

Coagulation disorders

Coagulation disorders are defined as prolongation of coagulation parameters as follows:

- in the absence of anticoagulant treatments:
  - o INR> 1.5,
  - o Prothrombin ratio < 50%,
  - o Prothrombin time > 1.5-fold the local laboratory normal values,
  - o aPTT > 1.2-fold the local laboratory normal values.
- in the presence of anticoagulant treatments:
  - o INR > 4 (in presence of vitamin K antagonists),
  - o Prothrombin ratio < 25% (in presence of vitamin K antagonists),
  - o Prothrombin time > 3-fold the local laboratory normal values (in presence of vitamin K antagonists),
  - o aPTT > 4-fold the local laboratory normal values (in presence of heparin),
  - o aPTT > 2-fold the local laboratory normal values (in presence of vitamin K antagonists).

Thrombocytopenia

Thrombocytopenia is defined as:

- platelets values < 100 G/L and,
- for platelets between 100 G/L and 150 G/L: all decreases > 30% compared to baseline.

Agranulocytosis

Agranulocytosis is defined as neutrophils values < 0.5 G/L.

Hemorrhages

Hemorrhages identified using a pre-defined list of events based on MedDRA.

Bleeding grade and classification

From *Webert KB, Arnold DM, Lui Y, Carruthers J, Arnold E, Heddle NM. A new tool to assess bleeding severity in patients with chemotherapy-induced thrombocytopenia. Tansfusion. 2012;52:2466-2474.*

3. Other Events

Falls

Defined as to drop suddenly from an erect position, to descend by the force of gravity from a higher to a lower place.

All falls, mechanical or not, will be adjudicated. Consequences of falls such as fractures, contusion, hematoma etc.… will not be adjudicated.

Medical consequences:

- Severe: with death or hospitalization.
- Not severe: other cases different from none.

Arterial hypotension:

Defined as systolic BP < 100 mmHg and/or diastolic BP < 60 mmHg measured in supine position.

Medical consequences:

- Severe: with death or hospitalization.
- Not severe: other cases different from none.

Orthostatic hypotension

Defined as a reduction of MORE THAN 20 mmHg (> 20 mmHg) for systolic BP and/or MORE THAN 10 mmHg (> 10 mmHg) for diastolic BP at 1 AND 3 minutes after standing– up as compared to the measurement in the supine position.

Serious skin disorders

A serious skin disorder is a disease affecting the skin and/or a mucous membrane considered as serious by the investigator.

Acute Generalized Exanthematous Pustulosis is an acute febrile drug eruption characterized by numerous small, primarily non-follicular, sterile pustules, arising within large areas of edematous erythema. The eruption follows a self-limiting course and will end before a week provided the causative agent (e.g. medication) is discarded. It is accompanied by fever, neutrophilia, and sometimes by facial edema, hepatitis and eosinophilia. The aetiology is 60-80 % iatrogenic *[Roujeau JC et al. Acute generalized exanthematous pustulosis. Analysis of 63 cases. Arch Dermatol 1991, 127, 1333-8.].* The mortality rate is about 5% and the differential diagnosis includes Stevens–Johnson syndrome (SJS). Contrary to SJS, in AGEP, mucosa are not affected, which means that there are no blisters in the mouth or vagina *[Rapini, Ronald P.; Bolognia, Jean L.; Jorizzo, Joseph L. (2007). Dermatology: 2-Volume Set. St. Louis: Mosby. pp. 297, 303, 308, 309]*.

DRESS is a Drug Reaction with Eosinophilia and Systemic Symptoms.

Hepatic disorders

Hepatic disorders may include events such as:
- ALAT and/or ASAT elevation > 3 ULN, alkaline phosphatase > 2 ULN without clear etiological diagnosis,
- hepatitis,
- icterus, jaundice without clear etiological diagnosis,
- biliary/gall bladder disorders (bile ducts morphological anomalies, neoplasms, infections, inflammation, lithiasis and obstruction, fibrosis),
- hepato-biliary neoplasms/mass (benign and malignant),
- hepatic vascular disorders (including ischemia, hemorrhage hemangioma, portal vein disorders, veno-occlusive disease ...),
- hepatic metabolic disorders,
- hepatic auto-immune disorders.

Supplementary Table S3: Baseline characteristics of patients of the trimetazidine group with elective or urgent index PCI - Intent to treat analysis set (n= 6007)

	Elective PCI (n=1742)	Urgent PCI (n=1256)
Demography	..	..
Age (years)	61·3 (9·2)	60·8 (10·1)
Age >=70 years old	312 (17·9%)	249 (19·8%)
Male	1345 (77·2%)	966 (76·9%)
Ethnic origin	..	..
Caucasian	1391 (79·9%)	1155 (92·0%)
Asian	213 (12·2%)	28 (2·2%)
Other	138 (7·9%)	73 (5·8%)
History of ischaemic heart disease	..	..
Number of stenosed vessels	..	..
1	917 (52·6%)	704 (56·1%)
2	571 (32·8%)	380 (30·3%)
3	254 (14·6%)	172 (13·7%)
CCS class*	..	..
I	167 (9·6%)	24 (1·9%)
II	881 (50·6%)	342 (27·2%)
III+IV	694 (39·8%)	889 (70·8%)
Left ventricular ejection fraction (%)	..	..
<40	29 (1·9%)	25 (2·3%)
40-49	150 (9·9%)	146 (13·3%)
≥50	1331 (88·1%)	931 (84·5%)
Medical history	..	..
Previous myocardial infarction	642 (36·9%)	806 (64·2%)
Previous coronary revascularization	662 (38·0%)	340 (27·1%)
Hypertension	1444 (82·9%)	1046 (83·3%)
Stroke	74 (4·3%)	47 (3·7%)
Peripheral artery disease	133 (7·6%)	79 (6·3%)
Diabetes	521 (29·9%)	310 (24·7%)
Concomitant treatment ongoing at inclusion	..	..
Anti-platelets agents	1735 (99·6%)	1253 (99·8%)
Aspirin	1703 (97·8%)	1227 (97·7%)
Clopidogrel	1475 (84·7%)	927 (73·8%)
Ticagrelor	224 (12·9%)	270 (21·5%)
Other P2Y12 inhibitors	21 (1·2%)	43 (3·4%)
Anticoagulants	77 (4·4%)	62 (4·9%)
Lipid-lowering agents	1675 (96·2%)	1212 (96·5%)
Statins	1668 (96·8%)	1210 (96·3%)
Other lipid-lowering agents	80 (4·6%)	59 (4·7%)
Angiotensin-converting enzyme inhibitors	986 (56·6%)	840 (66·9%)
Angiotensin receptor blockers	408 (23·4%)	228 (18·2%)
Diuretics (excluding aldosterone antagonists)	424 (24·3%)	290 (23·1%)
Antianginal therapy	1630 (93·6%)	1148 (91·4%)
Beta-blockers	1436 (82·4%)	1072 (85·4%)
Long-acting nitrates or molsidomine	282 (16·2%)	89 (7·1%)
CCB (dihydropiridine or not)	523 (30·0%)	305 (24·3%)
Other antianginal therapy **	404 (23·2%)	261 (20·8%)

Data are number of patients (%) or mean (SD). CCS: Canadian Cardiovascular Society. CCB: Calcium-channel blocker
* Worst class within 4 weeks before index PCI
** Short-acting nitrates, ivabradine, nicorandil, ranolazine, perhexiline and open-label trimetazidine

Supplementary Table S4: Reasons for hospitalisation for cardiac event - Intent to treat analysis set (n= 6007)

Data are number of patients having experienced the event (% calculated on patients with a primary composite endpoint for hospitalisation for cardiac event)

	Trimetazidine (n=2998)	**Placebo (n=3009)**
Hospitalisation for cardiac event	314 (100%)	320 (100%)
Acute myocardial infarction	88 (28·0%)	96 (30·0%)
Unstable angina	117 (37·3%)	111 (34·7%)
Angina and/or ischemia leading to revascularisation	73 (23·3%)	71 (22·2%)
Heart failure	48 (15·3%)	46 (14·4%)
Resuscitated cardiac arrest	4 (1·3%)	3 (0·9%)
Sustained ventricular tachycardia	0	2 (0·6%)

Supplementary Table S5: CCS classification of angina - Intent to treat analysis set (n= 6007)

Data are the number of patients (%) according to their CCS class

CCS class	Trimetazidine (N=2998)	Placebo (N=3009)
Month 1 *	n=2986	n=2998
• <2	2448 (82·0%)	2453 (81·8%)
• ≥2	538 (18·0%)	545 (18·2%)
Month 12 **	n=2930	n=2930
• <2	2488 (84·9%)	2516 (85·9%)
• ≥2	442 (15·1%)	414 (14·1%)
Last post baseline visit **	n=2992	n=3004
• <2	2698 (90·2%)	2704 (90·0%)
• ≥2	294 (9·8%)	300 (10·0%)

* Severity of angina within the first month of treatment
** Severity of angina between previous and current visit

Supplementary Table S6: Serious Treatment Emergent Adverse Events by system organ class (frequency ≥3% under trimetazidine) - Safety analysis set (n= 5973)

	Trimetazidine (N=2983)		Placebo (N=2990)	
	Number of events	Number of patients with at least an event (%)	Number of events	Number of patients with at least an event (%)
All Serious Adverse Events	**3077**	**1219 (40·9)**	**2944**	**1230 (41·1)**
Cardiac disorders	1127	671 (22·5)	1121	683 (22·8)
Nervous system disorders	273	194 (6·5)	228	171 (5·7)
Vascular disorders	185	149 (5·0)	185	160 (5·4)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	137	126 (4·2)	155	136 (4·5)
Infections and infestations	169	121 (4·1)	173	128 (4·3)
Metabolism and nutrition disorders	129	105 (3·5)	135	113 (3·8)
Gastrointestinal disorders	142	111 (3·7)	126	99 (3·3)
Injury, poisoning and procedural complications	201	118 (4·0)	141	88 (2·9)
Respiratory, thoracic and mediastinal disorders	119	90 (3·0)	114	93 (3·1)

Supplementary Table S7: Serious Treatment Emergent Adverse Events by preferred term (frequency ≥3% under trimetazidine) - Safety analysis set (n= 5973)

	Trimetazidine (N=2983)		Placebo (N=2990)	
	Number of events	Number of patients with at least an event (%)	Number of events	Number of patients with at least an event (%)
All Serious Adverse Events	**3077**	**1219 (40·9)**	**2944**	**1230 (41·1)**
Angina unstable	322	258 (8·6)	324	247 (8·3)
Angina pectoris	218	196 (6·6)	236	207 (6·9)
Acute myocardial infarction	136	120 (4·0)	126	118 (3·9)
Atrial fibrillation	97	89 (3·0)	108	94 (3·1)

Supplementary Table S8: Treatment Emergent Adverse Events by preferred term (frequency ≥3% under trimetazidine) - Safety analysis set (n= 5973)

	Trimetazidine (N=2983)		Placebo (N=2990)	
	Number of events	Number of patients with at least an event (%)	Number of events	Number of patients with at least an event (%)
All Adverse Events	**9392**	**2152 (72·1)**	**9318**	**2187 (73·1)**
Hypertension	465	381 (12.8)	479	408 (13.6)
Angina pectoris	401	333 (11.2)	390	323 (10.8)
Angina unstable	342	272 (9.1)	339	260 (8.7)
Type 2 diabetes mellitus	209	193 (6.5)	194	183 (6.1)
Acute myocardial infarction	136	120 (4.0)	126	118 (3.9)
Hypertriglyceridaemia	120	117 (3.9)	152	139 (4.6)
Atrial fibrillation	138	117 (3.9)	160	131 (4.4)
Hypercholesterolaemia	109	103 (3.5)	117	112 (3.7)
Alanine aminotransferase increased	108	100 (3.4)	105	98 (3.3)
Fall	121	99 (3.3)	93	83 (2.8)

Supplementary Table S9: ATPCI Committees – Affiliation of members

Role	Title, Name	Affiliation
Executive Committee		
Chairman	Prof. R. FERRARI, Cardiology	Azienda Ospedaliero-Universitaria di Ferrara Ospedale di Cona Cona (Ferrara) - Italy
Member	Prof. N. DANCHIN, Cardiology	Hôpital Européen Georges Pompidou Unité Clinique des Maladies Coronaires Paris - France
Member	Prof. I. FORD, Statistics	Robertson Centre for Biostatistics University of Glasgow Glasgow - UK
Member	Prof. K. FOX, Cardiology	Royal Brompton National Heart and Lung Hospital London - UK
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Member	Prof. M. TENDERA, Cardiology	3rd Division of Cardiology Medical University of Silesia Katowice - Poland
Member	Prof. P. WIDIMSKÝ, Cardiology	Depts. of Cardiology & Cardiac Surgery Third Faculty of Medicine, Charles University Prague University Hospital Kralovske Vinohrady Praha - Czech Republic
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National coordinator	Dr. M. TRIVI	Instituto Cardiovascular de Buenos Aires CABA, Buenos Aires - Argentina
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National coordinator	Prof. L. H. W. GOWDAK	São Paulo -Brazil Universidade de São Paulo Departamento de Cardiopneumologia Incor São Paulo - Brazil
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National coordinator	Prof. R.J. GIL	Klinika Kardiologii Inwazyjnej CSK MSWiA Warszawa - Poland
National coordinator	Prof. F. PINTO	Centro Hospitalar de Lisboa Norte, E.P.E. – Hospital de Santa Maria Lisbo - Portugala
National coordinator	Prof. S.J. PARK	Division of Cardiology, Asan Medical Center University of Ulsan College of Medicine Seoul - Korea
National coordinator	Prof. C. ARSENESCU-GEORGESCU	Institutul de Boli Cardiovasculare "Prof. George I.M. GEORGESCU" Iasi - Romania
National coordinator	Prof. Y.A. KARPOV	Federal State “National Medical Research Cardiology Centre” Department of angiology Moscow - Russia
National coordinator	Prof. M. OSTOJIC	Medical faculty University of Belgrade Belgrade - Serbia
National coordinator	Prof. D. PELLA	Cardio D&R s.r.o. Kosice - Slovakia
National coordinator	Dr. E. LÓPEZ DE SA	Hospital la Paz. Servicio de Cardiología Madrid - Spain
National coordinator	Prof. V. SANSOY	Cardiology Institute - Istanbul University Aksaray-Istanbul - Turkey
National coordinator	Prof. A. PARKHOMENKO	Institute. of Cardiology of AMS of Ukraine Department of reanimation and intensive therapy

		Kiev - Ukraine
National coordinator	Prof. NGUYEN LAN VIET	Vietnam Heart Institute Bach Mai Hospital Ha Noi - Vietnam

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Member	Prof. G. FRAGASSO, Cardiology	Heart Failure Clinic Istituto Scientifico San Raffaele Milano - Italy
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Safety Endpoints Adjudication Committee

Chairman	**Prof. F. STOCCHI, Neurology**	**Clinical Trial center** **Centro per lo studio e Cura Morbo di Parkinson e disturbi del Movimento** **I.R.C.C.S. San Raffaele Pisana** **Roma - Italy**
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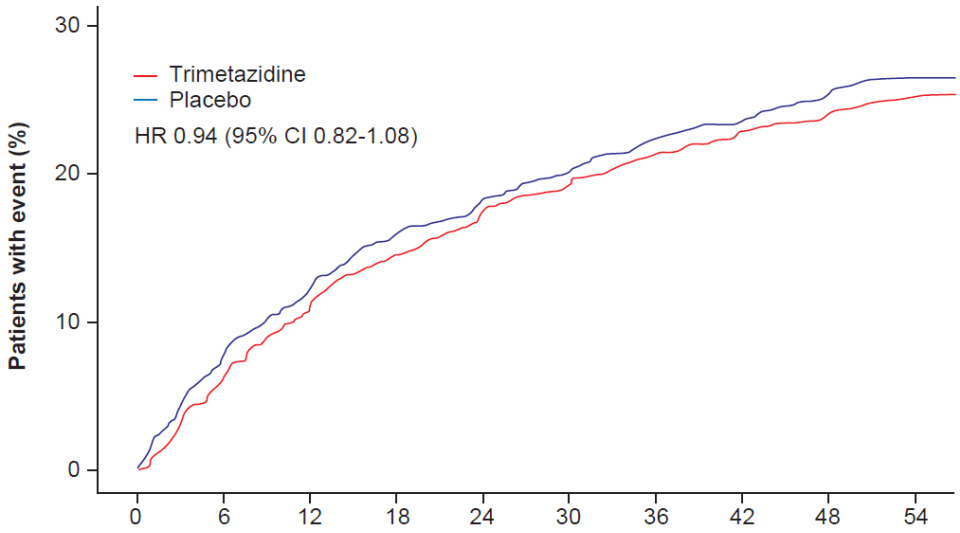
Member	Prof. O. HANON, Geriatrics	Service Gérontologie du Pr Rigaud Hôpital Broca Paris - France
Member	Prof. T. LECOMPTE, Haematology	Service d'Hématologie Département des Spécialités de Médecine Hôpitaux Universitaires de Genève Genève - Switzerland
Member	Prof. P. CACOUB, Internal Medicine	Service de médecine interne 2 Groupe hospitalier La Pitié Salpêtrière – Charles Foix Paris - France

Data Monitoring Committee

Chairman	**Prof. P.G. STEG, Cardiology**	**Hôpital Bichat-Claude-Bernard** **Service de Cardiologie** **Paris - France**
Member	Prof. C. RAPEZZI, Cardiology	Policlinico Sant'Orsola Malpighi Bologna - Italy
Member	Prof. M. VOLTERRANI, Cardiology	Cardiovascular Research Unit Department of Medical Sciences Centre for Clinical and Basic Research Istituto di Ricovero e Cura a Carattere Scientifico Rome - Italy
Member	Prof. J. BENICHOU, Statistics	Bihorel - France

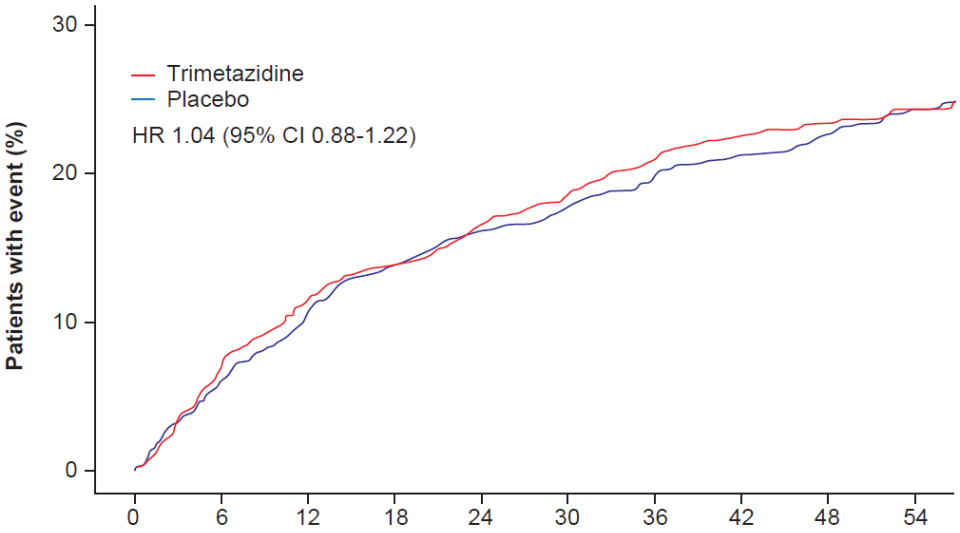
Supplementary Figure S1: Kaplan-Meier cumulative event curves for the primary efficacy composite endpoint in patients with elective and urgent PCI - Intent to treat analysis set (n= 6007)

Elective PCI subgroup



Number at risk										
Trimetazidine	1742	1622	1521	1454	1398	1349	1300	1055	634	246
Placebo	1748	1599	1512	1438	1381	1399	1289	1049	627	247

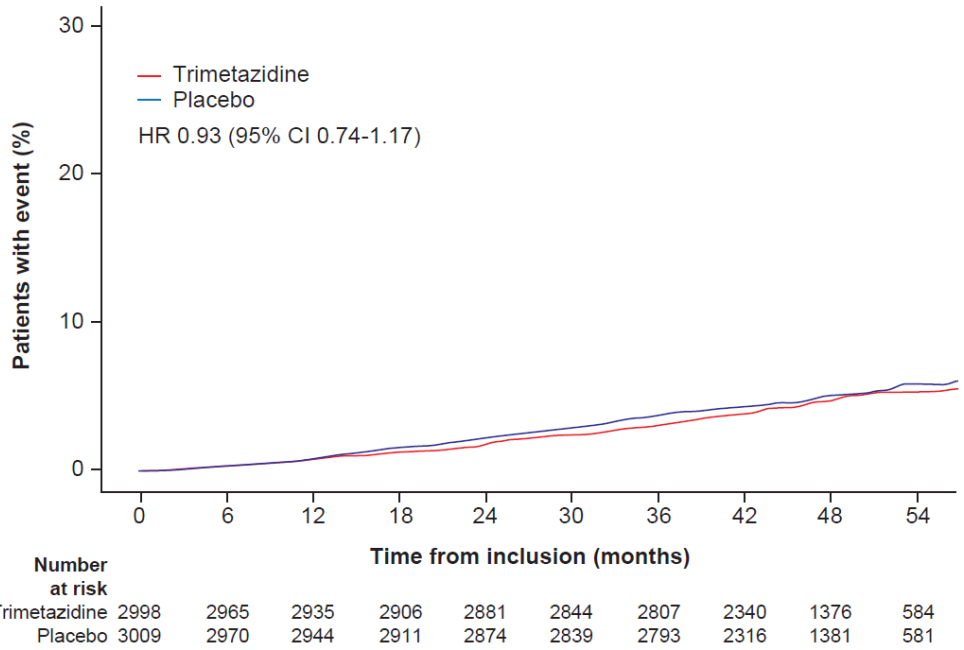
Urgent PCI subgroup



Number at risk										
Trimetazidine	1256	1162	1094	1058	1017	984	946	793	465	208
Placebo	1261	1173	1110	1061	1025	996	958	794	458	204

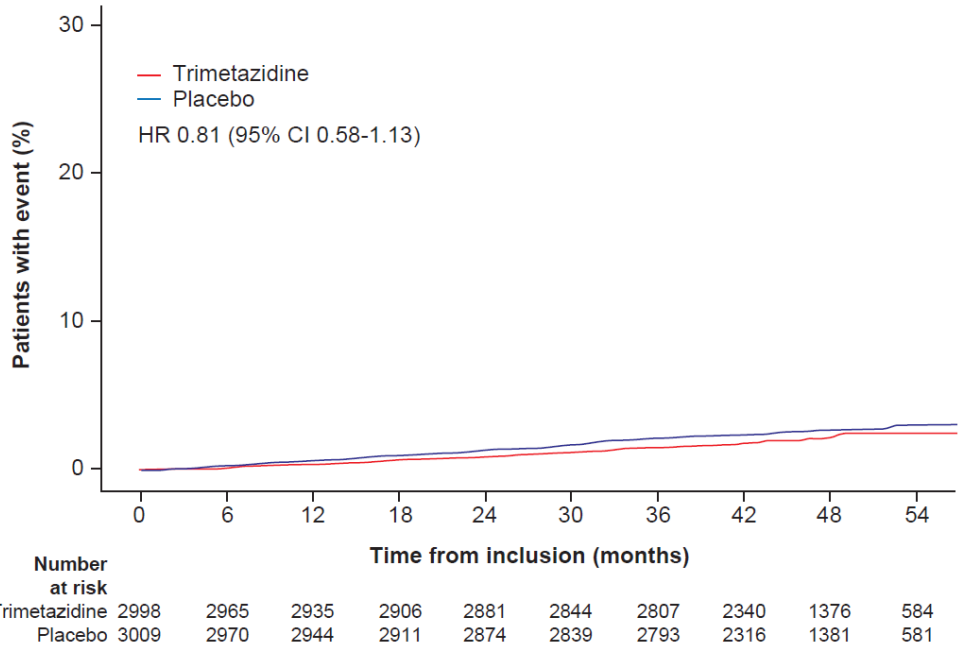
Supplementary Figure S2: Kaplan-Meier cumulative event curves for the main secondary efficacy composite endpoints - Intent to treat analysis set (n= 6007)

All cause mortality



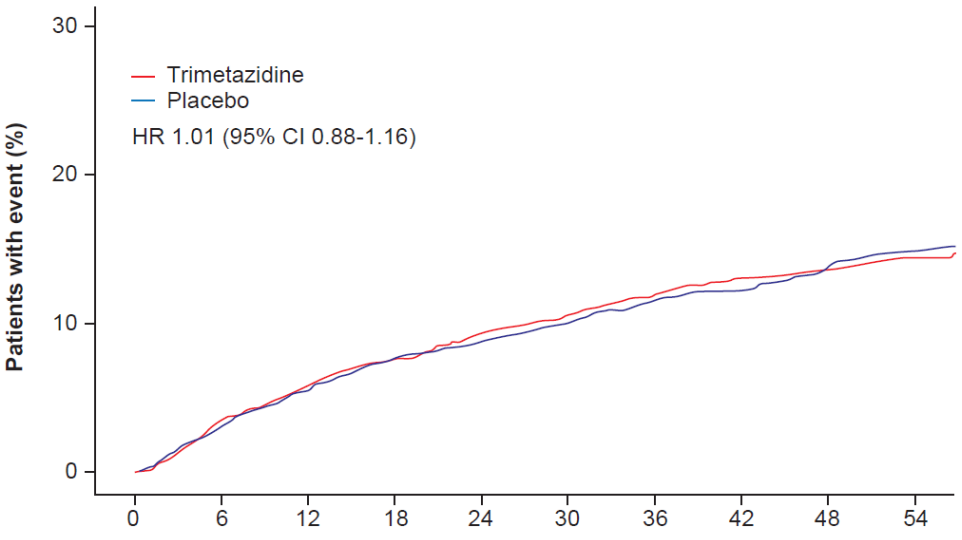
Number at risk										
Trimetazidine	2998	2965	2935	2906	2881	2844	2807	2340	1376	584
Placebo	3009	2970	2944	2911	2874	2839	2793	2316	1381	581

Cardiac death



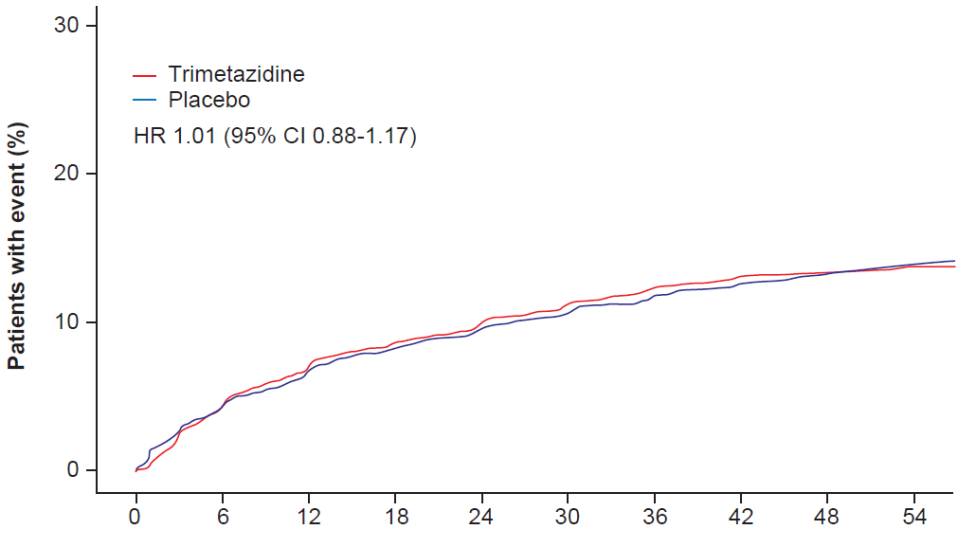
Number at risk										
Trimetazidine	2998	2965	2935	2906	2881	2844	2807	2340	1376	584
Placebo	3009	2970	2944	2911	2874	2839	2793	2316	1381	581

Hospitalization for cardiac event



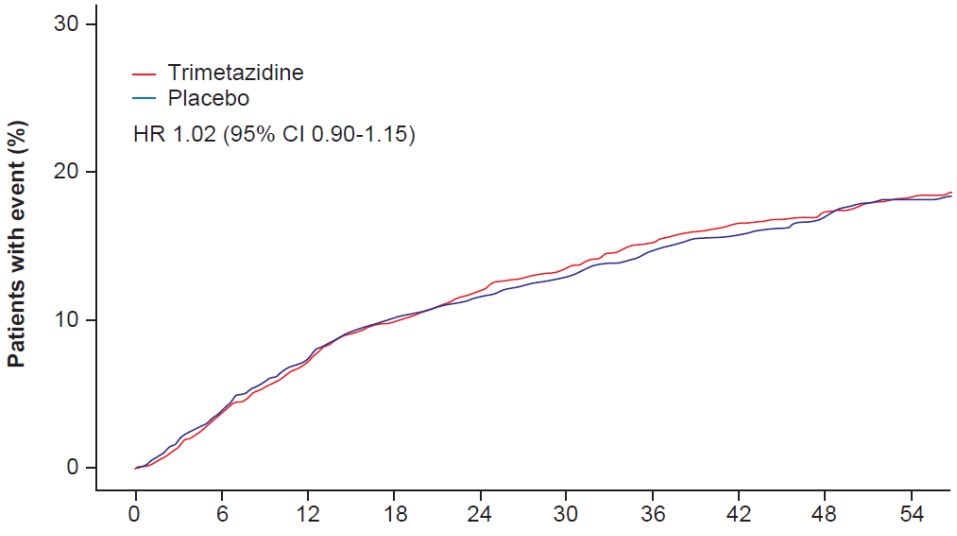
Number at risk										
Trimetazidine	2998	2868	2772	2697	2624	2560	2490	2057	1204	507
Placebo	3009	2880	2789	2698	2631	2565	2488	2049	1205	497

Angina leading to treatment change



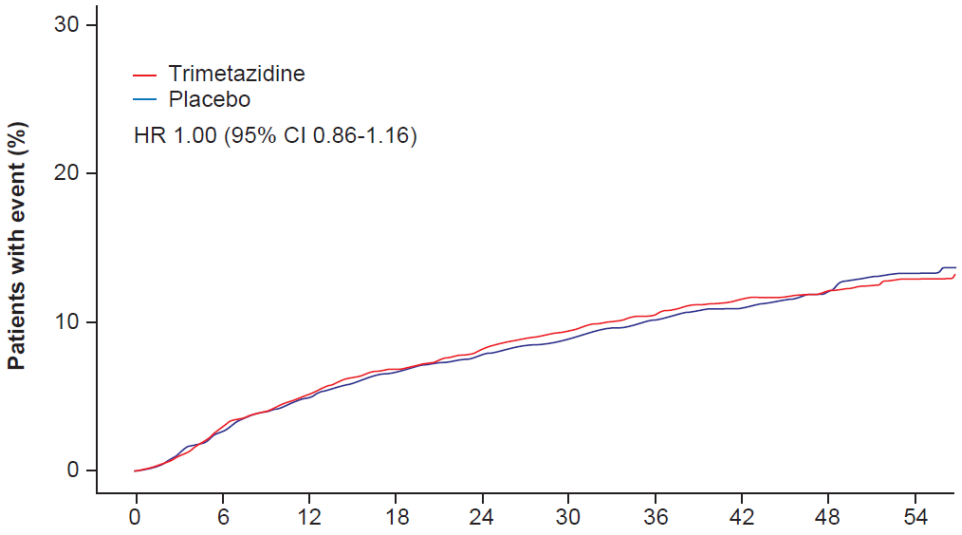
Number at risk										
Trimetazidine	2998	2843	2726	2655	2596	2530	2465	2039	1190	496
Placebo	3009	2844	2747	2675	2602	2542	2471	2039	1207	503

Angina leading to coronary angiography



Number at risk										
Trimetazidine	2998	2857	2728	2628	2546	2469	2391	1969	1157	481
Placebo	3009	2855	2730	2617	2543	2472	2382	1950	1153	476

Any coronary revascularisation



Number at risk										
Trimetazidine	2998	2879	2787	2715	2653	2585	2523	2080	1220	514
Placebo	3009	2890	2800	2719	2651	2587	2510	2067	1221	503

ATPCI Protocol

Document title	**AMENDED CLINICAL STUDY PROTOCOL**
Study title	**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.**
Test drug code	**S 06790 (Trimetazidine MR 35 mg)**
Indication	**Angina pectoris**
Development phase	**Phase III**
Protocol code	**CL3-06790-010**
EudraCT Number	**2010-022134-89**
Sponsor	**I.R.I.S.**
Date of the document	**04 February 2019**
Version of the document	**Final version**

Substantial Amendment integrated

No	Final version date	Countries concerned
1	**26 February 2014**	**BGR**
2	**14 April 2014**	**ALL**
3	**30 November 2015**	**ALL**
4	**10 May 2017**	**ALL**
5	**04 February 2019**	**ALL**

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FOLLOW-UP OF VERSIONS

Substantial amendment No	Final version date	Countries concerned	Nature of amendments
1	26 February 2014	BGR	This local amendment will never be implemented because Bulgaria is no longer involved in the study. Therefore, it is not included in appendix of this amended protocol.
2	14 April 2014	ALL	• treatment arm with the higher dose of trimetazidine removed, • number of required events for the primary efficacy endpoint reduced from 2 390 to 1 363 and total number of included patients reduced from 10 300 to 5 800, • number of participating countries reduced from 54 to 27 and number of centres from about 800 to about 400, • sections related to statistics, study treatments and other sections updated, • planned study initiation and completion dates updated, • patients with moderate renal failure allowed to enter the study, with dosage adjustment, • non-inclusion criterion “Time interval between PCI and inclusion > 30 days” added, • section regarding computerised medical files modified, • World Medical Association declaration of Helsinki version updated, • measurement of troponin before and after PCI limited to elective PCI, • administrative structure of the study updated, • typing errors corrected and items that needed clarifications rephrased.

Substantial amendment No	Final version date	Countries concerned	Nature of amendments
3	30 November 2015	ALL	• clarification of some selection and inclusion criteria, • modification of the section "Adverse Events of Interest" in order to introduce the Events of Interest not reported as adverse events, • change in the reporting rules of adverse events occurring between the randomization of the patient and the first administration of the study drug, • updating of the administrative structure of the study, • other clarifications and corrections of typing errors.
4	10 May 2017	ALL	• clarification on the management of blinding systems, • clarification on two Events of Interest (neurological symptoms and coagulation disorders) • precisions on the adverse events to be recorded, • updating of the composition of the Cardiovascular Endpoints Adjudication Committee, • precisions on the study data reporting, • updating of the administrative structure of the study, • modification of the specific storage conditions of the IMP.
5	04 February 2019	ALL	• correction of Appendix 5 of the protocol: Clinical Classification of Chest Pain, • change in archiving process of participants data: dematerialization of e-CRF data files process (CD-ROM logistics is removed), • update of administrative structures.

STUDY SUMMARY SHEET

<table>
<tr><td>Name of the Sponsor:
I.R.I.S.
50 rue Carnot
92284 Suresnes - France</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:
NA</td></tr>
<tr><td>Name of Active Ingredient:
Trimetazidine MR 35 mg
(S 06790)</td></tr>
<tr><td colspan="3">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</td></tr>
<tr><td colspan="3">Executive Committee Chairman: R. Ferrari (Italy).
National coordinators are listed in Appendix 1</td></tr>
<tr><td colspan="3">Study centres:
Total number of centres: about 400
Total number of countries: 27
Number of centres/country: about 15</td></tr>
<tr><td colspan="2">Study period:
Study duration for the participant: 2 to 4 years with the possibility to prolong it up to 5 years according to the number of observed events
Planned study initiation date: June 2014
Planned study completion date: June 2018 (event driven trial)</td><td>Study development phase:
Phase III</td></tr>
<tr><td colspan="3">Objectives:
The purpose of this study is 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).
Primary objectives: 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.
Secondary objectives: to evaluate the effect of trimetazidine on the other efficacy endpoints as well as the other safety parameters, clinical and biological.</td></tr>
<tr><td colspan="3">Methodology:
Target population: adult patients with coronary artery disease treated by PCI.
Phase III, international, multicentre, double-blind, placebo-controlled study randomised in 2 parallel and balanced arms (trimetazidine 35 mg b.i.d. and placebo) on top of post-PCI recommended treatment for Coronary Artery Disease (CAD), both secondary prevention and regular antianginal therapies as per current guidelines. Stratified randomisation at inclusion according to country and nature of PCI procedure (whether elective or urgent following an acute presentation).
Selection and Inclusion visits within 30 days of PCI, followed by a 2 to 4 year treatment period with a maximum of 10 visits (M001, M003, M006, M012, M018, M024, M030, M036, M042 & Final).</td></tr>
<tr><td colspan="3">Number of participants:
Planned: 5 800 included patients (2 900 per group).
Required number of events for the primary efficacy endpoint: 1 363</td></tr>
</table>

Name of the Sponsor: I.R.I.S. 50 rue Carnot 92284 Suresnes - France	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Diagnosis and main criteria for inclusion:

Selection/Inclusion criteria

Women or men ≥ 21 years old and <85 years old of any ethnic origin.

Patients presenting a single or multivessel coronary artery disease and having undergone PCI treating at least one stenosis to either a native coronary artery or a coronary graft where the PCI was:

- indicated because of angina pectoris occurring either in the context of stable angina (elective PCI) or in the context of an acute presentation such as unstable angina / NSTEMI, but excluding STEMI,
- achieved by stent implantation or by other acceptable interventional means successful as planned by the operator and with no further revascularization (either percutaneous or surgical) planned,
- uncomplicated, such that the patient's discharge was not, or will not be, delayed because of a cardiac or cerebrovascular problem.

A recent measurement (whatever the method) of Left Ventricular Ejection Fraction (LVEF) should have been performed within 3 months before inclusion (including the day of inclusion) for patients having undergone elective index PCI and between the acute coronary event leading to the index PCI and inclusion (including the day of inclusion) for patients having undergone index PCI performed in the context of an acute coronary syndrome. Otherwise, an estimate of the LVEF (≥ 40% or < 40%) should be provided.

Patients can be selected post PCI regardless of whether they are asymptomatic or symptomatic with regards to angina, and regardless of their CCS class, provided that they had experienced angina symptoms prior to the index PCI. The patients will be included after PCI as soon as the patient's antianginal treatment, if any, is stable (no changes made on the day of inclusion and no anticipated change in dose or drug after the inclusion visit).

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Non selection/Exclusion criteria

- General criteria: unlikely to co-operate with study procedures or visits; unlikely to comply with treatment; legal incapacity; pregnancy, breastfeeding or possibility of becoming pregnant during the study; current participation in another randomised study or inclusion in another randomised study within the preceding month (or according to local legislation if it requires more than 1 month); participant already included in the study; time interval between PCI and inclusion > 30 days.
- Criteria related to the coronary artery disease: index PCI carried out in the absence of prior chest pain considered to be angina pectoris, including where carried out for asymptomatic ischaemia; index PCI carried out as part of management of STEMI or within 4 weeks following a STEMI; procedure-related Q-wave MI; isolated periprocedural elevation of cardiac troponin (when measured) > 5x99th percentile upper reference limit in patients with normal baseline values (≤99th percentile URL) or rise of cardiac troponin values >20% if the baseline values are elevated and are stable or falling; further revascularization planned during the study period.
- Criteria related to clinical events between PCI and Inclusion: occurrence of an event which may prevent the patient to continue in the study correctly; acute myocardial infarction; repeat coronary revascularization; hospitalisation (or prolongation of hospitalisation) for cardiovascular event.
- Criteria related to concomitant diseases: severe uncontrolled rhythm disturbances; known severe aortic or mitral valve disease; NYHA class IV heart failure; hypertrophic obstructive cardiomyopathy or other forms of left ventricular outflow tract obstruction; congenital heart disease; history of pulmonary embolism within preceding 6 months; active myocarditis, pericarditis or endocarditis; history of thoracic aortic dissection; history of aortic aneurysm; severe uncontrolled arterial hypertension; known unpaced 2nd or 3rd degree atrioventricular block (except Mobitz type I AV block); known current anaemia (Hb <100 g/L); history of agranulocytosis, severe thrombocytopenia or severe coagulation disorder; known chronic severe renal failure, with eCrCl <30 mL/min or eGFR <30 mL/min/1.73m²; any state of severe physical or mental illness which may prevent compliance with study procedures or where the patient's life expectancy is <5 years; current or previous movement disorders such as Parkinsonian symptoms, restless leg syndrome, tremors, gait instability of central origin; severely reduced mobility.
- Criteria related to medication: hypersensitivity to trimetazidine or any of the product's or placebo's constituents; ongoing treatment by trimetazidine, perhexiline or ranolazine that cannot be discontinued at the time of inclusion.
- Laboratory criteria at inclusion: no available measurement of renal function, haemoglobin, AST or ALT, or no pregnancy test (for women who have childbearing potential); eCrCl <30 mL/min or eGFR <30 mL/min/1.73m²; haemoglobin <100g/L; AST or ALT >3-fold above the upper normal values; positive pregnancy test.
- ECG criteria at inclusion: unpaced 2nd or 3rd degree AV block except Mobitz Type I AV block.
- During the study patients should receive a standard post PCI regimen with regards to secondary prevention and regular antianginal therapies, in accordance with local or regional guidelines.

Test drug:
Trimetazidine MR 35 mg (active goup): one tablet swallowed at mealtimes in the morning and in the evening.
Patients with moderate renal failure: one tablet of trimetazidine MR 35 mg swallowed at mealtime in the morning.

Comparator:
Placebo (placebo group): one tablet swallowed at mealtimes in the morning and in the evening.
Patients with moderate renal failure: one tablet swallowed at mealtime in the morning.

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Duration of treatment:
Active treatment period: 2 to 4 years (according to the time of inclusion) with the possibility to prolong it up to 5 years according to the number of observed events.

Criteria for evaluation:

Efficacy measurements

- Pre-specified events (all visits during follow-up),
- CCS classification of angina symptoms (all visits except Inclusion visit),
- Number of angina episodes (all visits during follow-up),
- Number of doses of short acting nitrates taken (all visits during follow-up),
- Seattle Angina questionnaire (from M001 to M012) – in countries where a validated translation is available,
- EQ-5D-3L questionnaire (from M000 to M012),
- Cardiac troponin before each repeat elective PCI and between 6 and 24 hours after (treatment period)

Primary efficacy endpoint

Superiority of trimetazidine over placebo on the time to first occurrence of an event in the composite of:

- 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.

Secondary efficacy endpoints

Superiority of trimetazidine over placebo on the time to first occurrence of an event in the composite of:

- 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 ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
- Evidence of ischemia (documented by Stress Imaging) leading to performing a coronary angiography.

Effect of trimetazidine MR, compared with that of placebo, on the following endpoints:

Components of the primary endpoint

- 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.

Other secondary endpoints

- Evidence of ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies;
- Evidence of ischemia (documented by Stress Imaging) leading to performing a coronary angiography;

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- 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;
- Hospitalisation for heart failure;
- Any coronary revascularization;
- Repeat coronary revascularization in response to angina.

Other efficacy endpoints

- CCS class of angina symptoms;
- Number of angina episodes per week;
- Number of doses of short-acting nitrates taken per week;
- Number of antianginal drugs taken by the patient;
- Seattle Angina Questionnaire scores (in concerned countries);
- EQ-5D-3L Questionnaire scores;
- Level of cardiac troponin (before each repeat elective PCI and between 6 and 24 hours after).

Safety measurements

Primary safety endpoint

- Incidence of serious emergent adverse events with trimetazidine as compared with placebo (all visits).

Secondary safety endpoints

- Emergent adverse events – including clinically significant abnormalities observed from the ECG recordings and from laboratory parameters (all visits);
- Events of interest (all visits);
- Vital signs: blood pressure, heart rate (all visits except Selection visit)
- Weight (all visits except Selection visit);
- Laboratory examinations (all visits except Selection visit).

Statistical methods:

Efficacy analysis

The efficacy analysis will be performed in the randomised set and on the sub group of patients defined according to nature of PCI procedure at inclusion.

The superiority of trimetazidine (MR 35 mg b.i.d.) as compared with placebo will be tested on the primary endpoint using a Cox's proportional hazards model adjusted for the randomisation stratification factors: country and nature of the initial PCI –elective or urgent– at inclusion.

In order to assess the treatment effect, the estimate of the hazard ratio and the 95% confidence interval will be provided based on the same model.

This analysis will also be performed on the composite endpoint of the secondary endpoints, on each component of the primary endpoint and on each other secondary endpoints.

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For other efficacy criteria descriptive statistics by treatment group at each visit and on the change will be provided. Changes from baseline will be compared between treatment groups using 95% confidence intervals and superiority tests.

Safety analysis

The safety analysis will be carried-out on patients of the Safety Set.
Emergent adverse events, events of interest, vital signs and laboratory parameters will be studied using descriptive statistics.

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Contractual signatories

I, the undersigned, have read the foregoing amended protocol and agree to conduct the study in compliance with such documents, GCP and the applicable regulatory requirements.

NAME **DATE** **SIGNATURE**

COORDINATOR / INVESTIGATOR:

CENTER NUMBER	

DIRECTOR OF CLINICAL DEVELOPMENT: ***Emmanuel ARNAUD***

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GLOSSARY AND DEFINITIONS

AE	:	Adverse Event
AEI	:	Adverse Event of Interest
ALT	:	ALanine AminoTransferase
aPTT	:	Activated Partial Thromboplastin Time
ASSE	:	Selection visit
AST	:	ASpartate AminoTransferase
ATP	:	Adenosine Triphosphate
AV	:	AtrioVentricular
β-hCG	:	Beta-human Chorionic Gonadotrophin
b.i.d.	:	bis in die (twice a day)
BMS	:	Bare metal stent
BP	:	Blood Pressure
CAD	:	Coronary Artery Disease
CCS	:	Canadian Cardiovascular Society
CCSFOT	:	Centre for Clinical Studies France and Overseas Territories
CHD	:	Coronary Heart Disease
CHF	:	Congestive Heart Failure
CHMP	:	Committee for Medicinal Products for Human Use
CI	:	Confidence Interval
CKD-EPI	:	Chronic Kidney Disease - Epidemiology Collaboration
CK-MB	:	MB fraction of Creatine Kinase
CRO	:	Contract Research Organisation
CT	:	Computed Tomography
CV	:	Curriculum Vitae
DBP	:	Diastolic Blood Pressure
DES	:	Drug Eluting Stent
DMC	:	Data Monitoring Committee
EAE	:	Emergent Adverse Event
ECG	:	ElectroCardioGram
eCrCl	:	estimated Creatinine Clearance
eCRF	:	Electronic Case Report Form
e.g.	:	exempli gratia (for example)
eGFR	:	estimated Glomerular Filtration Rate
EI	:	Event of Interest
EMA	:	European Medicine Agency
EQ-5D-3L	:	EuroQol-5 Dimensions-3 Levels questionnaire
FFA	:	Free Fatty Acid
FFR	:	Fractional Flow Reserve
g	:	gram
GCP	:	Good Clinical Practice
HDL	:	High-Density Lipoprotein
HR	:	Heart Rate
ICH	:	International Conference on Harmonisation
ICTR	:	International Centre for Therapeutic Research
i.e.	:	id est (that is to say)
IMP	:	Investigational Medicinal Product (test drug or placebo)

INN	:	International Nonproprietary Names
INR	:	International Normalized Ratio
INCL	:	Inclusion visit
I.R.I.S.	:	Institut de Recherches Internationales Servier
IWRS	:	Interactive Web Response System
L	:	Litre
LDL	:	Low-Density Lipoprotein
LVEF	:	Left Ventricular Ejection Fraction
M	:	Month
MDRD	:	Modification of Diet in Renal Disease
MedDRA	:	Medical Dictionary for Regulatory Activities
mg	:	milligram
MI	:	Myocardial Infarction
min	:	minute
mL	:	Millilitre
mmHg	:	Millimetre of mercury
mm	:	Millimetre
MR	:	Modified Release
MRI	:	Magnetic Resonance Imaging
NA	:	Not Applicable
Nb	:	Number
NSTEMI	:	Non-ST Elevation Myocardial Infarction
NYHA	:	New York Heart Association
o.d.	:	Once a day
PCI	:	Percutaneous Coronary Intervention
POBA	:	Plain Old Balloon Angioplasty
PR	:	Prothrombin Ratio
PT	:	Prothrombin Time
PSE	:	Pre-specified Event
QoL	:	Quality of Life
s	:	Seconds
SA	:	Short Acting
SAE	:	Serious Adverse Event
SBP	:	Systolic Blood Pressure
SmPC	:	Summary of Product Characteristics
STEMI	:	ST segment Elevation Myocardial Infarction
SVT	:	SupraVentricular Tachycardia
TERM	:	Final Visit
Test drug	:	Servier product (S 06790)
TU	:	Therapeutic Unit(s)
TUTF	:	Therapeutic Units Tracking Form
VT	:	Ventricular Tachycardia
WHO-DD	:	World Health Organization, Drug Dictionary

1. ADMINISTRATIVE STRUCTURE OF THE STUDY

See Appendix 1.

2. BACKGROUND INFORMATION

Coronary heart disease (CHD), particularly in the form of angina, is a highly prevalent condition, reaching high levels in most developed countries. It is estimated that in most European countries between 20,000 and 40,000 individuals per million of the population suffer from angina (Fox, 2006). The treatment of CHD has two principal goals: 1) to relieve ischaemic symptoms, if present, and so improve quality of life, and 2) to prevent adverse outcomes - primarily myocardial infarction (MI) and premature death (Cassar, 2009; Fox, 2006; Fihn, 2012). The latter goal is achieved mainly through the combination of disease-modifying pharmacotherapy, such as statins, angiotensin converting enzyme inhibitors and antiplatelet agents, together with risk factor and lifestyle modification (Cassar, 2009; Fox, 2006; Gibbons, 2003). The relief of ischaemic symptoms may be initially attempted pharmacologically using antianginal drugs; however an ever increasing number of patients require revascularization procedures in addition to medication, either percutaneously (PCI) or by means of coronary artery surgery (British Heart Foundation, 2008; Moschovitis, 2010; Ludman, 2009). Indeed, a growing proportion of the population of patients with stable angina undergone myocardial revascularization even although, in the chronic setting, coronary revascularization has limited, if any, impact on prognosis (Boden, 2007; Bucher, 2000).

The first Percutaneous Coronary Intervention (PCI) was carried out using balloon angioplasty (POBA) in 1977 by Dr Andreas Grüntzig (Gruntzig, 1978) and coronary stents appeared in the mid 1980s. Stents have now largely replaced POBA owing to the demonstrated improvements in angiographic and clinical outcomes seen with their use (Carrie, 2000; de Feyter, 1994; Savage, 1994). Since their first appearance, extensive developments and advances in stent design and technology have led to PCI being one of the most frequently performed invasive medical procedures today (Garg, 2010). In 2006 just over 1.3 million PCIs were performed in the US (Lloyd-Jones, 2010) and just over a million in Europe, which represented a 10% rise on the preceding year (Moschovitis, 2010).

Shortly after the introduction of coronary stents there emerged the iatrogenic problem of in-stent neointimal hyperplasia and restenosis (Hoffmann, 1996) which was set to become the Achilles' heel of interventional cardiology (Moliterno, 2005). Studies have consistently shown a need for repeat revascularization in a proportion of patients which can be as high as 30% at one year with bare metal stents (BMS), depending on the patient and lesion characteristics (Garg, 2010). A partial solution was found in the form of drug-eluting stents (DES) which have largely fuelled the exponential growth of PCI during the last decade. Both randomised controlled trials and observational studies have shown a reduction in the need for target vessel revascularization of between 46% and 55% through the use of DES as compared with BMS (Kirtane, 2009). Although DES have reduced the need for repeat revascularization they have not altogether removed it. In the ARTS II study of multivessel PCI using DES 8.5% of patients underwent repeat revascularization during the first year and 20.8% by the end of five years (Serruys, 2010). In the SYNTAX trial (patients with more complex disease) the rate of repeat revascularization with DES was 13.7% at one year (Serruys, 2009). These figures

however may be considered to be the "best-case scenario", obtained in the context of highly controlled and highly selective clinical trials; most trials of multivessel disease have enrolled <10% of potentially eligible patients (Wijns, 2010). Additionally, these data do not include patients who had recurrent symptoms treated medically. Therefore, the rate of recurrent symptoms post PCI in the real life situation is likely to be much greater (Pursnani, 2012; Bangalore, 2013; Thomas 2013).

There are several mechanisms which can lead to either recurrent or persistent angina following initially successful PCI. Structural causes tend to cause angina several months post PCI and include 1) neointimal hyperplasia/restenosis, 2) disease progression, and 3) incomplete revascularization (Abbate, 2007). There are also functional causes of recurrent angina which may appear much earlier in the post-PCI period and include 1) coronary microvascular dysfunction, 2) epicardial coronary artery spasm, and 3) vasoconstriction at the stent edge (Abbate, 2007). Many patients treated with myocardial revascularization will therefore still require antianginal therapy (Danchin, 2006). A French registry (Dubois, 2004) which included 2,357 patients treated with PCI during January 2004 showed that at 6 month follow-up 66% of the patients were still receiving beta-blockers, 21.5% calcium antagonists and 23% nitrates.

Whatever the basis for it, recurrent or persistent angina after initially successful PCI is always a disappointment to both the patient and the cardiologist. For such patients, symptoms equate to a reduction in quality of life. Repeat coronary angiography and repeat PCI, particularly for chronic syndromes, bring both additional risk for the patient and cost to the healthcare system, with no major prognostic gain. Therefore, treating such symptoms medically would seem to be an alternative strategy worth pursuing.

The classical treatment of angina involves drugs that affect cardiovascular haemodynamics (β-blockers, calcium channel blockers and nitrates), thereby mainly reducing oxygen demand. **Trimetazidine** is a metabolic agent that acts neither by reducing oxygen consumption nor by increasing blood supply (thus devoid of any haemodynamic effect) but directly on the myocardial cells by shifting energy substrate utilisation away from free fatty acid (FFA) metabolism and towards glucose metabolism. It does so by inhibiting a key mitochondrial enzyme in fatty acid oxidation: long chain 3-ketoacyl coenzyme A thiolase (3-KAT) (Kantor, 2000, Lopaschuk 2010).

Under normal conditions the heart is capable of oxidising different substrates such as carbohydrates or FFAs to produce energy. The normal heart obtains 60-90% of its energy from FFA oxidation and the remainder from glucose and lactate. FFA metabolism produces less ATP per mole of oxygen used, and so more oxygen is required for ATP production when hearts are metabolising FFA than when they utilise glucose. Therefore, a switch to glucose metabolism by trimetazidine will particularly benefit hypoperfused, ischaemic myocardium.

Trimetazidine has been shown to be an effective antianginal therapy in the context of stable exertional angina. It is therefore licensed in more than 100 countries for the treatment of angina pectoris. Since it lacks any major haemodynamic properties it can be combined with all other classes of antianginal therapy. A recent meta-analysis, performed on the same methodological basis as that published in the Cochrane library, gathered 2,786 patients from 22 randomised, placebo-controlled, simple or double-blind, parallel or crossover design, trials conducted with trimetazidine in patients with stable angina (Danchin, 2009). It evaluated the effect on symptoms and exercise response achieved by treatment with trimetazidine, both in

monotherapy and in combination, and both in comparison with placebo or classic agents. The results of this meta-analysis showed that the overall treatment effect was statistically significant in favour of trimetazidine for all efficacy criteria – both clinical and exercise ECG test. The following differences between the trimetazidine and placebo groups at the end of treatment were observed: a reduction of 1.4 (95% CI 0.8 to 2.0) in the number of weekly episodes of angina; a decrease of 1.3 (95% CI 0.7 to 1.9) in the number of short acting nitrate doses per week; an increase of 23.3 s (95% CI 2.7 to 44.0 s) in total exercise duration and a delay of 33.9 s (95% CI 15.9 to 51.8 s) in the time to 1-mm ST-segment depression. A meta-analysis of the safety data showed a similar number of adverse effects in both groups (Danchin, 2009).

In order to allow the ranking of the efficacy of trimetazidine in terms of effect size relative to other anti-anginal agents, a network meta-analysis was recently performed (NP30724, 2011). It included 358 randomised, blind, controlled studies (27,058 patients treated for stable angina) carried out with dihydropyridines, nitrate derivatives, nicorandil, ranolazine, heart-rate lowering agents or trimetazidine. The effect size of trimetazidine was shown to be similar to its therapeutic alternatives whether analysed together or separately with consistency between the 3 different usual exercise tolerance test criteria as well as on the clinical criteria. These findings are reinforced by the statistically significant improvement by each of these anti-anginal agents including trimetazidine, of all ergometric and symptomatic criteria when compared to placebo.

Trimetazidine, in addition, has been studied in 94 patients who all developed recurrent angina symptoms following a revascularization procedure (PCI in 52%) at least six months prior. This was a subgroup analysis of the 426 patients enrolled in the TRIMPOL II study (Ruzyllo, 2004). All were symptomatic despite monotherapy with metoprolol. In comparison with placebo, the addition of trimetazidine resulted in improved exercise test parameters: time to 1-mm ST segment depression increased by 80 s; exercise test duration increased by 57 s; time to onset of angina increased by 75 s. Maximal ST-segment depression and total workload also improved. Clinical parameters improved with a reduction, in favour of trimetazidine, in both the mean number of weekly angina attacks and short acting nitrate consumption.

Trimetazidine may possibly improve prognosis in certain angina patients. The METRO study (Iyengar, 2009), was conducted amongst 353 survivors of MI who had been receiving medical therapy for stable angina at the time of their MI. In this relatively small study, amongst those who had been receiving trimetazidine there was a reduction in mortality, compared with those not receiving trimetazidine, seen to occur between hospital discharge and 6 months (HR 0.36 [95% CI 0.15-0.86], P=0.022). This effect was not seen with the other classes of antianginal therapy.

Trimetazidine has been shown to be safe and indeed beneficial during PCI procedures. A study conducted amongst 266 patients undergoing single vessel stenting (Bonello, 2007) observed the effects of administering a single 60 mg oral dose of trimetazidine shortly prior to PCI. The level of post-procedural troponin (calculated as area under the curve) was significantly reduced in the trimetazidine treated group as compared to the control group.

Trimetazidine has also been shown to significantly improve left ventricular function in patients with both ischaemic and non-ischaemic cardiomyopathy. The addition of trimetazidine to optimised standard CHF medication for a mean of 13 months in 65 patients with persistently symptomatic CHF and a LVEF <45% brought about an increase in LVEF

accompanied by a reduction in plasma B-type natriuretic peptide levels, an improvement in functional class, improved symptom and quality of life scores, and improved exercise capacity (Fragasso, 2006). There was also seen a lower use of diuretics and digoxin. Another study (Belardinelli, 2008) looked at 116 patients with ischaemic cardiomyopathy, all with a previous MI, 45 of whom had undergone a PCI previously. Trimetazidine improved functional capacity measured by cardiopulmonary exercise testing and this effect was additive to conventional cardiac rehabilitation with exercise training. Once again the LVEF improved in the trimetazidine group.

In June 2012, the European Medicine Agency (EMA) recognized the positive benefit risk-ratio of trimetazidine as an add-on to first-line antianginal therapies in symptomatic patients with stable angina pectoris insufficiently controlled by, or intolerant to first-line antianginal treatments.

In this study we intend studying the long-term efficacy and safety of trimetazidine in the reduction of cardiac events when added to standard treatment following PCI.

The study patients will be selected after a PCI indicated for angina pectoris occurring in the context of stable angina or in the context of an acute presentation such as unstable angina/NSTEMI, but excluding STEMI (because patients with STEMI require a specific management with a different risk profile). They will be randomly allocated to one of two treatment groups: placebo or trimetazidine 35 mg twice daily. This will be added to post PCI recommended treatment for CAD as set out by the relevant guidelines (Anderson, 2007; Fox, 2006; Gibbons, 2003) and according to the investigator's normal clinical practice.
The primary efficacy endpoint will be a composite endpoint of cardiac mortality, 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 recurrent or persistent angina leading to performing a coronary angiography

During this study, the assessment of long-term safety will be a major objective, with particular attention to events of interest such as neurological symptoms (including Parkinson's syndrome), coagulation disorders, thrombocytopenia, agranulocytosis, falls, arterial hypotension, hepatic disorders, and serious skin disorders.

In accordance with the European SmPC of trimetazidine MR 35 mg, patients with moderate renal failure will receive only one tablet of the study drug daily.

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

3. STUDY OBJECTIVES AND PURPOSE

The purpose of this study is 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 PCI.

The primary objectives are 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.

The secondary objectives are to evaluate the effect of trimetazidine on the other efficacy endpoints, as well as the other safety parameters, clinical and biological.

4. STUDY DESIGN

4.1. Endpoint(s)

4.1.1. Primary endpoints

4.1.1.1. Primary efficacy endpoint

Superiority of trimetazidine over placebo on the time to first occurrence of an event in the composite of:

- 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.

4.1.1.2. Primary safety endpoint

Incidence of serious emergent adverse events with trimetazidine as compared with placebo.

4.1.2. Secondary endpoints

4.1.2.1. Secondary efficacy endpoints

Superiority of trimetazidine over placebo on the time to first occurrence of an event in the composite of:

- 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 ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
- evidence of ischemia (documented by Stress Imaging) leading to performing a coronary angiography.

Effect of trimetazidine, compared with that of placebo, on the following endpoints:

Components of the primary endpoint

- 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.

Other secondary endpoints

- evidence of ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies;
- evidence of ischemia (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;
- hospitalisation for heart failure;
- any coronary revascularization;
- repeat coronary revascularization in response to angina.

4.1.2.2. Other efficacy endpoints

- CCS class of angina symptoms;
- number of angina episodes per week;
- number of doses of short-acting nitrates taken per week in response to angina;
- number of antianginal drugs taken by the patient;
- Seattle Angina Questionnaire scores (in countries where a validated translation is available);
- EQ-5D-3L Questionnaire scores;
- level of cardiac troponin (before each repeat elective PCI and between 6 and 24 hours after).

4.1.2.3. Secondary safety endpoints

- emergent adverse events (including clinically significant abnormalities observed from the electrocardiographic recordings and from laboratory examinations),
- events of interest (see Section 8.3),
- vital signs: supine and standing blood pressure (BP), heart rate (HR),
- weight,
- biochemical and haematological parameters.

4.2. Experimental design

4.2.1. Study plan

This is a phase III, international, multicentre, double-blind, placebo-controlled study randomised in 2 parallel and balanced groups:

- trimetazidine 35 mg b.i.d. (o.d. for patients with moderate renal failure),
- placebo b.i.d. (o.d. for patients with moderate renal failure).

Investigational medicinal product (IMP) will be given in addition to routine post-PCI treatment which includes secondary prevention therapy, as per current guidelines, with or without regular antianginal therapy as decided by the investigator according to his/her normal practice or specific requirements of local/national guidelines and the patient's clinical condition.

- Following the PCI and until the day before the inclusion visit regular antianginal therapy may be withdrawn (if any) or prescribed at the discretion of the investigator;
- The day of inclusion, regular antianginal therapy (if any) should not be changed (either drug or dose) or should not be initiated, whatever the reason;
- Following the inclusion visit, regular antianginal therapy (if any) should not be changed (either drug or dose) or should not be initiated, except for clinical reasons (see Section 6.3). The reasons for change must be detailed in the medical file and eCRF. Whatever the reason, all changes (*i.e.*, addition, switch or increase of the dose of the antianginal therapy, excluding short-acting nitrates) will be adjudicated.

The IMP will be allocated by centralised randomisation at the inclusion visit, with stratification by both country and by type of presentation (*i.e.* planned procedure for stable angina or urgent procedure following an acute/unstable presentation).

The sample size is based on the primary efficacy endpoint. No formal sample size calculation was done based on the primary safety criterion.

Assuming a power of 85% to show a significant 15% relative risk reduction in the occurrence of the primary efficacy endpoint between the placebo group and the trimetazidine group, based on an expected incidence in the placebo group of 10% and 2% of yearly withdrawals, and using a logrank test at a 5% type I error, 1,363 events and about 5,800 patients are required in this study (see Section 10.3). The estimated duration of the recruitment period is 24 months. The minimum follow-up duration for the last included patients will be 24 months. It is expected that the first included patients will be followed for 48 months (estimated mean follow-up duration of 36 months). Depending on the number of observed events, the follow-up duration may be prolonged up to 5 years (see Section 10.3).

All randomised patients should continue the study procedures and should attend the scheduled follow-up visits until the study end, even after the occurrence of an efficacy pre-specified event (PSE - see definition of efficacy PSE in Section 7.2.1) or after IMP withdrawal.

The patients will be selected as soon after PCI as possible, but preferably not on the actual day of the procedure. **The Selection Visit** (ASSE) should ideally be performed during the hospitalisation for the PCI, or failing that, shortly after discharge. With regards to angina, patients can be selected regardless of their symptomatic status post PCI (*i.e.* whether they are free from angina or not), and regardless of their CCS class, provided that they had experienced angina symptoms before the index PCI.

The Inclusion Visit (M000) will be performed as soon as the patient's antianginal treatment, if any, is stable (*i.e.*, with no change done on inclusion visit and no anticipated change in dose or drug after the inclusion visit). Depending on the organisation of the centre this visit may possibly be performed on the same day as the Selection Visit. However, in any case it must be performed no later than 30 days following the PCI procedure. At the Inclusion Visit (M000) patients will have their baseline evaluation performed and eligible patients will be randomised

to one of the two treatment groups: trimetazidine 35 mg b.i.d. (o.d. for patients with moderate renal failure) or placebo.

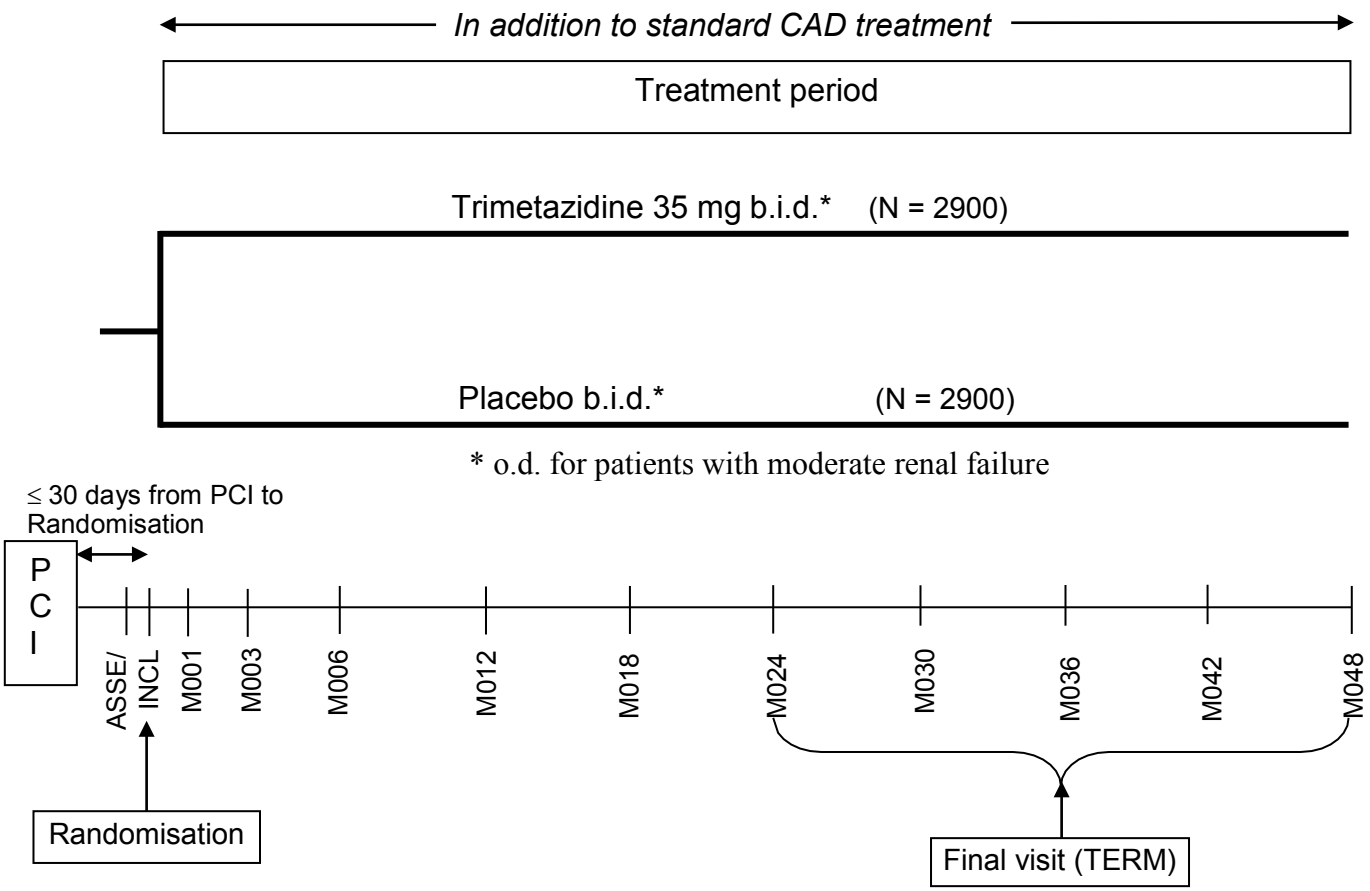
The treatment period will include visits at the following scheduled time-points: 1 month (M001), 3 months (M003), 6 months (M006) and then every 6 months, with a final visit which is expected to occur at the latest at 48 months (for the first included patients). However, the study may be prolonged up to 5 years if the number of expected events is not reached, in which case further visits (identical to the previous visits) will be added every 6 months during the fifth year of the treatment period. The actual number of visits for each patient will depend on the duration of follow-up for that patient.

At the end of the study, patients will be asked to attend the final visit (TERM) during a specific time window. The decision to terminate the study will be taken by the Executive Committee in collaboration with the Sponsor.

Five supervisory committees have been formed for this study. A summary of the responsibilities of these committees is given in Section 12.4.

The study plan is shown in Figure (4.2.1) 1 – Study plan.

Figure(4.2.1) 1 – Study plan



ASSE: Selection visit
INCL: Inclusion visit

4.2.2. Investigational schedule

Before randomisation, study procedures and investigations will be performed to check patient's eligibility and to obtain reference data. After randomisation, study procedures and investigations will be performed to record occurrences of cardiac events, other efficacy parameters and to assess safety and compliance. All planned visits are mandatory. Figure (4.2.2) 1 describes the measurements of both efficacy and safety assessed during the study. It details the visits to be performed for the first included patients with an expected follow-up of 48 months. The last included patients will have fewer follow-up visits with a final visit planned to occur 24 months after the Inclusion Visit. In case of prolongation of the study, visits will be similar to the previous visits.

During the study, all the relevant forms of the eCRF for each visit must be completed as soon as possible after the visit. It is essential that the investigator responds promptly to all data queries generated by the Sponsor or its agents, seeking to resolve them as soon as possible.

During the Selection Visit
The Selection Visit should take place as soon as after PCI as possible, but preferably not on the actual day of the procedure. It should ideally take place prior to discharge from hospital. In any case, it should be kept in mind that inclusion (which can be done on a different day or on the same day as selection) must occur within 30 days following the date of the PCI.

The investigator will obtain the patient's written informed consent after the PCI procedure has been completed and before any investigation specifically required by the study.

The investigator should try and obtain all relevant contact details for the patient *e.g.* home and office phone numbers, relatives or acquaintances, general practitioner and cardiologist contact if any.

The investigator will have to use the Interactive Web Response System (IWRS) via the internet in order to obtain a Patient Number.

The investigator will document the patient's medical/surgical history, current and previous medications and demographics. He/she will describe and classify the worst severity of anginal symptoms experienced by the patient in everyday life during the 4-week period prior to PCI using the Canadian Cardiovascular Society (CCS) classification which is described in Appendix 6. Thus, it is expected that at selection the CCS is at least class 1, as the assessment should take into consideration the worst severity of angina symptoms during the 4-week period prior to index PCI.

For patients meeting all selection criteria (see Section 5.1) and if no non-selection criterion is met (see Section 5.2), the investigator should:

- ask the patient to come to the next visit (inclusion). This visit will be performed as soon as the patient's antianginal treatment, if any, is stable (*i.e.*, with no change done on inclusion visit and no anticipated change in dose or drug after the inclusion visit) and may possibly be performed on the same day as the Selection Visit. In any case the Inclusion Visit must be performed no later than 30 days following the PCI procedure;
- schedule baseline fasting laboratory exams. The exams should be performed during the 7 days prior to the inclusion visit or at the latest on the same day as the inclusion visit. The investigator must ensure that the samples are scheduled so that the results are available for the inclusion visit. In particular, the results of estimated creatinine clearance (eCrCl) or estimated glomerular filtration rate (eGFR), blood haemoglobin, AST and ALT will have to be available before randomisation for the verification of the non-inclusion criteria. The investigator must be very careful to the time necessary in obtaining results when the selection and inclusion visits are performed on the same day;
- request a pregnancy test on a blood sample (β-hCG) for all women except those who are menopausal or who have had a hysterectomy or surgical sterilisation. Menopausal means that the last menstrual period occurred more than one year prior in a lady of appropriate age. The result must imperatively be available prior to randomisation (see Section 5.4). In case the β-hCG test cannot be performed, a urinary pregnancy test will be used.

After the informed consent has been signed by the patient, and for the duration of the study:

- if the investigator is informed that an event has occurred he/she will follow the instructions described in Section 8.4;
- the investigator will give to the patient a "patient card" containing the name of the study and the name/phone number of the investigator. Furthermore, the patient will be able to record all future appointments related to the study.

During the Inclusion Visit (M000)

- The investigator will ask the patient to fill in the EQ-5D-3L Questionnaire (see Appendix 8). This should be done prior to other study procedures at the beginning of the visit. The investigator should explain to the patient how to complete the questionnaire but neither he/she nor the research staff can assist the patient with its completion. The patient should complete the questionnaire by him/herself in a quiet place. If the patient is unable to read, an impartial witness (independent of the research staff) can help the patient to fill in the questionnaire. The questionnaire is printed in duplicate on copy paper. One copy of the questionnaire will be collected by the study monitor and the other will stay on site.
- In the likelihood that the Selection and Inclusion visits occur on separate days, the investigator will document any events which have occurred in the interval, as well as any changes in concomitant treatments including changes in dose. The events will be reported as AEs or as medical/surgical history according to the rule defined in Section 8.4.1.1.2.
- The investigator will proceed with a routine clinical examination including height, weight, blood pressure (supine after 10 mins of rest then 1 and 3 mins after standing up) and heart rate measurements. Any clinically significant abnormalities found on examination should be considered as events and reported as AEs or medical/surgical history according to the rule defined in Section 8.4.1.1.2.
- A standard resting 12-lead ECG will be performed and clinically significant abnormalities should be considered as events and reported as AEs or medical/surgical history according to the rule defined in Section 8.4.1.1.2. The investigator will check that the ECG does not meet any of the non-inclusion criteria (see Section 5.4). This ECG must be retained in the medical file as a source document. If the ECG is recorded on thermal paper, a certified paper copy of the tracing should be made.
- The investigator will review the results of all blood laboratory tests to verify the compliance with the non-inclusion criteria (namely eCrCl or eGFR, haemoglobin, AST, ALT and β-hCG blood test/urinary pregnancy test if required). The results of all tests should be reviewed and any clinically significant abnormalities considered as events and reported as AEs or medical/surgical history according to the rule defined in Section 8.4.1.1.2. If after reviewing the results the investigator considers it unsafe for the patient to continue in the study, the patient should not be included. All parameters should be entered into the appropriate form of the eCRF (see Section 8.2).
  The eCrCl or the eGFR will be calculated using a formula whose choice is left to the investigator according to the patient's characteristics (Cockcroft-Gault, MDRD or CKD-EPI formula ─ see formulas in Appendix 11). For a given patient, this formula should be the same throughout the study. If the renal function at baseline shows an eCrCl <30 mL/min or an eGFR <30 mL/min/1.73 m² the patient cannot be randomised. However, the test may be repeated within 7 days and if this is satisfactory (eCrCl ≥30 mL/min or eGFR ≥30 mL/min/1.73/m²) the patient can be randomised, provided all inclusion criteria are met. The test may also be repeated within 7 days for AST, ALT in case the values are > 3-fold the upper normal values, and if this is satisfactory (AST and ALT ≤ 3-fold the upper normal values) the patient can be randomised, provided all inclusion criteria are met.
- The investigator will document in the medical file and in the appropriate form of the eCRF the result of a recent measurement (whatever the method) of Left Ventricular Ejection Fraction (LVEF) performed:
  - within 3 months before inclusion (including the day of inclusion) for patients having undergone elective index PCI (see the definition of elective PCI in Section 5.1.2). If hospitalisation for cardiac event (except hospitalisation for the index PCI) occurs during this period, the measurement must be performed at the end or after the hospitalisation,

  - between the acute coronary event leading to the index PCI and inclusion (including the day of inclusion) for patients having undergone index PCI performed in the context of an acute coronary syndrome.

  If no precise measurement of LVEF was performed, the investigator should provide an estimate of LVEF (≥40% or <40%).
- The investigator will document the results of any relevant investigations (FFR, biomarkers dosage) if performed at the time of the index PCI. This information should be indicated in the medical file and entered in the eCRF.
- For patients meeting all inclusion criteria (and if no non-inclusion criterion is met) the investigator will randomise the patient to one of the 2 treatment groups by using the IWRS system. The IWRS will specify the number of the treatment kit (1 box) to be dispensed to the patient.
- The patient should be instructed to take the first dose of study medication the day after the Inclusion Visit in the morning at mealtime, then to take the second dose in the evening at mealtime and to continue taking it twice daily thereafter. Patients with moderate renal failure (eCrCl ≥30 and <60 mL/min, or eGFR ≥30 and <60 mL/min/1.73 m²) should be instructed to take only one tablet of study medication per day at mealtime in the morning. He/she will have to continue this dose until the end of the study even if eCrCl or eGFR rises ≥60 mL/min or 60 mL/min/1.73 m² during the study.
- The investigator will ask the randomised patient to attend the next visit planned 1 month later (first follow-up visit, M001).
- If applicable, the investigator will inform the patient that he will notify his/her primary care physician of his/her inclusion in the study.

During the intermediate visits (M001, M003, M006, M012, M018, M024, M030, M036 and M042)

- Only for M001, M003, M006 and M012: the investigator will ask the patient to fill in the Seattle Angina Questionnaire (see Appendix 7) in countries where a validated translation is available and the EQ-5D-3L Questionnaire (see Appendix 8). This should be done at the beginning of the visit prior to other study procedures. The investigator should explain to the patient how to complete these questionnaires but neither he/she nor the research staff can assist the patient with their completion. The patient should complete the questionnaires by him/herself in a quiet place. If the patient is unable to read, an impartial witness (independent of the research staff) can help the patient to fill in the questionnaires. The questionnaires are printed in duplicate on copy paper. One copy of each questionnaire will be collected by the study monitor and the other will stay on site.
- The investigator will document the inter-visit events including any AEs, AEs of interest or PSEs together with any changes in concomitant treatments including their respective doses (if any).
- The investigator will classify, using the CCS classification (see Appendix 6), the severity of any symptoms of angina experienced by the patient in everyday life since the last visit.
- If any exercise test and/or ischaemia/coronary imaging procedure has been performed since the last visit this should be documented in the medical file and in the appropriate form of the eCRF. Additionally, a copy of the corresponding reports should be kept in the medical file. A paper copy of the tracing of any exercise ECG should also be kept in the medical file. In the case that an exercise ECG has been performed using equipment capable of storing the data digitally, the electronic file should be kept in order to be sent to the Sponsor on request.

- Compliance with the Investigational medicinal product (IMP) will be documented at each biannual visit (no record at visits M001 and M003, except if IMP is prematurely discontinued between M000 and M003). Patients should be reminded to return all unused and used/empty blisters at next visits.
- The investigator will proceed with a clinical examination including blood pressure (supine after 10 mins of rest then 1 and 3 mins after standing up) and heart rate measurements. Weight will also be measured at each intermediate visit.
- The investigator will enter in the medical file and into the eCRF the mean number of angina attacks per week and the mean number of doses of short-acting nitrates per week taken by the patient in response to angina taking into account the four weeks preceding the current visit.
- One standard resting 12-lead ECG will be performed and any clinically significant abnormalities will be recorded as AEs. The ECG should be retained in the medical file. If the ECG is recorded on thermal paper, a certified paper copy of the tracing should be made.
- For each intermediate visit, the investigator should arrange for fasting blood samples to be taken for biochemistry and haematology at some point during the 7 days prior to the visit or else on the day of the visit, but not later. The investigator should make every effort to ensure that the results are available at each intermediate visit (at least the results of eCrCl or eGFR). The study drug prescription for the next period should be done after having reviewed the results of eCrCl or eGFR. If it is not possible to obtain the results at the time of the visit, they must be reviewed by the investigator as soon as they become available thus allowing to organise straightway a contact with the patient, if needed. All parameters should be entered into the appropriate form of the eCRF and any clinically significant abnormalities should be reported as AEs. If after reviewing the results the investigator considers it unsafe for the patient to continue the IMP, it should be withdrawn but patient should continue in the study (see Section 5.6).
- After obtaining the therapeutic unit (TU) number from the IWRS the investigator will dispense the treatment kit corresponding to the forthcoming period (except at visits M001 and M003 where there is no dispensation). If during the study eCrCl or eGFR drops below 60 mL/min or 60 mL/min/1.73 m² (but remains ≥30 mL/min or 30 mL/min/1.73 m²), the patient should be instructed to take only one tablet of study medication per day at mealtime in the morning. He/she will have to continue this dose until the end of the study even if eCrCl or eGFR comes back ≥60 mL/min or 60 mL/min/1.73 m².
- The investigator will program the next study visit and inform the patient. He should ask the patient to bring back the treatment box and the blisters (empty, incomplete or complete) to this visit. He should ensure that the patient's contact details are up to date.

During the final visit (TERM) – between M024 and M048

- The investigator will document the inter-visit events including any AEs, AEs of interest and PSEs and the changes in concomitant treatments and their respective doses (if any).
- The investigator will classify, using the CCS classification, the severity of any symptoms of angina experienced by the patient in everyday life since the last visit.
- If any exercise test and/or ischaemia/coronary imaging procedure has been performed since the last visit this should be documented in the medical file and in the appropriate form of the eCRF. Additionally, a copy of the corresponding reports should be kept in the medical file. A paper copy of the tracing of any exercise ECG should also be kept in the medical file. In the case that an exercise ECG has been performed using equipment capable

of storing the data digitally, the electronic file should be kept in order to be sent to the Sponsor on request.

- Compliance with the IMP will be documented.
- The investigator will proceed with a clinical examination including blood pressure (supine after 10 mins of rest then 1 and 3 mins after standing up) and heart rate measurements and weight.
- The investigator will enter in the medical file and into the eCRF the mean number of angina attacks per week and the mean number of doses of short-acting nitrates per week taken by the patient in response to angina taking into account the four weeks preceding the current visit.
- One standard resting 12-lead ECG will be performed and any clinically significant abnormalities will be recorded as AEs. The ECG should be retained in the medical file. If the ECG is recorded on thermal paper, a certified paper copy of the tracing should be made.
- The investigator should arrange for fasting blood samples to be taken for biochemistry and haematology at some point during the 7 days prior to the Final Visit or else on the day of the visit, but not later. The results should be reviewed as soon as they become available and any clinically significant abnormalities reported as AEs. All parameters should be entered into the appropriate form of the eCRF. However, if the final visit takes place ≤1 month following visit M024 or subsequent visits, and blood tests were performed at these visits, there is no requirement to repeat the blood tests at the final visit.
- The investigator will instruct the patient to stop the study medication immediately and should ensure that all unused medication has been returned by the patient.
- The investigator should review the patient's medication and current clinical status with a view to making appropriate modifications to the therapy after cessation of the study medication.

During the study period

- In case of repeat elective PCI performed after the inclusion the investigator should obtain measurements of troponin before the PCI and between 6 and 24 hours after, unless technically impossible (see Section 7.2.2). The results of these measurements will be entered into the appropriate form of the eCRF.
- Depending on local regulations, pregnancy tests can be repeated throughout the treatment period.

Figure (4.2.2) 1 describes the measurements of efficacy and safety assessed during the study.

Figure (4.2.2) 1 – Investigation schedule

	Selection	Inclusion	Treatment period Intermediate visits									Final Visit
	ASSE	M000	M001	M003	M006	M012	M018	M024	M030	M036	M042	TERM
Time Window from M000	after PCI	≤30 days after PCI	± 7 days	± 14 days	± 14 days	±14 days	± 21 days	± 21 days	± 21 days	± 21 days	± 21 days	#
Informed consent	X											
Selection/inclusion criteria	X	X										
Pregnancy test		X(1)	Depending on local regulations, it can be repeated throughout the treatment period									
Medical/Surgical history	X	X(2)										
Clinical examination		X	X	X	X	X	X	X	X	X	X	X
Height		X										
Concomitant treatments	X	X	X	X	X	X	X	X	X	X	X	X
IWRS connection (3)	X	X			X	X	X	X	X	X	X	
Allocation of treatments		X			X	X	X	X	X	X	X	
Compliance assessment					X	X	X	X	X	X	X	X
Efficacy measurements												
PSEs (4)			X(5)	X	X	X	X	X	X	X	X	X
CCS classification	X(6)		X	X	X	X	X	X	X	X	X	X
Anginal episodes/week			X	X	X	X	X	X	X	X	X	X
SA nitrates/week			X	X	X	X	X	X	X	X	X	X
Seattle Angina Quest. (7)			X	X	X	X						
EQ-5D-3L Quest.		X	X	X	X	X						
Measurement of troponin			After the inclusion, before each repeat elective PCI and between 6 and 24 hours after									
Safety measurements												
Adverse events	X(8)	X(8)	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, HR)		X	X	X	X	X	X	X	X	X	X	X
Weight		X	X	X	X	X	X	X	X	X	X	X
Laboratory examinations		X(9)	X(9)	X(9)	X(9)	X(9)	X(9)	X(9)	X(9)	X(9)	X(9)	X(10)
ECG		X	X	X	X	X	X	X	X	X	X	X

 # Final visit will occur during a period of time to be decided by the Executive Committee.

1. *A β-hCG test should be requested on a blood sample between Selection and Inclusion for women who have childbearing potential – as defined in Section 5.2.1 - since a result must be available prior to randomisation. In case the β-hCG test cannot be performed, a urinary pregnancy test will be used.*
2. *Events occurring before the first intake of the test drug and not associated with a procedure scheduled in the study protocol, a withdrawal of treatment related to the conditions of the protocol, a product other than the IMP, taken as part of the protocol will be recorded in the medical/surgical history (see Section 8.4.1.1.2 Recording methods). However, events considered as efficacy Pre-Specified Events by the investigator will be recorded in an Adverse Event form if they occur between the randomisation of the patient and the first administration of the study drug.*
3. *The investigator will connect with IWRS (Interactive Web Response System) at Selection visit for obtaining the patient's number, at M000 visit and subsequent 6-monthly visits to obtain the Therapeutic Units numbers.*
4. *As listed in Section 7.2.1*
5. *PSEs occurring since the randomisation.*
6. *Investigator will classify the worst severity of angina symptom experienced by the patient in everyday life during the 4-week period prior to PCI.*
7. *In countries where a validated translation is available.*
8. *Events occurring between the signing of the consent form and the first administration of the test drug and associated with a procedure scheduled in the study protocol, or a withdrawal of treatment related to the conditions of the protocol, or a product other than the IMP taken as part of the protocol will be recorded in an Adverse Event form. In addition, events considered as efficacy Pre-Specified Events by the investigator will be recorded in an Adverse Event form if they occur between the randomisation of the patient and the the first administration of the test drug (see Section 8.4.1.1.2. Recording methods).*
9. *Results of fasting blood tests need to be available for the inclusion of the patient; for all follow-up visits, it is highly recommended to have the results available at the time of the visit.*

10. If the final visit takes place ≤1 month following visit M024 or subsequent visits, and blood tests were performed at this visit, there is no requirement to repeat the blood tests at the final visit.

For further practical details, methods of measurement are provided in Sections 7 and 8.

4.3. Measures to minimise bias

The following measures have been taken in order to minimise bias:

- double-blind, placebo-controlled study;
- centralised balanced randomisation non adaptative using permuted blocks, with two stratification factors: country and nature of PCI procedure (whether an elective procedure for stable angina or an urgent procedure following an acute/unstable presentation);
- the randomisation list will be designed by the Methodology and Clinical Data Analysis Division of I.R.I.S. Treatment will be allocated through an Interactive Web Response System (IWRS);
- restricted access to the knowledge of which study medication has been prescribed to a specific patient. The investigators will have access, through the IWRS, to the name and dose of the medications administered only for patients under their responsibility. Investigators and other authorised persons will not break the treatment code unless it is absolutely necessary to ascertain the type of treatment received (trimetazidine or placebo) by a given patient and the dose in order to choose between crucial therapeutic options;
- identical number and appearance of the study tablets and packaging for all patients;
- the names of both components of the study medication (trimetazidine or placebo) will be blinded for investigators, patients and the Sponsor (or its agents) until the unblinding of the data;
- central blinded adjudication of the efficacy pre-specified events by a Cardiovascular Endpoints Adjudication Committee and of the events of interest by a Safety Endpoints Adjudication Committee. Statistical analyses will be performed using the results of the adjudication;
- none of the supervisory committees will have access to the code list of treatments allocated to patients, except authorised persons of the independent Data Monitoring Committee (DMC) who will be responsible for supervising all safety aspects of the study. The unblinded documentation will remain confidential and will not be made available to anyone outside the DMC;
- The Seattle Angina and the EQ-5D-3L Questionnaires will be completed by the patient, independently of the study personnel, at the beginning of each concerned visit prior to other study measures. The scoring of the questionnaire will be carried out independently of the investigator by the Data Management Department at I.R.I.S., France;
- the Seattle Angina Questionnaire will be used only if there is a validated translation available in the local language of the patient. To avoid selection bias, all centres within a country where a validated translation of the Seattle Angina Questionnaire is available will participate in this part of the study.

4.4. Study products and blinding systems

4.4.1. Products administered

Trimetazidine 35 mg and placebo will be provided in the form of tablets with an identical appearance for all treatment groups.

No Investigational medicinal product (IMP: trimetazidine or placebo) will be given to patients during the period between selection and inclusion. From inclusion onwards, patients will receive a fixed regimen of one tablet to be taken at mealtimes in the morning and evening:

- 1 tablet of placebo twice daily, or
- 1 tablet of trimetazidine twice daily.

This will be managed in a blinded manner by the IWRS.

Patients with moderate renal failure (eCrCl ≥30 and <60 mL/min, or eGFR ≥30 and <60 mL/min/1.73m²) at inclusion will receive a fixed regimen of one tablet to be taken at mealtime in the morning throughout the study:

- 1 tablet of placebo once a day, or
- 1 tablet of trimetazidine once a day.

If during the study eCrCl or eGFR drops below 60 mL/min or 60 mL/min/1.73 m² (but remains ≥30 mL/min or 30 mL/min/1.73 m²), the patient will have to receive only 1 tablet in the morning. The investigator should clearly inform the patient about the new posology. This posology will be continued, even if the eCrCl/eGFR comes back to ≥60 mL/min or 60 mL/min/1.73m².

Table (4.4.1) 1 provides a description of the study products and Table (4.4.1) 2 provides a description of the packaging of the study products.

Table(4.4.1) – 1 – Description of the study products

	Trimetazidine	**Placebo**
Pharmaceutical form*	Modified-release film-coated tablets	Film-coated tablets
Unit dosage	35 mg	NA
Appearance, colour	Pink	Pink
Composition**	Trimetazidine dihydrochloride 35 mg	Lactose monohydrate

** final dosage form administered to the participant*

*** quantitative active ingredient composition and qualitative excipient (only those known to have a recognised action) composition*

Table(4.4.1) – 2 – Description of packaging

Number of units of the pharmaceutical form per primary packaging	40 tablets per blister
Number of primary packaging per secondary packaging	12 blisters per box
Number of secondary packaging per participant and per treatment period	1 kit (*i.e.*, 1 box) dispensed every 6 months during the study (M000, M006, M012, M018, M024, M030, M036, M042)

The labelling of packages complies with the regulatory requirements of each country involved in the study, as well as the recommendations in Appendix 13 of the European Guide to Good Manufacturing Practice (European Commission, 2010).

4.4.2. Treatment management

Treatments will be directly delivered from the manufacturing site (Les Laboratoires Servier Industrie, 905 route de Saran, 45520 GIDY – France) to the study centres or to a national storage centre chosen by I.R.I.S. from where they will be further distributed to the study centres.

Drug management will be the responsibility of the investigator and/or the pharmacist of the medical institution and will be dispensed in accordance with the study plan.
The investigator and/or pharmacist or a person designated by them will take delivery of the treatments. The treatment should be stored in a secure area with restricted access. Specific storage conditions by country are described in Appendix 9.

In countries were specific conditions of temperature are required, the investigator and/or pharmacist or a person designated by them will be responsible for the TU temperature monitoring on a daily basis using the "Therapeutic Unit temperature log sheet". The Min-Max temperature should be recorded every working day.
In case of temperature deviation, the investigator and/or pharmacist or the person designated by them should immediately:

- block the IWRS for the concerned TUs and place them in quarantine,
- alert the monitor or the local project manager if the monitor is absent, forward him all needed information and implement the instructions received.

Furthermore, the investigator and/or pharmacist or a person designated by them must put in place an adequate corrective/preventive action once the first temperature deviation occurs in order to avoid recurrence.

The investigator and/or a designated person from his/her study team and/or the pharmacist of the medical institution will use the IWRS for the management of the treatments. A site users' manual will be available on the IWRS website detailing all procedures.

Patients will return all treatment units at each 6-monthly visit, including all used and unused blisters. Drug accountability will be under the responsibility of the investigator and/or the pharmacist of the medical institution. Treatment management will be verified on a regular basis by the study monitor.

Returned and unused treatments will subsequently be collected by the monitor or a person responsible for destruction. After verification, the treatments will be placed in a primary container stored at the centre or at a local unit until destruction. The destruction can be done all along the study period, taking into account the local regulation. The primary containers will be sent for destruction, which can be done either directly by the centre or by a Destruction Body or, if not available, the primary containers will be sent back to the Clinical Supplies Unit of Les Laboratoires Servier Industrie.

The investigator and/or the pharmacist of the medical institution and/or a designated person from their study team must complete in real time all the documents provided by the Sponsor concerning treatment management: therapeutic units tracking form (TUTF), TU label collection form are the source documents to be completed. The original forms will be kept by the investigator.

The investigator and/or the pharmacist of the medical institution should only use the treatment provided for the participants involved in the study.

All defects or deterioration of treatments or their packaging are to be reported to the study monitor and to the IWRS. The investigator will notify the monitor of all complaints made by a participant (*e.g.* change of taste, appearance, etc).
In the event of anticipated return of treatments to the Sponsor (batch recall), the Sponsor will prepare an information letter intended for the investigator and/or pharmacist of the medical

institution. This letter will be sent by the person locally responsible for the study to each study centre. On receipt of the letter, the investigator and/or the pharmacist will identify the participants in possession of the treatment at the moment the incident becomes known, by using, among other tools, the TUTF, and will contact them immediately.

4.4.3. Management of blinding systems

The system used for breaking the study allocation code is centralised by the IWRS. The IWRS can be accessed to break the code for any given randomised patient.

Investigators will be allowed to request the system to break the code only for patients under their responsibility. The code for any study participant should only be broken by the investigator or authorised person if it is absolutely necessary to ascertain the type of treatment given. If the code is broken for any patient, this will be recorded in the IWRS database.

If IWRS is not available, unblinding should be done by IVRS phone call.

If both IWRS and IVRS are not available, as a last resort, decoding will be possible by calling the Emergency Phone Number of I.R.I.S. (+33 1 55 72 60 00) 7/7d and 24/24h.

Unblinding is exceptional and is justified only when the therapeutic management of the patient is conditioned by the necessity of knowing the exact nature of the treatment dispensed to the patient.

4.5. Discontinuation of the study

4.5.1. Premature discontinuation of the study

If safety concerns are detected at any time during the study the DMC could recommend an early termination of the trial to the Executive Committee who will take the final decision in collaboration with the Sponsor.

The study can also be prematurely discontinued if new scientific knowledge or other information becomes available which indicates that continuation of the study would place the patients at undue risk.

After having informed the study committees and the investigators or coordinator(s), the Sponsor may terminate the study before its scheduled term. Two copies of the written confirmation will be dated and signed by the investigator or coordinator(s). The Ethics Committees and Competent Authorities will be informed according to local regulations.

4.5.2. Discontinuation of the study in the event of objective reached

Not applicable.

4.6. Source data

Source data will be required for all data recorded in the eCRF (*e.g.* patient's medical file, ECGs, laboratory reports, etc).

The calculation of estimated Creatinine Clearance (eCrCl) or of estimated Glomerular Filtration Rate (eGFR) is a source data. This calculation can be done either via the eCrCl/eGFR calculator of the eCRF homepage or the eCrCl/eGFR calculator of the provided

excel table. It should be reported in the patient's medical file as well as the used formula (see Appendix 11). Alternatively, a print-out of the calculation, dated, signed and identified with patient name and surname can be included in the medical file.

The Seattle Angina and the EQ-5D-3L Questionnaires will be completed as a paper version (duplicate) by the patient during the visit as per study plan. One anonymised copy of each will be collected by the monitor for data entry by the Sponsor and one copy will stay on site as a source document.

Source data and source documents of the centre should be clearly identified in a specific, detailed and signed document before the beginning of the study and updated on any change of source data managament at the centre.

5. SELECTION AND WITHDRAWAL OF PARTICIPANTS

5.1. Selection criteria

5.1.1. Demographic characteristics

1. Men or women of any ethnic origin,
2. ≥21 years old and <85 years old.

5.1.2. Medical and therapeutic criteria

3. Patients presenting a single or multivessel coronary artery disease and having undergone PCI treating at least one stenosis to either a native coronary artery or a coronary graft where the PCI was:
   - indicated because of angina pectoris*, occurring either in the context of stable angina (elective PCI**) or in the context of an acute presentation such as unstable angina / NSTEMI, but excluding STEMI;
   - achieved by stent implantation or by other acceptable interventional means***;
   - successful as planned by the operator and with no further revascularization (either percutaneous or surgical) planned;
   - uncomplicated, such that the patient's discharge was not, or will not be, delayed because of a cardiac or cerebrovascular problem.

The qualifying PCI will be referred to as the "index PCI". A patient undergoing staged PCI may be selected following the final procedure provided no further procedure is planned. This final procedure will be considered to be the index PCI for the purposes of this study. There is no time limit set for the interval between the first and final procedures of a staged PCI procedure.

Patients can be selected post PCI regardless of whether they are asymptomatic or symptomatic with regards to angina, and regardless of their CCS class, provided that they had experienced angina symptoms prior to the index PCI.

Patient should receive a standard post-PCI therapy regimen in accordance with local or regional guidelines (see Section 6.3).

**Angina pectoris is defined as being chest pain which meets the diagnostic criteria as outlined in Appendix 5. A PCI performed as a consequence of an angina equivalent or of an isolated angina attack experienced during an ischemia testing does not fulfill the selection criterion.*

***A PCI is considered elective when the PCI was performed during a hospitalisation planned specially for the procedure.*

****The following interventional means are considered as acceptable: balloon angioplasty without stent implantation, thrombectomy/ thrombolysis only if combined with a dilatation of the coronary artery.*

5.1.3. Informed consent

4. Obtained as described in Section 13.3 of the protocol.

5.2. Non-selection criteria

5.2.1. General criteria

5. Unlikely to co-operate with study procedures or visits.
6. Unlikely to comply with investigational medicinal product (IMP).
7. Legal incapacity.
8. Pregnancy, breastfeeding or possibility of becoming pregnant during the study (*i.e.*, not menopausal, non-hysterectomised, non-surgically sterilised women who are not using an effective method of contraception such as the contraceptive pill, intra-uterine device, subcutaneous contraceptive implant or patch – but this does not include barrier methods in isolation). Not menopausal means that the time since last menstrual period is <1 year.
9. Current participation in another randomised study or inclusion in another randomised study within the preceding month (or according to local legislation if it requires more than 1 month). Registry studies considered as strictly non-interventional may be permitted after consultation with the Executive Committee.
10. Participant already included in the study.

5.2.2. Medical and therapeutic criteria

Related to the coronary artery disease

11. Index PCI carried out in the absence of prior chest pain considered to be angina pectoris, including where carried out for asymptomatic ischaemia;
12. Index PCI carried out as part of the management of STEMI – including primary, rescue, facilitated or convalescent PCI (*i.e.* PCI performed during the recovery phase of an MI);
13. Index PCI carried out within 4 weeks following a STEMI;
14. Procedure-related Q wave MI;
15. Isolated periprocedural* elevation of cardiac troponin (when measured) > 5x99th percentile upper reference limit in patients with normal baseline values (≤99th percentile URL) or rise of cardiac troponin values >20% if the baseline values are elevated and are stable or falling;
16. Further revascularization planned during the study period, whether percutaneous or surgical.

** "periprocedural": at the time of the procedure and/or immediately after the procedure*

Related to concomitant diseases

17. Severe uncontrolled rhythm disturbances including paroxysmal VT and SVT (but this does not include isolated ventricular or supraventricular extrasystoles);
18. Known severe aortic or mitral valve disease;
19. Clinical signs and/or symptoms of heart failure corresponding to NYHA class IV;
20. Hypertrophic obstructive cardiomyopathy or other forms of left ventricular outflow tract obstruction;
21. Congenital heart disease, whether corrected or not;
22. History of pulmonary embolism within preceding 6 months;

23. Active myocarditis, pericarditis or endocarditis;
24. History of thoracic aortic dissection;
25. History of aortic aneurysm;
26. Known severe uncontrolled arterial hypertension;
27. Known 2nd or 3rd degree atrioventricular block, except Mobitz Type I AV block (Wenckebach), in the absence of a permanent pacemaker;
28. Known current anaemia with recent result of haemoglobin <100 g/L;
29. History of agranulocytosis, severe thrombocytopenia or severe coagulation disorder;
30. Known chronic severe renal failure, with eCrCl <30 mL/min or eGFR <30 mL/min/1.73 m²;
31. Any state of severe physical or mental illness which may prevent compliance with study procedures or where the patient's life expectancy is < 5 years;
32. Current or previous movement disorders such as Parkinsonian symptoms, restless leg syndrome, tremors, gait instability of central origin;
33. Severely reduced mobility.

Related to medication

34. Hypersensitivity to trimetazidine or any of the product's or placebo constituents.

5.3. Inclusion criteria

35. Availability of the result of a recent measurement (whatever the method) of Left Ventricular Ejection Fraction (LVEF) performed:
    - within 3 months before inclusion (including the day of inclusion) for patients having undergone elective index PCI. If hospitalisation for cardiac event (except hospitalisation for the index PCI) occurs during this period, the measurement must be performed at the end or after the hospitalisation.
    - between the acute coronary event leading to the index PCI and inclusion (including the day of inclusion) for patients having undergone index PCI performed in the context of an acute coronary syndrome.

    If no precise measurement of LVEF was performed, the investigator should provide an estimate of LVEF (≥ 40% or < 40%).
36. The patient's antianginal treatment, if any, is stable (no changes in dose or drug made on the day of inclusion and no anticipated change in dose or drug after the inclusion visit).
37. Selection criteria must still be fulfilled at the time of the inclusion visit.

5.4. Non-inclusion criteria

General criteria

38. As per non selection criteria;
39. Occurrence of an event which may prevent the patient to continue in the study correctly.
40. Time interval between PCI and inclusion > 30 days.

Clinical criteria

41. The occurrence of one or more of the following since the index PCI:
    - acute myocardial infarction including acute or subacute stent thrombosis;
    - repeat coronary revascularization procedure;
    - hospitalisation or prolongation of hospitalisation for cardiovascular event (except admission to a cardiac rehabilitation centre);
42. Uncontrolled arterial hypertension with SBP ≥180 mmHg and/or DBP ≥110 mmHg at rest.

Laboratory criteria

43. No available measurement of renal function (eCrCl/eGFR), haemoglobin, AST or ALT, or no pregnancy test (for women who have childbearing potential) at inclusion.
44. eCrCl < 30 mL/min or eGFR < 30 mL/min/1.73 m²*.
45. Haemoglobin <100 g/L.
46. AST or ALT > 3-fold above the upper normal values*
47. Positive pregnancy test (β-hCG blood test or, alternatively, urinary pregnancy test)

**Retests performed within 7 days are acceptable, provided that the values are available for review before inclusion and are within the defined limits values mentioned hereabove.*

ECG criteria

48. 2nd or 3rd degree atrioventricular block, except Mobitz Type I AV block (Wenckebach), in the absence of a permanent pacemaker.

Criteria related to medication

49. Ongoing treatment by trimetazidine, perhexiline or ranolazine that cannot be discontinued at the time of inclusion.

5.5. Additional information recorded at the Selection/Inclusion visit

- Results of any investigations (FFR, biomarkers dosage) if performed at the time of the index PCI;
- History of coronary artery disease, including family history;
- Other relevant medical and surgical history, including risk factors for CAD;
- Occurrence of any exercise test and/or ischaemia/coronary imaging procedure prior to PCI;
- Smoking habits – patients having stopped smoking <6 months prior to selection will be regarded as current smokers;
- Contraception;
- Physical activity;
- All treatments during the 3 months before selection;
- Ethnic origin *i.e.* caucasian, asian, black or other;
- Height.

5.6. Participant withdrawal criteria

5.6.1. Withdrawal criteria

At the start of the study the investigator should try and obtain all relevant contact details for the patient *e.g.* home and office phone numbers, relatives or acquaintances, general practitioner and cardiologist contacts, if any, together with any other useful measures in agreement with the patient to facilitate making contact with the patient, if necessary.

Before randomisation, a patient will be withdrawn from the study when the investigator is aware that a selection/non-selection criterion or an inclusion/non-inclusion criterion is not verified.

All randomised patients should continue the study procedures and should attend the scheduled follow-up visits until the study end, even after the occurrence of an efficacy pre-specified event (PSE- See section 7.2.1) or after IMP discontinuation.

After randomisation, all patients will be asked to take the Investigational Medicinal Product (IMP) until the sponsor declares the termination of the study (following the decision of the Executive Committee) or until the investigator decides the discontinuation of IMP. They should be encouraged to continue on the IMP, even following an efficacy pre-specified event (PSE – see Section 7.2.1) or a change in regular antianginal therapy, and to restart the IMP after an interruption, except when the patient's safety would be compromised according to the investigator's opinion.

IMP should be prematurely discontinued for a patient for one of the following reasons:

- onset of an adverse event which, according to the investigator, makes it unsafe for the patient to continue with the IMP. This includes clinically significant abnormal biochemical and haematological parameters;
- pregnancy (see Sections 8.4.1.1.1 and 8.4.1.3). The IMP should be stopped permanently;
- the occurrence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability of central origin should lead to definitive withdrawal of IMP. In those cases a neurologist opinion is to be sought as soon as possible and not later than 1 month after treatment withdrawal; the visit with the neurologist will be repeated 4 months after treatment withdrawal for follow-up or at least at the end of the study. A specific questionnaire is to be completed by the neurologist in these cases (see Appendix 10);
- the eCrCl (or the eGFR) is found during the treatment period to be <30 mL/min (<30 mL/min/1.73 m²) and remains so on repeat testing performed within 7 days;
  In the event that following randomisation, and during the treatment period, the eCrCl (or the eGFR) is found to be <30 mL/min (<30 mL/min/1.73 m²) the investigator should stop the IMP. He may repeat the test within 7 days and if this is satisfactory the IMP can be restarted twice daily (or once daily in case eCrCl or eGFR is below 60 mL/min or 60 mL/min/1.73 m²) if the investigator considers it safe to do so. Should the second result however be eCrCl <30 mL/min (or eGFR <30 mL/min/1.73 m²) the IMP should be stopped permanently;
- major protocol deviation which, in the opinion of the investigator, makes it unsafe for the patient to continue to take the study medication;
- non-medical reason (*e.g.,* patient's personal decision to stop treatment).

If the IMP has been discontinued, it might be restarted at the same dose upon the investigator's decision if there are no safety concerns for the patient:

- in case of adverse event or major protocol deviation if in the opinion of the investigator there is no safety issue,
- in case of non-medical reason if the patient changes his/her mind.

5.6.2. Procedure

In case of **premature discontinuation of the Investigational medicinal product (IMP)**, the investigator must record the reason for discontinuation and the exact date of the last intake of IMP in the patients's medical file and in the eCRF. If there is more than one reason, the investigator must indicate the main one.

If a **definitive discontinuation of the IMP** is decided, the patient will be asked to attend the scheduled visits until the study end is declared. All study procedures planned during the follow-up visits for patients receiving the IMP will also be carried out in patients having

discontinued it, except prescription/dispensation of the IMP and treatment compliance assessment. If the patient is unable or unwilling to attend all the scheduled visits, then as far as possible the follow-up should be completed by other means (*e.g.* alternate visits, home visits, phone follow-up through General Practitioners and/or relatives/acquaintances, or verification of national mortality registries if available), in order to document any endpoint occurring after the IMP discontinuation.
At the beginning of the study, the investigator should inform the patient that even in case of withdrawal of consent he/she should be able to give minimal information on his/her status of health at the end of the study or alternatively should authorize the investigator to contact a person indicated by him/her or his/her General Practitionner or Care Taking Physician in order to obtain this information. In case of withdrawal of consent, the reason should as far as possible be explained with details in the medical notes and on the eCRF.

In the case of **treatment withdrawal due to an adverse event** (event requiring immediate notification or not), the investigator must make every effort to collect the information relating to the outcome of the event. If necessary the information will be collected afterwards (see Section 8.4.1.2). This information is recorded in the part of the eCRF which concerns adverse events. If the investigator cannot collect the information by means of a patient visit, he must collect it from the doctor dealing with the follow-up of the participant.

If the investigator has **no news of a patient**, he/she must make every effort to contact him/her, to obtain the date when the IMP was discontinued, to establish the reason for the discontinuation, to ask the patient to resume the study procedures or to suggest that he/she provides the contact details of his/her physician. The key study data will be obtained from this physician. If all attempts to contact the patient failed –it will be requested that all actions implemented are documented and kept in the medical file– and if the key study data cannot be obtained before the end of the study, the investigator will then declare the patient "lost to follow-up".

The dispositions to be taken after the treatment discontinuation are described in Section 6.5.

6. TREATMENT OF PARTICIPANTS

6.1. Treatments administered

All patients are randomly assigned at the inclusion visit in a double-blind manner to receive one of the following treatments:

- Trimetazidine 35 mg b.i.d. group: the daily study regimen will be one tablet of trimetazidine MR 35 mg swallowed twice daily - at mealtimes in the morning and evening;
- placebo group: the daily study regimen will be one tablet of matching placebo to be swallowed twice daily - at mealtimes in the morning and evening.

In both groups, patients with moderate renal failure at inclusion (eCrCl ≥30 and <60 mL/min or eGFR ≥30 and <60 mL/min/1.73m²) will take one tablet once a day at mealtime in the morning throughout the study, in accordance with the European SmPC of trimetazidine 35 mg.

If during the study eCrCl or eGFR drops below 60 mL/min or 60 mL/min/1.73 m² (but remains ≥30 mL/min or 30 mL/min/1.73 m²), the patient will have to receive only 1 tablet per day in the morning. The investigator should clearly inform the patient about the new

posology. This posology will be continued, even if the eCrCl/eGFR comes back ≥60 mL/min or 60 mL/min/1.73m².

The patient should be instructed to take the first dose of study medication the day after the Inclusion Visit, in the morning, and to continue taking it twice daily (or once daily for patients with moderate renal failure) thereafter.

6.2. Treatment dispensing

In this section a therapeutic unit (TU) corresponds to one treatment kit consisting of one box containing 6 months of treatment.

Connection to the IWRS via the internet will have to be made in order to obtain the number of the TU to be given to the patient at Inclusion (M000), M006, M012, M018, M024, M030, M036 and M042 visits. The TU number will be different on each biannual visit.

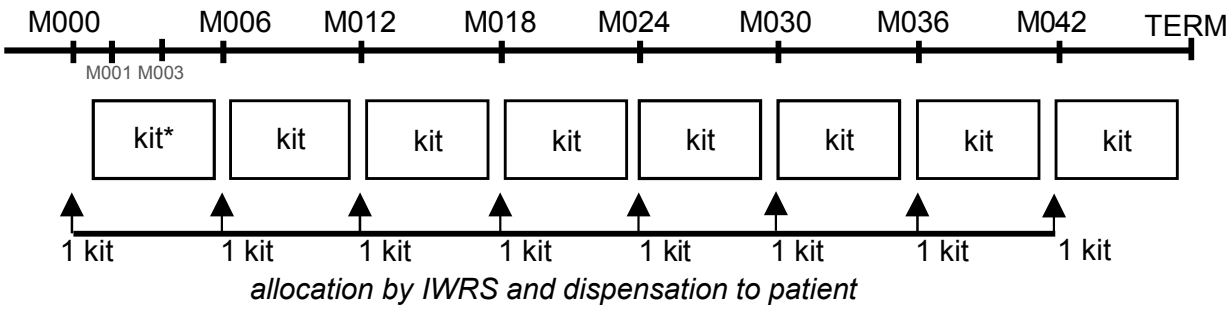
During these biannual visits, the IWRS will assign the patient one box with 6 months of treatment i.e. one TU number will be issued by the IWRS corresponding to the box (see Figure (6.2) 1.
There will be no dispensing of treatment at M001 and M003 as sufficient treatment for 6 months will have been given at the Inclusion Visit (M000).

The investigator should indicate on the TU box, the administration schedule for each patient (one in the morning and one in the evening or one in the morning only) by ticking the corresponding icon.

The detachable portion of the treatment labels must be stuck on the "TU label collection form" by the investigator. The study monitor will check IMP allocation by checking this document with the information entered in the eCRF by the investigator, with the IWRS confirmation fax or e-mail regarding the IMP allocation and with the TU tracking form. The original "TU label collection form" will be kept by the investigator and a copy of this document will be given to the monitor at the end of the study and archived in the Sponsor file.

The IMP will only be dispensed during the study. At the last visit of the study (TERM), the investigator will prescribe ongoing treatment suitable for the clinical state of the patient (see Section 6.5).

Figure (6.2) 1) – Allocation and Dispensing of Medication to Patient -



*1 kit = 1 box

6.3. Previous and concomitant treatments

Previous treatments refer to any treatment taken by the patient and stopped within 3 months prior to the Selection Visit or at this visit.

Concomitant treatments refer to any treatment taken by the patient at the time of the Selection Visit and any new treatment that will be prescribed during the study.

Regular antianginal therapy may include drugs from the following therapeutic classes: beta-blockers, calcium channel blockers (dihydropyridine and non-dihydropyridine), nitrates (but excluding short-acting nitrates taken buccally or sublingually), nicorandil, ivabradine and molsidomine.

All treatments except perhexiline, ranolazine and open-labelled trimetazidine are authorised during the study. In the case that the patient was taking perhexiline, ranolazine or trimetazidine before the study, these treatments should be discontinued at the latest the day of inclusion visit (see Section 5.4, criteria related to medication).

Following the index PCI, and prior to inclusion, regular antianginal therapy may be withdrawn (if any) or prescribed at the discretion of the investigator in keeping with his/her routine practice and the patient's clinical condition.
However, regular antianginal therapy should not be changed (drug or dose) or should not be initiated on the day of inclusion, whatever the reason.
Following inclusion of the patient, the antianginal therapy should remain unchanged (drug or dose) except for clinical reasons. Clinical reasons include the case of antianginal therapy modified or discontinued in a patient who becomes asymptomatic. In all cases, the reasons for the change in antianginal therapy must be detailed in the eCRF and in the clinical notes. Whatever the reason, all changes in antianginal therapy (addition, switch of antianginal therapy or increase of the dose, excluding short-acting nitrates) will be adjudicated.
Details of previous and concomitant treatments should be documented in medical records and recorded by the investigator in the appropriate forms of the eCRF.

6.4. Treatment compliance

The number of tablets dispensed and the number of tablets returned by the participant are to be counted by the investigator, or a designated person from his/her team, and recorded in the eCRF and the TUTF.

At each 6-monthly visit during the treatment period (M006, M012, M018, M024, M030, M036, M042 and Final Visit), the patient will return the entire treatment box along with the used and unused blisters. The box and blisters will be retained by the investigator (or the pharmacist or other delegated person).
Compliance will be assessed at M006, M012, M018, M024, M030, M036, M042 and Final Visit (TERM) using the method described above or from the questionning of the patient [if the patient does not return the IMP box]. Compliance will not be formally recorded at visits M001 and M003.

6.5. Arrangements after the discontinuation of the IMP

After discontinuation of the Investigational medicinal product (IMP), the participant will receive appropriate treatment and/or have access to other appropriate care by his doctor.

7. ASSESSMENT OF EFFICACY

7.1. Efficacy measurements

Efficacy measurements performed for each visit or treatment period are indicated in Figure (4.2.2) 1 – Investigation schedule.

Primary endpoint:
Superiority of trimetazidine over placebo on the time to first occurrence of an event in the composite of:

- 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.

"Hospitalisation" includes day care.

"Angina" is defined as being cardiac chest pain which meets the criteria as outlined in Appendix 5.

"Switching" means replacing an antianginal drug by another. Replacing a drug by another with the same INN (e.g., generic) is not considered as a switch.

The date of occurrence for the primary endpoint will be the date of the death, the date of the first hospitalisation for a cardiac event, the date of the adding/switching/intensification of the evidence-based therapy or the date of the angiography.

Secondary endpoints:
Superiority of trimetazidine over placebo on the time to first occurrence of an event in the composite of:

- 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 ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
- Evidence of ischemia (documented by Stress Imaging) leading to performing a coronary angiography.

Effect of trimetazidine, compared with that of placebo, on the following endpoints:
Components of the primary endpoint

- 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;

Other secondary endpoints

- Evidence of ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies;

- Evidence of ischemia (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;
- Hospitalisation for heart failure;
- Any coronary revascularization;
- Repeat coronary revascularization in response to angina.

"Ischaemic chest pain" includes all cases where the diagnosis is considered to be myocardial infarction, acute coronary syndrome, unstable angina or episode of angina.

Other efficacy endpoints

- CCS class of angina symptoms,
- Number of angina episodes per week,
- Number of doses of short-acting nitrates taken per week,
- Number of antianginal drugs taken by the patient,
- Seattle Angina Questionnaire scores (in countries where a validated translation is available),
- EQ-5D-3L Questionnaire scores,
- Level of cardiac troponin (before each repeat elective PCI and between 6 and 24 hours after).

7.2. Methods and measurement times

7.2.1. Efficacy Pre-specified events (after randomisation)

The following **Pre-Specified Events (PSE)** will be reviewed by an independent Cardiovascular Endpoints Adjudication Committee:

- all deaths,
- all hospitalisations for cardiovascular reason,
- all coronary angiographies,
- all coronary revascularizations,
- all changes in antianginal therapy (addition, switch or increase of the dose of one of the antianginal therapies ─ excluding short-acting nitrates ─ whatever the reason).

Note: all medical and non-medical reasons should be considered, including those leading to add and/or switch and/or increase the dose of an antianginal therapy for other clinical purposes than angina symptoms relief (*e.g.*, treatment of arterial hypertension). Contrariwise, non-medical reasons such as a temporary discontinuations (omission or treatment unavailibility) up to 2 calendar days, followed by the restart of the treatment at the same dosage, are not considered as PSE.

The PSE should be reported in the medical file and appropriate forms of the eCRF as soon as the investigator is informed about them.

For each PSE the Cardiovascular Endpoints Ajudication Committee will be provided with a file containing data from the eCRF together with additional documents provided by the investigator. This will happen each time a PSE is reported after the randomisation. All efforts should be made by the investigator to collect as soon as possible the requested documentation/information for each PSE, even in the case of hospitalisation and even if the investigation or procedure was performed in another hospital. These documents will be collected by the study monitor and will thereafter be translated into English. The translation will be provided to the Cardiovascular Endpoints Adjudication Committee. The Sponsor will be responsible for the management of document workflow.

During the adjudication process, the committee may request from the investigator further documentation or information. These requests will come via the study monitor and should be dealt with as quickly as possibly by the investigator.
The committee will be blinded to IMP and the patient data will have been anonymised.

These PSEs will allow the Cardiovascular Endpoints Adjudication Committee to adjudicate the following events:

- cardiac death,
- hospitalisation for a cardiac event,
- angina leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
- angina leading to performing a coronary angiography,
- ischemia leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
- ischemia leading to performing a coronary angiography,
- all-cause mortality,
- hospitalisation for fatal myocardial infarction,
- hospitalisation for non-fatal myocardial infarction,
- hospitalisation for ischaemic chest pain,
- hospitalisation for heart failure,
- repeat coronary revascularization,
- repeat coronary revascularization in response to angina.

The PSEs considered by the Cardiovascular Endpoints Adjudication Committee as fulfilling the endpoint definitions will be called the **adjudicated study efficacy endpoints**.

The definitions used for adjudication of these PSEs as well as the adjudication procedure will be specified in the Cardiovascular Endpoints Adjudication Committee charter.

Documentation/information to be provided by the investigator for the Cardiovascular Endpoints Adjudication Committee adjudication are listed in the associated documents (PSE check list).

7.2.2. Other measurements

- CCS classification of angina symptoms (See Appendix 6)
  To be assessed and reported in the eCRF at visits Selection (relating to symptoms prior to index PCI), M001, M003, M006, M012, M018, M024, M030, M036, M042 and Final Visit. The investigator will classify the severity of anginal symptoms experienced by the patient in everyday life during the 4 week period prior to index PCI at selection visit and since the last visit for the follow-up visits. At selection visit, the worst severity of angina pectoris during the period should be reported.
- Number of episodes of angina
  At visits M001, M003, M006, M012, M018, M024, M030, M036, M042 and Final Visit, the investigator will record the mean number of episodes of angina per week experienced by the patient during the four weeks preceding the current visit.
- Number of doses of short-acting nitrates taken in response to angina
  At visits M001, M003, M006, M012, M018, M024, M030, M036, M042 and Final Visit, the investigator will record the mean number of doses of short-acting nitrates per week taken by the patient in response to angina during the four weeks preceding the current visit – excluding any doses taken solely as prophylaxis prior to exertion.
- Seattle Angina Questionnaire (see Appendix 7) – will only apply in countries where there is a valid translation of the questionnaire into the local language of the patients.
  The questionnaire will be filled in by the patient at visits M001, M003, M006 and M012.
- EQ-5D-3L questionnaire (see Appendix 8)
  The questionnaire will be filled in by the patient at visits Inclusion (M000), M001, M003, M006 and M012.

  These 2 questionnaires should be filled in at the beginning of the visit prior to other study procedures. The investigator should explain to the patient how to complete the questionnaires but neither he/she nor the research staff can assist the patient with their completion. The patient should complete the questionnaires by him/herself in a quiet place. If the patient is unable to read, an impartial witness (independent of the research staff) can help the patient to fill in the questionnaires. The questionnaires are printed in duplicate on copy paper. One copy of each questionnaire will be collected by the study monitor and the other will stay on site. The Data Management Department of I.R.I.S. will score the questionnaires and enter the data.
- Cardiac troponin
  Measurements of cardiac troponin will be performed for all repeat elective PCI performed to the patient after the inclusion, except if not possible (see the definition of elective PCI in Section 5.1.2.). Measurements of troponin will be performed at the following periods:
  - before the PCI,
  - between 6 and 24 hours after PCI.

  The result of the measurement before the PCI will be considered as the baseline value.
  The measurement will be preferably performed using high-sensitivity troponin. When results of measurements are available, they will be entered in the appropriate form of the eCRF.

8. ASSESSMENT OF SAFETY

8.1. Safety measurements

Safety measurements performed for each visit or treatment period are indicated in Figure (4.2.2) 1 – Investigation schedule.

Primary endpoint:
Incidence of serious emergent adverse events with trimetazidine as compared with placebo.

"Serious adverse events": serious adverse events reported by the investigators and adverse events upgraded by the sponsor (see Section 8.4.2).

Secondary endpoints:

- Emergent adverse events (including clinically significant abnormalities observed from the electrocardiographic recordings and from laboratory examinations),
- Events of interest,
- Vital signs: supine and standing blood pressure (BP), heart rate (HR),
- Weight,
- Biochemical and haematological parameters.

8.2. Methods and measurement times

Medical/surgical history will be recorded by the investigator at Selection and Inclusion visits, particularly to identify any medical condition which would make an individual unsuitable for inclusion:

- history of coronary artery disease, including family history,
- other relevant medical and surgical history, including risk factors for CAD,
- smoking habits – patients having stopped smoking <6 months prior to Selection will be regarded as current smokers,
- contraception for non menopausal women,
- physical activity,
- treatments during the 3 months before selection.

Adverse events
All clinical adverse events will be recorded during the study and will be accurately documented in the eCRF (see Section 8.4).

Events of interest are detailed in Section

8.3. Clinical examination

- The patient examination will be systematically performed at all the visits except Selection. Any abnormalities on clinical examination will be evaluated by the investigator as being either clinically significant or not. Any clinically significant abnormality should be reported as adverse event (or medical/surgical history).
- Height will be measured at Inclusion visit only.
- Body weight will be measured at each visit except Selection visit.
- Vital signs (blood pressure – supine after 10 mins of rest then 1 and 3 mins after standing up – and heart rate) will be measured at each visit, except Selection Visit.

Laboratory tests

- Baseline fasting laboratory tests will be performed between the Selection and Inclusion visits and the same measurements will be repeated for all visits during follow-up.
- For all these visits, the tests should be performed during the 7 days prior to, or at the latest, on the day of visit. The results need to be available for the inclusion visit. Every effort should be made to ensure that the results are available for the follow-up visits (at least the results of eCrCl or eGFR). If it is not possible to obtain the results at the time of these follow-up visits, they must be reviewed by the investigator as soon as they become available.
- If the final visit (TERM) takes place ≤1 month following visit M024 or subsequent visits, and blood tests were performed at this visit, there is no requirement to repeat the blood tests at the final visit.
- For a premature withdrawal visit, the investigator must make every effort to obtain a final laboratory test.
- Analysed parameters:
  - **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, HDL-cholesterol, LDL-cholesterol, triglycerides, International Normalized Ratio (INR) or alternatively Prothrombin Time (PT) / Prothrombin ratio (PR), and activated Partial Thromboplastin Time (aPTT).

    The eCrCl or the eGFR should be determined using a formula whose choice is left to the investigator according to the patient's characteristics (Cockcroft-Gault, MDRD or CKD-EPI formula ─ see formulas in Appendix 11). For a given patient, this formula should be the same throughout the study. The calculation of this parameter can be done either via the eCrCl/eGFR calculator of the eCRF homepage or the eCrCl/eGFR calculator of the provided excel table.
- A pregnancy test (β-hCG) should be requested on a blood sample, and the result reviewed, prior to randomisation for women who have childbearing potential (*i.e.* non-menopausal, non-hysterectomised or non-sterilised women), even if she is using an effective method of contraception (see Section 5.2.1). In case the β-hCG test cannot be performed, a urinary pregnancy test will be used. Depending on local regulations, pregnancy tests can be repeated throughout the treatment period.

For all parameters, the investigator or a designated person from his/her team will have to complete the eCRF with the values at the visits including the relevant reference ranges according to their local lab. In addition, if there are any clinically significant abnormalities these should be reported as adverse events (or medical history) in the eCRF and documented in the medical file.

All the laboratory tests will be performed by local laboratories. The same laboratory should perform all the laboratory testings for all the patients for one centre in order to simplify the assessment of results. The volume of blood taken during the study will be approximately 30 ml per visit with sampling.

Electrocardiogram (ECG)

A standard ECG (12 leads) will be performed locally at all visits except Selection. For a premature withdrawal visit, the investigator must make every effort to obtain a final electrocardiogram. The ECG should be read by the investigator with any clinically significant

abnormality being reported as adverse event (or medical/surgical history) in the eCRF. The ECG should be retained by the investigator in the medical file as a source document. If the ECG is recorded on thermal paper, a certified paper copy of the tracing should be made. All study measurements will be recorded in the medical file and the eCRF at the study visit. Training for investigators on study procedures will be carried out by the study monitors at the beginning of the trial and thereafter as appropriate.

8.3. Events of interest

The following **Events of Interest (EI)** will be adjudicated by an independent Safety Endpoints Adjudication Committee**:**

- neurological symptoms, including Parkinson's syndrome, disorientation, hallucination and convulsion, according to a predefined list drawn up by the neurologists of the Safety Adjudication Committee,
- coagulation disorders including non-traumatic haemorrhages, thrombocytopenia (<150 G/L), agranulocytosis (neutrophils <0.5 G/L),
- falls,
- arterial hypotension, including orthostatic hypotension,
- serious skin disorders,
- hepatic disorders.

Note: A neurologist opinion is to be sought as soon as possible, and not later than one month after Investigational Medicinal Product (IMP) withdrawal, in case of occurrence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability of central origin. The visit with the neurologist will be repeated 4 months after IMP withdrawal for follow-up or at least at the end of the study. A specific questionnaire is to be completed by the neurologist in these cases (see also Section 5.6.1.).

- If one of the above-mentioned EI is reported as Adverse Event by the investigator, it will be called "**Adverse Event of Interest" (AEI)** and all relevant clinical information will be collected, in order to allow its adjudication by the Safety Endpoints Adjudication Committee. All these events must be followed-up until either full recovery, stabilisation or death.

  For each of these **AEI**, the Safety Endpoints Ajudication Committee will be provided with a file containing data from the eCRF together with additional documents provided by the investigator. All efforts should be made by the investigator to collect as soon as possible the requested documentation/information for each of these **AEI**, even in the case of hospitalisation and even if the investigation or procedure was performed in another hospital. These documents will be collected by the study monitor and will thereafter be translated into English. The translation will be sent to the Safety Endpoints Adjudication Committee. The Sponsor will be responsible for the management of document workflow.

- If not reported as Adverse Events, the following EI will be still detected by the Sponsor through post-baseline* biological/clinical values reported in the eCRF and adjudicated:
  - Coagulation disorders:
    - INR > 1.5 or Prothrombin ratio < 50% or Prothrombin time > 1.5-fold the local laboratory upper normal value in the absence of anticoagulation treatments,
    - aPTT > 1.2-fold the local laboratory upper normal value in the absence of anticoagulation treatments,
    - INR > 4 or Prothrombin ratio < 25% or Prothrombin time > 3-fold the local laboratory upper normal values in the presence of vitamin K antagonists,

  - aPTT > 4-fold the local laboratory upper normal values in the presence of heparin,
  - aPTT > 2-fold the local laboratory upper normal values in the presence of vitamin K antagonists,
- Thrombocytopenia:
  - Platelets: All cases of platelets < 100 G/L,
  - For platelets between 100 G/L and 150 G/L: any decrease > 30% compared to baseline value,
- Agranulocytosis: Neutrophils < 0.5 G/L,
- Arterial hypotension, including orthostatic hypotension:
  - Systolic blood pressure < 100 mmHg and /or diastolic blood pressure < 60 mmHg measured in supine position,
  - Reduction of more than 20 mmHg (> 20 mmHg) for systolic BP and/or more than 10 mmHg (> 10 mmHg) for diastolic BP at 1 and 3 minutes after standing-up as compared to the measurement in the supine position,
- Hepatic disorders: AST and/or ALT > 3-fold the upper normal values.

**Baseline biological and clinical data are not adjudicated.*

For the above-mentioned **EI not reported as AE**, all relevant clinical information will be collected, in order to allow adjudication by the independent Safety Endpoints Adjudication Committee.

During the adjudication process, the committee may request from the investigator further documentation or information. These requests will come via the study monitor and should be dealt with as quickly as possible by the investigator.
The committee will be blinded to IMP and the patient data will have been anonymised.
The definitions used for adjudication of these events as well as the adjudication procedure will be specified in the Safety Endpoints Adjudication Committee charter.

Documentation/information to be provided by the investigator for the Safety Endpoints Adjudication Committee adjudication are listed in the associated documents (EI check list).

8.4. Adverse events

All adverse events and other situations relevant to the safety of the participants must be followed up and fully and precisely documented in order to ensure that the sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical trial.

The same procedure applies whether the participant receives the test drug or placebo.

8.4.1. Responsibilities of investigator

8.4.1.1. Recording of adverse events

8.4.1.1.1. Events to be recorded

An **adverse event** is defined as any untoward medical occurrence in a subject participating in a clinical study, whether or not there is a causal relationship with the Investigational medicinal product (IMP) and/or experimental procedures, occurring or detected from the

participant's signature of information and consent form, whatever the period of the study (periods without administration of the IMP are also concerned).

An adverse event can therefore be:

- any unfavourable and unintended sign, including an abnormal finding from an additional examination (lab tests, X-rays, ECG…) deemed clinically relevant by the investigator;
- any symptom or disease;
- any worsening during the study of a symptom or a disease already present when the participant entered the study (increase in frequency and/or intensity), including the studied pathology,

and detected during a study visit or at an additional examination or occurred since the previous study visit.

Of note:

- Any **hospitalisation for social reasons, educational or rehabilitation purpose** or routine check-up should not be considered as an adverse event and should not be reported in the Adverse Event form of the eCRF.
- The following procedures, whether planned before the study or not, whether leading to hospitalisation or not, should be reported in the specific form **"Procedures not subsequent to an adverse event"** of the eCRF:
  - coronary angiographies related to a non-aggravated medical history,
  - therapeutic procedures related to a non-aggravated medical history (*e.g.* cataract extraction not due to an aggravation of the cataract during the study, haemodialysis sessions related to a renal insufficiency not aggravated during the study),
  - prophylactic procedures (*e.g.* sterilisation, wisdom teeth removal),
  - comfort procedures (*e.g.* cosmetic surgery),
  - control procedures of a pre-existing condition without aggravation (*e.g.* colonoscopy to control the remission of colon cancer).

An adverse event must be **notified immediately** (*i.e.* within 24 hours) when it is:

1. A serious adverse event *i.e.* an event which, whatever the dose of the IMP administered:

- results in the death of the participant;
- is life-threatening;
  Note: the term "life-threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- is medically important;
  Note: any event that may not be immediately life threatening or result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of these outcomes (for example: oedema or allergic bronchospasm that required intensive treatment at home, blood dyscrasia, convulsions that do not result in hospitalisation, or development of drug dependence or drug abuse). The investigator should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to Sponsor.
- requires in participant hospitalisation or prolongation of existing hospitalisation (except for PSE, see below);
- results in persistent or significant disability / incapacity;

Note: any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.

- is a congenital anomaly / birth defect: exposure to the IMP before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.

2. A case of excessive intake* of the IMP by a participant:

- if there are serious signs or symptoms;
- if there are no signs or symptoms or if there are non-serious signs or symptoms, in the following cases:
  - if the intake of treatment is intentional (including suicide attempt),
  - if the intake of treatment represents more than 4 tablets in any one 24 hour period.

* excessive intake corresponds to any intake greater than two tablets per day.

3. A case of IMP intake by a person around the participant:

- if there are serious or non-serious signs or symptoms,
- if there are no signs or symptoms, in the following cases:
  - if the person is a minor subject,
  - if the intake of treatment represents more than 4 tablets in any one 24 hour period.

Summary tables of the different cases of overdose to be notified immediately are available in Appendix 4.

4. A pregnancy occurring during the study.
In the case of a pregnancy occurring the IMP must be stopped immediately and the patient withdrawn from the study.

***5.* A suspected Parkinsonian symptom, a restless legs syndrome, tremors, or a gait instability of central origin.**
Other adverse events of interest do not need to be notified immediately if they are not serious.

On the other hand, in the framework of this protocol, the following complications of the disease constituting a potential efficacy endpoint for the study do not need to be notified immediately (*i.e.*, within 24 hours), even if they are considered as serious by the investigator:

- cardiac events leading to hospitalisation or complicating a hospitalisation,
- coronary revascularizations,
- angina or evidence of ischemia leading to:
  - adding, switching or increasing the dose of one of the evidence-based therapies,
  - or leading to performing a coronary angiography.

These events should be recorded as soon as possible by the investigator in the medical file and in the appropriate eCRF forms, and will be transferred to the DMC on a regular basis. They will not be sent to the Medical Safety Division of I.R.I.S. and will not be subject to systematic unblinding and expedited reporting by the Sponsor to the relevant authorities.

All deaths and all hospitalisations for non-cardiac or unknown reasons must be notified immediately.

8.4.1.1.2. Recording methods

Any event meeting the above mentioned definitions (see 8.4.1.1.1 Events to be recorded) must be reported on the appropriate "Adverse Event" form of the eCRF, according to the general instructions for completion available in the eCRF.

However, events occurring before the first administration of the test drug must be reported as medical/surgical history in the dedicated form of the eCRF if they are not associated with:

- a procedure scheduled in the study protocol,
- withdrawal of treatment related to the conditions of the protocol,
- a product other than the Investigational medicinal product (IMP), taken as part of the protocol.

Moreover, events considered as Pre-Specified Events by the investigator or linked to a Pre-Specified Event (see 7.2.1 Efficacy Pre-specified events) must be reported in an "Adverse Event" form of the eCRF if they occur between the randomisation of the patient and the first administration of the test drug. These events are the following:

- deaths,
- hospitalisations for cardiovascular reason,
- events leading to a coronary angiography,
- events leading to a coronary revascularization,
- events leading to a change in antianginal therapy (addition, switch or increase of the dose of one of the antianginal therapies, whatever the reason).

A summary of the process is available in Appendix 3.

In the case of a chronic disease characterised by exacerbations:

- if the disease is known when the participant enters the study (*i.e.* documented as part of the medical/surgical history), only worsening (increased frequency and/or intensity of the episodes/attacks) will be documented as an adverse event;
- if the disease is detected during the study and if repeated episodes enable diagnosis of a chronic disease, the episodes will be grouped on the same "Adverse Event" form, which will clearly describe the diagnosis.

8.4.1.2. Follow-up of adverse events

The investigator must ensure that follow-up of the participant is appropriate to the nature of the event, and that it continues until resolution. He/she must as soon as possible inform the Sponsor of any secondary worsening.

Any change in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding an adverse event already reported must be written up in a new complete evaluation of the event documented on the "Adverse event" form previously created for the event.

If the adverse event has not resolved at the participant's final visit in the study, the participant must be followed up suitably and any information on the outcome of the event will be noted on the "Adverse Event" form previously created for the event.

If the follow-up of the participant is not done by the investigator him/herself (hospitalisation, followed by a specialist or the participant's general practitioner…), the investigator will do everything to establish/maintain contact with the person/department in charge of follow-up of

the participant, so as to have additional information and report it on the "Adverse Event" form previously created for the event.

8.4.1.3. Procedure for an event requiring immediate notification

The Seriousness should be evaluated according to international guidances (see definition in Section 8.3 in accordance with ICH Topic E2A and DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April).

In the case of an event requiring immediate notification that occurs:

- during the study:
  - after the first intake of the test drug,
  - or before the first intake of the test drug if associated with a procedure scheduled in the study protocol, or a withdrawal of treatment relating to the conditions of the protocol, or a product other than the Investigational medicinal product (IMP) taken as part of the protocol,
- during the 30 calendar days after the participant's last study visit, regardless of the supposed role of the research (IMP or experimental procedures required by the clinical study protocol); or,
- after these 30 days, irrespective of the time of onset after the end of the study in case of serious adverse event likely due to the research (IMP or experimental procedure).

The investigator must:

- **note** in the participant's medical file the date on which he/she learned of the event (at a follow-up visit or a telephone contact with the participant or a third person…);
- **immediately** after being informed of this event, **fill in** the appropriate "Adverse Event" form of the eCRF according to the general instructions available in the eCRF, without waiting for the results of the clinical outcome or of additional investigations. When data is entered into the eCRF, an e-mail will be immediately and automatically sent to the Sponsor (Cardiovascular Innovation Therapeutic Pole, ICTR concerned and the Pharmacovigilance Department);
- if the eCRF is not available when the investigator learned of the event:
  - immediately inform by telephone or fax:
    - the ICTR concerned, or the CCSFOT, or the contract research organisation (CRO) in charge of the monitoring (please refer to the specific instructions provided to each centre);
    - or, one of the persons of the Cardiovascular Innovation Therapeutic Pole
      (Fax: +33 1 55 72 59 87):
      Dr J.P. Challeton Telephone: +33 1 55 72 70 57
      Dr B. Tallot Telephone: + 33 1 55 72 61 03
    - or, outside working hours, the 24-hour phone line of I.R.I.S.: +33 1 55 72 60 00.
  - immediately fill in a paper "Adverse event - Initial information" form and send it immediately by fax to the persons designated above. As soon as the eCRF becomes available, the investigator should enter these data in the "Adverse Event" form of the eCRF;
- provide the persons designated above, as they become available, with anonymous copies of the documents which provide additional useful information, such as hospital admission reports, reports of further consultations, laboratory test reports, reports of other examinations aiding diagnosis (where possible, the results from pre-treatment assessments

should be appended for comparison with the results obtained under treatment), or the autopsy report, if autopsy is performed;
- fulfil his/her regulatory obligations to the Competent Authorities and/or to the Ethics Committee, in accordance with local regulations.

If an adverse event initially non-serious worsens and becomes serious, this must be reported **immediately** by updating the already completed "Adverse event" form of the eCRF. If the eCRF is unavailable when the investigator was informed of this worsening, he/she should:
- report the event initially non-serious on a paper "Adverse event - Initial information" form;
- report the worsening leading to seriousness on a paper "Adverse event - Additional information" form; and
- send them by fax **immediately** to the persons designated above.

As soon as the eCRF becomes available, the investigator should enter these data in the "Adverse Event" form of the eCRF.

If a female participant in the study becomes pregnant, the investigator must:
- stop the participant's treatment;
- fill in the "Adverse Event" form of the eCRF (if the eCRF is not available, the process described above should be complied with);
- complete a paper pregnancy follow-up report form (1st page);
- track the follow-up of this pregnancy and provide the Sponsor with information concerning this follow-up (notably using the 2nd page of the pregnancy follow-up report).

8.4.1.4. Evaluation of causality

It is important that the investigator gives his/her opinion regarding the cause-effect relationship between an adverse event and the Investigational medicinal product (IMP), for the following reason: certain adverse events that occur during clinical investigations can prove sufficiently significant to lead to changes in the drug development program (for example: change in dose, study population or in the information given to participants that may lead to the preparation of new information and consent forms). This is particularly true for events suspected to be related to the IMP (adverse drug reaction) and which, in their most severe forms, are life threatening.

The causality must be assessed when reporting the AE in the AE form. Only cases ticked "related" by the investigator or judged by the Sponsor as having a reasonable suspected causal relationship to the investigational medicinal product (AE linked to the mechanism of action of the IMP…) will be considered as suspected Adverse Drug Reaction**.**

In general, the expression reasonable causal relationship means to convey that there is evidence or arguments to suggest a causal relationship.

8.4.1.5. Evaluation of intensity

The intensity of adverse events must be assessed by the investigator (and reported in the AE form) according to the following rule:
- mild: signs or symptoms, easily tolerated, relieved with symptomatic treatment,
- moderate: enough discomfort to cause interference with usual activity, only partially relieved with symptomatic treatment,

- severe: incapacity in some regular activities, not easily relieved with symptomatic treatment.

8.4.2. Responsibilities of Sponsor

In accordance with international guidances, the seriousness and the causality of adverse events must be assessed by the sponsor, and may be upgraded (but never downgraded). If the assessments of the investigator and the sponsor are different, both will be reported in the clinical study report.

Independently of the regulatory obligations of the investigator, the Sponsor must report the pharmacovigilance data to the appropriate Authorities and to all the investigators involved, according to the requirements stated in ICH Good Clinical Practice guidelines and local regulations.

8.4.3. Responsibilities of the Data Monitoring Committee

The role and composition of the Data Monitoring Committee (DMC) are summarised in Section 12.4.5 and detailed in a specific Charter.
According to local regulations, the sponsor will inform as soon as possible the Competent Authorities and the Ethics Committees of recommendations of the DMC, where relevant for the safety of participants.

9. OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO EFFICACY OR SAFETY

9.1. Measurement of drug concentration

Not applicable.

9.2. Other

Not applicable.

10. STATISTICS

10.1. Interim analyses

During the study, the safety will be periodically reviewed by a DMC. These reviews will be partially unblinded (*i.e.* edited by treatment group A/B) and prepared by an independent statistician. When needed, the DMC could break the code (with confidential envelopes disclosing the correspondence between A/B and trimetazidine 35 mg b.i.d./placebo) at any time during the study.

On the basis of these reviews, the DMC should make a recommendation about stopping or not the trial for harmful effect. In order to assess trimetazidine on a long term period, efficacy and futility will not be a reason for stopping the trial. Therefore, Cardiovascular Endpoints will only be evaluated in safety context and no statistical test will be implemented for statistical monitoring guidelines.

All these considerations are detailed in the DMC charter (Ellenberg, 2002).

10.2. Final analysis

10.2.1. Introduction

This section deals with the final statistical analysis of the main study, handled by the Methodology and Clinical Data Analysis Division of I.R.I.S.
A statistical analysis plan will be written during the study and finalised before breaking the blind. These specifications will detail the implementation of all the planned statistical analyses in accordance with the principal features stated in the protocol and amendments.

10.2.2. Evaluation criteria

10.2.2.1.Efficacy criteria

Endpoints adjudicated by the Cardiovascular Endpoint Validation Committee will be considered for the analyses.

Primary endpoint

- Time to first occurrence of an event in the composite of:
  - 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.

Secondary endpoints

- Time to first occurrence of an event in the composite of:
  - 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 ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
  - Evidence of ischemia (documented by Stress Imaging) leading to performing a coronary angiography.

<u>Components of the primary endpoint</u>:

- Time to occurrence of cardiac death;
- Time to first occurrence of hospitalisation for a cardiac event;
- Time to first occurrence of recurrent or persistent angina leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies;
- Time to first occurrence of recurrent or persistent angina leading to performing a coronary angiography.

<u>Other secondary endpoints</u>:

- Time to first evidence of ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies;
- Time to first evidence of ischemia (documented by Stress Imaging) leading to performing a coronary angiography;
- Time to first occurrence of event among:
  - cardiac death,

  - hospitalisation for a cardiac event.
- Time to first occurrence of 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;
- Time to occurrence of all cause mortality;
- Time to first hospitalisation for non-fatal MI;
- Time to first hospitalisation for fatal or non-fatal MI;
- Time to first occurrence of event among:
  - hospitalisation for fatal MI,
  - hospitalisation for non-fatal MI,
  - cardiac death.
- Time to first occurrence of hospitalisation for ischaemic chest pain;
- Time to first hospitalisation for heart failure;
- Time to first occurrence of any coronary revascularization;
- Time to first occurrence of repeat coronary revascularization in response to angina.

A cardiac event corresponds to one of the following events: resuscitated cardiac arrest, acute coronary syndrome including unstable angina and STEMI/NSTEMI, heart failure, revascularization, sustained ventricular tachycardia.

The time to occurrence of an event is defined as the time between the date of randomisation and the date of the first occurrence of this event.

If the studied event does not occur during the study, a censorship process will be applied. The duration of follow-up from randomisation will be taken into account. In the time to event analysis, each patient's follow-up will be censored by the earliest of the end of study date, date of death (when death or nature of death is not considered in the studied event) or loss to follow-up date.

Other efficacy criteria

- CCS classification of angina severity
- Number of angina episodes per week
- SA nitrates consumption per week in response to angina
- Number of antianginal drugs taken by the patient
- Seattle Angina Questionnaire
- EuroQoL-5D-3L Questionnaire
- Level of cardiac troponin

10.2.2.2.Safety criteria

- Emergent adverse events
- Events of interest
  Events of interest adjudicated by the Safety Endpoints Adjudication Committee will be considered for the analyses
- Vital signs (BP, HR)
- Weight
- Laboratory tests abnormalities

10.2.3. Statistical elements

A two-sided p-value will be provided and compared to a 5% type I error rate.

Moreover 95% confidence intervals (two-sided) will be provided.

The following descriptive statistics will be supplied by treatment group depending on the nature of criteria:

- Time to occurrence:
  - number of patients having experienced the event,
  - number of patients at risk for the event,
  - global incidence: ratio between the number of patients having experienced the event and the number of patients at risk for the event,
  - number of patients-years at risk for the event,
  - annual incidence: ratio between the number of patients having experienced the event and the number of patients-years at risk for the event,
  - estimates of cumulative incidence over time, using the Kaplan-Meier method. These estimates will be plotted.
- ***Quantitative:*** number of observed values, mean, median, standard deviation, minimum and maximum
- ***Qualitative:*** absolute and relative frequencies per class

10.2.4. Analysed patients sets

RANDOMISED SET	All randomised patients according to the intention-to-treat principle (ICH E9, 1998)
SAFETY SET	All patients having received at least one dose of Investigational medicinal product (IMP)
SUBGROUP	Nature of PCI procedure at inclusion

The definition of these analysed sets will be finalised in statistical analysis plan before breaking the blind.

10.2.5. Statistical methodology

10.2.5.1. Study outcome

Characteristics of patients

Demography, medical/surgical history, risk factors and some efficacy and safety criteria at baseline will be described by treatment group and overall on randomised patients.

Follow-up of patients

Duration of follow-up, duration of treatment, compliance to treatment, status of patients, protocol deviations and concomitant drug treatments will be described by treatment group on randomised patients.

10.2.5.2. Efficacy analysis

The following analyses will be carried-out on patients of the Randomised Set.

Primary endpoint

The superiority of trimetazidine (MR 35 mg b.i.d.) as compared to placebo will be tested on the primary endpoint using a Cox's proportional hazards model (Collett, 1994) adjusted for the randomisation stratification (EMEA/CHMP/EWP/2863/99, 2003): country and nature of PCI procedure at inclusion.
In order to assess the treatment effect, the estimate of the hazard ratio and the 95% confidence interval will be provided based on the same model.

The treatment effect will be estimated within the subgroup (EMEA/CHMP/EWP/908/99, 2002).

Secondary endpoints

The analysis described for the primary endpoint will be performed on the composite endpoint of the secondary endpoints, on each component of the primary endpoint (EMEA/CHMP/EWP/908/99, 2002) and on each other secondary endpoints. Moreover, the recurrence of each endpoint will be also studied.

Other efficacy criteria

Descriptive statistics will be provided by treatment group at each visit and on the change from baseline. Changes from baseline will be compared between treatment groups using 95% confidence intervals and superiority tests.

10.2.5.3. Safety analysis

The safety analysis will be carried-out on patients of the Safety Set.

Adverse events

Global and annual incidences of emergent adverse events (*i.e. *all events occurring, worsening or becoming serious after the first Investigational medicinal product [IMP] intake) will be given by system organ class and preferred term, for each treatment group.

The same description will be performed for serious emergent adverse events (EAE), severe EAE, EAE treatment related and EAE leading to IMP withdrawal.

The emergent adverse events will be studied during the study and during the treatment period.

Events of interest

The incidences of events of interest will be specifically studied and compared between treatment groups.

Vital signs and weight

Descriptive statistics will be performed by treatment group at each visit and on the change from baseline.

Laboratory tests

The number and percentage of patients having a value out of reference laboratory range (respectively out of potentially clinically significant range) will be provided by treatment group.

Patients with emergent abnormal values will also be described.

10.3. Determination of sample size

The number of events required and the sample size are estimated for the time to first occurrence of primary endpoint, in order to detect a true difference between the placebo and trimetazidine (35 mg b.i.d.), using a two-sided log rank test.

For **85% power and 5% type I error rate**, **1,363 events and 5,800 patients** (Machin, 1987) are necessary to show a difference between the survival distribution of placebo group and trimetazidine (35 mg b.i.d.) corresponding to a **15%** relative risk reduction, assuming an annual incidence rate of the primary endpoint of **10%** in placebo group over a mean follow-up duration of 3 years. This number of patients takes into account an annual withdrawal rate (non-cardiac deaths and consent withdrawals) of **2%** in all groups.
If, during the study, it is estimated that the number of events required for the primary endpoint will not be reached at the scheduled end of study, the sample size and/or the duration of follow-up may be adjusted in order to maintain the power.
Similarly, if the number of events is estimated, during the study, to be more than expected at the scheduled end of study, the sample size and/or the duration of follow-up may be adjusted bearing in mind a minimum duration of follow-up for last included patients.

11. DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

The investigator will allow the monitors, the persons responsible for the audit, the representatives of the Ethics Committee, and of the Competent Authorities to have direct access to source data/documents.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Study monitoring

12.1.1. Before the study

The investigator will allow the monitor to visit the site and facilities where the study will take place in order to ensure compliance with the protocol requirements.

An initiation visit will be organised in each investigational centre involved in the study in order to allow the monitor to meet the local teams (including but not limited to the main investigator's team, persons involved in the pharmacy department if any, and persons involved in the local laboratories) and to review in detail the study procedures before the selection of the first patient.

Investigators meetings will be organised by the Sponsor before the study start. During these meetings, the study protocol and the study procedures will be explained to investigators.

12.1.2. During the study

The investigator will allow the monitor to:

- inspect the site, the facilities and the materials used for the study,
- meet all members of his/her team involved in the study,
- have a suitable working space within the centre,
- consult all of the documents relevant to the study,
- have access to the eCRF (*i.e.* access to an internet connection),
- check that the eCRF has been filled out correctly,
- directly access source documents for comparison of data therein with the data in the eCRF,
- verify that the study is carried out in compliance with the protocol and local regulatory requirements.

The study monitoring will be carried out at regular intervals, depending on the recruitment rate, and arranged between the investigator and monitor.
All information dealt with during these visits will be treated as strictly confidential.

12.2. Computerised medical file

If computerised medical files are used, and if the computer system allows, no change made in the medical files by the investigator should obscure the original information. The record must clearly indicate that a change was made and clearly provide a means to locate and read the prior information (*i.e*. audit trail). The investigator will save data at regular intervals.

The investigator must guarantee the integrity of the study data in the medical files by implementing security measures to prevent unauthorised access to the data and to the computer system.

If the computerised medical files are considered as not validated by the sponsor, the investigator undertakes:

- at the start of the study, to print the medical files of all participants allowing a reliable verification of the study criteria (e.g. medical history/previous treatments/ characteristics of the studied disease documented within the period of time defined by the study protocol),
- during the study, to print in real time each data entry and each data change.

The investigator will personally sign, date and give the number of pages on the first or last page of each print-out. At each visit by the monitor, the investigator will provide all the print-outs of the medical files of the participants. The monitor will personally sign and date the first (or last) page then initial all pages in each paper print-out.

If the computer system allows the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the medical files of the participants and the records of the changes made. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

If the computerised medical files are considered as validated by the sponsor, the investigator undertakes to give access to the monitor to the computerised medical files of all participants. If the monitor cannot access to the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the records of the changes made to the medical files of the participants. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

The investigator undertakes to keep:

- all medical file print-outs signed and dated by him/her and by the monitor when the computer system is considered as not validated by the sponsor,
- if the computer system used allows changes to be made, the print-outs of the audit trail when the computer system is considered as not validated by the sponsor or when the monitor cannot access to the audit trail in the computer system,
- all original source-documents (originals of specific examinations, informed consent forms, therapeutic unit tracking form…).

12.3. Audit – Inspection

The investigator should be informed that an audit may be carried out during or after the end of the study.
The investigator should be informed that the Competent Authorities may also carry out an inspection in the facilities of the Sponsor and/or the study centre(s). The Sponsor will inform the investigators concerned immediately upon notification of a pending study centres inspection. Likewise, the investigator will inform the Sponsor of any pending inspection.

The investigator must allow the representatives of the Competent Authorities and persons responsible for the audit:

- to inspect the site, facilities and material used for the study,
- to meet all members of his/her team involved in the study,
- to have direct access to study data and source documents,
- to consult all of the documents relevant to the study.

If computerised medical files are used, the investigator undertakes to provide all the source-documents and the printouts of the medical files of the participants and, if the computer system used allows, the record of the changes made during the study.

12.4. Supervisory committees

Five Committees will be involved in the study.

12.4.1. Executive Committee

The composition of the Executive Committee is described in table (12.4.1) - 1.

Table(12.4.1) – 1 Composition of the Executive Committee

Role	Title. Initial Forename. Name, Speciality	Work address and telephone number
Chairman	Prof. R. FERRARI, Cardiology	Chair of Cardiology Azienda Ospedaliero-Universitaria di Ferrara Ospedale di Cona - 2/C/3° piano lOCALE 3:13:03 Via Aldo Moro 8 44124 Cona (Ferrara) - Italy Email: fri@unife.it
Member	Prof. N. DANCHIN, Cardiology	Hôpital Européen Georges Pompidou Unité Clinique des Maladies Coronaires 20 rue Leblanc 75908 Paris cedex 15 - France Email: nicolas.danchin@egp.aphp.fr
Member	Prof. I. FORD, Statistics	Robertson Centre for Biostatistics Boyd Orr Building University of Glasgow Glasgow G12 8QQ - UK Email: Ian.Ford@glasgow.ac.uk
Member	Prof. K. FOX, Cardiology	Royal Brompton National Heart and Lung Hospital Sydney Street London SW3 6NP - UK Email: K.Fox@rbht.nhs.uk
Member	Prof. M. MARZILLI, Cardiology	Dipartimento Cardiotoracico Azienda Ospedaliera Univesitaria di Pisa Unità Operativa di Malattie Cardiovascolari I via Paradisa, 2 56124 Pisa - Italy Email: marzilli@med.unipi.it
Member	Prof. M. TENDERA, Cardiology	3rd Division of Cardiology Medical University of Silesia Ziolowa 45/47 40-635 Katowice - Poland Email: michal.tendera@gmail.com
Member	Prof. P. WIDIMSKÝ, Cardiology	Head of the Cardiocenter Depts. of Cardiology & Cardiac Surgery Third Faculty of Medicine, Charles University Prague University Hospital Kralovske Vinohrady Srobarova 50 100 34 Praha 10 - Czech Republic Email: petr.widimsky@fnkv.cz

The Executive Committee is responsible for the development of the study protocol in collaboration with the Sponsor. It will advise the Steering Committee (see below) on possible changes in the study design and administration in order to guarantee achievement of the study main goal. It will supervise the study progress and advise the Steering Committee on stopping or modifying the study (if applicable). It will give approval on the definitions and process of adjudication produced by both the Cardiovascular and Safety Endpoints Adjudication Committees. It will plan and implement all publications; abstracts and presentations related to the study and advise the Steering Committee on this. It will decide on ancillary studies in collaboration with the Sponsor. The Executive Committee will only have access to blinded data until the study is completed.

12.4.2. Steering Committee

The Steering Committee comprises the Executive Committee and the national coordinators. The members of this Committee will be the representative body of the study investigators. The Chairman of the Steering Committee is Prof. N. DANCHIN (see address and details in Section 12.4.1).

12.4.3. Cardiovascular Endpoints Adjudication Committee

The composition of the Cardiovascular Endpoints Adjudication Committee is described in Table (12.4.3) – 1.

Table(12.4.3) – 1 Composition of the Cardiovascular Endpoints Adjudication Committee

Role	Title. Initial Forename. Name, Speciality	Work address and telephone number
Chairman	Prof. P. GUERET, Cardiology	14 rue de Cambrai 75019 Paris – France Email: pascalgueret46@gmail.com
Member	Prof. Y. COTTIN, Cardiology	Centre Hospitalier Universitaire Le Bocage Service de Cardiologie 2, Bd Mal De Lattre De Tassigny 21079 Dijon cedex - France Email: yves.cottin@chu-dijon.fr
Member	Prof. G. FRAGASSO, Cardiology	Heart Failure Clinic Istituto Scientifico San Raffaele Via Olgettina 60 20132 Milano - Italy Email: gabriele.fragasso@hsr.it
Member	Prof. R. HATALA, Cardiology	National Cardiovascular Institute - NÚSCH Dept.of Arrhythmias and Pacing, Pod Krásnou hôrkou 1, SK-833 48 Bratislava - Slovak Republic E-mail: robert.hatala@nusch.sk

The members of the Cardiovascular Endpoints Adjudication Committee will independently and blindly adjudicate the efficacy pre-specified events as mentioned in Section 7.2.1. A separate and specific document will describe the role and organisation of this committee.

12.4.4. Safety Endpoints Adjudication Committee

The composition of the Safety Endpoints Adjudication Committee is described in Table (12.4.4) – 1.

Table(12.4.4) – 1 Composition of the Safety Endpoints Adjudication Committee

Role	Title. Initial Forename. Name	Work address and telephone number
Chairman	Prof. F. STOCCHI, Neurology	Clinical Trial center Centro per lo studio e Cura Morbo di Parkinson e disturbi del Movimento I.R.C.C.S. San Raffaele Pisana Via della Pisana, 216 00163 Roma - Italy Email: fabrizio.stocchi@sanraffaele.it
Member	Prof. Y. AGID, Neurology	Institut du Cerveau et de la Moelle Epinière (ICM) CHU Pitié-Salpêtrière 47 boulevard de l'Hôpital 75013 Paris - France Email: yves.agid@icm-institute.org

Role	Title. Initial Forename. Name	Work address and telephone number
Member	Prof. O. HANON, Geriatrics	Service Gérontologie du Pr Rigaud Hôpital Broca 54-56 rue Pascal 75013 Paris- France Email: olivier.hanon@brc.aphp.fr
Member	Prof. T. LECOMPTE, Haematology	Service d'Hématologie Département des Spécialités de Médecine Hôpitaux Universitaires de Genève Rue Gabrielle Perret-Gentil 4 1211 Genève 14 - Switzerland Email: thomaspierre.lecompte@hcuge.ch
Member	Prof. P. CACOUB, Internal Medicine	Service de médecine interne 2 Groupe hospitalier La Pitié Salpêtrière – Charles Foix 47-83 boulevard de l'Hôpital 75651 Paris cedex 13 – France Email : patrice.cacoub@psl.aphp.fr

The members of the Safety Endpoints Adjudication Committee will independently and blindly adjudicate the emergent events of interest as mentioned in Section 8.3. A separate and specific document will describe the role and organisation of this committee. The committee will have the possibility to ask additional specialists (*e.g.* dermatologists) to give their opinion on some specific events.

12.4.5. Data Monitoring Committee (DMC)

The composition of the Data Monitoring Committee is described in Table (12.4.5) – 1.

Table(12.4.5) – 1 Composition of the Data Monitoring Committee

Role	Title. Initial Forename. Name	Work address and telephone number
Chairman	Prof. P.G. STEG, Cardiology	Hôpital Bichat-Claude-Bernard Service de Cardiologie 46 rue Henri Huchard 75722 Paris cedex 18 - France Email: gabriel.steg@bch.aphp.fr
Member	Prof. C. RAPEZZI, Cardiology	Policlinico Sant'Orsola Malpighi Via Massarenti, 9 40138 Bologna - Italy Email: crapezzi@orsola-malpighi.med.unibo.it
Member	Prof. M. VOLTERRANI, Cardiology	Cardiovascular Research Unit Department of Medical Sciences Centre for Clinical and Basic Research Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Pisana via della Pisana 235 00163 Rome - Italy E-mail: maurizio.volterrani@sanraffaele.it
Member	Prof. J. BENICHOU, Statistics	23 rue Philibert Caux 76420 Bihorel - France Email: Jacques.Benichou@chu-rouen.fr

On the basis of safety summaries the DMC will make appropriate recommendations to the Executive Committee concerning the safety aspects of the study (EMEA/CHMP/EWP/5872/03, 2005). Unblinded data that may be assessed by the DMC will

be kept confidential and will not be disclosed outside of the DMC. Safety summaries may lead to a premature stopping of the study. The DMC will develop its own processes, which will be described in a specific document (DMC charter).

DMC recommendations will be forwarded to the Ethics Committees/Competent Authorities only if relevant for the safety of participants.

13. ETHICS

13.1. Ethics Committee(s)

The study protocol, the "Participant information and consent form" document, the list of investigators document, the insurance documents, the SmPC of administered treatments (if available) will be submitted to independent Ethics Committees by the investigators or the national coordinators or the Sponsor in accordance with local regulations.

The study will not start in a centre before written approval by corresponding Ethics Committee(s) has been obtained, the local regulatory requirements have been complied with, and the signature of the clinical study protocol of each contractual party involved has been obtained.

13.2. Study conduct

The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Fortaleza, 2013 (see Appendix 2).

13.3. Participant information and informed consent

The investigator or a person designated by him/her is to collect written consent from each participant before his/her participation in the study. Prior to this, the investigator or his/her delegate must inform each participant of the objectives, benefits, risks and requirements imposed by the study, as well as the nature of the Investigational medicinal product (IMP).

The participant will be provided with an information and consent form in clear, simple language. He/she must be allowed ample time to inquire about details of the study and to decide whether or not to participate in the study.

Two original information and consent forms must be completed, dated and signed personally by the participant and by the person responsible for collecting the informed consent.

If the participant is unable to read, an impartial witness (independent of the research staff) should be present during the entire informed consent discussion. The participant must give consent orally and, if capable of doing so, complete, sign and personally date the information and consent form. The witness must then complete, sign and date the form together with the person responsible for collecting the informed consent.

The participant will be given one signed original information and consent form, the second original will be kept by the investigator.

A copy of the information and consent form in the language(s) of the country is given in the “Participant information and consent form” document attached to the protocol.

13.4. Modification of the information and consent form

Any change to the information and consent form constitutes an amendment to this document and must be submitted for approval to the Ethics Committee(s), and if applicable to the Competent Authorities.

A copy of the new version of the information and consent form in the language(s) of the country will be given in the amendment to the "Participant Information and consent form".

Such amendments may only be implemented after written approval of the Ethics Committee has been obtained and compliance with the local regulatory requirements, with the exception of an amendment required to eliminate an immediate hazard to the study participants.

Each participant affected by the amendment must complete, date and sign two originals of the new version of the information and consent form together with the person who conducted the informed consent discussion. He/she will receive one signed original amendment to the information and consent form.

14. DATA HANDLING AND RECORD KEEPING

14.1. Study data

An electronic data capture system is going to be used for this study. An electronic case report form (eCRF) is designed to record the data required by the protocol and collected by the investigator.

The eCRF will be produced by I.R.I.S., in compliance with its specifications. The investigator and the designated person (if any) from his/her team will be trained for the use of the eCRF by the Sponsor.

Data entry at the investigator's site will be performed by the investigator or by the designated person from his/her team after completion of Medical File.

Upon entry data will be transmitted via the Internet from the study centre to the study database.

In concerned countries the Seattle Angina Questionnaire will be used. The Seattle Angina and the EQ-5D-3L questionnaires are printed in duplicate on copy paper. One copy will be collected by monitor and the other will stay on site. The clinical data division will score the questionnaire in accordance with a specification manual and enter the data.

The investigator or the designated person from his/her team agrees to complete the eCRF, at each participant visit, and all other documents provided by the Sponsor (*e.g.* documents relating to the treatment management…).
All relevant forms of the eCRF must be completed as soon as possible following each visit. In particular, data concerning the Creatinine Clearance or Glomerular Filtration Rate calculated and documented in the Source Data according to section 4.6, are key for the decision on the study treatment dosage and should be promptly entered in the eCRF.

All corrections of data on the eCRF must be promptly made by the investigator or by the designated person from his/her team according to the provided instructions. All data modification will be recorded using the audit trail feature of INFORM™ software, including

date, reason for modification and identification of the person who has made the change. It is essential that the investigator responds promptly to all data queries generated by the Sponsor or its agents, seeking to resolve them as soon as possible.

In order to ensure confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorised personnel only, whether resident within the investigator's sites, the Sponsor or third parties.

The monitor must make certain that data are completed on the eCRF.
Key data subject to monitor's verification are defined in the monitoring guide. After comparing these data to the source documents, the monitor will request correction / clarification from the investigator using electronic data clarifications that should be answered and closed as quickly as possible.

Data can be frozen during the study after their validation. However the investigator has the possibility to modify a data if deemed via a request to the sponsor.

After the last visit of the participant, the investigator or co-investigator must attest the authenticity of the data collected in the eCRF by entering his/her user name and password.

After the data base lock, the investigator or an authorized member of his/her team will have to download from the e-CRF an electronic file containing participant data of his/her centre for archiving it in the study file (see section 14.3).

14.2. Data management

Data are collected via an e-CRF and stored in a secured database.

For data collected on paper forms (*e.g.* EQ-5D-3L Questionnaire, Seattle Angina Questionnaire in concerned countries), the Clinical Data Division of I.R.I.S. is responsible for data processing including:

- data entry: independent, blind, double data entry with a third person resolving any discrepancy between first and second entry,
- data validation performed according to a specification manual describing the checks to be carried out. As a result of data validation, data may require some changes. A data clarification form is sent to the investigator for confirmation or correction and signature. In some cases, mentioned in the specification manual, changes (obvious errors) are not subject to the investigator's approval. A record of these data changes is provided to the investigator when the study is completed.

For data collected on the eCRF, the Clinical Data Division of I.R.I.S. is responsible for data processing including data validation performed according to a specification manual describing the checks to be carried out. As a result of data validation, data may require some changes. An electronic data clarification form is sent to the investigator who is required to respond to the query and make any necessary changes to the data.

The IWRS CRO and the Endpoint Adjudication CRO will provide electronic transfer of computerised data to the database held by the Data Management Department of I.R.I.S. according to a transfer protocol issued by the I.R.I.S. data manager.

The Medical Data Department of I.R.I.S. is responsible for data coding including:

- medical/surgical history, adverse events, procedures using MedDRA,

- medications using WHO-DD.

The coding process is described in a specification manual.

Intermediate blind reviews of data will be organised regularly during the study according to the Sponsor's standard operating procedure. When data validation is achieved, a final blind review of the data will be performed according to the Sponsor's standard operating procedure. When the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for the data analysis.

14.3. Archiving

The investigator will keep all information relevant to the study for at least 15 years after the end of the study.

At the end of the study, the investigator or an authorized member of his/her team will download an electronic copy of each participant's data from the e-CRF and should keep it in a reliable, secure and durable location. The file must include appropriate restrictions (password protection) and adequate protection from loss, physical damage or deterioration for the duration of the archiving period. These data include the completed eCRF, all electronic CRF comments, history of all queries; all signature history and the full audit trail reports.

15. INSURANCE

I.R.I.S., or any parent company of SERVIER GROUP in charge of the management of clinical trials, is insured under the liability insurance program subscribed by LES LABORATOIRES SERVIER to cover its liability as Sponsor of clinical trials on a worldwide basis.

Where an indemnification system and/or a mandatory policy are in place, I.R.I.S. or any parent company of SERVIER GROUP will be insured under a local and specific policy in strict accordance with any applicable law.

All relevant insurance documentation is included in the file submitted to any authorities approval of which is required.

16. OWNERSHIP OF THE RESULTS – PUBLICATION POLICY

I.R.I.S., acting as the study Sponsor, assumes full responsibility relating to this function and retains exclusive property rights over the results of the study, which it may use as it deems fit.

As the study is a multicentre one, the first publication must be performed only with data collected from several centres and analysed under the responsibility of the Methodology and Clinical Data Analysis Division of I.R.I.S. The investigator commits himself not to publish or communicate data collected in only one centre or part of the centres before the publication of the complete results of the study, unless prior written agreement from the other investigators and I.R.I.S. has been provided.

Any project of publication and/or communication relative to the study and/or relative to the obtained results during the study or after the study end, shall be submitted to the Sponsor at least 30 days for a publication and 15 days for an abstract before the forecasted date of communication and/or submission for a publication. The Sponsor shall make comments on the project within 15 days for a publication and 7 days for an abstract, of receipt of the project. The investigator, who submitted the project, shall take the Sponsor's comments into

due consideration. In any case, should the investigator who submitted the project decide not to modify the project according to the Sponsor's comments, he/she shall provide the Sponsor with the grounds of its decision in writing.

However, in the case where the Sponsor is in the process of filing a patent application on the results of the study, the Sponsor will be able to delay its authorisation for publication or communication of the results of the study until the date of international registration of the patent.

17. ADMINISTRATIVE CLAUSES

17.1. Concerning the Sponsor and the investigator

17.1.1. Persons to inform

In accordance with local regulations, the investigator and/or the Sponsor will inform, the Director of the Medical Institution, the pharmacist involved in the study and the Director of the analysis laboratory that the study is to be performed in the institution.

With the agreement of the participant, the investigator will inform the participant’s general practitioner about his/her patient’s participation in a clinical study.

17.1.2. Substantial protocol amendment

If the protocol must be altered after it has been signed, the modification or substantial amendment must be discussed, in the case of a potential impact on all patients, by the Executive Committee and the company I.R.I.S. (Sponsor) and, in the case of a potential impact on the patients in a local area, by the relevant national coordinator and the company I.R.I.S. The final document will be approved, in the case of a potential impact on all patients, by the Steering Committee and, in the case of a potential impact on the patients in a local area, by the relevant national coordinator.

The substantial protocol amendment must be drafted in accordance with the Sponsor’s standard operating procedure and an amended protocol must be signed by both parties. Both documents must be kept with the initial protocol.

All substantial amendments and corresponding amended protocols must be sent by the investigator or the coordinator or the Sponsor, in accordance with local regulations, to the Ethics Committee that examined the initial protocol. They can only be implemented after a favourable opinion of the Ethics Committee has been obtained, local regulatory requirements have been complied with, and the amended protocol has been signed, with the exception of a measure required to eliminate an immediate hazard to the study participants.

When the submission is performed by the investigator or the coordinator, the latter must transmit a copy of Ethics Committee’s new written opinion to the Sponsor, immediately upon receipt.

Furthermore, the substantial amendment and amended protocol are to be submitted to the Competent Authorities in accordance with local regulations.

17.1.3. Final study report

The study report will be drafted by I.R.I.S. in close collaboration with the International Coordinator (Chairman of the Executive Committee) and in compliance with I.R.I.S. standard operating procedure.

The Sponsor's representative and the chairman of the Executive Committee must mutually agree on the final version. One copy of the final report, must be dated and signed by the International Coordinator and the Director of the Innovation Therapeutic Pole.

17.2. Concerning the Sponsor

The Sponsor undertakes to:

- supply the investigator with adequate and sufficient information concerning the treatment administered during the study to enable him/her to carry out the study,
- supply the investigator with SmPC, the one best suited to ensure patient safety, and any potential updated version during the study,
- obtain any authorisation to perform the study and import licence for the treatment administered that may be required by the local authorities before the beginning of the study,
- provide the coordinators annually, or with another frequency defined by the local regulations, with a document describing study progress to be sent to the Ethics Committees.

17.3. Concerning the investigator

17.3.1. Confidentiality - Use of information

All documents and information given to the investigator by the Sponsor with respect to trimetazidine and study CL3-06790-010 are strictly confidential.

The investigator expressly agrees that data on his/her professional and clinical experience is collected by the Sponsor on paper and computer, and stored for its sole use relating to its activities as the Sponsor of clinical trials, in accordance with GCP. He/she has a right to access to, modify, and delete any personal data by applying to the study monitor.

The investigator agrees that he/she and the members of his/her team will use the information only in the framework of this study, for carrying out the protocol. This agreement is binding as long as the confidential information has not been disclosed to the public by the Sponsor. The clinical study protocol given to the investigator may be used by him/her or his/her colleagues to obtain the informed consent of study participants. The clinical study protocol as well as any information extracted from it must not be disclosed to other parties without the written authorisation of the Sponsor.

The investigator must not disclose any information without the prior written consent from I.R.I.S., except to the representatives of the Competent Authorities, and only at their request. In the later case, the investigator commits himself to informing I.R.I.S. prior to disclosure of information to these authorities.

A subject screening log and a full identification and enrolment list of each participant will be completed and kept by the investigator who should agree to provide access on site to the

auditor and/or the representatives of the Competent Authorities. The information will be treated in compliance with professional secrecy.
The subject-screening log must be completed from the moment the investigator checks that a participant could potentially take part in the study (by assessment of participant medical/surgical history during a visit or by examination of the medical file).

17.3.2. Organisation of the centre

Every person to whom the investigator delegates under his/her responsibility a part of the follow-up of the study (co-investigator, nurse…) and any other person involved in the study for this centre (cardiologist, pharmacist) must figure in the "Organisation of centre" document.

This document should be filled in at the beginning of the study and updated at any change of a person involved in the study in the centre.

17.3.3. Documentation supplied to the Sponsor

The investigator undertakes before the study begins:

- to provide his/her dated and signed English Curriculum Vitae (CV) (maximum 2 pages) or to complete in English the CV form provided by the Sponsor and to send it to the Sponsor, together with that of his/her co-investigator(s),
- to provide a detailed description of the methods, techniques, and investigational equipment, and the reference values for the parameters measured,
- to send (if appropriate), a copy of the Ethics Committee's opinion with details of its composition and the qualifications of its constituent members.

The CVs of other members of the team involved in the study (if possible in English) will be collected during the course of the study.

18. REFERENCES

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19. APPENDICES

Appendix 1: Administrative Structure of the Study

1. Non Sponsor Parties

Table (19) 1 – Non Sponsor parties - Global Level

Role	Title. Initial Forename. Name	Work address and telephone number
Chairman of the Executive Committee	Prof. R. FERRARI	Chair of Cardiology Azienda Ospedaliero-Universitaria di Ferrara Ospedale di Cona - 2/C/3° piano lOCALE 3:13:03 - Via Aldo Moro 8 44124 Cona (Ferrara) - Italy Email: fri@unife.it
Chairman of the Steering Committee	Prof. N. DANCHIN	Hôpital Européen Georges Pompidou Unité Clinique des Maladies Coronaires 20 rue Leblanc 75908 Paris cedex 15 - France Tel: +33 (0)1 56 09 25 71 Email: nicolas.danchin@egp.aphp.fr

Name	Tasks	Address and telephone number
Perceptive eClinical Limited	Interactive Web Response System	The Quays 101-105 Oxford Road Uxbridge - Middlesex United Kingdom UB8 1LZ Tel: +44 (0) 845 365 9879
Syneos Health	Endpoints management	4 The Fleming Building Edinburgh Technopole, Milton Bridge, Penicuik, Midlothian EH26 0BE Tel: +44 (0) 131 448 1300

Table (19) 2 – Non Sponsor parties – List of the national coordinators

Country	Title. Initial Forename. Name	Work address and telephone number
Algeria	Prof. M.T. BOUAFIA	CHU Frantz Fanon Clinique de Medecine interne et Cardiologie Centre Zabana - Route de H'Tatba 9000 BLIDA Tel: +213 77 016 29 19
Argentina	Dr. M. TRIVI	ICBA Av. Del Libertador 6302 (C1428ART) CABA-Argentina Tel: +54 11 4787 7500 ext: 3182
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Country	Title. Initial Forename. Name	Work address and telephone number
Belarus	Prof. A.G. MROCHEK	Republican Scientific and Clinical Institute "Cardiology" of Ministry of Health of the Republic of Belarus 220036, R. Luxemburg str, 110, Minsk Republic of Belarus; Tel: +375 17 207 37 62
Bosnia and Herzegovina	Prof. M. KULIC	Cardioteam Sarajevo Reisa Džemaludina Čauševića 2 71000 Sarajevo Tel: +387 33209800 Fax: +387 33209801 Mob: +387 61 149 491
Brazil	Prof. L.A.M. CÉSAR	Universidade de São Paulo Departamento de Cardiopneumologia Incor Av. Dr. Enéas de Carvalho Aguiar, 44 Cerqueira Cesar 05403-000 São Paulo, SP Tel: +55 11 3069 5387
	Prof. L. H. W. GOWDAK	Universidade de São Paulo Departamento de Cardiopneumologia Incor Av. Dr. Enéas de Carvalho Aguiar, 44 Cerqueira Cesar 05403-000 São Paulo, SP Tel: +55 11 2661 5929
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Croatia	Prof. D. MILICIC	Clinical Hospital Centre Zagreb Kišpatićeva 12 10000 Zagreb Tel: +385 1 2367501
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France	Prof. P. COSTE	Hôpital cardiologique Avenue Magellan 33604 Pessac Tel: +33 5 57 65 64 57
Georgia	Dr. T.SHABURISHVILI	Tbilisi Heart and Vascular Clinic 18/20 Ljubljana Str. Tbilisi 0159 Tel: +995 599 50 22 44
Greece	Dr. V. VOUDRIS	Onassis Cardiac Surgery Center 356 Sygrou Av. 17674 Athens Tel: +30 210 9493354

Country	Title. Initial Forename. Name	Work address and telephone number
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Poland	Prof. R.J. GIL	Klinika Kardiologii Inwazyjnej CSK MSWiA Ul Woloska 137 02-507 Warszawa Tel: +48 22 508 11 00
Portugal	Prof. F. PINTO	Centro Hospitalar de Lisboa Norte, E.P.E. – Hospital de Santa Maria Av. Prof. Egas Moniz 1649-035 Lisboa Tel : +351 217 985 113 // +351 217 969 305 // +351 966 046 210
Republic of Korea	Prof. S.J. PARK	Division of Cardiology, Asan Medical Center University of Ulsan College of Medicine 88, Olympic-ro 43-gil, Songpa-gu Seoul, 05505 Tel: +82 2 3010 4812
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Country	Title. Initial Forename. Name	Work address and telephone number
Turkey	Prof. V. SANSOY	Cardiology Institute - Istanbul University Haseki caddesi 34303 Aksaray-Istanbul Tel: +90 212 343 21 66
Ukraine	Prof. A. PARKHOMENKO	Institute. of Cardiology of AMS of Ukraine Department of reanimation and intensive therapy 5, Narodnogo Opolchennia Str. 03151 Kiev Tel: +380 50 353 16 33
Vietnam	Prof. NGUYEN LAN VIET	Vietnam Heart Institute Bach Mai Hospital 78 Giai Phong – Dong Da HA NOI, Vietnam Tel: +84 913 507 007

The composition and role of the supervisory committees (Executive Committee, Steering Committee, Cardiovascular Endpoints Adjudication Committee, Safety Endpoints Adjudication Committee and Data Monitoring Committee) are described in Sections 8.4.3 and 12.4.
The list of investigators is given in a document attached to the protocol for each country.

2. Sponsor(s) Parties

Table (19) 3 – Institut de Recherches Internationales Servier (I.R.I.S.)

I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex (France)
Tel: +33.1.55.72.60.00 - Fax: +33.1.55.72.54.11

Role	Title. Initial Forename. Name	Work address and telephone number
Director of Cardiovascular Innovation Therapeutic Pole	Dr. I. TUPINON-MATHIEU	+33 1 55 72 64 90
Director of Clinical Development	Mr. E. ARNAUD	+33 1 55 72 67 92
Project Director	Ms. S. ROBERT	+33 1 55 72 65 32
Biostatistician	Ms. A. CORREGES	+33 1 55 72 39 67

Table (19) 4 – Local Sponsors

Country	Name of the Sponsor	Title, Initial, Forename, Name of the protocol's signatory*	Work, address and telephone number
Portugal	Servier Portugal – Especialidades Farmacêuticas, Lda.	Dr. C. GOROSTIAGA AYESTARÁN	Servier Portugal Av. António Augusto Aguiar, 128-130 1069-133 Lisboa Portugal +351 21 312 20 00
Russia	Les Laboratoires Servier (L.L.S)	Director of ICTR-EAEU Dr. A. ANDREEV	50 Rue Carnot 92284 Suresnes Cedex France Tel: +33 1 55 72 60 00 Les Laboratoires Servier Russia Representative Office Lesnaya str., 7, Moscow, 125196 +7 495 937 07 00

3. Departments/organisations responsible for local management of the study

Table (19) 5 – Departments/organisations responsible for local management of the study

Country	Name of the department/organisation	Work address and telephone number
Argentina, Belarus, Bosnia and Herzegovina, Brazil, China, Croatia, Georgia, Greece, Montenegro, Peru, Russia, Serbia, Spain, Turkey	Medical Trials Analysis Swiss SA	6, Via Antonio Riva 6900 Lugano Switzerland Tel: +41 91 960 54 30
Italy	Medical Trials Analysis Italy	6, Via Walter Tobagi, 20143 Milan, Italy Tel: +39 02 36798200
Czech Republic, Poland, Romania, Slovakia, Ukraine	Vesalius Trials LTD	66 Prescott Street London E1 8NN, UK Tel: +44 207 351 8626
Algeria, Austria, Colombia, Republic of Korea, Vietnam	PAREXEL International Sarl	190, rue Championnet 75018 Paris, France Tel: +33 1 44 90 32 00
Portugal	Associação para a Investigação e Desenvolvimento da Faculdade de Medicina de Lisboa (AIDFM)	Av. Prof. Egas Moniz, piso 01 1649-028 Lisboa, Portugal Tel: +351 210008500
France	Action Coeur	Institut de Cardiologie Centre Hospitalier Universitaire Pitié-Salpêtrière 47-83 Boulevard de l´Hôpital 2ème étage 75013 Paris, France Tel: +33142162959

Appendix 2: World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risk, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor on-going studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the

physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

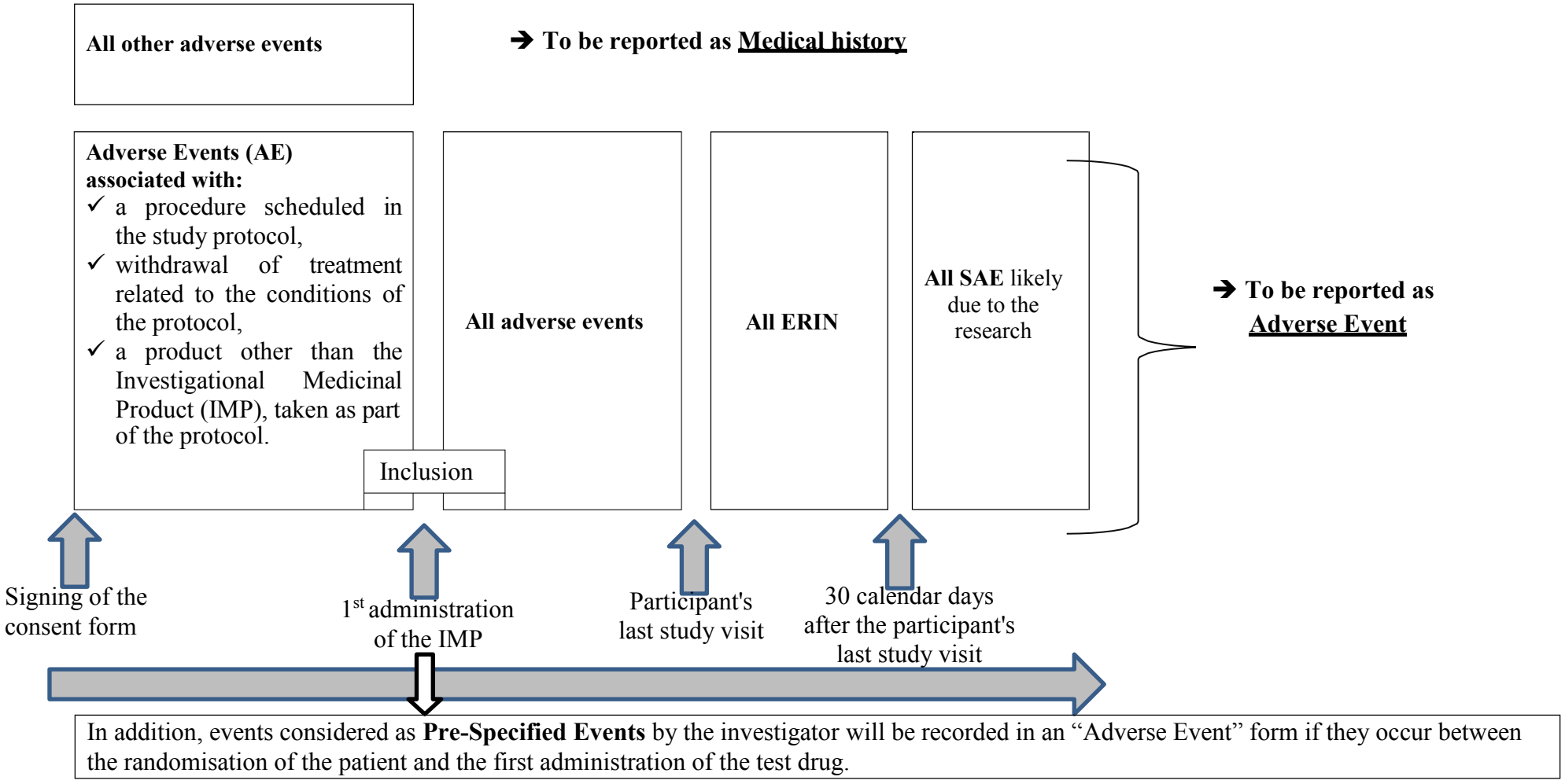
35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Intervention in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 3: Recording of events in the Case Report Form



Appendix 4: Overdose

<table>
<tr><th colspan="6">Excessive intake of the IMP by a study participant</th></tr>
<tr><th rowspan="4">Dose</th><th colspan="5">Adult</th></tr>
<tr><th colspan="3">Intentional intake</th><th colspan="2">Accidental intake</th></tr>
<tr><th rowspan="2">Absence of signs and symptoms</th><th colspan="2">Presence of signs and symptoms</th><th rowspan="2">Absence of signs and symptoms</th><th colspan="2">Presence of signs and symptoms</th></tr>
<tr><th>Non serious AE</th><th>SAE</th><th>Non serious AE</th><th>SAE</th></tr>
<tr><td>> 2 tablets daily and ≤ 4 tablets in any 24 hour period</td><td rowspan="2">To be notified immediately</td><td rowspan="2">To be notified immediately</td><td rowspan="2">To be notified immediately</td><td></td><td></td><td rowspan="2">To be notified immediately</td></tr>
<tr><td>> 4 tablets in any 24 hour period</td><td>To be notified immediately</td><td>To be notified immediately</td></tr>
</table>

AE: Adverse Event SAE: Serious Adverse Event

<table>
<tr><th colspan="5">Intake of the IMP by a person around the study participant</th></tr>
<tr><th rowspan="3">Dose</th><th rowspan="3">Minor subject</th><th colspan="3">Adult</th></tr>
<tr><th rowspan="2">Absence of signs and symptoms</th><th colspan="2">Presence of signs and symptoms</th></tr>
<tr><th>Non serious AE</th><th>SAE</th></tr>
<tr><td>≤ 4 tablets in any 24 hour period</td><td rowspan="2">To be notified immediately</td><td></td><td rowspan="2">To be notified immediately</td><td rowspan="2">To be notified immediately</td></tr>
<tr><td>> 4 tablets in any 24 hour period</td><td>To be notified immediately</td></tr>
</table>

AE: Adverse Event SAE: Serious Adverse Event

Appendix 5: Clinical Classification of Chest Pain

For the purposes of this study angina pectoris will be defined as chest pain of cardiac nature which fulfills the following criteria:

Clinical classification of chest pain		
Exertional angina	Definite exertional angina	Meets **three** of the following characteristics: ▪ Chest discomfort of characteristic quality and duration ▪ Provoked by exertion or emotional stress ▪ Relieved by rest and/or short acting nitrates
	Probable exertional angina	▪ Chest discomfort of characteristic quality and duration and one of the two other characteristics: ▪ provoked by exertion or emotional stress, ▪ OR, relieved by rest and/or short acting nitrates
Resting angina		Chest discomfort of characteristic quality and duration, irrespective of the circumstances in which it occurs

Adapted from:

Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F et al. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006;27(11):1341-81.

Appendix 6: Canadian Cardiovascular Society (CCS) Classification of Symptoms of Angina

Class 1
"Ordinary activity does not cause angina"
Angina with strenuous or rapid or prolonged exertion only

Class 2
"Slight limitation of ordinary activity"
Angina on walking or climbing stairs rapidly, walking uphill or exertion after meals, in cold weather, when under emotional stress, or only during the first few hours after awakening

Class 3
"Marked limitation of ordinary physical activity"
Angina on walking one or two blocks[(a)] on the level or one flight of stairs at a normal pace under normal conditions

Class 4
"Inability to carry out any physical activity without discomfort"
or "angina at rest"

[(a)] Equivalent to 100-200 meters

From: Campeau L. Letter: grading of angina pectoris. Circulation 1976;54:522–-

Appendix 7: The Seattle Angina Questionnaire

This questionnaire will only apply in countries where there is a valid translation of the questionnaire into the local language of the patients.

1. The following is a list of activities that people often do during a normal week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness, or anginal attacks over the past 4 weeks:**

Place an x in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not Limited at all	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Walking indoors on level ground	☐	☐	☐	☐	☐	☐
Showering or bathing	☐	☐	☐	☐	☐	☐
Climbing a hill or a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Gardening, vacuuming, or carrying groceries	☐	☐	☐	☐	☐	☐
Walking more than a hundred yards at a brisk pace	☐	☐	☐	☐	☐	☐
Running or jogging	☐	☐	☐	☐	☐	☐
Lifting or moving heavy objects such as furniture, or lifting children	☐	☐	☐	☐	☐	☐
Participating in strenuous sports (e.g. swimming, tennis)	☐	☐	☐	☐	☐	☐

2. Compared with 4 weeks ago, how often do you have **chest pain**, **chest tightness**, or **anginal attacks** when doing your **most strenuous** activities?

I have **chest pain**, **chest tightness**, or **anginal attacks**...

Much more often	**Slightly more** often	About **the same**	**Slightly less** often	**Much less** often	I have had **no chest pain** over the last 4 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 4 weeks, on average, how many times have you had **chest pain**, **chest tightness**, or **anginal attacks**?

I have had **chest pain**, **chest tightness**, or **anginal attacks**...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

4. Over the past 4 weeks, on average, how many times have you had to take GTN (nitroglycerin tablets or spray) for your **chest pain**, **chest tightness**, or **anginal attacks**?

I have taken GTN...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

5. How bothersome is it for you to take your pills for **chest pain**, **chest tightness** or **anginal attacks** as prescribed?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not** bothersome at all	My doctor has **not prescribed** pills
☐	☐	☐	☐	☐	☐

6. How satisfied are you that everything possible is being done to treat your **chest pain**, **chest tightness**, or **anginal attacks**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

7. How satisfied are you with the explanations your doctor has given you about your **chest pain**, **chest tightness**, or **anginal attacks**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

8. Overall, how satisfied are you with the current treatment of your **chest pain**, **chest tightness**, or **anginal attacks**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

9. Over the past 4 weeks, how much has your **chest pain**, **chest tightness**, or **anginal attacks** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not** limited my enjoyment of life at all
☐	☐	☐	☐	☐

10. If you had to spend the rest of your life with your **chest pain**, **chest tightness**, or **anginal attacks** the way it is at the moment, how would you feel about this?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

11. How often do you think or worry that you may have a heart attack or die suddenly?

I think or worry about it **all the time**	I **often** think or worry about it	I **occasionally** think or worry about it	I **rarely** think or worry about it	I **never** think or worry about it
☐	☐	☐	☐	☐

SAQ – UK (English)

Appendix 8: The EQ-5D-3L Questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

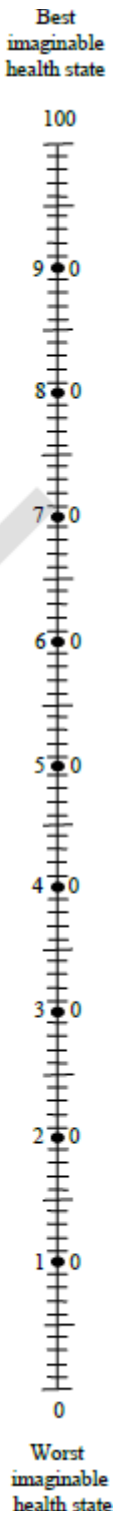
Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 9: Specific storage conditions by country

COUNTRY	SPECIFIC STORAGE CONDITIONS
ALGERIA	STORE UP TO 30°C
ARGENTINA	STORE UP TO 30°C
AUSTRIA	NO SPECIFIC STORAGE CONDITIONS
BELARUS	STORE UP TO 30°C
BOSNIA & HERZEGOVINA	STORE UP TO 30°C
BRAZIL	PROTECT FROM LIGHT, PROTECT FROM MOISTURE, STORE AT ROOM TEMPERATURE 15-30°C
CHINA	NO SPECIFIC STORAGE CONDITIONS (REGARDING TEMPERATURE), PRESERVE IN A WELL CLOSED CONTAINER
COLOMBIA	STORE UP TO 30°C
CROATIA	STORE UP TO 30°C
CZECH REPUBLIC	NO SPECIFIC STORAGE CONDITIONS
FRANCE	NO SPECIFIC STORAGE CONDITIONS
GEORGIA	NO SPECIFIC STORAGE CONDITIONS
GREECE	NO SPECIFIC STORAGE CONDITIONS
ITALY	NO SPECIFIC STORAGE CONDITIONS
KOREA (REPUBLIC OF)	STORE BETWEEN 1-30°C
MONTENEGRO	NO SPECIFIC STORAGE CONDITIONS
PERU	STORE UP TO 30°C
POLAND	NO SPECIFIC STORAGE CONDITIONS
PORTUGAL	NO SPECIFIC STORAGE CONDITIONS
ROMANIA	NO SPECIFIC STORAGE CONDITIONS
RUSSIAN FEDERATION	NO SPECIFIC STORAGE CONDITIONS
SERBIA	NO SPECIFIC STORAGE CONDITIONS
SLOVAKIA	STORE UP TO 25°C
SPAIN	NO SPECIFIC STORAGE CONDITIONS
TURKEY	STORE UP TO 30°C
UKRAINE	NO SPECIFIC STORAGE CONDITIONS
VIETNAM	STORE UP TO 30°C

Appendix 10: Questionnaire for neurologists (template)

PARKINSON'S SYNDROME

☐ Initial consultation ☐ Follow-up consultation

TO BE COMPLETED BY THE INVESTIGATOR

DATE:……. /……. /…….
DD MM YYYY

PATIENT INFORMATION
Patient n° : I__I__I__I__I__I Center n° : I__I__I__I__I
☐ Female ☐ Male Age: ……. year-old Weight .....kg
EVENT (verbatim)**:** .....

ONSET DATE: ……. /……. /…….
DD MM YYYY
DATE OF FIRST INTAKE OF THE INVESTIGATIONAL MEDICINAL PRODUCT: ……./……. /…….
DD MM YYYY
DATE OF LAST INTAKE OF THE INVESTIGATIONAL MEDICINAL PRODUCT: ……. /……. /…….
DD MM YYYY

TO BE COMPLETED BY THE NEUROLOGIST

SYMPTOMATOLOGY	YES	NO	UNK
Rapid onset of symptomatology	☐	☐	☐
BRADYKINESIA ☐ YES ☐ NO			
If yes, please complete:			
1- Slowness of gait	☐	☐	☐
2- Unexpressive face	☐	☐	☐
3- Micrographia	☐	☐	☐
4- Decreased arm swing	☐	☐	☐
5- Other……			
TREMOR ☐ YES ☐ NO			
If yes, please complete:			
☐ Unilateral ☐ Bilateral			
1- Onset circumstances:			
- Resting	☐	☐	☐
- Postural	☐	☐	☐
2- Head and voice involved	☐	☐	☐
3- Other……			
HYPERTONIA ☐ YES ☐ NO			
If yes, please complete:			
☐ Unilateral ☐ Bilateral			
1- Wrist rigidity	☐	☐	☐
2- Other……			
OTHER			
1- Gait disturbance	☐	☐	☐
2- Postural instability	☐	☐	☐
3- Micturition disorders	☐	☐	☐
4- Dyskinesia	☐	☐	☐
5- Cognitive disorders	☐	☐	☐
6- Pyramidal or cerebellar signs	☐	☐	☐
7- Restless leg syndrome	☐	☐	☐
8- Other……			

INVESTIGATIONS	YES	NO	UNK	DATE	DETAILS
IMAGING FINDINGS					
Cerebral MRI	☐	☐	☐	/……. /……. /……. DD MM YYYY	……
DAT scan	☐	☐	☐	/……. /……. /……. DD MM YYYY	……
L-Dopa test					
☐ positive ☐ negative				/……. /……. /……. DD MM YYYY	
Other					

Relevant past medical history:

.....
.....
.....
.....
.....
.....
.....

Improvement after drug withdrawal*
☐ YES ☐ NO ☐ UNK

Evolution since last consultation**
☐ Unchanged ☐ Worsening ☐ Improving ☐ Recovering ☐ Unknown

General comments:

.....
.....
.....
.....
.....
.....
.....

*Initial consultation
**Follow-up consultation

Appendix 11: Calculation of estimated creatinine clearance (eCrCl) and estimated glomerular filtration rate (eGFR)

Calculation of Estimated Creatinine Clearance (eCrCl) Using Cockcroft-Gault Formula

Required data:

- Age
- Sex
- Weight - kilograms
- Creatinine – units: either mg/dL or μmol/L

For creatinine in **mg/dL:**

For FEMALE patients

$$eCrCl = \frac{(140 - age) \times Wt \times 0.85}{72 \times \text{Serum creatinine (}\mathbf{mg/dL}\text{)}}$$

For MALE patients

$$eCrCl = \frac{(140 - age) \times Wt}{72 \times \text{Serum creatinine (}\mathbf{mg/dL}\text{)}}$$

For creatinine in **μmol/L:**

For FEMALE patients

$$eCrCl = \frac{(140 - age) \times Wt \times 1.04}{\text{Serum creatinine (}\boldsymbol{\mu}\mathbf{mol/L}\text{)}}$$

For MALE patients

$$eCrCl = \frac{(140 - age) \times Wt \times 1.23}{\text{Serum creatinine (}\boldsymbol{\mu}\mathbf{mol/L}\text{)}}$$

Calculation of estimated glomerular filtration rate (eGFR) using MDRD formula

Required data:

- Age
- Sex
- Ethnicity
- Creatinine – units: either mg/dL or µmol/L

For creatinine in **mg/dL:**

For FEMALE patients

For **black female** patients
eGFR= [186 x Serum creatinine $^{-1.154}$ x (Age) $^{-0.203}$] x 0.742 x 1.210 x 0.95
For **white or other race female** patients

eGFR= [186 x Serum creatinine $^{-1.154}$ x (Age) $^{-0.203}$] x 0.742 x 0.95

For MALE patients

For **black male** patients
eGFR= [186 x (Serum creatinine) $^{-1.154}$ x (Age) $^{-0.203}$] x 1.210 x 0.95

For **white or other race male** patients
eGFR= [186 x (Serum creatinine) $^{-1.154}$ x (Age) $^{-0.203}$] x 0.95

For creatinine in **µmol/L:**

For FEMALE patients
For **black female** patients
eGFR= [186 x (Serum creatinine x 0.0113)$^{-1.154}$ x (Age) $^{-0.203}$] x 0.742 x 1.210 x 0.95

For **white or other race female** patients
eGFR= [186 x (Serum creatinine x 0.0113)$^{-1.154}$ x (Age) $^{-0.203}$] x 0.742 x 0.95

For MALE patients
For **black male** patients
eGFR= [186 x (Serum creatinine x 0.0113)$^{-1.154}$ x (Age) $^{-0.203}$] x 1.210 x 0.95

For **white or other race male** patients
eGFR= [186 x (Serum creatinine x 0.0113)$^{-1.154}$ x (Age) $^{-0.203}$] x 0.95

Calculation of estimated glomerular filtration rate (eGFR) using CKD-EPI formula

Required data:

- Age
- Sex
- Ethnicity
- Creatinine – units: either mg/dL or µmol/L

For creatinine in **mg/dL:**

For FEMALE patients

Black female

If serum creatinine <= 0.7:
$eGFR = 166 \times (Serum\ creatinine / 0.7)^{-0.329} \times 0.993^{Age}$

If serum creatinine > 0.7:
$eGFR = 166 \times (Serum\ creatinine / 0.7)^{-1.209} \times 0.993^{Age}$

White or other race female

If serum creatinine <= 0.7:
$eGFR = 144 \times (Serum\ creatinine / 0.7)^{-0.329} \times 0.993^{Age}$

If serum creatinine > 0.7:
$eGFR = 144 \times (Serum\ creatinine / 0.7)^{-1.209} \times 0.993^{Age}$

For MALE patients

Black male

If serum creatinine <= 0.9:
$eGFR = 163 \times (Serum\ creatinine / 0.9)^{-0.411} \times 0.993^{Age}$

If serum creatinine > 0.9:
$eGFR = 163 \times (Serum\ creatinine / 0.9)^{-1.209} \times 0.993^{Age}$

White or other race male

If serum creatinine <= 0.9:
$eGFR = 141 \times (Serum\ creatinine / 0.9)^{-0.411} \times 0.993^{Age}$

If serum creatinine > 0.9:
$eGFR = 141 \times (Serum\ creatinine / 0.9)^{-1.209} \times 0.993^{Age}$

For creatinine in **µmol/L:**

For FEMALE patients

Black female

If serum creatinine <= 61.9:
$eGFR = 166 \times (Serum\ creatinine / 61.9)^{-0.329} \times 0.993^{Age}$

If serum creatinine > 61.9:
$eGFR = 166 \times (Serum\ creatinine / 61.9)^{-1.209} \times 0.993^{Age}$

White or other race female

If serum creatinine <= 61.9:
$eGFR = 144 \times (Serum\ creatinine / 61.9)^{-0.329} \times 0.993^{Age}$

If serum creatinine > 61.9:
$eGFR = 144 \times (Serum\ creatinine / 61.9)^{-1.209} \times 0.993^{Age}$

For MALE patients

Black male

If serum creatinine <= 79.6:
$eGFR = 163 \times (Serum\ creatinine / 79.6)^{-0.411} \times 0.993^{Age}$

If serum creatinine > 79.6:
$eGFR = 163 \times (Serum\ creatinine / 79.6)^{-1.209} \times 0.993^{Age}$

White or other race male

If serum creatinine <= 79.6:
$eGFR = 141 \times (Serum\ creatinine / 79.6)^{-0.411} \times 0.993^{Age}$

If serum creatinine > 79.6:
$eGFR = 141 \times (Serum\ creatinine / 79.6)^{-1.209} \times 0.993^{Age}$

ATPCI Charter of the Cardiovascular Endpoints Adjudication Committee

Document title	**CARDIOVASCULAR ENDPOINTS ADJUDICATION COMMITTEE PROCEDURE**
Study title	**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.**
Study drug	**S 06790 (Trimetazidine MR 35mg)**
Indication	**Angina pectoris**
Development phase	**Phase III**
Protocol code	**CL3-06790-010**
Chairman of the Cardiovascular Endpoints Adjudication Committee	**Prof. Pascal GUERET** **14, rue de Cambrai** **75019 Paris** **France**
Sponsor	**I.R.I.S.**
Date of the document	**Final version including amendment n°6 - 18 February 2020**

Amendment integrated

No	Final version date
1	23 April 2015
2	15 September 2015
3	7 June 2016
4	18 October 2017
5	20 November 2019
6	18 February 2020

CONFIDENTIAL

CONFIDENTIALITY CLAUSE

FOLLOW-UP OF VERSIONS

Amendment No	Final version date	Nature of amendments

1	23 April 2015	• Update of following definitions:
		  • Sudden death,
		  • Unstable angina,
		  • Date of event for coronary angiography, for change in evidence-based antianginal therapy, for death, for hospitalization for angina leading to performing a coronary angiography or leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies.
		• Update of adjudication forms for hospitalisation, coronary angiography, coronary revascularization, change in antianginal therapy, death.
		• Changes related to adjudication process: order of adjudications, update of readjudication process, update of process for unreported events.
		• Addition of details regarding training of adjudicators
		• Clarification of I.R.I.S. ITP role in the review of PSE

2	15 September 2015	• Clarification of CVAC members role
		• Clarification of the I.R.I.S. ITP and Syneos Health role during the CVAC face-to-face meetings
		• Update of the definition of unstable angina
		• Clarifications related to date of event:
		  • Auto-population of date in TrialEAS
		  • Incomplete date
		  • Date of change of antianginal therapy
		• Update of information to be provided by the investigators for coronary revascularization

3	7 June 2016	• Update of the CVAC members list • Adjustment of the time window for adjudication • Update of the definition of hospitalization for coronary revascularization • Update of the definition of unstable angina • Update of the adjudication form for hospitalization

4	18 October 2017	• Creation of unreported event Hospitalisation by the adjudicators for each Coronary angiography without hospitalization for cardiovascular reason • Update of evidence-based antianginal therapy list with trimetazidine
5	20 November 2019	• Update regarding creation of Unreported events Hospitalisation by the adjudicators • Hospitalisations for stable angina or ischemia leading to revascularisations – particular cases to be confirmed by the adjudicators • Events downgraded after adjudication • Update of the time window for the adjudication at the end of the study • Update of the list of situations when PSE will be adjudicated during a face-to-face meeting • Update of rules regarding adjudication decided during the CVAC meetings • Update of table "List of PSE, adjudicators' diagnoses and study endpoints" • Update of name of the CRO in charge of adjudication: INC Research changed its name into Syneos Health starting from January 2018.
6	18 February 2020	• Clarification of events to be reviewed directly by committee (first and last face-to-face meetings) • Possibility to have a phone meeting at the end of the study • Update of particular cases to be confirmed by the adjudicators

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1. LOSSARY

AE	:	Adverse event
BNP	:	B-type Natriuretic Peptide
CABG	:	Coronary Artery Bypass Graft
CAD	:	Coronary Artery Disease
CK-MB	:	Creatine Kinase-Myocardial Band
CCS	:	Canadian Cardiovascular Society
CRO	:	Contract Research Organisation
CT	:	Computerised Tomography
cTn	:	Cardiac troponin
CV	:	Curriculum Vitae
CVAC	:	Cardiovascular Endpoints Adjudication Committee
DCF	:	Data Clarification Form
ECG	:	ElectroCardioGram
e-CRF	:	Electronic Case Report Form
HF	:	Heart Failure
I.R.I.S.	:	Institut de Recherches Internationales Servier
ITP	:	Innovation Therapeutic Pole
LBBB	:	Left Bundle Branch Block
LVH	:	Left Ventricular Hypertrophy
MI	:	Myocardial Infarction
MR	:	Magnetic Resonance
MRI	:	Magnetic Resonance Imaging
NSTEMI	:	Non-ST Segment Elevation Myocardial Infarction
PCI	:	Percutaneous Coronary Intervention
PCS	:	Patient Case Summary
PSE	:	Pre-Specified Event
STEMI	:	ST Segment Elevation Myocardial Infarction
URL	:	Upper Reference Limit

2. INTRODUCTION

The CL3-06790-010 study entitled **"The efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention. ATPCI study"**, is a phase III study planned to obtain 1363 primary endpoints after inclusion of about 5800 patients, with an estimated recruitment period of 2 years and a minimum follow-up duration of 2 years.

The primary objective is to demonstrate the superiority of trimetazidine MR 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.

The secondary objective is to evaluate the effect of trimetazidine on the other efficacy endpoints as well as the other safety parameters, clinical and biological (*see appendix 1*).

This procedure describes the role of the Cardiovascular Endpoint Adjudication Committee (CVAC), the requirements for membership, the description of the adjudication process, the organisation of the CVAC meetings, and the required definitions and documents for Pre-Specified Events adjudication.

3. ROLE OF THE CARDIOVASCULAR ENDPOINTS ADJUDICATION COMMITTEE

Before the start of the adjudication process, the CVAC members will produce working definitions for the purpose of endpoints classification. The definitions to be used for adjudication are presented in appendix 2.

Throughout the study, all Pre-Specified Events (PSE) occuring after randomisation until the end of the study, whether or not the patient is under treatment, will be adjudicated by an independent Cardiovascular Endpoint Adjudication Committee which is blinded to the patient's identity and treatment. These PSE are:

- all deaths,
- all hospitalisations for cardiovascular reason,
- all coronary angiographies,
- all coronary revascularizations,
- all changes in antianginal therapy (addition, switch or increase of the dose of one of the antianginal therapies, whatever the reason).

The PSE considered by the CVAC as fulfilling the endpoint definitions will be called the adjudicated study efficacy endpoints.

4. EMBERS OF THE CARDIOVASCULAR ENDPOINT ADJUDICATION COMMITTEE

The CVAC is an independent committee formed of four cardiologists including the Chairman Prof P. Guéret (*see appendix 3*). New members can be added during the study if required (for example, if there is a delay in the adjudication process due to work overload).

Each CVAC member will supply I.R.I.S. with a copy of their curriculum vitae (CV) in English, dated and signed, before participating in the adjudication process.

Each CVAC member will be trained to the adjudication system by Syneos Health. In addition, a training session will be organised before starting the adjudication process in order to train the CVAC members on the adjudication procedures. During this meeting the CVAC members will review several dummy cases and will adjudicate the first PSE files of the study.

CVAC members must sign a financial contract describing, among other, the role of the CVAC, the confidentiality rules and the financial agreement relationship between the CVAC members and I.R.I.S.

All adjudications must be made by the CVAC in a fair and unbiased manner. All members will be free of direct involvement in the study and will be independent from I.R.I.S. Thus, no CVAC member will act as an investigator or co-investigator in the study.

CVAC members will have to fulfil the conditions described in the "Conflict of interest statement" and sign it *(see appendix 4)*.

Then, if during the trial CVAC members develop a conflict of interest, they are responsible for informing the Chairman concerning any other relevant financial interest in pharmaceutical companies, biotechnology companies or Contract Research Organisations (CROs). The Chairman will be responsible for deciding whether or not consultancy or financial interests of the member materially impact upon his objectivity.

The Chairman will ask for resignation of a CVAC member who develops a material conflict of interest. If the Chairman himself or another member develops such a conflict, the Chairman will inform I.R.I.S. In order to maintain the CVAC at full complement throughout the trial, the CVAC Chairman in cooperation with I.R.I.S. shall designate a replacement for any member who resigns. If the member to be replaced is the CVAC Chairman himself, the designation of his successor will be decided by the Executive Committee on cooperation with I.R.I.S.

5. ORGANISATION

In order to allow the adjudication of the events by the CVAC members, a website will be conceived by Syneos Health, a dedicated CRO which is under the responsibility of I.R.I.S. The specifications of the tasks of Syneos Health are detailed in a separate specific document. Syneos Health will be independent from the CVAC members and will be under contract with I.R.I.S.

In cooperation with the Chairman, I.R.I.S. and Syneos Health will ensure the good running of the adjudication of the PSE by:

- organising each meeting,
- providing all documents and additional information to the CVAC members,
- attending each meeting for ensuring a logistic support during the meeting.

5.1. Pre-Specified Events data flow

5.1.1. Adjudication process

The adjudication process is detailed below:

Each event will be adjudicated electronically, independently, and in parallel by two randomly chosen CVAC members.

PSEs occurring in a same patient and related to the same Adverse Event will be adjudicated at the same time (as far as possible) and by the same pair of adjudicators.

In addition:

- in case of death, the death cannot be adjudicated before the event which is considered by the investigator as the cause of death, when this event is to be adjudicated,
- in case of death, the death cannot be adjudicated if an MI occurred within the 28 calendar days preceding the death, as long as the hospitalisation for the MI has not been adjudicated.

The above mentioned cases will be adjudicated by the same pair of adjudicators.

The CVAC members in charge of the adjudication of a new PSE will be provided with the available results of adjudications of previous PSE that occurred to the same patient.

A flow chart of the adjudication process is presented in *appendix 5*.

The time window for the adjudication of an event is 14 calendar days, from the availability of the PSE file on the website. If the adjudication is not carried out within this time, the CRO will remind the concerned CVAC member by e-mail:

- after 14 calendar days, the CVAC member will receive a remindermessage,
- then every 2 weeks after additional 14 calendar days, the CVAC member will receive a second reminder containing a cumulative list of all events allocated to him that have overpassed the 14 days since allocation,
- after a period of > 42 calendar days the CVAC member will be informed that the time window is over and that the PSE dossier will be allocated to another CVAC member.

CVAC members will check at least once a week directly on the INC website if they have events to be adjudicated. The time window for adjudication can be readjusted during the study by I.R.I.S. in cooperation with the Chairman, particularly at the end of the study (7 calendar days or less, if necessary) when the timelines can be shortened to allow database lock 6 weeks after Last Visit Last Patient.

In case of unavailability of a CVAC member, allocation of PSE dossiers to this member may be temporarily discontinued.

At any time during the review of the PSE and before adjudication, a member may ask for additional information. In that case, the additional information will be sent to the CVAC member who requested the additional information. From the availability of the additional information, the CVAC member will have 14 calendar days to adjudicate the event.

When the two CVAC members have the same adjudication results on both the date of event and the diagnosis (i.e. “matching result”), the adjudication process will be considered as completed.
By default, the “event date” reported in the adjudication form on INC website will be the date of the related event reported in the e-CRF (date of hospitalisation, date of angiography, date of revascularization, date of change in antianginal therapy). If necessary, the CVAC member will have to change this “event date” according to his judgment based on the documents provided in the adjudication file.

In the following situations, the PSE will be adjudicated during a face-to-face meeting of the committee:

- in case of disagreement between the adjudication results of the 2 CVAC members (i.e. “mismatching result”),

- if one/both CVAC members declare(s) to be "unable to adjudicate" the case (i.e. the member cannot adjudicate the event),
- in case of events created by the CVAC (i.e. events detected by the adjudicators during individual adjudications and not reported by the investigators in the e-CRF),
- in case a complementary PSE file with new or changed relevant information is received by Syneos Health after the final adjudication (readjudication),
- in case I.R.I.S. Data Management department issues a Data Clarification Form (DCF) related to the completion of the adjudication form to be answered by the adjudicators,
- in case of other discrepancies identified by I.R.I.S. following coherence checks,
- first events received for the first face-to-face meeting (to reinforce the training on adjudication procedures),
- last events received for review just before the last face-to-face meeting (to speed up the process and avoid potential additional mismatches).

During the face-to-face meetings, after discussion between the CVAC members and vote, the CVAC chairman will enter the result of adjudication corresponding to the opinion of the majority of the members. If there is no majority during the face-to-face meetings when the CVAC members are in pair number, the Chairman will be given 2 votes.

During the face to face meetings and if necessary, CVAC members may ask for additional information. If so, the corresponding event will be reviewed at the next face-to-face meeting.

During the course of the study, the definitions of PSE to be used for adjudication (ppendix 2) could be modified by amending this procedure (after providing justifications). In that case, according to the type of change it will be decided whether the cases of PSE already adjudicated will have to be re-adjudicated or not with the amended definition. In case a re-adjudication is necessary it will be decided whether the case will be re-opened with a normal process or during a face-to-face meeting. A re-adjudication will also be triggered in case of any relevant modification or relevant new information made available by the investigator after the initial adjudication that can have an impact on the adjudication results. The monitoring CRO Medical Reviewer will review the case and will discuss with the investigator in order to decide whether or not this case needs to be resubmitted to the adjudicators. If yes, I.R.I.S. ITP will perform the medical review and will give the green light to Syneos Health. During the next face-to-face meeting the adjudicators will decide if it is necessary to re-adjudicate the case and if yes, the case will be re-adjudicated during the same meeting.

During the adjudication process, the adjudicators may identify when reviewing the documents related to a PSE, another potential PSE, and they may wonder if this event has been reported by the investigator in the e-CRF as a PSE. In this situation, the adjudicators have the possibility to ask I.R.I.S. whether this event was reported or not, and if not I.R.I.S will ask the investigator to declare it as an event so that regular data flow can be initiated. In case the investigator does not agree to declare it as an event, the event will be presented to the adjudicators during the next face to face meeting. The adjudicators will check if it is necessary or not to create an unreported event and if yes, they will adjudicate it during the same meeting. I.R.I.S., after performing the medical review of the documents related to a PSE, may, in some cases, directly present potential unreported PSE to the adjudicators during the next face to face meeting.

During the study I.R.I.S. will follow up the % of mismatches per adjudicator and, if necessary, will perform a retraining of the adjudicators.

5.1.2. Data flow of the documents related to PSE and adjudication

The PSE data flow will be organised in three steps:

1. From investigator's centre to Syneos Health: the investigator will record the PSE in the e-CRF and, in addition, collect pre-defined appropriate documents and put them at the disposal of the monitor who will constitute the "Pre-specified event dossier". Documents to be provided by the investigator for the adjudication are listed in *appendix 6.*

The PSE dossier will be sent to Syneos Health after source data verification and checking of the documents by the monitor, initial medical review done by the medical reviewer from the local monitoring structure and translation in English by the monitoring CRO. This should be done within 8 weeks after notification of the event to the monitoring CRO. If the timelines are not kept, Syneos Health will send a reminder e-mail to the monitoring CRO.

2. From Syneos Health to the CVAC: Syneos Health is in charge of making available electronically for the 2 CVAC members the documentation related to the PSE to be adjudicated including:

- PSE checklist (list of documents provided by the investigator for the event),
- relevant information extracted from the e-CRF (patient case summary [PCS] provided by I.R.I.S. ITP),
- required documents (see *appendix 6)*.

The documents needed for the event adjudication will be put at the CVAC members' disposal through a website they will have access to, using among other the equipment provided by the sponsor (iPad, high speed internet connection, if necessary). Syneos Health will check the completeness of the PSE dossier and will forward it to I.R.I.S. ITP after having requested and obtained any missing information/document if any. ITP will perform medical review of the PSE files and if necessary will issue queries regarding missing information or inconsistency between different information, etc, or might also request additional documents. Once I.R.I.S. has given the green light for the case by providing the PCS, Syneos Health will allocate it to the adjudicators.

Each CVAC member will be provided with a specific and separate handbook explaining the use of the computerized system. The system (especially the legibility of the documents: e.g. ECG) will be tested before starting the study.

3. From the CVAC to Syneos Health*:* an electronic adjudication form will be completed independently and in parallel by both CVAC members (*appendix 7*). The same electronic procedure will be followed for adjudication during face-to-face meetings (*see § 5.1.1 and 5.2*).

The results of adjudication will be transferred from Syneos Health to I.R.I.S. on a regular basis throughout the study but not to the investigator.

5.2. Cardiovascular Endpoint Adjudication Committee meetings

Face-to-face meetings will be organised by or in close collaboration with I.R.I.S. whenever needed according to the study progress, in order to definitively adjudicate mismatching cases, or when necessary in agreement with the Chairman, in particular in the view of preparation of Data Monitoring Committee meetings.

At the end of the study, if necessary, the committee meeting could be held by telephone in order to solve the last mismatch events or any other outstanding issue.

For events adjudicated during these face-to-face meetings, the adjudication will be entered electronically by the CVAC chairman. In case of technical problems during any face-to-face

meeting a back-up system will be used: the chairman will complete paper adjudication forms and will enter the adjudication results electronically once the system is working again.

General information on the study and on the adjudication progress will be provided to CVAC members at the beginning of each meeting before the adjudication work. Only blinded data will be discussed during all the CVAC meetings.

All members of the CVAC are asked to attend the meetings. In case of impossibility, they have to inform the CVAC Chairman.

A CVAC meeting can be organised when at least 3 members of the CVAC including the Chairman are present.

Exceptionally, when the Chairman cannot attend a meeting, he will delegate the chairmanship to another CVAC member.
Participants to the CVAC meeting other than the CVAC members:

- I.R.I.S. and/or CRO representative(s) will participate in order to:
    - provide the CVAC members with general information on the study and on the adjudication progress at the beginning of the meetings before the adjudication tasks,
    - take minutes of the meetings and provide all attendees with them for validation after the meeting,
    - ensure a logistic support during the meeting (e.g.: functioning of the website).
- I.R.I.S. members are listed in *appendix 8*.

Syneos Health and I.R.I.S. ITP representatives will not make any decisions on adjudication.

6. CARDIOVASCULAR ENDPOINTS ADJUDICATION COMMITTEE MEMBERS SIGNATURES

Members of the Cardiovascular Endpoints Adjudication Committee have read and agreed to the above on the dates below:

Role	*Name*	*Country*	*Date*	*Signature*
Chairman *Cardiology*	Prof. P. GUERET	***France***		
Cardiology	Prof. Y. COTTIN	***France***		
Cardiology	Prof. R. HATALA	***Slovakia***		
Cardiology	Prof. G. FRAGASSO	***Italy***		

7. APPENDICES

7.1. Appendix 1: Efficacy and safety criteria of the protocol

1. Primary endpoints

1.1 Primary efficacy endpoint

Superiority of trimetazidine over placebo on the time to first occurrence of an event in the composite of:
- 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.

1.2 Primary safety endpoint

Incidence of serious emergent adverse events with trimetazidine as compared with placebo.

2. Secondary endpoints

2.1 Secondary efficacy endpoints

Superiority of trimetazidine over placebo on the time to first occurrence of an event in the composite of:
- 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 ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
- evidence of ischemia (documented by Stress Imaging) leading to performing a coronary angiography.

Effect of trimetazidine, compared with that of placebo, on the following endpoints:

Components of the primary endpoint
- 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.

Other secondary endpoints
- evidence of ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
- evidence of ischemia (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,
- hospitalisation for heart failure,
- any coronary revascularization,
- repeat coronary revascularization in response to angina.

2.2 Other efficacy endpoints

- CCS class of angina symptoms,
- number of angina episodes per week,
- number of doses of short-acting nitrates taken per week in response to angina,
- number of antianginal drugs taken by the patient,
- Seattle Angina Questionnaire scores (in countries where a validated translation is available),
- EQ-5D-3L Questionnaire scores,
- level of cardiac troponin (before each repeat elective PCI and between 6 and 24 hours after).

2.3 Secondary safety endpoints

- emergent adverse events (including clinically significant abnormalities observed from the electrocardiographic recordings and from laboratory examinations),
- emergent adverse events of interest,
- vital signs: supine and standing blood pressure (BP), heart rate (HR),
- weight,
- biochemical and haematological parameters.

7.2. Appendix 2: Definition to be used for adjudication

The definitions to be used by the CVAC members for the adjudication are detailed below:

1 ALL CAUSE-MORTALITY

This will consist of all deaths.

2 CARDIAC DEATH

- Classify the cause of cardiac death:
    - Acute MI,
    - Heart Failure,
    - Coronary artery procedures,
    - Other cardiac procedures,
    - Arrhythmia,
    - Other cardiac death.

3 DEATH FROM ACUTE MYOCARDIAL INFARCTION

Death occurring up to 28 days after a documented acute MI unless there is an obvious other cause of death, or autopsy findings showing a recent MI or an intracoronary thrombus.

4 DEATH FROM HEART FAILURE

Death occurring when at least one of the components of the heart failure definition is present even if the terminal event is arrhythmia, unless there is an obvious other cause of death.

5 DEATH RELATED TO CORONARY ARTERY PROCEDURE

Death related to a coronary artery procedure (investigation/procedure/operation), unless there is an obvious other cause of death.

6 DEATH RELATED TO OTHER CARDIAC PROCEDURE

Death related to a cardiac procedure (investigation/procedure/operation, other than coronary artery procedure), unless there is an obvious other cause of death.

7 ARRHYTHMIC DEATH

Death related to a documented fatal arrhythmia.

8 OTHER CARDIAC DEATH

Death caused by a cardiac cause, other than the ones mentioned before.

9 OTHER CARDIOVASCULAR DEATH

The pre-defined causes of other non-cardiac cardiovascular deaths are:
- Stroke,
- Pulmonary embolism,
- Acute aortic syndrome,
- Peripheral arterial ischemia,
- Other.

10 NON-CARDIOVASCULAR DEATH

Death will be considered non-cardiovascular only if an unequivocal and documented cause can be established.
Pre-defined causes of non-cardiovascular death are:
- Cancer,
- Gastrointestinal causes,
- Infection,
- Liver disease,
- Renal failure,
- Respiratory failure,
- Suicide,
- Trauma / violent death,
- Other.

11 DEATH OF UNKNOWN CAUSE

Deaths of unknown cause will correspond to deaths for which it is not possible to specify whether they are cardiovascular or not.
When there are multiple potential causes of death, the adjudicators should define the most probable cause.
The mode of death (sudden, not sudden, non-classifiable) should be indicated for the deaths of unknown cause.

12 SUDDEN DEATH

Sudden death refers to a death that occurs unexpectedly and includes the following scenarios:
- death witnessed and occurring without new or worsening symptoms,
- death witnessed within 60 min of the onset of new or worsening symptoms,
- unwitnessed death in a subject seen alive and clinically stable ≤24 h before being found dead without any evidence supporting a specific cause of death.

13 CARDIAC EVENT

In the context of this study cardiac event corresponds to one of these events:
- Acute Myocardial Infarction (STEMI/NSTEMI/Unknown),
- Unstable angina,
- Heart Failure,
- Sustained ventricular tachycardia,
- Resuscitated cardiac arrest,
- Coronary revascularization.

14 ACUTE MYOCARDIAL INFARCTION

14.1. Criteria for acute myocardial infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI:
- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
    - Symptoms of ischaemia.

  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous Coronary Intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

According to: Third universal definition of myocardial infarction, Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Eur Heart J, 2012; 33:2551-2567

14.2. Universal classification of myocardial infarction

Type 1: Spontaneous myocardial infarction
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2: Myocardial infarction secondary to an ischaemic imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)
Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Type 4b: Myocardial infarction related to stent thrombosis
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
According to: Third universal definition of myocardial infarction, Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Eur Heart J, 2012; 33:2551-2567

15 HEART FAILURE

Heart failure is defined by the presence of symptoms such as dyspnoea or fatigue either at rest or during exercise, and/or signs of fluid retention (e.g. peripheral oedema, pulmonary oedema, raised jugular venous pressure, ascites…), leading to hospitalisation (or prolongation of hospitalisation).
These symptoms should be associated with:
- The objective evidence of HF such as abnormal chest X-ray (congestion signs, pleural fluid…), or abnormal echocardiography (dysfunction, pericardial fluid…), or abnormal cardiac imaging, or BNP increase; AND;
- The requirement or increase of dedicated treatment for HF such as intravenous/intramuscular or oral medications for HF (diuretics, vasodilators, positive inotropic agents…).

Patients with cardiogenic shock will fulfill the definition of heart failure.

16 ANGINA PECTORIS

<table>
<tr><th colspan="3">Clinical classification of chest pain</th></tr>
<tr><td rowspan="2">Exertional angina</td><td>Definite exertional angina</td><td>Meets three of the following characteristics:
Chest discomfort of characteristic quality and duration
Provoked by exertion or emotional stress
Relieved by rest and/or short acting nitrates</td></tr>
<tr><td>Probable exertional angina</td><td>Chest discomfort of characteristic quality and duration
and one of the two other characteristics:
provoked by exertion or emotional stress,
OR, relieved by rest and/or short acting nitrates</td></tr>
<tr><td colspan="2">Resting angina</td><td>Chest discomfort of characteristic quality and duration, irrespective of the circumstances in which it occurs</td></tr>
</table>

In the adjudication forms for “coronary angiography”, “coronary revascularization” and “change in antianginal therapy”, the term “as a result of angina” includes acute coronary syndrome (ACS)

17 ISCHEMIA (documented by stress imaging)

Confirmed ischemia documented by:
- Stress echography,
- Scintigraphic stress test,
- Stress cardiac magnetic resonance,
- Stress myocardial CT perfusion.

18 EVIDENCE-BASED ANTIANGINAL THERAPY

Evidence-based antianginal therapy include drugs with a current antianginal indication as well as drugs that will obtain an antianginal indication during the study.
Currently evidence-based antianginal therapy includes drugs from the following therapeutic classes:
- Beta-blockers,
- Calcium channel blockers (dihydropyridine and non-dihydropyridine),
- Long acting nitrates ,
- Nicorandil,
- Ivabradine,
- Molsidomine,
- Ranolazine,
- Perhexiline,
- Trimetazidine.

19 CHANGE ANTIANGINAL THERAPY

Defined as being either:
- an increase in the dose of an existing antianginal medication,
- or the addition of an antianginal medication,
- or a switching of one antianginal medication for another.

Additionally the followings rules were specified:
- In case of successive changes of the same drug for the same reason during the same hospitalization, only one change (the most relevant) compared to immediate pre-admission should be taken into account as a possible endpoint. The other ones will be considered as double reporting. *(02/12/2015 meeting).*
- Administration of antianginal IV drugs will not be considered as changes in antianginal therapy. It will be adjudicated as "Not an endpoint" and "No changes in evidence based antianginal therapy" will be ticked in the adjudication form. *(02/12/2015 meeting).*
- If a patient discontinues or reduces by himself an antianginal treatment and resumes it later at the initial dose, this should not be considered as an endpoint. *(02/12/2015 meeting).*
- In case of change of treatment, the date of the decision to change the treatment should be taken into account as date of the event and not the date of the first intake of modified therapy. *(29/04/2015 meeting).*
- If for a same patient 2 or more changes in Concomitant Antianginal Treatment are reported on a same date: no more than one should be reported as an Endpoint. (*14/02/2017 meeting*).

20 CORONARY REVASCULARIZATION

Coronary revascularization includes:
- PCI,
- CABG.

21 HOSPITALISATION FOR CORONARY REVASCULARIZATION

The coronary revascularizations in response to angina (ACS or not) and/or ischemia should be considered as hospitalization for coronary revascularization.

The following revascularizations should not fall within the definition of "hospitalization for coronary revascularization":
- the second planned revascularization (and the following) in case of staged procedure for cardiac event (including revascularization planned during the study but decided before inclusion, without respecting the selection criteria),
- a revascularization following a planned angiography not performed in response to angina or ischemia.

Hospitalisations for stable angina or ischemia leading to revascularisations and other particular cases to be confirmed by the adjudicators:

1) Revascularisations / death are reported by the investigator in the CRF as related to an Adverse Event number. For some of these cases, the adjudicators will confirm during a face-to-face CVAC meeting if the revascularisation / death is indeed related to that Adverse Event number or to another Adverse Event

2) Some revascularisations are adjudicated "as a result of documented ischemia without angina", but the related hospitalization is adjudicated as "Not an endpoint, hospitalization for other reason", according to the options present in the adjudication form. Adjudicators will confirm during a face-to-face CVAC meeting that the corresponding hospitalization is indeed related to this revascularization.
3) Other particular cases might need confirmation from the adjudicators.

The information confirmed by the adjudicators will be printed, dated and signed during the face-to-face meeting and will be included in an Excel table that will be imported as a manual correction by the I.R.I.S. Data Management in the data base.

Additionally the followings rules were specified:

- If a revascularization is planned before the inclusion of the patient in the study, the event should be considered as Not an endpoint, double reporting. (Executive Committee decision on 28/02/2019);
- If a revascularization is performed due to findings on a planned coronary angiography performed as control, the event should be considered as an endpoint, revascularization for other reason: PCI after planned angiography. (07/06/2016 meeting);
- In case of a staged revascularization, the second revascularization should be adjudicated as a double reporting. (28/03/2018 meeting);
- The 1st unsuccessful PCI should be adjudicated as a real PCI (endpoint, …) while the 2nd PCI (successful) should be adjudicated as "not endpoint, double reporting" (26/09/2018 meeting).

4) ISCHEMIC CHEST PAIN

Ischemic chest pain includes:

- Acute MI
  - NSTEMI
  - STEMI
  - Unknown
- Unstable angina.
- Angina leading to performing a coronary angiography or leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies.

5) HOSPITALISATION / PROLONGATION OF HOSPITALISATION

An admission to hospital is defined as any attendance at hospital requiring completion of the hospital admission procedures (hospitalisation includes day care).
An event leading to the prolongation of an ongoing hospitalisation decided for another reason, with or without the transfer of the patient to a specialised hospital department, will be considered as a hospitalisation.
All coronary revascularizations will be considered as hospitalisation.
An unreported event Hospitalisation will be created by the adjudicators for each Coronary angiography adjudicated "as a result of angina" or "as a result of documented ischemia without angina" for which a hospitalization for cardio-vascular reason is not reported by the investigator.

6) CORONARY ANGIOGRAPHY

Invasive coronary angiography (with coronary catheterisation). This excludes coronary CT angiography and coronary MR angiography.

7) SUSTAINED VENTRICULAR TACHYCARDIA

A row of ventricular ectopic beats lasting more than 30 seconds.

26. UNSTABLE ANGINA

Unstable angina is defined as recurrence or worsening of angina pectoris (or equivalent type of ischemic discomfort) sufficient to warrant hospitalisation (or prolongation of hospitalisation).

In addition, recurrence or worsening of angina should be confirmed by one or more of the following:

- ECG changes: new or worsening ST or T waves changes on ECG in the absence of LVH and permanent LBBB,
- Evidence of ischemia at low threshold on functional testing,
- Coronary revascularization performed as a consequence of ischemic symptoms".

27. DATE OF EVENT

The date of the adjudicated event will be:

- **For acute MI**: the date of hospitalisation. In case of prolongation of hospitalisation: the date of onset of symptoms,
- **For unstable angina:** the date of hospitalisation. In case of prolongation of hospitalisation: the date of onset of symptoms,
- **For heart failure:** the date of hospitalisation. In case of prolongation of hospitalisation: the date of onset of symptoms,
- **For sustained ventricular tachycardia:** the date of hospitalisation. In case of prolongation of hospitalisation: the date of onset of symptoms,
- **For resuscitated cardiac arrest:** the date of hospitalisation. In case of prolongation of hospitalisation: the date of onset of symptoms,
- **For coronary revascularization**: the date of the procedure,
- **For coronary angiography (as a result of angina or documented ischemia):** the date of the coronary angiography,
- **For change in evidenced-based antianginal therapy (as a result of angina or documented ischemia):** the date of adding/switching/intensification of the evidence-based antianginal therapy. If both the date of decision to change the treatment and the date of first treatment intake are available, the date of the decision to change the treatment should be taken into account as date of the event,
- **For hospitalisation for angina leading to performing a coronary angiography or leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies:** the date of hospitalization,
- **For hospitalisation for coronary revascularization:** the date of hospitalisation for the event (angina, ACS or not, and/or ischemia) leading to revascularization. In case of prolongation of hospitalisation: the date of onset of symptoms,
- **For death:** the date of death.

If the date provided by the investigator is not complete and the adjudicators cannot find other information in the PSE file, the adjudicators will report the incomplete date in the adjudication form. The partial date will be converted in a complete date by the I.R.I.S. Data Management by using the following rules:
- missing day will be replaced by 01,
- missing month will be replaced by January.

NB: in case a patient is admitted to an emergency room and officially hospitalised on the following day, the date of admission to the emergency room will be chosen as the date of hospitalisation, even if the hospitalisation report reads the official date of hospitalisation.

28. EVENTS DOWNGRADED AFTER ADJUDICATION

Some events were downgraded by the investigator after the adjudication by the CVAC. Some of these events have been replaced by another event with a different identification (other Adverse Event/ Procedure number, visit number, etc) and other have not been replaced at all. These events will be upgraded by the sponsor and will be re-adjudicated during face-to-face meetings based on complementary information received regarding the change after adjudication.

List of PSE, adjudicators' diagnoses and study endpoints

AE/PSE form (investigators' diagnoses)	Adjudicators' diagnoses	Study endpoints and corresponding adjudicators' diagnoses
Death	**1.1 Cardiac death** 1.1.1 Death from acute MI 1.1.2 Death from HF 1.1.3 Death related to coronary artery procedure 1.1.4 Death related to other cardiac procedure 1.1.5 Arrhythmic death 1.1.6 Other cardiac death **1.2 Other cardiovascular death** **1.3 Non-cardiovascular death** **1.4 Death of unknown cause**	Cardiac death (1.1) All cause mortality (1.1 / 1.2 / 1.3 / 1.4)
Hospitalisation or prolongation of hospitalisation for a cardiovascular reason	**2. HOSPITALISATION OR PROLONGATION OF HOSPITALISATION FOR CARDIAC EVENT** **2.1 ACUTE MI** **2.1.1 MI type** o Type 1 o Type 2 o Type 3 o Type 4a o Type 4b o Type 5 o Unclassified **2.2 UNSTABLE ANGINA** **2.3 HEART FAILURE** **2.4 SUSTAINED VENTRICULAR TACHYCARDIA** **2.5 RESUSCITATED CARDIAC ARREST** **3. HOSPITALISATION FOR ANGINA OTHER THAN MYOCARDIAL INFARCTION 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 cardiac event (2.1 / 2.2 / 2.3 / 2.4 / 2.5) Hospitalisation for cardiac event (4.1.1 /4.1.2 + 4.2.1 / 4.2.2/ 4.2.3) – updated definition is included in the Statistical Analysis Plan Hospitalisation for non-fatal MI (2.1 without related Cardiac death 1.1.1) Hospitalisation for fatal MI (2.1 + Cardiac death 1.1.1) Hospitalisation for Heart Failure (2.3) Hospitalisation for ischemic chest pain (2.1 / 2.2/ 3)
Coronary revascularization	**4. CORONARY REVASCULARIZATION** **4.1 Type** 4.1.1 PCI 4.1.2 CABG **4.2 Reason of coronary revascularization** 4.2.1 As a result of angina 4.2.2 As a result of documented ischemia (imaging test) without angina 4.2.3 As a result of angina AND documented ischemia (imaging test) 4.2.4 As a result of exercise ECG without imaging, without angina 4.2.5 Other	Any coronary revascularization (4.1.1 / 4.1.2 + 4.2.1 / 4.2.2 / 4.2.3 / 4.2.4/4.2.5) Repeat coronary revascularization in response to angina (4.1.1 /4.1.2 + 4.2.1 / 4.2.3)

AE/PSE form (investigators' diagnoses)	Adjudicators' diagnoses	Study endpoints and corresponding adjudicators' diagnoses
Coronary angiography	**5. CORONARY ANGIOGRAPHY** **5.1 Type** 5.1.1 As a result of angina 5.1.2 As a result of documented ischemia (imaging test) without angina 5.1.3 As a result of angina AND documented ischemia (imaging test)	Recurrent or persistent angina leading to performing a coronary angiography (5.1.1 / 5.1.3)) Evidence of ischemia leading to performing a coronary angiography (5.1.2 / 5.1.3)
Change in antianginal therapy	**6. Change in evidence-based antianginal therapy** **6.1 Type** 6.1.1 As a result of angina 6.1.2 As a result of documented ischemia (imaging test) without angina 6.1.3 As a result of angina AND documented ischemia (imaging test)	Recurrent or persistent angina leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies (6.1.1 / 6.1.3) Evidence of ischemia leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies (6.1.2 / 6.1.3)

7.3. Appendix 3: Cardiovascular Events Adjudication Committee members

Role	Title. Initial Forename. Name, Speciality	Work address and telephone number
Chairman	Prof. P. GUERET, Cardiology	14, rue de Cambrai 75019 Paris, France Email: pascalgueret46@gmail.com
Member	Prof. Y. COTTIN, Cardiology	Centre Hospitalier Universitaire Le Bocage Service de Cardiologie 2, Bd Mal De Lattre De Tassigny 21079 Dijon cedex - France Email: yves.cottin@chu-dijon.fr
Member	Prof. R. HATALA, Cardiology	National Cardiovascular Institute - NÚSCH Dept.of Arrhythmias and Pacing, Pod Krásnou hôrkou 1, SK-833 48 Bratislava, Slovak Republic E-mail: robert.hatala@nusch.sk
Member	Prof. G. FRAGASSO, Cardiology	Heart Failure Clinic Istituto Scientifico San Raffaele Via Olgettina 60 20132 Milano - Italy Email: gabriele.fragasso@hsr.it

7.4. Appendix 4: Conflict of Interest Statement

CERTIFICATION/DISCLOSURE OF FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS	
Please complete all of the information below. You must retain a copy of this form in your study files for at least 15 years after the end of the study.	
1. Protocol Title: The efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention. ATPCI study	
2. Protocol Number: CL3-06790-010	
3. Name:	I am participating in this study as a voting member of the Cardiovascular Endpoints Adjudication Committee
4. Full Address:	
5. Telephone:	**6. Email** :

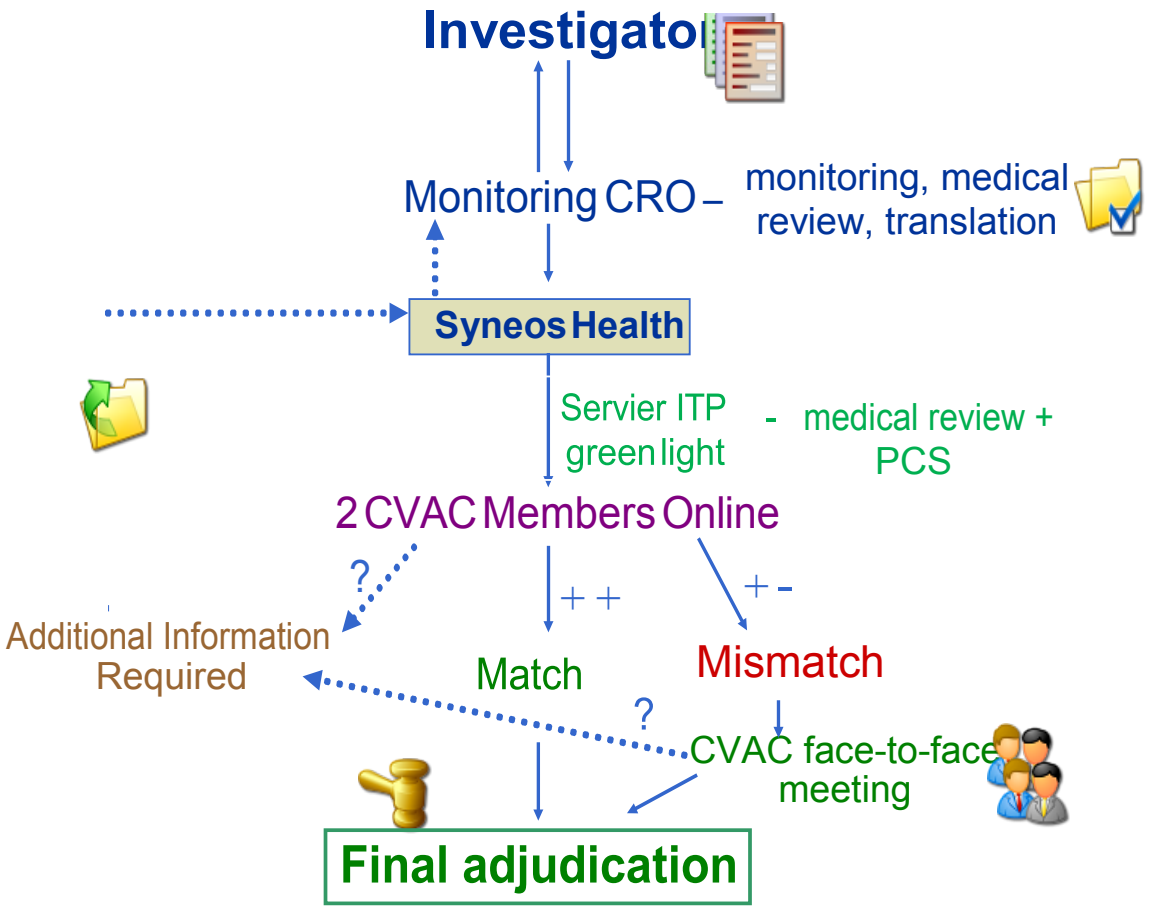
7. Indicate by marking YES or NO if you, your spouse, or your dependent children hold financial interests as described below:

YES	NO	
☐	☐	Any financial arrangement entered into between you and the Sponsor of the study, whereby the compensation to you for reviewing the study could be influenced by the outcome of the study. If so, please attach details to this form.
☐	☐	Any proprietary interest in the product tested in the study, including but not limited to, property, patents, trademarks, copyrights, or licensing agreements. If so, please attach details to this form.
☐	☐	Any significant equity interest in the Sponsor of the study, such as ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices, or any equity interest in the Sponsor that exceeds $50,000 in aggregate. If so, please attach details (e.g., the number of stock shares and current trading price) to this form.

I declare the information that is provided on this form is, to the best of my knowledge and belief, true, correct, and complete. Furthermore, if my financial interests and arrangements, or those of my spouse and dependent children, change from the information provided above during the course of the study, and within 1 year after the last patient has completed this study as specified in the protocol, I will notify I.R.I.S. with specific details immediately.

• **Signature**	**9. Date**

7.5. Appendix 5: Flow Chart of the Adjudication Process



7.6. Appendix 6: Documents to be provided by the investigator for adjudication

Documentation/information to be provided by the investigator for the Cardiovascular Endpoints Adjudication Committee adjudication are listed below:

- **in the case of death:**
    - detailed description of the event written in the e-CRF including details of the mode of death,
    - most relevant ECGs performed during the study (at least at inclusion and at the last visit before the event),
    - other relevant ECGs related to the event,
    - hospital report and/or report of the physician responsible for the management of patient care including details of events preceding death,
    - death certificate (if available),
    - autopsy report (if available),
    - other information: any additional information concerning mode of death and suspected cause of death will be collected,
    - other essential documents, if applicable.

- **in the case of hospitalisation for cardiovascular reason:**
    - detailed description of the event written in the e-CRF,
    - most relevant ECGs performed during the study (at least at inclusion and at the last visit before the event),
    - hospital report and/or report of the physician responsible for the management of patient care,
    - details of any changes made to therapy as a consequence of reported event,
    - in case of hospitalisation for cardiac cause:
        - the most recent ECG performed before the event,
        - the first ECG performed on admission to hospital,
        - the most abnormal ECG performed during the event/hospitalisation,
        - the last ECG performed during the hospitalisation,
        - other relevant ECGs,
        - specific cardiac biomarkers performed at the time of the event (if available) with local MI decision limits (preferably troponin and if not available then CK-MB). In the particular case of acute coronary syndrome, the investigator should report the peak value of troponin in the e-CRF (if available),
          N.B.: ECG and cardiac biomarkers should be performed in all patients with chest pain of suspected ischaemic origin as recommended by international guidelines.
        - reports of all ischaemia testing (such as stress echo, exercise ECG, scintigraphy etc) and/or cardiac CT or MRI scans related to the event,
        - any report of other investigations related to the cardiac event (echocardiography, chest X-ray, etc),
        - coronary revascularization procedures related to the event should be reported if any.
    - in a case with death as the outcome: information as listed above together with autopsy report and death certificate as available (see above),
    - other essential documents, if applicable.

- **in case of coronary angiography:**
    - detailed description of the event leading to performing angiography written in the e-CRF,
    - details of any symptoms prompting angiography,
    - most relevant ECGs performed during the study (at least at inclusion and at the last visit before the event),
    - hospital report and/or report of the physician responsible for the management of patient care including reports of all ischaemia testing (such as stress echo, exercise ECG, scintigraphy etc) and/or cardiac CT or MRI scans related to the event,
    - report of the angiogram performed,
    - in a case with death as the outcome: autopsy report and death certificate (see above),
    - other essential documents, if applicable.
- **in case of coronary revascularization:**
    - detailed description of the event written in the e-CRF,
    - details of any symptoms prompting revascularization,
    - most relevant ECGs performed during the study (at least at inclusion and at the last visit before the event),
    - hospital report and/or report of the physician responsible for the management of patient care including reports of all ischaemia testing (such as stress echo, exercise ECG, scintigraphy etc) and/or cardiac CT or MRI scans related to the event,
    - ECGs before and after coronary revascularization and specific cardiac biomarkers (troponin) performed during the hospitalisation before and after coronary revascularization (if available) with local MI decision limits,
    - report of any coronary angiograms performed,
    - report of the revascularization procedure performed including an operation note in the case of surgical revascularization,
    - in a case with death as the outcome: autopsy report and death certificate (see above),
    - other essential documents, if applicable.
- **in case of change in antianginal therapy (*i.e.*, addition, switch or increase of the dose of one of the antianginal therapies):**
    - detailed description of the event leading to changing therapy written in the e-CRF,
    - details of the reason prompting the change (symptoms, etc),
    - most relevant ECGs performed during the study (at least at inclusion and at the last visit before the event),
    - hospital report and/or report of the physician responsible for the management of patient care, if any,
    - details of any changes made to therapy,
    - details of any tests/ investigations performed related to the change made to therapy,
    - reports of all ischaemia testing (such as stress echo, exercise ECG, scintigraphy, etc) and/or cardiac CT or MRI scans performed related to the change made to therapy,
    - other essential documents, if applicable.

7.7. Appendix 7: Adjudication forms

ADJUDICATION FORM FOR HOSPITALISATION

PSE N° : |__|__|__| - |__|__|__|__| - |__|__|__|__|__|__| - |__|__|__|__| - |__|__|__|__| - |__|__|__|__| - |__|__|
Country Centre Patient Sequence n° AE/Procedure n° Visit n° PSE code

1. Is this an Endpoint?	o NO ➹ If no, please indicate reason: • No hospitalisation or prolongation of hospitalisation • Hospitalisation for other reason • Double reporting • Not enough documentation provided o YES ➹ If yes, indicate your adjudication by ticking the appropriate boxes: o **HOSPITALISATION OR PROLONGATION OF HOSPITALISATION FOR CARDIAC EVENT** • **Type** o Hospitalisation o Prolongation of hospitalisation • **Cause of hospitalisation / prolongation of hospitalisation** o **Acute myocardial infarction** Clinical classification o Type 1 o Type 2 o Type 3 o Type 4a o Type 4b o Type 5 o Unclassified Category of MI based on ECG o STEMI (including new left bundle branch block) o NSTEMI (including normal or undetermined ECG) o Unknown (no ECG available) o **Unstable angina** o **Heart failure** o **Sustained ventricular tachycardia** o **Resuscitated cardiac arrest** o **HOSPITALISATION FOR ANGINA (OTHER THAN MYOCARDIAL INFARCTION 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**
1. Please indicate the date of the event	**Date of event:** |_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
2. CVAC member notes	Not to be transferred to IRIS
3. Date of adjudication (Automatic)	|_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
4. Name of the CVAC member (Automatic) Electronic signature	…… …….... ……....

ADJUDICATION FORM FOR CORONARY ANGIOGRAPHY

PSE N° : |__|__|__| - |__|__|__|__| - |__|__|__|__|__|__| - |__|__|__| - |__|__|__| - |__|__|__|__| - |__|__|
Country Centre Patient Sequence n° AE/Procedure n° Visit n° PSE code

1. Is this an Endpoint?	o NO ➔ If no, please indicate reason: o No coronary angiography performed o Coronary angiography as a result of exercise ECG without imaging, without angina o Coronary angiography performed for another reason o Double reporting o Not enough documentation provided o YES ➔ If yes, indicate your adjudication by ticking the appropriate boxes: o **CORONARY ANGIOGRAPHY** o As a result of angina (angina includes ACS) o As a result of documented ischemia (imaging test) without angina o As a result of angina AND documented ischemia (imaging test)
2. Please indicate the date of the event	**Date of event:** |_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
3. CVAC member notes	Not to be transferred to IRIS
4. Date of adjudication (Automatic)	|_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
5. Name of the CVAC member (Automatic) Electronic signature	……... ……... …….....

ADJUDICATION FORM FOR CORONARY REVASCULARIZATION

PSE N° : |__|__|__| - |__|__|__|__| - |__|__|__|__|__| - |__|__|__| - |__|__|__| - |__|__|__|__| - |__|__|
Country Centre Patient Sequence n° AE/Procedure n° Visit n° PSE code

1. Is this an Endpoint?	o NO ➔ If no, please indicate reason: o No revascularization performed o Double reporting o Not enough documentation provided o YES ➔ If yes, indicate your adjudication by ticking the appropriate boxes: o **CORONARY REVASCULARIZATION** o PCI o CABG Reason of coronary revascularization o As a result of angina (angina includes ACS) o As a result of documented ischemia (imaging test) without angina o As a result of angina AND documented ischemia (imaging test) o As a result of exercise ECG without imaging, without angina o Other: _ _ _ _ _ _ _ _ _ _
2. Please indicate the date of the event	**Date of event:** |_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
3. CVAC member notes	Not to be transferred to IRIS
4. Date of adjudication (Automatic)	|_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
5. Name of the CVAC member (Automatic) Electronic signature	……... ……... ……

ADJUDICATION FORM FOR CHANGE IN ANTIANGINAL THERAPY

PSE N° : |__|__|__| - |__|__|__|__| - |__|__|__|__|__|__| - |__|__|__|__| - |__|__|__|__| - |__|__|__|__|__| - |__|__|
Country Centre Patient Sequence n° AE/Procedure n° Visit n° PSE code

1. Is this an Endpoint?	o NO ➔ If no, please indicate reason: o No change in evidence-based antianginal therapy (i.e. treatment not changed or decrease of dose only or discontinuation of treatment only) o Change of treatment as a result of exercise ECG without imaging, without angina o Change of treatment for another reason o Double reporting o Not enough documentation provided o YES ➔ If yes, indicate your adjudication by ticking the appropriate boxes: o **CHANGE IN EVIDENCE-BASED ANTIANGINAL THERAPY (ADDING, SWITCHING OR INCREASING THE DOSE OF ONE OF THE EVIDENCE-BASED ANTIANGINAL THERAPY)** o As a result of angina (angina includes ACS) o As a result of documented ischemia (imaging test) without angina o As a result of angina AND documented ischemia (imaging test)
2. Please indicate the date of the event	**Date of event:** |_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
3. CVAC member notes	Not to be transferred to IRIS
4. Date of adjudication (Automatic)	|_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
5. Name of the CVAC member (Automatic) Electronic signature	……... ……... ……...

ADJUDICATION FORM FOR DEATH

PSE N° : |__|__|__| - |__|__|__|__| - |__|__|__|__|__|__| - |__|__|__|__| - |__|__|__| - |__|__|__|__| - |__|__|
Country Centre Patient Sequence n° AE/Procedure n° Visit n° PSE code

1. Is this an Endpoint?	o NO ➔ If no, please indicate reason: o Double reporting o Erroneous information o YES ➔ If yes, indicate your adjudication by ticking the appropriate boxes: o Cardiac Death o Acute MI o Heart failure o Coronary artery procedures o Other cardiac procedures o Arrhythmic death o Other:_ _ _ _ _ _ _ _ _ _ o Other cardiovascular death o Stroke o Pulmonary embolism o Acute aortic syndrome o Peripheral arterial ischemia o Other:_ _ _ _ _ _ _ _ _ _ o Non-cardiovascular death o Cancer o Gastrointestinal causes o Infection o Liver disease o Renal failure o Respiratory failure o Suicide o Trauma / Violent death o Other:_ _ _ _ _ _ _ _ _ _ o Death of unknown cause Mode of death o Sudden o Not sudden o Non-classifiable
2. Please indicate the date of death	Date of death: |_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
3. CVAC member notes	Not to be transferred to IRIS
4. Date of adjudication (Automatic)	|_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
5. Name of the CVAC member (Automatic) Electronic signature	…… …… ……

7.8. Appendix 8: Cardiovascular Innovation Therapeutic Pole Members

Development Director	Mr Emmanuel ARNAUD
Project Director	Ms S. ROBERT
Senior Clinical Development Leader	Dr J.P. CHALLETON
Clinical Development Leader	Ms R. BARBAROSIE
Clinical Development Leader	Ms S. BRACQ

ATPCI Charter of the Safety Endpoints Adjudication Committee

Document title	**SAFETY ENDPOINTS ADJUDICATION COMMITTEE PROCEDURE**
Study title	**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.**
Study drug	**S 06790 (Trimetazidine MR 35mg)**
Indication	**Angina pectoris**
Development phase	**Phase III**
Protocol code	**CL3-06790-010**
Chairman of the Safety Endpoint Adjudication Committee	**Prof. Fabrizio STOCCHI** **Clinical Trial center** **Centro per lo studio e Cura Morbo di Parkinson e disturbi del Movimento** **I.R.C.C.S. San Raffaele Pisana** **Via delle Pisana, 216** **00163 Roma** **Italy**
Sponsor	**I.R.I.S.**
Date of the document	**Final version including amendment n°2 – 10 September 2019**

Amendment integrated

No	Final version date
1	**23 July 2018**
2	**10 September 2019**

CONFIDENTIAL

CONFIDENTIALITY CLAUSE

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FOLLOW-UP OF VERSIONS

Amendment No	Final version date	Nature of amendments
1	**23 July 2018**	• Clarification of the Unreported AEI process: in order to be adjudicated, the unreported AEI has to be confirmed by the investigator and reported as AEI. If the investigator does not confirm, the unreported AEI will be manually created by Syneos Health and adjudicated at the end of the study. • Clarification of the "unable to adjudicate" EI process: these events will be considered as a mismatch which will be discussed and re-adjudicated during a phone meeting. No EI can remain with the status "unable to adjudicate" at the end of the study. • Update of the EI not reported as AE adjudication: these events will be adjudicated during the last 3 months of the study. • Addition of the documentation archiving: at least 25 years after the end of the study. • Update of the Pr Cacoub address. • New name of INC Research: Syneos Health.
2		• Update of the Adjudication form in Appendix 9: o Neurological events adjudication form o Agranulocystosis adjudication form o Arterial Hypotension adjudication form o Hepatic disorders adjudication form

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1. GLOSSARY

AE	:	Adverse Event
AEI	:	Adverse Event of Interest
ASSP		Adjudicated Study Safety endPoint
ATPCI	:	The efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention. ATPCI study
BP	:	Blood Pressure
e-CRF	:	electronic Case Report Form
CRO	:	Contract Research Organisation
CV	:	Curriculum Vitae
DMC	:	Data Monitoring Committee
ECG	:	ElectroCardioGram
EI	:	Event of Interest
HR	:	Heart Rate
ITP	:	Innovation Therapeutic Pole
I.R.I.S.	:	Institut de Recherches Internationales Servier
MDD	:	Medical Data Department
MI	:	Myocardial Infarction
MR	:	Modified Release
PCI	:	Percutaneous Coronary Intervention
PCS	:	Patient Case Summary
SAC	:	Safety-endpoint Adjudication Committee
SDV	:	Source Data Verification
ULN	:	Upper Limit of Normal

2. INTRODUCTION

The CL3-06790-010 study entitled **"The efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention. ATPCI study."** is a phase III study planned to obtain 1363 primary efficacy endpoints after inclusion of about 5800 patients, with an estimated recruitment period of 2 years and a minimum follow-up duration of 2 years.

The primary objective is to demonstrate the superiority of trimetazidine MR 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.
The secondary objective is to evaluate the effect of trimetazidine on the other efficacy endpoints as well as the other safety parameters, clinical and biological (see *6.1 appendix 1*).

This procedure describes the role of the Safety Endpoint Adjudication Committee (SAC), the requirements for membership, the description of the adjudication process, the organisation of the SAC meetings, and the required definitions and documents for Events of Interest (EI) adjudication. The Events of Interest (EI), Adverse Events of Interest (AEI) and Events of Interest not reported as Adverse Event (EI not reported as AE) are defined below.

Before the start of the adjudication process, the SAC members will produce working definitions for the purpose of endpoints classification. The definitions to be used for adjudication are presented in *6.2 appendix 2*.

Throughout the study, all EI occuring after the first study drug intake until the end of the study will be adjudicated by an independent SAC which is blinded to the patient's identity and treatment.

Events of Interest (EI)
The following events are considered as **EI**:
- central neurological symptoms, including Parkinson's syndrome, disorientation, hallucination and convulsion (the corresponding Preferred Terms based on the MedDRA updated version are listed in a separate document *),*
- coagulation disorders including non-traumatic haemorrhages (for non-traumatic haemorrhages, the corresponding Preferred Terms based on the MedDRA updated version are listed in a separate document),
- thrombocytopenia (platelets <150G/L),
- agranulocytosis (neutrophils <0.5 G/L),
- falls,
- arterial hypotension including orthostatic hypotension,
- serious skin disorders,
- hepatic disorders.

Each of these items corresponds to one type of EI.

The EI include AEI and EI not reported as AE:

- **AEI**
  Any of the above-mentioned EI reported as AE in the eCRF by the investigator will be considered as AEI and will be adjudicated.
- **EI not reported as AE**
  In addition, even if they are not reported as AE by the investigator, the following EI will be detected by I.R.I.S. Innovation Therapeutic Pole (ITP) through post-baseline biological/clinical values and will also be adjudicated.

- Coagulation parameters:
  - In the absence of anticoagulation treatments:
    - INR > 1.5 or Prothrombin ratio < 50% or Prothrombin time > 1.5-fold the local laboratory normal values,
    - aPTT > 1.2-fold the local laboratory normal values.
  - In the presence of anticoagulation treatments:
    - INR > 4 or Prothrombin ratio < 25% or Prothrombin time > 3-fold the local laboratory normal values (in presence of vitamin K antagonists),
    - aPTT > 4-fold the local laboratory normal values (in presence of heparin),
    - aPTT > 2-fold the local laboratory normal values (in presence of vitamin K antagonists).
- Platelets:
  - All cases of platelets < 100 G/L,
  - For platelets between 100 G/L and 150 G/L: all decreases > 30% compared to baseline.
- Neutrophils < 0.5 G/L.
- Systolic blood pressure < 100 mmHg and / or diastolic blood pressure < 60 mmHg measured in supine position.
- Reduction of MORE THAN 20 mmHg (> 20 mmHg) for systolic BP and/or MORE THAN 10 mmHg (> 10 mmHg) for diastolic BP at 1 AND 3 minutes after standing–up as compared to the measurement in the supine position.
- AST and/or ALT > 3-fold above the upper normal values.

I.R.I.S. Medical Data Division (MDD) will be in charge of identifying the EI not reported as AE, checking if they are not already reported as AE by the investigators in a AE form, and informing I.R.I.S ITP who will inform a dedicated CRO (Syneos Health) (via I.R.I.S. Data Management) and the Monitoring CRO (see § *4.1.3.2*).

The EI considered by the SAC as fulfilling the endpoint definitions will be called the adjudicated study safety endpoints (ASSP).

Unreported AEI
During the adjudication process, new AEI (not previously reported as AEI by the investigator) may be identified and created by the SAC members: they will be called unreported AEI. In order to be adjudicated, the unreported AEI has to be confirmed by the investigator and reported as AEI. If the investigator does not confirm, the unreported AEI will be manually created by Syneos Health and adjudicated at the end of the study.

Suspected AEI
If an investigator does not confirm the new AEI after the split, multicoding or creation of an unreported AEI, this AEI becomes a Suspected AEI and will be adjudicated as the other AEI.

3. MEMBERS OF THE SAFETY ENDPOINT ADJUDICATION COMMITTEE

The SAC is an independent committee formed of five members including the Chairman: 2 neurologists, one haematologist, one geriatrician and one internist (see *6.3 appendix 3*). New members can be added during the study if required (for example, if there is a delay in the adjudication process due to work overload). The committee will have the possibility to ask additional specialists (*e.g.* dermatologists) to give their opinion on some specific events.

Each SAC member will supply I.R.I.S. with a copy of their curriculum vitae (CV) in English, dated and signed, before participating in the adjudication process.

Each SAC member will be trained to the adjudication system by Syneos Health. In addition, the SAC members will be trained on the adjudication procedures before starting the adjudication process by adjudicating together some real cases during a face-to-face meeting.

SAC members must sign a financial contract describing: the role of the SAC, the confidentiality rules and the financial agreement relationship between the SAC members and I.R.I.S.

All adjudications must be made by the SAC in a fair and unbiased manner. All members will be free of direct involvement in the study and will be independent from I.R.I.S. Thus no SAC member will act as an investigator or co-investigator in the study.

SAC members will have to fulfil the conditions described in the "Conflict of interest statement" and sign it *(*see *6.4 appendix 4*).

Then, if during the trial, SAC members develop a conflict of interest, they are responsible for informing the Chairman about any other relevant financial interest in pharmaceutical companies, biotechnology companies or Contract Research Organisations (CROs). The Chairman will be responsible for deciding whether or not consultancy or financial interests of the member materially impact upon his objectivity.

The Chairman will ask for resignation of a SAC member who develops a material conflict of interest. If the Chairman himself or another member develops such a conflict, the Chairman will inform I.R.I.S. In order to maintain the SAC at full complement throughout the trial, the SAC Chairman in cooperation with I.R.I.S. shall designate a replacement for any member who resigns. If the member to be replaced is the SAC Chairman himself, the designation of his successor will be decided by the Executive Committee on cooperation with I.R.I.S.

4. ORGANISATION

In order to allow the adjudication of the EI by the SAC members, a website TrialEAS will be conceived by Syneos Health, a dedicated CRO which is under the responsibility of I.R.I.S. The specifications of the tasks of Syneos Health are detailed in a separate specific document. Syneos Health will be independent from the SAC members and will be under contract with I.R.I.S.
I.R.I.S. and/or Syneos Health will ensure the good running of the adjudication of the EI by providing all documents and additional information to the SAC members. To resolve the mismatches between SAC members, some meetings will be organized: phone meetings or

face-to-face meetings if needed. If a face-to-face meeting is needed, Syneos Health and I.R.I.S. will organise and attend the meeting to ensure a logistic support during the meeting.

4.1. Events of interest (EI) data flow

4.1.1. General aspects of the adjudication process

4.1.1.1. Involved Experts

The adjudication process is detailed below:

Each EI will be adjudicated electronically, independently, and concomitantly by two SAC members chosen according to their expertise (see *6.5 appendix 5*).

EI file will be allocated for adjudication by Syneos Health to SAC members according to the type of the event and the expertise of the SAC members:

- **Neurological events**

Two neurologists will adjudicate neurological symptoms (listed in a separate document based on the MedDRA updated version), including Parkinson's syndrome, disorientation, hallucination and convulsion. Haemorrhagic and non-haemorrhagic strokes will be adjudicated by the neurologists.

- **Haematological events**

One haematologist and one internist will adjudicate coagulation disorders, thrombocytopenia, agranulocytosis events and non-traumatic haemorrhages (listed in a separate document based on the MedDRA updated version), except haemorrhagic stroke which will be adjudicated by the neurologists.

- **Other events**

One geriatrician and one internist will adjudicate falls, arterial hypotension including orthostatic hypotension, serious skin disorders and hepatic disorders.

4.1.1.2. Major points of the adjudication process

AEIs occurring in the same patient will be adjudicated independently without respecting the chronological order.

For a given patient, if two or more EI of the same type are detected at different visits through post-baseline biological/clinical values (i.e.: EI not reported as AE), they will be adjudicated all together (i.e.: only one adjudication form will be completed for several biological/clinical values corresponding to the same EI type detected in the same patient). The adjudication will be performed per patient and type of event and not per values not reported as AE.

The SAC members in charge of the adjudication of a new EI will be able to look at the results of the adjudications of previous (closed) EI that occurred to the same patient, if needed.

A flow chart of the adjudication process is presented in *6.6 appendix 6*.

SAC members will check at least once a week directly on the Syneos Health website if they have events to be adjudicated. The time window for the adjudication of an EI is 14 calendar days, from the availability of the EI file on the website. If the adjudication is not carried out within this time, the CRO will remind the concerned SAC member by e-mail:

- after 14 calendar days, the SAC member will receive a remindermessage,
- then every 14 calendar days in case the event is not yet adjudicated.

The time window for adjudication can be readjusted during the study by I.R.I.S. in cooperation with the Chairman.

SAC members will inform Syneos Health of any period of unavailability of more than 14 calendar days.

At any time during the review of the EI and before adjudication, a member may ask for additional information. In that case, the additional information will be sent to the concerned SAC member who requested the additional information. From the availability of the additional information, the SAC members will have 14 calendar days to adjudicate the event.

If a member cannot adjudicate an event despite the requested information availability he may declare that he is "unable to adjudicate". Every EI assessed as "unable to adjudicate" will be considered as a mismatch which will be discussed and re-adjudicated during a phone meeting. No EI can remain with the status "unable to adjudicate" at the end of the study.
When the two SAC members have the same adjudication results including diagnosis, classification, possible causes, specific box re-adjudication, etc. (as applicable), dates of events and outcome (i.e. "matching result"), the adjudication process will be considered as completed.

By default, the "date of the event" reported in the adjudication form on Syneos Health website will be the date of the related event reported in the e-CRF (date of onset of adverse event for AEI and date of sampling or clinical examination for Events of Interest not reported as AE). If necessary, the SAC member will have to change this "date of the event" according to his judgment based on the documents provided in the adjudication file.

In the following situations, the EI will be adjudicated during a phone meeting or, if needed, during a face-to-face meeting:

- in case of disagreement between the adjudication results of the 2 SAC members (i.e. "mismatching result"),
- if one/both SAC members declare(s) the case to be "unable to adjudicate",
- in case of events created by the SAC (i.e. events detected by the adjudicators during individual adjudications and not reported by the investigators in the CRF),
- in case a complementary EI file with new or changed relevant information is received by Syneos Health after the final adjudication (re-adjudication),
- in case I.R.I.S. Data Management department issues a Data Clarification Form (DCF) related to the completion of the adjudication form to be answered by the adjudicators.

During the phone or face-to-face meetings, after discussion between the two SAC members, one of the SAC members (the main adjudicator see *6.5 appendix 5*) will enter the result of adjudication corresponding to the joint opinion of the members and will electronically sign the form (password). Syneos Health will extract from the database the list of the cases discussed during the meeting and the results of the adjudications entered in the database by one of the two adjudicators. Syneos Health will send this list to I.R.I.S. ITP for information.

In case of phone meeting, Syneos Health will send a paper version of this list to the second adjudicator for validation and handwritten signature. Then, the second adjudicator will send back to Syneos Health the signed list.

During the meetings and if needed, SAC members may ask for additional information. If so, the corresponding event will be reviewed at the next meeting after the additional data will be received by Syneos Health.

During the course of the study, the definitions of EI and the biological/clinical value limits for the EI not reported as AE to be used for adjudication (*6.2 appendix 2*) can be modified (after justification). In that case, the concerned SAC members will discuss whether all concerned EI already adjudicated will have to be re-adjudicated or not with the amended definition.
During the adjudication process, when reviewing the documents related to an EI, the adjudicators may identify a potential AEI, and they may wonder if this event has been reported by the investigator in the e-CRF as an AEI. In this situation, the adjudicators have the possibility to check in the Patient Case Summary (PCS) i.e. a summary of the main eCRF data, whether this event was reported or not as an AEI.
In case of not reported potential AEI, I.R.I.S. ITP will ask the investigator if he considers that the event must be reported as an AEI so that regular data flow can be initiated. In case the investigator does not agree to report it as an event, the unreported AEI will be manually created by Syneos Health and adjudicated at the end of the study.

During the study I.R.I.S. will follow up the % of mismatches per adjudicator and, if necessary, will perform a retraining of the adjudicators.

4.1.2. Initial adjudication, Follow up adjudication and Re-Adjudication of the events

4.1.2.1. Initial adjudication

An initial adjudication will be performed as follows:

- for AEIs:
  - Each AEI will have an initial adjudication after completion and validation of the EI file. AEIs occurring in the same patient will be adjudicated independently without respecting the chronological order.
  - The adjudicators will decide during the initial adjudication if it is useful to re-adjudicate the event at the end of the study by ticking a specific box (YES) in the adjudication form, by default, this specific button will be unticked (NO).
  - For the movement disorders such as Parkinsonian symptoms, restless leg syndrome, tremors, gait instability of central origin, the initial adjudication will be performed after the neurologist visit, within 1 month after the study drug withdrawal (as planned in the study protocol). For these events, a follow-up adjudication is planned 4 months after the study drug withdrawal,
- for EIs not reported as AE:
  - Abnormal values of same type not reported as AE will be adjudicated during the last 3 months of the study in order to take into account follow-up data. EIs (of same type) not reported as AE, occurring in the same patient will be adjudicated all together. The adjudication will be performed per patient and type of event and not per values.
  - If the patient is not recovered at the last available visit before adjudication, and if this visit is not the last study visit, the EI not reported as AE must be re-adjudicated at the end of the study.

- If the patient is recovered at the last available visit before adjudication, the adjudicators will decide during the initial adjudication if it is useful to re-adjudicate the event at the end of the study by ticking a specific button (YES) in the adjudication form, by default, this specific button will be unticked (NO).

If several parameters of coagulation disorders (e.g INR, PR, PT, aPTT) are identified as potential EI not reported as AE for a patient at the same visit, only one file will be prepared and sent for adjudication.

4.1.2.2. Follow up adjudication

For movement disorders such as Parkinsonian symptoms, restless leg syndrome, tremors, gait instability of central origin, a follow up adjudication will be performed after the neurologist visit, 4 months after treatment withdrawal as planned in the study protocol.

4.1.2.3. Re-adjudication

In order to take into account the evolution of the events, the SAC members will review again the events as follows:

For AEIs:

- re-adjudication will be performed at the end of the study for each AEI considered by the adjudicators, during the initial adjudication, to be re-adjudicated,
- re-adjudication will be performed in case of new relevant available data about the AEI,
- if the patient withdraws from the study after the event, the re-adjudication will be performed at the time of withdrawal for each AEI considered by the adjudicators, during the initial adjudication, to be re-adjudicated.

For movement disorders such as Parkinsonian symptoms, restless leg syndrome, tremors, gait instability of central origin:

- re-adjudication will be performed at the end of the study if the adjudicators consider, during the follow-up adjudication (4 months after the onset of the event), that the event has to be re-adjudicated,
- re-adjudication will be performed in case of new available data about the AEI,
- if the patient withdraws from the study, the re-adjudication will be performed at the time of withdrawal if the adjudicators consider during the follow-up adjudication (at 4 months) that the event has to be re-adjudicated.

For EIs not reported as AE:

- re-adjudication taking into account all subsequent changes of the same parameter or related to the same parameter will be performed at the end of the study except for patients :
  - with normalized values at the last visit before initial adjudication,
  - and without new abnormal values until the end of the study,
  - and without ticking of the specific button “re-adjudication” in the initial adjudication form.

4.1.2.4. General aspect of adjudication

The initial adjudication, follow-up adjudication and re-adjudication will be performed independently and concomitantly by two SAC members. In case of mismatch, the cases will be discussed during a meeting.

The initial adjudication, follow-up adjudication and re-adjudication of the events will be performed no matter if the study treatment is continuing or has been stopped.

Only the results of the last adjudication will be taken into account in the analysis.

4.1.3. Data flow of the documents related to EI and adjudication

The EI data flow will be organised in three steps:

4.1.3.1. From Syneos Health to the SAC:

Syneos Health is in charge of making available electronically for the SAC members the documentation related to the EI to be adjudicated including:

- AEI/EI not reported as AE checklist (list of documents provided by the investigator for the event).
- Relevant information extracted from the e-CRF (PCS provided by I.R.I.S. ITP).
- Required documents (see *6.7 appendix 7* and *6.8 appendix 8*).

The documents needed for the event adjudication will be put at the SAC members disposal through a website they will have access to, using among other the equipment provided by the sponsor (iPad, high speed internet connection). For cases where a file has been sent to Syneos Health by the investigators, Syneos Health will check the EI file and will make it available to the I.R.I.S. ITP after having requested and obtained any missing information/document if any. I.R.I.S. ITP will perform medical review of the EI files and if necessary will issue queries regarding missing information or inconsistency between different information, etc., or might also request additional documents. I.R.I.S. ITP will give the green light for the case by providing the PCS to Syneos Health.

Each SAC member will be provided with a specific and separate handbook explaining the use of the computerized system. The system (especially the quality of the documents: e.g. neuroimaging) will be tested before starting the adjudication process.

4.1.3.2. From investigator's centre to Syneos Health:

For AEIs: the investigator will record the AEI in the e-CRF and, in addition, collect pre-defined appropriate documents and put them at the disposal of the monitor who will constitute the "AEI dossier". Documents to be provided by the investigator for the adjudication are listed in *6.7 appendix 7*.

The AEI file will be sent by the monitoring CRO to Syneos Health after source data verification (SDV) and checking of the documents by the monitor, translation into English by the monitoring CRO and initial medical review done by the medical reviewer from the local monitoring structure. This should be done within 8 weeks after notification of the event to the monitoring CRO. If the timelines are not kept, Syneos Health will send a reminder e-mail to the monitoring CRO.

For EIs not reported as AE : I.R.I.S. MDD will identify the case, will check if it is not already identified in the AE form, and if not will inform I.R.I.S ITP who will inform Syneos Health (via IRIS Data Management) and the Monitoring CRO about the case. The monitor will organize the SDV, will collect pre-defined appropriate available documents and will constitute the "EI not reported as AE file". Documents to be collected for the adjudication are listed in *6.8 appendix 8.* During the SDV, only abnormal values reported in the eCRF will be compared to the patient medical file (source documents).

If additional investigations were performed for the EI not reported as AE, a file will be sent by the monitoring CRO to Syneos Health after the SDV, checking of the documents by the monitor and translation into English by the monitoring CRO. No local medical review is foreseen for the EIs not reported as AE as in most of the cases, no extra-documentation will be expected in addition to CRF information.

This should be done within 8 weeks after notification of the event to the monitoring CRO. If the timelines are not kept, Syneos Health will send a reminder e-mail to the monitoring CRO.

If no additional investigations were performed, no file will be sent by the monitoring CRO to Syneos Health (however, the monitor has to tick the SDV box after the monitoring visit). The adjudicators will only receive the Patient Case Summary (PCS) provided by I.R.I.S. ITP and the list of all the values concerned by the adjudication.

4.1.3.3. From the SAC to Syneos Health:

An electronic adjudication form will be completed independently and in parallel by both SAC members (*6.9 appendix 9*). The same electronic procedure will be followed for adjudication during phone or face-to-face meetings (see § *4.2.2*)

The results of adjudication including intermediate adjudication results (match/mismatch) will be transferred from Syneos Health to I.R.I.S. on a regular basis throughout the study but not to the investigator.

4.2. Safety Endpoint Adjudication Committee meetings

4.2.1. Training meeting

A first face-to-face meeting has been organised by I.R.I.S. for training purposes (adjudication procedures and adjudication forms) on Monday, 02 May 2016. During this meeting, fictitious adjudications have been performed by the SAC members on paper adjudication forms, using the first reported cases. I.R.I.S. ITP representatives participated to the meeting, but were not involved in the discussions on the adjudications. I.R.I.S. ITP wrote the minutes of the meeting.

During a following WebEx meeting, Syneos Health will train the adjudicators on the adjudication system. Syneos Health will prepare minutes of this meeting.

The first cases adjudicated on paper forms during the training meeting will be adjudicated again in the real database independently and concomitantly by the 2 SAC members, according to the regular data flow.

4.2.2. Mismatch meeting

Phone meetings (or face-to-face meetings, if needed) will be organised by SAC members according to the study progress, in order to definitively adjudicate mismatching cases or when necessary in agreement with the Chairman, in particular in the view of preparation of Data Monitoring Committee meetings. I.R.I.S. ITP will not participate to the phone meetings.

If face-to-face meetings are needed, I.R.I.S. ITP will participate to these meetings. Syneos Health will participate to the face-to-face meetings and will prepare minutes of the meetings.

During the meetings, after discussion between the two SAC members, one of the SAC members (the main adjudicator see § *6.5 appendix 5*) will enter the result of adjudication corresponding to the joint opinion of the members and will electronically sign the form (password). Syneos Health will extract from the database the list of the cases discussed during the meeting and the results of the adjudications entered in the database by one of the two adjudicators. Syneos Health will send this list to IRIS ITP for information.

For events adjudicated during phone meetings, the adjudication will be entered electronically by one of the two SAC members (the main adjudicator see § *6.5 appendix 5*). Then, Syneos Health will send a paper version of this list to the second adjudicator for validation and handwritten signature. Then, the second adjudicator will send back to Syneos Health the signed list. Syneos Health will send this signed list to IRIS ITP for information.

In case of technical problems during any phone or face-to-face meeting a backup system will be used: the main adjudicator (see § *6.5 appendix 5*) will complete paper adjudication forms and will enter the adjudication results electronically once the system works again.

Only blinded data will be discussed during all the SAC meetings.
General information on the study and on the adjudication progress will be provided to SAC members on a regular basis.

4.3. Archiving

The adjudicators will keep all information relevant to the study for at least 25 years after the end of the study.

5. SAFETY ENDPOINTS ADJUDICATION COMMITTEE MEMBERS SIGNATURES

Members of the Safety Endpoint Adjudication Committee have read and agreed to the above on the dates below:

Role	*Name*		*Date*	*Signature*
Chairman Neurologist	Prof F. STOCCHI	*Italy*		
Neurologist	Prof. Y. AGID	*France*		
Haematologist	Prof. T. LECOMPTE	*Switzerland*		
Geriatrician	Prof O. HANON	*France*		
Internist	Prof P. CACOUB	*France*		

6. APPENDICES

6.1. Appendix 1: Efficacy and safety criteria of the protocol

1. Primary endpoints

1.1 Primary efficacy endpoint

Superiority of trimetazidine over placebo on the time to first occurrence of an event in the composite of:
- 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.

1.2 Primary safety endpoint

Incidence of serious emergent adverse events with trimetazidine as compared with placebo.

2. Secondary endpoints

2.1 Secondary efficacy endpoint

Superiority of trimetazidine over placebo on the time to first occurrence of an event in the composite of:
- 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 ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
- evidence of ischemia (documented by Stress Imaging) leading to performing a coronary angiography.

Effect of trimetazidine, compared with that of placebo, on the following endpoints:

Components of the primary endpoint
- 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.

Other secondary endpoints
- evidence of ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
- evidence of ischemia (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,
- hospitalisation for heart failure,
- any coronary revascularization,
- repeat coronary revascularization in response to angina.

2.2 Other efficacy endpoints

- CCS class of angina symptoms,
- number of angina episodes per week,
- number of doses of short-acting nitrates taken per week in response to angina,
- number of antianginal drugs taken by the patient,
- Seattle Angina Questionnaire scores (in countries where a validated translation is available),
- EQ-5D-3L Questionnaire scores,
- level of cardiac troponin (before each repeat elective PCI and between 6 and 24 hours after).

2.3 Secondary safety endpoints

- emergent adverse events (including clinically significant abnormalities observed from the electrocardiographic recordings and from laboratory examinations),
- events of interest,
- vital signs: supine and standing blood pressure (BP), heart rate (HR),
- weight,
- biochemical and haematological parameters.

6.2. Appendix 2: Definition of adverse event of interest used for adjudication

NEUROLOGICAL EVENTS

1. Definitions

1.1 Neurological symptoms

This will consist of clinically significant symptoms resulting from any disorder of the body central nervous system.

1.2 Parkinson' syndrome

A Parkinson's syndrome or parkinsonism is a set of symptoms including bradykinesia (or slowness with decrement and degradation of repetitive movements) and plastic rigidity, most often associated with rest tremor and caused by a central dopaminergic deficiency. Parkinson's disease is the most common neurodegenerative cause of parkinsonism.

In addition to neurodegenerative causes, Parkinsonism can also be a symptom of drug-related (drug-induced Parkinsonism), vascular, infectious, toxic, structural causes.

1.3 Parkinson's disease

Parkinson's disease is a motor clinical syndrome, with levodoparesponsive parkinsonism, typical clinical characteristics (rest tremor, rigidity, bradykinesia, and gait impairment), and an absence of markers suggestive of other disease.

- probable: at least 2 out of rest tremor, bradykinesia, rigidity,
- possible: only 1 out of rest tremor, bradykinesia, rigidity,

1.4 Atypical parkinsonism

Parkinson's syndrome including other symptoms than those of Parkinson's disease (rest tremor, rigidity, bradykinesia, and gait impairment) and not responding to Ldopa.

1.5 Drug induced Parkinsonism

Patient with Parkinson's syndrome treated with drugs known to induce Parkinsonism.

1.6 Abnormal involuntary movements other than tremor

Movement disorders characterized by involuntary movements that may occur in isolation or in combination other than tremor.

1.7 Mild Cognitive impairment

Mild cognitive impairment is a syndrome defined as cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life. The criteria for Mild Cognitive Impairment include: memory problems, objective memory disorder, absence of other cognitive disorders or repercussions on daily life, normal general cognitive functioning and absence of dementia.

1.8 Severe Cognitive impairment

Dementia.

1.9 Somnolence

Somnolence is a subjective feeling of an imperious need of sleep in unusual time and environmental conditions.

1.10 Tremor

Tremor is an unintentional (involuntary), rhythmical alternating movement that may affect the muscles of any part of the body. Tremor is caused by the rapid alternating contraction and relaxation of muscles and is a common symptom of diseases of the nervous system.
Among them, essential tremor is the most common. It's an action tremor, postural (patients typically experience tremors when the arms are held up, such as while reading a newspaper) or kinetic (occur during voluntary movements like eating, drinking or writing). The tremors also may affect the head, voice, tongue and legs and worsen with stress, fatigue and stimulant medications.

1.11 Disorientation

A disorientation is defined as inadequate or incorrect perception of place, time, or identity. Disorientation is one of the symptoms of confusional syndrome and may be due to multiples causes as organic (dementia, brain tumor, metabolic, vascular, or infectious …), toxic (drug or alcohol intoxication), or psychiatric (less commonly after severe stress).

1.12 Hallucination

A hallucination is a profound distortion in a person's perception of reality. A hallucination is a « perception without object to perceive » with complete conviction that it exists in reality, this is a wrong perception. A hallucination may be a sensory experience in which a person can see, hear, smell, taste, or feel something. Hallucinations may also occur in confusional syndromes and have multiple aetiologies.

1.13 Convulsion

A convulsion is an abnormal, involuntary contraction of muscles most typically seen with certain seizure disorders. These contractions may be tonic or clonic and they may be focal or generalized. Possible causes of convulsions include vascular, metabolic, toxic, hypoxic and traumatic (head injury) causes.

1.14 Restless legs syndrome

Restless legs syndrome (RLS) is a neurological disorder characterized by throbbing, pulling, or other unpleasant sensations in the legs with an uncontrollable urge to move them. Symptoms occur primarily at night when a person is relaxing or at rest and can increase in severity during the night. Moving the legs relieves the discomfort.
In most cases, the cause of RLS is unknown, but appears to be related to the following factors or conditions: low levels of iron, kidney failure, diabetes, and peripheral neuropathy. Certain medications, alcohol and sleep privation may aggravate symptoms.

1.15 Gait instability

Gait instability is any walking abnormality.
Only gait instability suspected of being of central origin will be adjudicated.

1.16 Stroke

Stroke is an acute episode ≥ 24h (according to AHA/ASA) of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

1.17 Transient ischemic attack

Transient ischemic attack is a transient episode < 24h (according to AHA/ASA) of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia without acute infarction.

2. Events to be adjudicated

The following events will be adjudicated by the SAC:

- Neurological events reported by the investigator as Adverse Event in the eCRF and corresponding to the Preferred Term listed in a separate document base on an updated MedDRA version (list N°3411).

HAEMATOLOGICAL EVENTS

1. Definitions

1.1 Coagulation disorders

Coagulation disorders are defined as prolongation of coagulation parameters as follows:

- in the absence of anticoagulant treatments:
  - INR> 1.5,
  - Prothrombin ratio < 50%,
  - Prothrombin time > 1.5-fold the local laboratory normal values,
  - aPTT > 1.2-fold the local laboratory normal values.
- in the presence of anticoagulant treatments:
  - INR > 4 (in presence of vitamin K antagonists),
  - Prothrombin ratio < 25% (in presence of vitamin K antagonists),
  - Prothrombin time > 3-fold the local laboratory normal values (in presence of vitamin K antagonists),
  - aPTT > 4-fold the local laboratory normal values (in presence of heparin),
  - aPTT > 2-fold the local laboratory normal values (in presence of vitamin K antagonists).

The following events will be adjudicated by the SAC:

- coagulation disorders reported by the investigator as Adverse Events in the eCRF
- the following coagulation parameters with values beyond the following limits:
  - in the absence of anticoagulant treatments:
    - INR > 1.5 or Prothrombin ratio < 50% or Prothrombin time > 1.5-fold the local laboratory normal values,
    - aPTT > 1.2-fold the local laboratory normal values.
  - in the presence of anticoagulant treatments:
    - INR> 4 or Prothrombin ratio < 25% or Prothrombin time > 3-fold the local laboratory normal values (in presence of vitamin K antagonists),
    - aPTT > 4-fold the local laboratory normal values (in presence of heparin),
    - aPTT > 2-fold the local laboratory normal values (in presence of vitamin K antagonists).

1.2 Thrombocytopenia

Thrombocytopenia is defined as:

- platelets values < 100 G/L and,
- for platelets between 100 G/L and 150 G/L: all decreases > 30% compared to baseline.

The following events will be adjudicated by the SAC:

- thrombocytopenia reported by the investigator as Adverse Event in the eCRF,
- platelets values < 100 G/L,
- for platelets between 100 G/L and 150 G/L: all decreases > 30% compared to baseline.

1.3 Agranulocytosis

Agranulocytosis is defined as neutrophils values < 0.5 G/L.

The following events will be adjudicated by the SAC:

- agranulocytosis reported by the investigator as Adverse Event in the eCRF,
- neutrophils values < 0.5 G/L.

1.4 Haemorrhages

Preferred Term list in a separated document based on an updated MedDRA version (list N°3193 « *TME Haemorrhages excl contusions SMQnp* »).

1.5 Bleeding grade and classification (Webert. 2012)

Webert KB, Arnold DM, Lui Y, Carruthers J, Arnold E, Heddle NM. A new tool to assess bleeding severity in patients with chemotherapy-induced thrombocytopenia. Tansfusion. 2012;52:2466-2474.

TABLE 2. Examples of bleeding signs or symptoms and their classification*

	Grade 1: not clinically significant bleeding		Grade 2: clinically significant bleeding		
	Grade 1(a): trace bleeding	Grade 1(b): mild bleeding	Grade 2(a): serious bleeding	Grade 2(b): serious bleeding with significant morbidity	Grade 2(c): fatal bleeding
Type or site of bleeding	Minimal bleeding or bleeding detectable by laboratory measures only. Bleeding does not have any impact on patient or care provided to patient.	Non–clinically significant bleeding. Bleeding associated with no impact on patient or level of care provided to patient. (Bleeding does not meeting criteria listed for "Grade 2/ Clinically significant bleeding.")	Any bleeding resulting in one or more of the following: pain; need for interventions (including transfusion, surgery, invasive procedures, administration of medication); or need for invasive investigations or increased monitoring.	Any bleeding meeting one of the following criteria: all central nervous system bleeding, resulting in hemodynamic instability, resulting in vision loss, resulting in significant morbidity.	Any bleeding directly contributing to patient's death.
Oral and nasal	Trace blood in nasal secretions. Oral petechiae (new). Trace blood from gums with brushing teeth.	Oral mucosal blood blisters (new or increased in number). Epistaxis not requiring intervention or transfusion.	Epistaxis requiring intervention (i.e., nasal packing, cautery), medical treatment, transfusion.		Bleeding directly contributing to death.
Skin, soft tissue, musculoskeletal	Petechiae (new or increased in number). Bruising of skin (new or increased size).	Hematoma (new or increased in size).		Joint bleeding. Hematoma causing compartment syndrome.	Bleeding directly contributing to death.
Abdominal and GI	Occult blood in stool. Mild hemorrhoidal bleeding (blood present on toilet paper only). Blood-tinged nasogastric drainage. Trace blood in peritoneal fluid.	Melena or hematochezia Hematemesis, coffee ground emesis. Frank blood in peritoneal fluid.	GI bleeding requiring endoscopy to investigate.	GI bleeding resulting in hemodynamic instability.	Bleeding directly contributing to death.
Genitourinary	Laboratory evidence of Hb or RBC in the urine. Vaginal spotting not at time of normal period.	Gross hematuria. Vaginal bleeding not at time of normal period or vaginal bleeding at time of normal period but of greater quantity or duration than normal period.	Hematuria causing renal impairment or necessitating bladder irrigation. Vaginal bleeding requiring transfusion.		Bleeding directly contributing to death.
Cardiopulmonary	Blood-tinged sputum. Trace blood in pleural fluid. Trace blood in pericardial fluid.	Hemoptysis (gross blood in sputum).	Hemoptysis associated with shortness of breath, hypoxia, new or increased requirement of supplemental oxygen. Hemoptysis requiring bronchoscopy. Hemoptysis necessitating transfusion of blood product.		Bleeding directly contributing to death.
Central nervous system	Laboratory evidence of blood in CSF with no symptoms	Retinal bleeding with no visual impairment.		Retinal bleeding with visual impairment. Hemorrhagic stroke (asymptomatic, temporary symptoms, or permanent morbidity).	Bleeding directly contributing to death.
Related to invasive procedures	Mild oozing at the site of a placement of venous catheter, venipuncture site, or other invasive surgical site.	Brisk bleeding at the site of placement of a venous catheter, venipuncture site, or other invasive surgical site.	Bleeding at surgical site necessitating return to OR to investigate.		Bleeding directly contributing to death.
Other				Bleeding occurring in critical area or organ (e.g., intraocular).	Bleeding directly contributing to death.

* Note that this list is meant to be illustrative rather than exhaustive.
CSF = cerebrospinal fluid; GI = gastrointestinal; OR = operating room.

OTHER EVENTS

1. Definitions

1.1 Falls
Defined as to drop suddenly from an erect position, to descend by the force of gravity from a higher to a lower place.

The following events will be adjudicated by the SAC:
- Falls reported by the investigator as Adverse Event in the eCRF.

All falls, mechanical or not, will be adjudicated.
Consequences of falls such as fractures, contusion, hematoma etc…will not be adjudicated.

Medical consequences:
- Severe: with death or hospitalization.
- Not severe: other cases different from none.

The adjudicators may ask an advice to the neurologist for the fall cases adjudication.

1.2 Arterial hypotension:
Defined as systolic BP < 100 mmHg and/or diastolic BP < 60 mmHg measured in supine position.

The following events will be adjudicated by the SAC:
- arterial hypotension reported by the investigator as Adverse Event in the eCRF,
- all values of systolic BP < 100 mmHg and/or diastolic BP < 60 mmHg measured in supine position.

Medical consequences:
- Severe: with death or hospitalization.
- Not severe: other cases different from none.

1.3 Orthostatic hypotension
Defined as a reduction of MORE THAN 20 mmHg (> 20 mmHg) for systolic BP and/or MORE THAN 10 mmHg (> 10 mmHg) for diastolic BP at 1 AND 3 minutes after standing–up as compared to the measurement in the supine position.

The following events will be adjudicated by the SAC:
- orthostatic hypotension reported by the investigator as Adverse Event in the eCRF,
- all reductions of MORE THAN 20 mmHg (> 20 mmHg) for systolic BP and/or MORE THAN 10 mmHg (> 10 mmHg) for diastolic BP at 1 AND 3 minutes after standing–up as compared to the measurement in the supine position.

If both arterial hypotension and orthostatic hypotension are reported for the same patient as EI not reported as AE, the events will be adjudicated together.

1.4 Serious skin disorders:
A serious skin disorder is a disease affecting the skin and/or a mucous membrane considered as serious by the investigator.

Acute Generalized Exanthematous Pustulosis is an acute febrile drug eruption characterized by numerous small, primarily non-follicular, sterile pustules, arising within large areas of edematous erythema. The eruption follows a self-limiting course and will end before a week provided the causative agent (e.g. medication) is discarded. It is accompanied by fever, neutrophilia, and sometimes by facial edema, hepatitis and eosinophilia. The aetiology is 60-80 % iatrogenic *[Roujeau JC et al. Acute generalized exanthematous pustulosis. Analysis of 63 cases. Arch Dermatol 1991, 127, 1333-8.]*.
The mortality rate is about 5% and the differential diagnosis includes Stevens–Johnson syndrome (SJS). Contrary to SJS, in AGEP, mucosa are not affected, which means that there are no blisters in the mouth or vagina *[Rapini, Ronald P.; Bolognia, Jean L.; Jorizzo, Joseph L. (2007). Dermatology: 2-Volume Set. St. Louis: Mosby. pp. 297, 303, 308, 309]*.

DRESS is a Drug Reaction with Eosinophilia and Systemic

Symptoms. The following events will be adjudicated by the SAC:

- serious skin disorders reported by the investigator as serious Adverse Event in the eCRF.

1.5 Hepatic disorders:

Hepatic disorders may include events such as:

- ALAT and/or ASAT elevation > 3 ULN, alkaline phosphatase > 2 ULN without clear aetiological diagnosis,
- hepatitis,
- icterus, jaundice without clear aetiological diagnosis,
- biliary/gall bladder disorders (bile ducts morphological anomalies, neoplasms, infections, inflammation, lithiasis and obstruction, fibrosis),
- hepato-biliary neoplasms/mass (benign and malignant),
- hepatic vascular disorders (including ischemia, hemorrhage haemangioma, portal vein disorders, veno occlusive disease ..),
- hepatic metabolic disorders,
- hepatic auto-immune disorders.

The following events will be adjudicated by the SAC:

- hepatic disorders reported by the investigator as Adverse Event in the eCRF,
- all cases of ALAT and/or ASAT elevation > 3 ULN.

6.3. Appendix 3: Safety Endpoints Adjudication Committee members

	Name	*Country*	*Address*
Chairman Neurologist	Prof. Fabrizio STOCCHI	Italy	Clinical Trial center Centro per lo studio e Cura Morbo di Parkinson e disturbi del Movimento I.R.C.C.S. San Raffaele Pisana Via della Pisana, 216 00163 Roma- ITALY Tel : +39 3358412976 fabrizzio.stocchi@sanraffaele.it fabrizio.stocchi@tin.it
Neurologist	Prof. Yves AGID	France	Institut du Cerveau et de la Moelle épinière (ICM) CHU Pitié-Salpêtrière Bâtiment Paul Castaigne 47 boulevard de l'Hôpital 75013 Paris - FRANCE Tel : + 33 1 42 16 19 93 ; + 33 1 57 27 40 24 yves.agid@icm-institute.org
Haematologist	Prof. Thomas LECOMPTE	Switzerland	Service d'Hématologie Département des Spécialités de Médecine Hôpitaux Universitaires de Genève Rue Gabrielle Perret-Gentil 4 1211 Genève 14 - SWITZERLAND thomaspierre.lecompte@hcuge.ch
Geriatrician	Prof. Olivier HANON	France	Service Gérontologie du Pr Rigaud Hôpital Broca 54-56 rue Pascal 75013 Paris - FRANCE TEL : + 33 1 44 08 36 36 ; + 33 1 44 08 35 10 olivier.hanon@brc.aphp.fr
Internist	Prof. Patrice CACOUB	France	Department of Internal Medicine and Clinical Immunology National Reference Center for Autoimmune Systemic and Rare Diseases Hôpital La Pitié Salpêtrière – Charles Foix 83 boulevard de l'Hôpital 75651 Paris cedex 13 – FRANCE Tel : + 33 1 42 17 80 27 patrice.cacoub@psl.aphp.fr

6.4. Appendix 4: Conflict of Interest Statement

CERTIFICATION/DISCLOSURE OF FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS	
Please complete all of the information below. You must retain a copy of this form in your study files for at least 15 years after the end of the study.	
1. Protocol Title: The efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention. ATPCI study.	
2. Protocol Number: CL3-06790-010	
3. Name:	I am participating in this study as a voting member of the Safety Endpoint Adjudication Committee
4. Full Address:	
5. Telephone:	**6. Email**:

7. Indicate by marking YES or NO if you, your spouse, or your dependent children hold financial interests as described below:

YES	**NO**	
☐	☐	Any financial arrangement entered into between you and the Sponsor of the study, whereby the compensation to you for reviewing the study could be influenced by the outcome of the study. If so, please attach details to this form.
☐	☐	Any proprietary interest in the product tested in the study, including but not limited to, property, patents, trademarks, copyrights, or licensing agreements. If so, please attach details to this form.
☐	☐	Any significant equity interest in the Sponsor of the study, such as ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices, or any equity interest in the Sponsor that exceeds $ 50,000 in aggregate. If so, please attach details (e.g., the number of stock shares and current trading price) to this form.

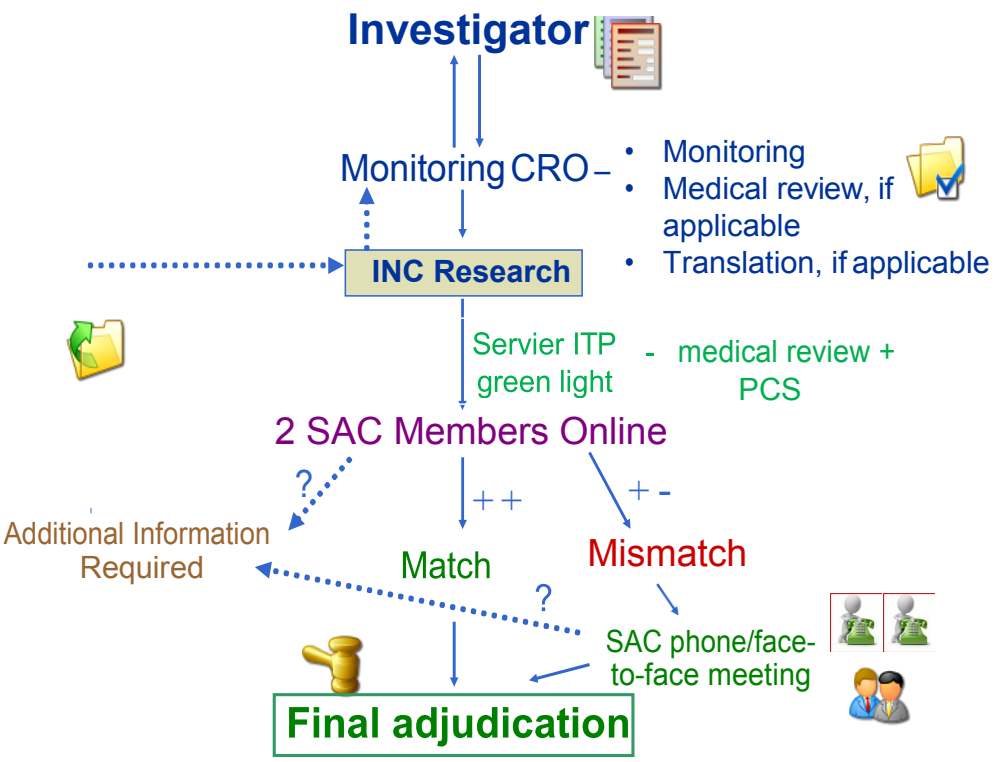
I declare the information that is provided on this form is, to the best of my knowledge and belief, true, correct, and complete. Furthermore, if my financial interests and arrangements, or those of my spouse and dependent children, change from the information provided above during the course of the study, and within 1 year after the last patient has completed this study as specified in the protocol, I will notify I.R.I.S. with specific details immediately.

8. Signature	**9. Date**

6.5. Appendix 5: Allocation of Events of Interest to Adjudicators

EVENTS OF INTEREST	ADJUDICATION BY				
	2 Neurologists	1 Hematologist	1 Geriatrician	1 Internist	**Main Adjudicator**
Neurological events and Strokes	✓				**Pr Stocchi**
Coagulation disorders including haemorrhages		✓		✓	**Pr Lecompte**
Thrombocytopenia		✓		✓	**Pr Lecompte**
Agranulocytosis		✓		✓	**Pr Lecompte**
Falls			✓	✓	**Pr Hanon**
Arterial hypotension			✓	✓	**Pr Hanon**
Serious skin disorders			✓	✓	**Pr Cacoub**
Hepatic disorders			✓	✓	**Pr Cacoub**

6.6. Appendix 6: Flow Chart of The Adjudication Process



6.7. Appendix 7: Documents to be provided by the investigator for adjudication of AEIs

Documentation/information to be provided by the investigator for the Safety Adjudication Committee adjudication are listed below:

In the case of neurological symptoms:

- detailed description of the event written in the eCRF,
- report of consultation with neurologist linked to study centre in case of occurence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability of central origin. This report should include results of investigations performed, if any. A specific questionnaire is also to be completed by the neurologist in this case (see Appendix 10 of the protocol),
- hospital report and/or report of the physician responsible for the management of patient care, if any,
- report of DAT scan/MRI scan related to the event, if any and reports within the previous 2 years, if available. Digitized images should be provided for MRI scans.

In the case of coagulation disorders (including non traumatic haemorrhages), thrombocytopenia or agranulocytosis:

- detailed description of the event written in the eCRF,
- report of consultation with haematologist, including results of any investigations performed,
- hospital report and/or report of the physician responsible for the management of patient care, if any,
- report of bone marrow biopsy/aspiration, if any,
- information regarding presence or not of bleeding for coagulation disorders and thrombocytopenia, presence or not of anticoagulant treatments for coagulation disorders, presence or not of transfusion for haemorrhages, presence of anti-infective treatment and growth factors for agranulocytosis.

In the case of falls:

- detailed description of the event written in the eCRF (including information regarding consequences and cause, if known),
- results of any investigations performed,
- report of any consultations related to this event,
- hospital report and/or report of the physician responsible for the management of patient care, if any,
- information regarding number of falls, mechanical or not, traumatic or not traumatic fall (presence or not of a fracture).

In the case of arterial hypotension, including orthostatic hypotension:

- detailed description of the event written in the eCRF, (including BP values at onset and recovery dates, if available),
- results of any investigations performed,
- report of any consultations related to this event,

- hospital report and/or report of the physician responsible for the management of patient care, if any,
- information regarding relevant symptoms such as vertigo, dizziness, malaise, fall, fatigue, postural instability, diarrhoea, relevant symptoms present the day of the visit and/or within the previous 6 months, hypotension detected during previous blood pressure measurements.

In the case of serious skin disorders:

- detailed description of the event written in the eCRF,
- report of consultation with dermatologist, if any, including results of any investigations performed,
- hospital report and/or report of the physician responsible for the management of patient care, if any,
- information regarding extension of the lesions (% of the body surface), presence or not of mucosal lesions, presence or not of skin detachment, presence or not of skin pain, presence or not of face oedema, presence or not of fever,
- pictures of the lesions taken by the investigator, results of skin lesions biopsy,
- lab report including WBC, creatinine, liver enzymes, presence or not of hypereosinophilia at time of event.

In the case of hepatic disorders:

- detailed description of the event written in the eCRF (please report if event is related to a concomitant treatment),
- results of any investigation performed, including abdominal ultrasound report, abdominal MRI report, hepatic biopsy report,
- report of any consultations related to this event,
- hospital report and/or report of the physician responsible for the management of patient care, if any,
- information regarding past medical history of alcoholism, liver enzymes (transaminases, Gamma Glutamyl Transferase, bilirubine, alkaline phosphatases, CPK), prothrombin time, blood albumin, viral serology (Hepatitis A, B, C, D, E).

6.8. Appendix 8: Documents to be provided by the investigator for adjudication of EIs not reported as AE

In case of coagulation disorders, thrombocytopenia, agranulocytosis, arterial hypotension, orthostatic hypotension, hepatic disorders identified by I.R.I.S Innovation Therapeutic Pole and not reported as AE:

- physician note (presence/absence of signs and symptoms, relevant information regarding the event, etc.), if necessary,
- any relevant document, if available (additional lab report, investigations related to the event, etc.) found during the SDV monitoring visit.

6.9. Appendix 9: Adjudication forms

AGRANULOCYTOSIS ADJUDICATION FORM

EI N° : |__|__|__| - |__|__|__|__| - |__|__|__|__|__| - |__|__|__| - |__|__|__| - |__|__|__|__| - |__|__|
Country Centre Patient Sequence n° AE/Procedure n° Visit n° EI code

AGRANULOCYTOSIS (Neutrophils < 0.5 G/L)

1. Is the event fulfilling the definition of Event of Interest?	❍ NO ❍ YES → If yes, please indicate your adjudication by ticking the appropriate boxes below: **PRESENCE OF CONCOMITANT BLOOD CELLS COUNT ANOMALY:** ❍ NO ❍ UNKNOWN ❍ YES **PRESENCE OF FEVER:** ❍ NO ❍ UNKNOWN ❍ YES **USE OF GROWTH FACTOR** ❍ NO ❍ UNKNOWN ❍ YES **PROBABLE CAUSE** (several causes could possibly be ticked): ☐ Infection ☐ In the context of a known autoimmune disorder ☐ Bone marrow disorder ☐ Toxic / Radiation ☐ Previous / concomitant treatment (INN in English): _ _ _ _ _ _ _ ☐ Other ☐ Unknown cause
2. Date of the event	|_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
3. Outcome	❍ Recovered / recovering ❍ Not recovered ❍ Unknown
4. Readjudication	Please indicate if you consider that the event needs to be readjudicated at the end of the study: ❍ NO ❍ YES
5. SAC member comments	Not to be transferred to IRIS
6. Date of adjudication (Automatic)	|_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
7. Name of the SAC	……

4 May 2016

member (Automatic) Electronic signature	…… ……

4 May 2016

ARTERIAL HYPOTENSION ADJUDICATION FORM

EI N° : |__|__|__| - |__|__|__|__|__| - |__|__|__|__|__|__|__| - |__|__|__| - |__|__|__| - |__|__|__|__| - |__|__|
Country Centre Patient Sequence n° AE/Procedure n° Visit n° EI code

ARTERIAL HYPOTENSION

1. Is the event fulfilling the definition of Event of Interest?	❍ NO ❍ YES → If yes, please indicate your adjudication by ticking the appropriate boxes below: **HYPOTENSION (SUPINE POSITION):** ❍ NO ❍ YES **ORTHOSTATIC HYPOTENSION:** ❍ NO ❍ YES **SYMPTOMATIC HYPOTENSION:** ❍ NO ❍ YES **SEVERE HYPOTENSION (SBP<90 mmHg):** ❍ NO ❍ YES **MEDICAL CONSEQUENCE:** ❍ None ❍ Not severe ❍ Severe (Death or Hospitalisation) **PROBABLE CAUSE** (several causes could possibly be ticked): □ Hypovolemia including dehydration (diarrhea, vomiting) □ Venous insufficiency □ Cardiac insufficiency □ Neurological □ Previous/ concomitant treatment □ Other □ Unknown cause
2. Date of the event	|_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
3. Outcome	❍ Recovered / recovering ❍ Not recovered ❍ Unknown
4. Readjudication	Please indicate if you consider that the event needs to be readjudicated at the end of the study: ❍ NO ❍ YES
5. SAC member comments	Not to be transferred to IRIS
6. Date of adjudication (Automatic)	|_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
7. Name of the SAC	……

4 May 2016

member (Automatic) Electronic signature	…… ……

4 May 2016

COAGULATION DISORDERS AND HAEMORRHAGES ADJUDICATION FORM

EI N° : |__|__|__| - |__|__|__|__| - |__|__|__|__|__| - |__|__|__| - |__|__|__| - |__|__|__|__| - |__|__|
Country Centre Patient Sequence n° AE/Procedure n° Visit n° EI code

COAGULATION DISORDERS and HAEMORRHAGES

1. Is the event fulfilling the definition of Event of Interest?	❍ NO ❍ YES → If yes, please indicate your adjudication by ticking the appropriate boxes below:
	PRESENCE OF COAGULATION DISORDERS ❍ NO ❍ UNKNOWN ❍ YES, IF YES, **CLASSIFICATION** (several boxes could possibly be ticked): ☐ INR > 1.5 or Prothrombin ratio < 50% or Prothrombin time > 1.5-fold the local laboratory normal values in the absence of anticoagulant treatment ☐ aPTT > 1.2-fold the local laboratory normal values in the absence of anticoagulant treatment ☐ INR > 4 or Prothrombin ratio < 25% or Prothrombin time > 3-fold the local laboratory normal values in the presence of treatment with a vitamin K antagonist ☐ aPTT > 4-fold the local laboratory normal values in the presence of a treatment with heparin ☐ aPTT > 2-fold the local laboratory normal values in the presence of treatment with a vitamin K antagonist ☐ Other concomitant coagulation disorders, such as low fibrinogen **PRESENCE OF BLEEDING:** ❍ NO (GRADE 0) ❍ UNKNOWN ❍ YES IF YES, SIGNIFICANCE? ❍ NOT CLINICALLY SIGNIFICANT: TRACE OF BLEEDING (GRADE 1A) ❍ NOT CLINICALLY SIGNIFICANT: MILD BLEEDING (GRADE 1B) ❍ CLINICALLY SIGNIFICANT: SERIOUS BLEEDING (GRADE 2A) ❍ CLINICALLY SIGNIFICANT: SERIOUS BLEEDING CAUSING SIGNIFICANT MORBIDITY (GRADE 2B) ❍ CLINICALLY SIGNIFICANT: FATAL BLEEDING (GRADE 2C) IF YES, ORIGIN? ❍ SPONTANEOUS ❍ RELATED TO PROCEDURE ❍ POST TRAUMATIC ❍ UNKNOWN IF YES, LOCATION? (several boxes could possibly be ticked): ☐ SUBCUTANEOUS ☐ RETROPERITONEAL ☐ URINARY ☐ EAR-NOSE-THROAT ☐ GINGIVAL ☐ INTRACRANIAL

24 June 2016

	☐ GYNECOLOGICAL ☐ GASTROINTESTINAL ☐ PROCEDURE OR SURGICAL SITE ☐ INTRAOCULAR ☐ OTHER LOCATION ☐ UNKNOWN **PROBABLE CAUSE** (several causes can be possibly ticked): ☐ Hepatic failure ☐ Vitamin K deficiency, but treatment with a vitamin K antagonist ☐ Autoimmune (lupus anticoagulant, antibody against a clotting factor) ☐ DIC (Disseminated Intravascular Coagulation) ☐ Clotting factor deficiency(ies) of any other causes ☐ Previous/ concomitant treatment (INN in English): _ _ _ _ _ _ _ _ ☐ Other ☐ Unknown cause
2. Date of the event	__| / __| / |2|0|__| *(DD / MM / YYYY)*
3. Outcome	❍ Recovered / recovering ❍ Not recovered ❍ Unknown
4. Readjudication	Please indicate if you consider that the event needs to be readjudicated at the end of the study: ❍ NO ❍ YES
5. SAC member comments	Not to be transferred to IRIS
6. Date of adjudication (Automatic)	__| / __| / |2|0|__| *(DD / MM / YYYY)*
7. Name of the SAC member (Automatic) Electronic signature	……... ……... ……...

FALL ADJUDICATION FORM

EI N° : |__|__|__| - |__|__|__|__| - |__|__|__|__|__| - |__|__|__| - |__|__|__| - |__|__|__|__| - |__|__|
Country Centre Patient Sequence n° AE/Procedure n° Visit n° EI code

FALL

1. Is the event fulfilling the definition of Event of Interest?	❍ NO ❍ YES → If yes, please indicate your adjudication by ticking the appropriate boxes below: **PROBABLE CAUSE** (several causes could possibly be ticked): ☐ Mechanical (accidental cause) ☐ Loss of consciousness ☐ Cardiovascular ☐ Neurological ☐ Previous/ concomitant treatment (INN in English): _ _ _ _ _ _ ☐ Other ☐ Unknown cause **FRACTURE** ❍ NO ❍ YES **MEDICAL CONSEQUENCE:** ❍ None ❍ Not severe ❍ Severe (Death or Hospitalization)
2. Date of the event	__/__/|2|0|__| *(DD / MM / YYYY)*
3. Outcome	❍ Recovered / recovering ❍ Not recovered ❍ Unknown
4. Readjudication	Please indicate if you consider that the event needs to be readjudicated at the end of the study: ❍ NO ❍ YES
5. SAC member comments	Not to be transferred to IRIS
6. Date of adjudication (Automatic)	__/__/|2|0|__| *(DD / MM / YYYY)*
7. Name of the SAC member (Automatic) Electronic signature	……... ……... ……...

19 May 2016

HEPATIC DISORDERS ADJUDICATION FORM

EI N° : |__|__|__| - |__|__|__|__| - |__|__|__|__|__| - |__|__|__| - |__|__|__| - |__|__|__|__| - |__|__|
Country Centre Patient Sequence n° AE/Procedure n° Visit n° EI code

HEPATIC DISORDERS

1. Is the event fulfilling the definition of Event of Interest?	❍ NO ❍ YES → If yes, please indicate your adjudication by ticking the appropriate boxes below: **LIVER FUNCTION ABNORMALITIES:** ❍ NO ❍ UNKNOWN ❍ YES, please specify (several boxes could possibly be ticked): ☐ ASAT/ALAT > 3-fold the local laboratory upper normal values ☐ Alkaline phosphatases > 2-fold the local laboratory upper normal values ☐ Other **PROBABLE CAUSE** (several causes could possibly be ticked): ☐ Viral infection ☐ Autoimmune ☐ Biliary disorder ☐ Cirrhosis ☐ Alcoholism ☐ Hepatic failure ☐ Tumour ☐ Previous/ concomitant treatment (INN in English):_ _ _ _ _ _ _ ☐ Other ☐ Unknown cause
2. Date of the event	__| / __| / |2|0|__| *(DD / MM / YYYY)*
3. Outcome	❍ Recovered / recovering ❍ Not recovered ❍ Unknown
4. Readjudication	Please indicate if you consider that the event needs to be readjudicated at the end of the study: ❍ NO ❍ YES
5. SAC member comments	Not to be transferred to IRIS
6. Date of adjudication (Automatic)	__| / __| / |2|0|__| *(DD / MM / YYYY)*
7. Name of the SAC member (Automatic) Electronic signature	…… …… ……

4 May 2016

NEUROLOGICAL EVENTS ADJUDICATION FORM

EI N° : |__|__|__| - |__|__|__|__| - |__|__|__|__|__| - |__|__|__| - |__|__|__| - |__|__|__|__| - |__|__|
Country Centre Patient Sequence n° AE/Procedure n° Visit n° EI code

NEUROLOGICAL EVENTS

1. Is the event fulfilling the definition of Event of Interest?	❍ NO ❍ YES → If yes, please indicate your adjudication by ticking the appropriate boxes below: **DIAGNOSIS / POSSIBLE CAUSES** ❍ **Parkinson's disease:** ❍ Probable (at least 2 out of Rest tremor, Bradykinesia, Rigidity) ❍ Possible (only 1 out of Rest tremor, Bradykinesia, Rigidity) ❍ **Atypical Parkinsonism** ❍ **Drug induced Parkinsonism,** INN in English: _ _ _ _ _ _ _ ❍ **Other than Parkinsonian syndrome** (several causes could possibly be ticked) ☐ Tremor (other than Parkinson's) ☐ Abnormal involuntary movements other than tremor ☐ Gait instability and/or fall of central neurological origin (other than Parkinson's disease) ☐ Restless leg syndrome ☐ Mild Cognitive impairment ☐ Severe Cognitive impairment ☐ Somnolence ☐ Disorientation / confusionnal state ☐ Hallucination ☐ Convulsion ☐ Recent stroke / Transient Ischemic Attack ☐ Other ☐ **Possibly linked to a previous / concomitant treatment** INN in English: _ _ _ _ _ _ _
2. Date of the event	__ / __ / 2 0 __ *(DD / MM / YYYY)*
3. Outcome	❍ Recovered / recovering ❍ Not recovered ❍ Unknown
4. Readjudication	Please indicate if you consider that the event needs to be readjudicated at the end of the study: ❍ NO ❍ YES
5. SAC member comments	Not to be transferred to IRIS
6. Date of adjudication (Automatic)	__ / __ / 2 0 __ *(DD / MM / YYYY)*
7. Name of the SAC member (Automatic) Electronic signature	…… …… ……

4 May 2016

SERIOUS SKIN DISORDERS ADJUDICATION FORM

EI N° : |__|__|__| - |__|__|__|__| - |__|__|__|__|__| - |__|__|__| - |__|__|__| - |__|__|__|__| - |__|__|
Country Centre Patient Sequence n° AE/Procedure n° Visit n° EI code

SERIOUS SKIN DISORDERS

1. Is the event fulfilling the definition of Event of Interest?	❍ NO ❍ YES → If yes, please indicate your adjudication by ticking the appropriate boxes below: **DIAGNOSIS:** ❍ Acute generalised exanthematous pustulosis (AGEP) ❍ Generalised urticaria / angioedema ❍ Steven Johnsons syndrome ❍ Toxic epidermal necrolysis ❍ DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) ❍ Other **PROBABLE CAUSE** (several causes could possibly be ticked): □ Allergic cause □ Bacterial infection □ Viral infection □ Mycosis □ Parasitosis □ Tumour □ Previous /concomitant treatment (INN in English): _ _ _ _ _ _ _ _ □ Other □ Unknown cause
2. Date of the event	|_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
3. Outcome	❍ Recovered / recovering ❍ Not recovered ❍ Unknown
4. Readjudication	Please indicate if you consider that the event needs to be readjudicated at the end of the study: ❍ NO ❍ YES
5. SAC member comments	Not to be transferred to IRIS
6. Date of adjudication (Automatic)	|_|_| / |_|_| / |2|0|_|_| *(DD / MM / YYYY)*
7. Name of the SAC member (Automatic) Electronic signature	……... ……... ……...

19 May 2016

THROMBOCYTOPENIA ADJUDICATION FORM

EI N° : |__|__|__| - |__|__|__|__| - |__|__|__|__|__|__| - |__|__|__| - |__|__|__| - |__|__|__|__| - |__|__|
Country Centre Patient Sequence n° AE/Procedure n° Visit n° EI code

THROMBOCYTOPENIA Platelet count < 100 G/L or between 100 G/L and 150 G/L

1. Is the event fulfilling the definition of Event of Interest?	❍ NO ❍ YES → If yes, please indicate your adjudication by ticking the appropriate boxes below: **PRESENCE OF CONCOMITANT BLOOD CELLS COUNT ANOMALY:** ❍ NO ❍ UNKNOWN ❍ YES **PRESENCE OF BLEEDING** ❍ NO ❍ UNKNOWN ❍ YES **PLATELET TRANSFUSION** ❍ NO ❍ UNKNOWN ❍ YES **PROBABLE CAUSES** (several causes could possibly be ticked): □ Primary immune thrombocytopenia □ In the context of a known autoimmune disorder (such as SLE...) □ Infection □ Bone marrow disorder □ Active cancer □ Other causes of DIC (Disseminated Intravascular Coagulation) □ Splenomegaly □ Toxic / Radiation □ Previous /concomitant treatment (INN in English): _ _ _ _ _ _ _ □ Other □ Unknown cause
2. Date of the event	|__| / |__| / |2|0|__| *(DD / MM / YYYY)*
3. Outcome	❍ Recovered / recovering ❍ Not recovered ❍ Unknown
4. Readjudication	Please indicate if you consider that the event needs to be readjudicated at the end of the study: ❍ NO ❍ YES
5. SAC member comments	Not to be transferred to IRIS
6. Date of adjudication (Automatic)	|__| / |__| / |2|0|__| *(DD / MM / YYYY)*
7. Name of the SAC member (Automatic) Electronic signature	……... ……...

19 May 2016

6.10. Appendix 10: Cardiovascular Innovation Therapeutic Pole Members

Development Director	Emmanuel ARNAUD
Project Director	Sophie ROBERT
Clinical Development Leader	Dr Jean-Pascal CHALLETON
Clinical Development Scientist	Ramona BARBAROSIE
Clinical Development Leader	Sylvie BRACQ
Clinical Department Leader	Dr Benoît TALLOT

ATPCI Charter of the Data Monitoring Committee

Document title	**Data Monitoring Committee Charter**
Study title	**The efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention.** **An international, multicentre, randomised, double-blind, placebo-controlled study in patients treated for 2 to 4 years.**
Study name	**ATPCI**
Test drug	**S 06790 (Trimetazidine MR 35 mg)**
Indication	**Angina pectoris**
Development phase	**Phase III**
Protocol code	**CL3-06790-010**
Chairman of the Data Monitoring Committee	**Prof. Philippe Gabriel STEG** **Hôpital Bichat - Service de Cardiologie** **46 rue Henri Huchard - 75018 Paris (France)** **Tel: +33 (0) 1 40 25 86 69** **Fax: +33 (0) 1 40 25 88 65** **e-mail: gabriel.steg@bch.aphp.fr**
Sponsor	**Institut de Recherches Internationales Servier** **50 rue Carnot** **92284 SURESNES Cedex** **France**
Date of the charter	**Final version including amendment n°1 – 5 September 2014**

CONFIDENTIAL

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GLOSSARY

3-KAT	:	3-ketoacyl coenzyme A thiolase
AE	:	Adverse Event
AEI	:	Adverse Events of Interest
b.i.d.	:	*bis in die* (twice a day)
BP	:	Blood Pressure
CAD	:	Coronary Artery Disease
CCS	:	Canadian Cardiovascular Society
CITP		Cardiovascular Innovation Therapeutic Pole
CRO	:	Clinical Research Organisation
CSU	:	Clinical Supply Unit of Servier
CVAC	:	CardioVascular endpoints Adjudication Committee
DM	:	Data Manager
DMC	:	Data Monitoring Committee
e.g.	:	*exempli gratia* / for example
EC	:	Executive Committee
e-CRF	:	electronic Case Report Form
EMA	:	European Medicine Agency
EQ-5D-3L	:	EuroQol-5 Dimensions-3 Levels questionnaire
FFA	:	Free Fatty Acid
HR	:	Heart Rate
IMP	:	Investigational Medicinal Product
IRIS	:	Institut de Recherches Internationales Servier
mg	:	milligram
MI	:	Myocardial Infarction
NSTEMI	:	Non-ST segment Elevation Myocardial Infarction
PCI	:	Percutaneous Coronary Intervention
PCS	:	Patient's Case Summary
PSE	:	Pre-Specified Event
SAC	:	Safety endpoints Adjudication Committee
SAP	:	Statistical Analysis Plan
STEMI	:	ST segment Elevation Myocardial Infarction

1. INTRODUCTION

Trimetazidine is a metabolic agent which acts directly on the myocardial cells to shift energy substrate utilisation away from free fatty acid (FFA) metabolism and towards glucose metabolism. It does so by inhibiting a key mitochondrial enzyme in fatty acid oxidation: long chain 3-ketoacyl coenzyme A thiolase (3-KAT). It does not act neither by reducing oxygen consumption nor by increasing blood supply and so is devoid of any haemodynamic effect.

In June 2012, the European Medicine Agency (EMA) recognized the positive risk-ratio of trimetazidine as an add-on to first-line antianginal therapies in symptomatic patients with angina pectoris insufficiently controlled by, or intolerant to first-line antianginal treatments.

The purpose of this phase III clinical study (Servier number CL3-06790-010) is 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 title of the study is "*The efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention. An international, multicentre, randomised, double-blind, placebo-controlled study in patients treated for 2 to 4 years".* The acronym of the study is ATPCI.

Patients to be recruited in this study are patients presenting a single or multivessel coronary artery disease and having undergone PCI treating at least one stenosis to either a native coronary artery or a coronary graft where the PCI was:

- indicated because of angina pectoris, occurring either in the context of stable angina (elective PCI) or in the context of an acute presentation such as unstable angina / NSTEMI, but excluding STEMI;
- achieved by stent implantation or by other acceptable interventional means;
- successful as planned by the operator and with no further revascularization (either percutaneous or surgical) planned;
- uncomplicated such that the patient's discharge was not, or will not be, delayed because of a cardiac or cerebrovascular problem.

Patients will randomly be allocated to one of the following treatments:

- trimetazidine 35 mg *b.i.d.*,
- placebo.

The investigational medicinal product (IMP) will be given in addition to routine post-PCI treatment which includes secondary prevention therapy, as per current guidelines, with or without regular antianginal therapy as decided by the investigator according to his/her normal practice or specific requirements of local/national guidelines and the patient's clinical condition.

The primary objectives are 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.

The secondary objectives are to evaluate the effect of trimetazidine on the other efficacy endpoints, as well as the other safety parameters, clinical and biological.

The primary efficacy endpoint of the study is the time to first occurrence of an event in the composite of:

- 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.

The primary safety endpoint is the incidence of serious emergent adverse events with trimetazidine as compared with placebo.

The secondary efficacy endpoints are:

- Time to first occurrence of an event in the composite of:
  - 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 ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
  - evidence of ischemia (documented by Stress Imaging) leading to performing a coronary angiography.
- Each component of the primary endpoint:
  - 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.
- Other secondary endpoints:
  - evidence of ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
  - evidence of ischemia (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,
  - hospitalisation for heart failure,
  - any coronary revascularization,
  - repeat coronary revascularization in response to angina.

The other efficacy endpoints are:

- CCS class of angina symptoms,
- number of angina episodes per week,
- number of doses of short-acting nitrates taken per week in response to angina,

- number of antianginal drugs taken by the patient,
- Seattle Angina Questionnaire scores (in countries where a validated translation is available),
- EQ-5D-3L Questionnaire scores,
- level of cardiac troponin (before each repeat elective PCI and between 6 and 24 hours after).

The secondary safety endpoints are:

- emergent adverse events (including clinically significant abnormalities observed from the electrocardiographic recordings and from laboratory examinations),
- emergent adverse events of interest:
  - all neurological symptoms, including Parkinson's syndrome, disorientation, hallucination and convulsion,
  - coagulation disorders, thrombocytopenia (<150 G/L), agranulocytosis (neutrophils <0.5 G/L),
  - falls,
  - arterial hypotension, including orthostatic hypotension,
  - Serious skin disorders,
  - hepatic disorders,
- vital signs: supine and standing blood pressure (BP), heart rate (HR),
- weight,
- biochemical and haematological parameters.

The charter describes the responsibilities of the Data Monitoring Committee (DMC), the requirements for membership, its relationships with other parties of the trial and the contents of the reports to be reviewed by the DMC during the study (safety and efficacy summaries). This charter also provides the purpose and timing of the DMC meetings (open and closed sessions), the types of recommendations to be made by the DMC and procedures for ensuring confidentiality and proper communication.

2. MAIN RESPONSIBILITIES OF THE DMC

The DMC is responsible for:

- periodically monitoring the overall conduct of the trial for safeguarding the interests of trial participants by assessing safety and efficacy during the trial,
- periodically reviewing all cardiovascular and non-cardiovascular events, serious or not, with or without suspected causal relationship with the study drug,
- providing the Executive Committee (EC) with recommendations about stopping or continuing the trial, about amending the protocol or changing the conduct of the study to ensure patients safety. The EC will assess these recommendations in collaboration with the Sponsor (IRIS).

A detailed list of DMC members' responsibilities is given in appendix 1.

3. DMC MEMBERS AND ORGANISATION

3.1. DMC Members

The DMC is an independent multidisciplinary group composed of 4 members: 3 clinicians and a statistician who collectively have experience in the management of patients with CAD and in the conduct and monitoring of morbidity-mortality randomised clinical trials. The DMC members listed hereafter are voting members.

Members of the Data Monitoring Committee:

DMC Chairman	**Prof. P-G. STEG**	Hôpital Bichat-Claude-Bernard Service de Cardiologie 46 rue Henri Huchard 75722 Paris Cedex 18 - France e-mail: gabriel.steg@bch.aphp.fr Phone : +33 1 40 25 86 69
DMC Statistician	**Prof. J. BENICHOU**	Unité de Biostatistique CHU de Rouen 1 rue de Germont 76031 Rouen Cedex - France e-mail: Jacques.Benichou@chu-rouen.fr Phone: +33 2 32 88 83 89
DMC member: Cardiologist	**Prof. C. RAPEZZI**	Policlinico Sant'Orsola Malpighi Via Massarenti, 9 40138 Bologna - Italy e-mail: crapezzi@orsola-malpighi.med.unibo.it Phone: +39 051 6364529
DMC member: Cardiologist	**Prof. M. VOLTERRANI**	Cardiovascular Research Unit Department of Medical Sciences Centre for Clinical and Basic Research Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Pisana via della Pisana 235 00163 Rome – Italy e-mail: maurizio.volterrani@sanraffaele.it Phone+39 06 522 52455

All voting members will be required to sign a confidentiality agreement and the DMC charter (appendix 6). They will supply IRIS with a copy of their curriculum vitae in English, originally dated and signed.
DMC membership is to be for the duration of the clinical trial. If any member leaves the DMC during the course of the trial, IRIS in consultation with the DMC and the EC will promptly appoint his replacement.

Moreover a statistician, from a statistical centre independent from the Sponsor, will support the DMC statistician. This independent statistician and IRIS representatives are presented in appendix 4.

3.2. Conflicts of interest

The DMC membership has been restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific or regulatory in nature. There is an intrinsic need for judgment in the process of developing recommendations about important study conduct issues. All recommendations must be perceived to have been made in a fair and unbiased manner. Thus, neither study investigators, nor study Executive Committee or Endpoints Adjudication Committees or Steering Committee members, nor individuals

employed by IRIS, nor individuals who may have regulatory responsibilities for the trial product, are DMC members.

The DMC members should not own stock in the companies having products being evaluated by the clinical trial. The DMC members will disclose to the chairman any consulting agreements or financial interests that could impact their objectivity they have with IRIS, with any Clinical Research Organization (CRO) involved in the trial or having products that are competitive with those being evaluated in the trial. The DMC members will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.

The DMC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the course of the trial. Any DMC member who develops significant conflicts of interest during the course of the trial should resign from the DMC.
All DMC members and the independent statistician must complete and sign a non-conflict of interest statement (appendix 5) to that effect at the time they are asked to participate.

It is expressly understood that the DMC member is, and shall remain at all times, an independent contractor pursuant to this Agreement and nothing herein shall be construed as constituting, either directly or indirectly the expert as an agent, servant, representative or employee of ADIR.

3.3. Organisation

The persons involved in the process leading to a DMC recommendation and their role are:

- The ***DMC Members*** who will:
  1. periodically review the safety/efficacy summaries. These summaries and analyses are presented in sections 4.2 and 4.3 respectively, and will be detailed in the DMC statistical analysis plan (DMC SAP),
  2. provide recommendations to the EC during the study;

- The Independent Statistician who will:
  1. write the DMC SAP in collaboration with the DMC statistician before the sending decoding elements,
  2. write the *Specifications of derived data* document dedicated to describe the rules used to prepare the derived data. These rules will be discussed with the DMC statistician,
  3. produce reports including the safety/efficacy summaries. The independent statistician will program the analyses described in the DMC SAP based on the datasets periodically sent by the IRIS data manager.
  4. periodically send these reports to the DMC members,
  5. perform any additional or modified analyses requested by the DMC members during the study without the knowledge of IRIS. The independent statistician will also update the statistical document dedicated to the description of these analyses (*Modifications of the DMC SAP*);

- The IRIS Statistician who will perform the final analysis;

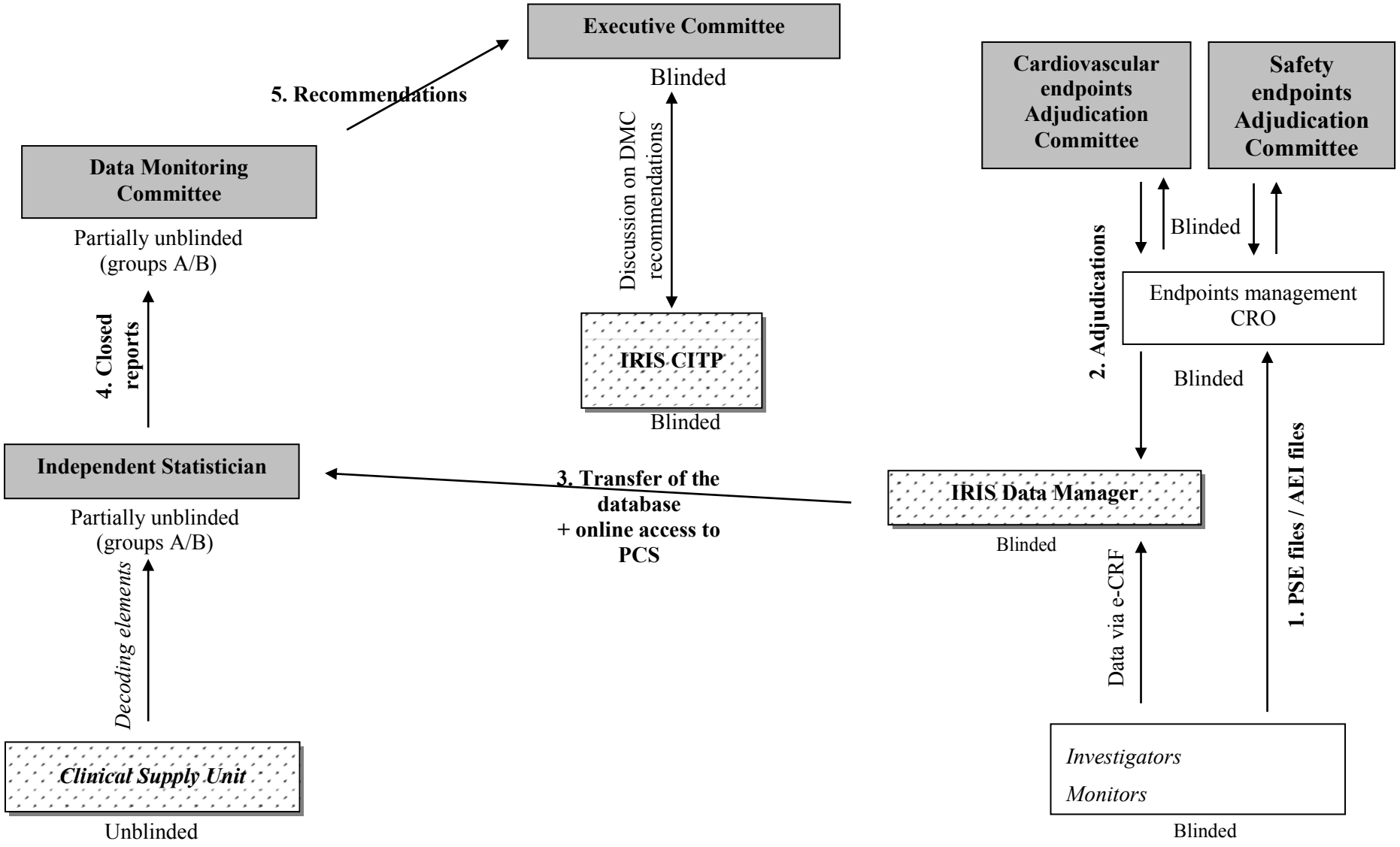
- The IRIS Data Manager who will:
  1. validate the data collected in the e-CRF and the results of endpoints adjudication by Endpoints Adjudication Committees members,
  2. periodically send the database for the independent statistician,

3. prepare and put Patient's Case Summaries (PCS) at the independent statistician's disposal through a collaborative workspace;

- The ***Clinical Supply Unit (CSU)*** of Servier which will supply decoding elements only to the independent statistician (the CSU is not involved in any meeting or discussion with the DMC);
- The ***Cardiovascular endpoints Adjudication Committee (CVAC)*** which will adjudicate the endpoints from the PSE files created by the investigators;
- The ***Safety endpoints Adjudication Committee (SAC)*** which will adjudicate the adverse events of interest from the events files created by the investigators;
- The ***Endpoints management CRO*** which will be in charge of the submission of PSE files to CVAC members and the adverse events of interest (AEI) files to SAC for adjudication of endpoints and of the periodic transfer of the endpoints database to the IRIS data manager;
- The IRIS ***Cardiovascular Innovation Therapeutic Pole*** (CITP) which, with the Endpoints management CRO, will make all efforts to provide the DMC with events already adjudicated in a timely manner;
- The ***Investigators*** who will collect the data of patients via the e-CRF and will collect the documents for the PSE and adverse events of interest files.

The relationships between the DMC and other functional structures involved in the trial are shown on the following flow chart.
The responsibilities of the DMC members, the independent statistician and the different Servier structures are detailed in appendix 1. Data flow and timelines are summarised in appendix 2.

Flow chart: Relationships between the DMC and other structures involved



4. REPORTS RECEIVED BY THE DMC

Reports on study data will be periodically sent to the DMC members. The first part of this section provides the contents and some organisational elements on the reports. The following parts describe specific elements about the safety/efficacy summaries. The last part of this section deals with the management of the blind which is a crucial point regarding the reports.

More details on the contents of the reports will be provided in the DMC SAP written by the independent statistician in collaboration with the DMC statistician.

4.1. Contents and timing of reports

The closed reports will be prepared by the independent statistician and reviewed by the DMC members. These reports will include the safety/efficacy summaries edited by treatment group A/B. The independent statistician will program the analyses described in the DMC SAP. Based on the database received from the IRIS Data Manager and on the decoding elements received from the CSU of Servier, the partially unblinded reports will be periodically generated by the independent statistician and sent to the DMC members at least 2 weeks before each DMC meeting. The DMC members will receive hard copies of the closed reports, with possibility to have an electronic access.

The first report will be performed when the data on the first 500 randomised patients with 3-month follow-up will have been collected into the database. This report will be sent to all DMC members in view of the first planned meeting.
Afterwards these reports will be sent to:

- the DMC chairman and the DMC statistician every 4 months during the whole study,
- all DMC members: approximately every 8 months.

In order that the independent statistician can produce the closed reports, the IRIS Data Manager will send to the independent statistician the data files at the appropriate time points.

Moreover at any time during the study, the DMC members may ask the independent statistician for further information. In this case, the independent statistician will write the programs and prepare the corresponding additional analyses. Concomitantly, the independent statistician will update the *Modifications of the DMC SAP* document, which details the additional analyses and modifications of the planned analyses. This document will be given to the IRIS statistician after IRIS has broken the blind in order that IRIS is not aware of what is being discussed by the DMC during the study.

Those reports will be prepared using the most up-to-date information available in the database, which means validated and not validated data, and adjudicated and not yet adjudicated endpoints.

The closed reports received by all DMC members will be discussed during the corresponding DMC meetings. Concerning the reports reviewed only by the DMC chairman and the DMC statistician, the DMC chairman may contact the other DMC members for advice or organise meetings if necessary. Such discussions may be held with or without the knowledge of IRIS.

After each meeting, the DMC members (except the DMC chairman) must destroy the documents they have received for the meeting.

The independent statistician will archive:

- the *DMC SAP*, signed by the DMC statistician and the independent statistician,
- the *Modifications of the DMC SAP* document signed by the DMC statistician and the independent statistician each time it is updated,
- the *closed reports* signed by the DMC statistician and the independent statistician,

- the programs used to generate the closed reports together with the validation report, associated programs and derived data used to generate the validation report (signed by the person in charge of validation).
- the derived data used to prepare the reports.

A copy of these documents will be provided to IRIS after IRIS has broken the blind. The DMC members should have access to the reports if needed.

4.2. Safety and efficacy summaries

Safety and efficacy will be assessed by the DMC during the study based on descriptive analyses of the following parameters:

- efficacy endpoints (adjudicated and not yet adjudicated),
- emergent adverse events (all emergent, serious or not, related to study drug or not, leading to treatment discontinuation or not), with particular emphasis on cardiovascular events including all disease-related events, and treatment-related events,
- emergent adverse events of interest (adjudicated and not yet adjudicated),
- blood laboratory parameters,
- blood pressures,
- patients' baseline characteristics,
- study progress, quality of recruitment and adherence (duration of follow-up, discontinuations of study treatment, doses of study treatment, compliance to study treatment, co-medications).

The first report and the reports sent every 8 months to all DMC members will include complete safety/efficacy summaries. The reports sent every 4 months to the DMC chairman and the DMC statistician will only present a description of major safety criteria: all emergent adverse events and emergent adverse events of interest.

PCS will be prepared by IRIS. They will be available for consultation at any time by the independent statistician.
Moreover the DMC chairman will be informed of any case for which unblinding of the study treatment code was done, either unblindings by the investigator or by Servier 24/24 helpdesk in case of medical emergency, or unblindings for regulatory purposes by the Pharmacovigilance Department of Servier. IRIS Cardiovascular Innovation Therapeutic Pole (CITP) will inform the DMC chairman on the cases of unblinding for medical emergency, the Pharmacovigilance Department of Servier will inform the DMC chairman on the unblindings for regulatory purposes (IRIS CITP will not be informed on regulatory unblindings until the end of the study).

4.3. Formal interim analyses

No formal interim analyses are planned during this study. The recommendations about stopping the trial will be the decision of the DMC based on a global consideration of all available data from the trial, including information on efficacy endpoints and adverse events, along with relevant information external to the trial, without statistical monitoring guidelines.

4.4. Management of the blind

To enhance the integrity and credibility of the trial, the DMC members will have exclusive access to unblinded results on safety and efficacy data and have to maintain confidentiality of these results.

When the DMC charter is signed by all DMC members and the DMC SAP is finalised, the independent statistician will receive from the CSU of Servier the decoding elements in two separate parts:

- first, the packaging list partially unblinded containing the link between the kit number allocated to a patient and the treatment group A/B,
- then, two sealed and confidential envelopes disclosing the correspondence between A/B and trimetazidine 35 mg *b.i.d.*/ placebo.

The packaging list and one envelope will be kept by the independent statistician. The second envelope will be transmitted by courier to the DMC chairman by the independent statistician before the first report.
When needed, the DMC chairman can open the envelope disclosing what A and B stand for. The data will remain blinded to IRIS. Any opened envelope will be signed and completed with the date and the justification of opening.
The packaging list and the envelopes will be returned to IRIS after IRIS will have broken the blind.

5. DMC MEETINGS

5.1. Organisational meeting

The initial meeting of the DMC will be an organisational meeting. It will aim at discussing some organisational elements, checking the process leading to the production of the reports and modifying the DMC charter if needed. This meeting will be attended by the DMC members and IRIS representatives, and will be held before the transfer of decoding elements to the independent statistician.
After this meeting the final version of the DMC charter will be signed by all DMC members.

5.2. Planned meetings

During the study, meetings will be organised aiming at reviewing the closed reports (including safety/efficacy summaries) with particular emphasis on cardiovascular events and adverse events of interest, and consequently at providing recommendations to the EC concerning the conduct of the trial. During these meetings, the DMC will weigh evidence for benefits and risks to determine whether there remains an adequate balance of benefit to risk in order to ethically and scientifically justify trial continuation.

The first meeting will be held when the data of the first 500 randomised patients with 3-month follow-up will have been collected. Subsequently, meetings will be held twice a year.
These meetings will be one-hour conference calls but may be replaced by face-to-face meetings if needed. They will be arranged by IRIS.
At least 2 weeks before each planned meeting, the independent statistician will send the report to be reviewed to all DMC members.

Planned meetings will include:

- an ***open session*** which will be attended by the DMC members, the independent statistician, IRIS representatives and the EC chairman (or his representative) or any other partners. The Sponsor may provide any complementary information to the DMC on the follow-up and management of the study, on the safety of the product… The open session will also give the DMC an opportunity to query IRIS about issues that have arisen during the review of the previous closed session. With this arrangement, important interactions will be facilitated through which problems affecting trial integrity can be identified and resolved. The open session must be conducted in a manner that fully maintains confidentiality of all unblinded information. Only blinded information will be discussed during this session;
- a ***closed session*** aiming at reviewing the results of the most recently sent report, which will be attended only by the DMC members and the independent statistician (as non-voting member);

- an additional ***open session*** at DMC request with the first open session attendees allowing to clarify the points raised by the DMC members during the closed session.

Two different access codes will be defined for the conference calls, one for the open session and one for the closed session.

All DMC members must make all efforts to participate to all DMC meetings. A planned meeting can only be held if the DMC chairman, the DMC statistician and one other member can attend. Otherwise another meeting will have to be organised.
A DMC member who will not be able to attend the meeting should send his comments on the report to the DMC chairman for consideration during the discussion.

5.3. Unplanned meetings

If a relevant concern is raised from the results present in a report or at any other time during the study, the DMC chairman may request an additional meeting with or without informing IRIS. This meeting, arranged by the DMC chairman, can be a conference call or a face-to-face meeting. An unplanned meeting can only be held if the DMC chairman, the DMC statistician and one other member can attend.
The main part of these meetings will consist in a closed session. If needed, the DMC chairman may ask for an open session in order to get more information on the trial from chosen non DMC representatives.

5.4. End-of-study debriefing meeting

At the study end, after the database has been frozen and the blind broken by the Sponsor, an "End-of-study debriefing meeting" will be held to review the closed reports produced throughout the conduct of the trial. All DMC members, the independent statistician and IRIS representatives will take part in this meeting.

6. DMC RECOMMENDATIONS

Following each planned DMC meeting, on the basis of safety summaries and efficacy summaries (taking into account the proportion of adjudicated endpoints), the DMC will make a recommendation concerning the conduct of the trial to the EC.
Unplanned meetings may also lead the DMC to provide a recommendation.

The DMC could recommend:

- to continue the study as *per* protocol,
- to continue the study with changes in the protocol,
- to stop the study for harmful effect.

In order to assess the registered treatment of trimetazidine on a long term period, it is not planned to stop the study for efficacy or futility.

A template for the DMC recommendation is proposed in appendix 3.

A recommendation should correspond to a consensus reached by the DMC members. In case of disagreement, the DMC members will vote (the independent statistician is a non-voting member) and the recommendation will correspond to the opinion of the majority. If there is no majority, the DMC chairman will have two voting rights.

The DMC chairman will send the recommendation to the EC chairman by email, with a confirmation paper, within the 7 days following a DMC meeting. Then, the chairman of the EC will

inform the Sponsor. The appropriate Authorities will be notified as soon as possible by the Sponsor of the DMC recommendation regarding the conduct of the study.
In case of recommendation to stop the study or modify the protocol and for any major issues, the DMC chairman will urgently contact the EC chairman who will take the appropriate decisions in collaboration with the Sponsor.
The DMC chairman will send a copy of this recommendation to the independent statistician who will archive it.

7. MINUTES OF DMC MEETINGS

The ***minutes of closed sessions*** will be prepared by the independent statistician following each meeting (planned or unplanned). These minutes will document the major issues discussed, any actions and any additional information needed for future meetings. They will be sent to the DMC chairman one week after the meeting and, when agreed, subsequently sent to all DMC members (having attended the meeting or not) in order that they may give their comments or their agreement. The DMC chairman will be the only one to sign the minutes of closed sessions. Then the DMC chairman will send the final version of the minutes of closed sessions to all DMC members.
The DMC members (except the DMC chairman) must destroy the minutes of closed sessions after having reviewed them. The DMC chairman will send the signed version of these minutes to the independent statistician who will archive them. The DMC members may have access to the minutes if needed. The minutes of closed sessions will not be communicated to IRIS before IRIS has broken the blind.

If appropriate, the minutes of closed sessions may include an open part dedicated to informing IRIS of some points discussed during the closed sessions that deserve the attention of IRIS, without giving any information likely to disclose the treatment blind. This open part will be sent to IRIS during the study.

The ***minutes of open sessions*** will be prepared by IRIS in collaboration with the DMC chairman following each meeting (planned or unplanned) including an open session. These minutes will include blinded information regarding study follow-up and study management. IRIS will send the minutes of open sessions to the attendees who will give their comments or their agreement. The DMC chairman will be the only one to sign the final version of this document. Then IRIS will send the final version of these minutes to the DMC members, the other meeting attendees and the EC chairman.
The DMC chairman will send a signed version of the minutes of open sessions to the independent statistician in order to archive them.

8. APPENDICES

Appendix 1: Check-list of responsibilities of all persons involved

	DMC chairman	All DMC members	DMC statistician	Independent statistician	Servier structures	Timelines
DOCUMENTS						
DMC Statistical Analysis Plan						before sending the decoding elements
- write the document				X		
- review the document			X			
Decoding elements						before the first report
- send the packaging list decoding partially treatment groups and envelopes disclosing the treatment group					CSU	
Specifications of derived data for the DMC planned analysis						
- write and update the document				X		every 4 months*
- review the document			X			
Modifications of the DMC planned analysis						
- write and update the document				X		
- validate and sign the document each time it is updated			X	X		
PROGRAMS						
- write the programs relative to the analyses described in the *DMC SAP*				X		
- update the programs required for any additional or modified analyses				X		
- run the programs				X		
- validate tables of results			X	X		
DATA						
- send the data to the independent statistician					IRIS DM	every 4 months*
- add the decoding elements to the data				X		
- put PCS at the independent statistician's disposal					IRIS DM	
- inform the DMC chairman on patients for which unblinding of treatment code was done					IRIS	

**: the first document/derived data will be prepared after 500 patients have been followed for 3 months*

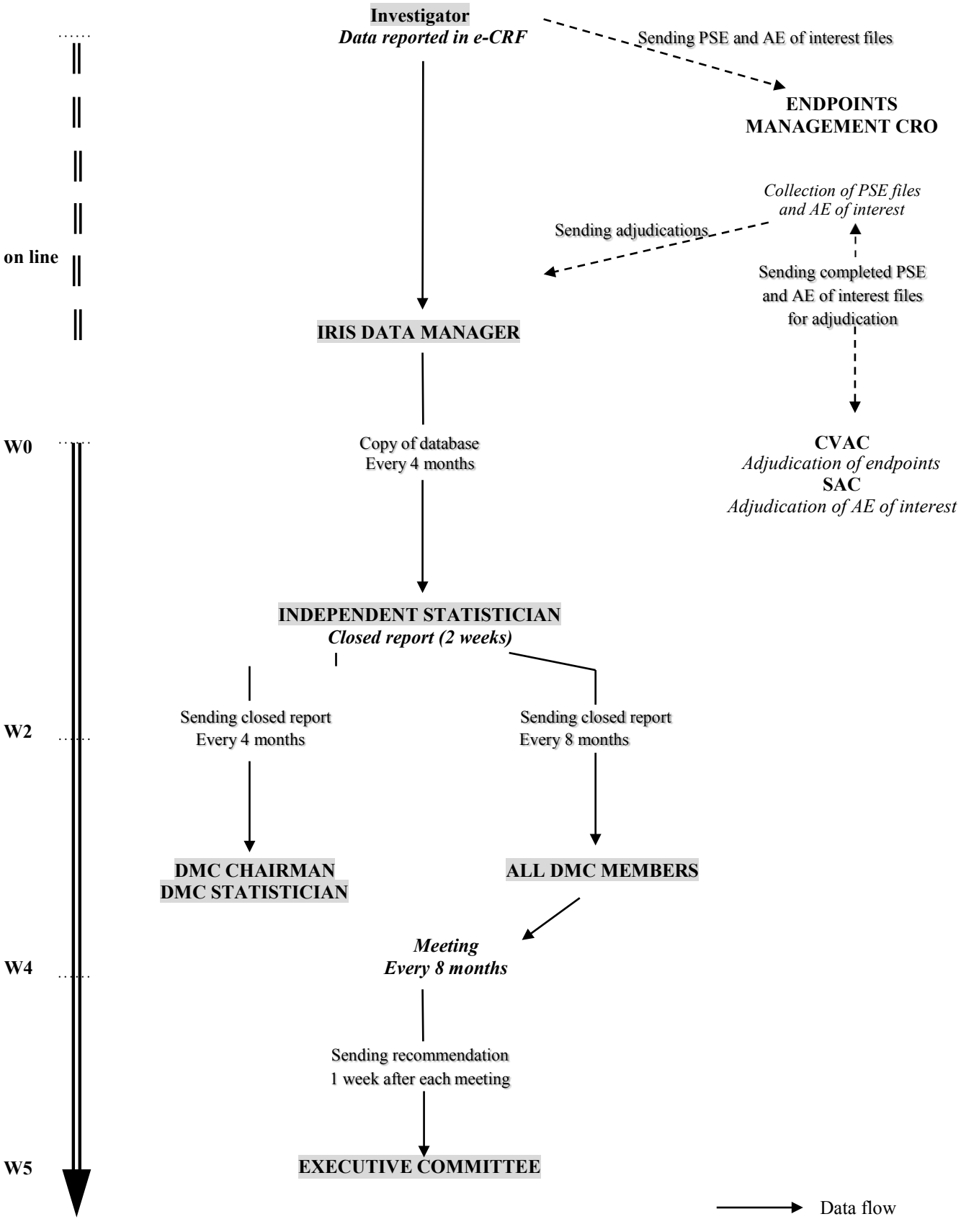
	DMC chairman	All DMC members	DMC statistician	Independent statistician	Servier structures	Timelines
PERIODIC REPORTS						
- prepare the closed reports on the basis of the programs and datasets provided by the IRIS statistician and from the decoding elements				X		
- validate the closed reports			X			
- sign the closed reports (the signed reports will be archived)			X	X		
- send the closed reports to the DMC chairman and the DMC statistician				X		every 4 months*
- send the closed reports to all DMC members at least 2 weeks before each DMC meeting				X		every 8 months*
- review the closed reports	X	X	X			
- provide the DMC with any additional information requested by the DMC members and prepare the programs to do so				X		
- destroy the reports after having reviewed them		X	X			
DMC MEETINGS						
- decide the date of meetings (planned or unplanned), set the agenda and chair the DMC meetings	X					every 8 months*
- organise the planned meetings on the request of the DMC chairman					IRIS CITP	
- organise the unplanned meetings (if any)	X					
- ensure that the DMC statistician and at least one other DMC member attend any meeting	X					
- attend and actively participate in each meeting of the DMC	X	X	X	X		
- if they cannot attend a meeting, inform the DMC chairman and pass their comments on the report to be reviewed for the meeting	NA	X	NA			
- present the results of the reports during the DMC meetings			X	X		
- participate in the open session of DMC meetings	X	X	X	X	IRIS	
DMC RECOMMENDATIONS						
- give their opinion concerning recommendations to be provided to the EC and IRIS and reach a consensus to make the recommendations	X	X	X			
- ensure that any recommendation is given according to the procedure defined in section 6	X					
- send the recommendations to the EC chairman	X					within the 7 days following a DMC meeting
- contact the EC chairman urgently in case of a recommendation to stop the study and decide with them of the next steps to be implemented	X					
- examine the DMC recommendations carefully and notify the DMC recommendations to the appropriate Authorities					IRIS	

*NA: not applicable; *: the first meeting will be held after 500 patients have been followed for 3 months*

	DMC chairman	**All DMC members**	**DMC statistician**	**Independent statistician**	**Servier structures**	**Timelines**
MINUTES OF DMC MEETINGS						
Closed session						
- prepare the minutes of closed sessions				X		
- review the minutes of closed sessions	X	X	X			
- ensure that the minutes are approved by all members	X					
- sign the minutes of closed sessions	X					
- send the final version of the minutes to all DMC members	X					
- send the open part of the minutes of closed sessions to IRIS, if any	X					
- read the open part of the minutes of closed sessions if any					IRIS	
- destroy these minutes after having reviewed them		X	X			
Open session						
- prepare the minutes of open sessions					IRIS	
- help IRIS in writing the minutes of open sessions	X					
- review the minutes of open sessions	X	X	X		IRIS	
- sign the minutes of open sessions	X					
- send the final version of the minutes of open sessions to the meeting attendees, the DMC members and the EC chairman					IRIS	
ARCHIVING						
- archive the DMC SAP and the *Modifications of the DMC planned analysis* document (signed) and specification of derived data used to prepare the reports				X		
- archive the programs and derived data used to generate the closed reports together with the validation report and associated programs and derived data used to generate the validation report				X		
- archive the signed reports				X		
- archive the signed versions of the minutes of closed and open sessions, the written recommendations and any other document used by the DMC during the study				X		
- provide a copy of the above documents to IRIS when IRIS will have broken the blind				X		
- return the decoding elements to IRIS when IRIS will have broken the blind.				X		

	DMC chairman	**All DMC members**	**DMC statistician**	**Independent statistician**	**Servier structures**	**Timelines**
OTHER						
- take any disposition to ensure and maintain the blind of study treatment and the confidentiality of decisions and documents	X	X	X	X		at any time until the blind is broken by IRIS
- provide the scientific awareness on all new findings that may influence the conduct of the study and, in this case, inform the DMC chairman / IRIS within a short time frame		X				
- maintain communication with other members of the DMC and ask them for specific expertise as judged necessary	X					
- provide the DMC members with his statistical expertise at any time during the study			X	X		
- supply the DMC chairman with adequate and sufficient information concerning the study drug development program, such as study manuscripts and international newsletters, or information following the regular signal detection performed by the Sponsor					IRIS	

Appendix 2: Data Flow and Timelines for DMC and other partners (for information only)



Appendix 3: Template for DMC Recommendation

PROTOCOL N° CL3-06790-010

DATA MONITORING COMMITTEE RECOMMENDATION

From: Prof. P-G. STEG (*DMC chairman*)

To: Prof. R. FERRARI (*Executive Committee chairman*)

DMC Meeting

Date of the meeting:

Voting members who attended the meeting:

- ❒ Prof. P-G. STEG
- ❒ Prof. J. BENICHOU
- ❒ Prof. C. RAPEZZI
- ❒ Prof. M. VOLTERRANI

Number of randomized patients:

Average follow-up:

DMC Recommendation

Following the review of accumulated safety and efficacy data of these patients (in particular cardiovascular events and adverse events of interest), the Data Monitoring Committee recommend to:

- ❒ Continue the study as per protocol
- ❒ Continue the study with the changes described hereafter
- ❒ Stop the study
- ❒ Other, please specify

Comments:

……

……

……

……

……

……

Date:

Signature: Prof. P-G. STEG

Appendix 4: IRIS Representatives & Other Persons involved

EXECUTIVE COMMITTEE		
Chairman	**Prof. R. Ferrari**	Azienda Ospedaliero-Universitaria di Ferrara Ospedale di Cona - 2/C/3° piano Via Aldo Moro 8 44124 Cona (Ferrara) Italy phone: +39 0532 239882 e-mail: fri@unife.it
INDEPENDENT STATISTICIAN		
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IRIS REPRESENTATIVES 50 rue Carnot - 92284 Suresnes Cedex / FRANCE		
Cardiovascular Innovation Therapeutic Pole		
Director of Clinical Development	**L. Feldmann**	phone: +33 1 55 72 72 29 e-mail: luc.feldmann@fr.netgrs.com
International Clinical Project Director	**C. Bourguignon**	phone: +33 1 55 72 68 40 e-mail: christian.bourguignon@fr.netgrs.com
Methodology Division		
Biostatistics Project Leader	**N. Gendrot**	phone: +33 1 55 72 36 50 e-mail: nathalie.gendrot@fr.netgrs.com
Clinical Supply Unit		
Project Leader	**G. Coquin**	phone: +33 2 38 23 84 40 e-mail: guenola.coquin@fr.netgrs.com
Data Management Department		
Data Manager	**M. Dagues de la Hellerie**	phone: +33 1 55 72 61 25 e-mail: muriel.daguesdelahellerie@fr.netgrs.com

Appendix 5: Non-Conflict of Interest Statement

<table>
<tr><td colspan="3">CERTIFICATION/DISCLOSURE OF FINANCIAL INTERESTS
AND ARRANGEMENTS OF CLINICAL INVESTIGATORS</td></tr>
<tr><td colspan="3">Please complete all of the information below. You must retain a copy of this form in your study files for at least 15 years after the end of the study.</td></tr>
<tr><td colspan="3">1. Study Title:
The Efficacy and Safety of Trimetazidine in patients with Angina pectoris having been treated by Percutaneous Coronary Intervention</td></tr>
<tr><td colspan="3">2. Protocol Number: CL3-06790-010</td></tr>
<tr><td colspan="2">3. Name:</td><td>I am participating in this study as a voting member of the Data Monitoring Committee.
(to be adapted for the independent statistician)</td></tr>
<tr><td colspan="3">5. Full Address:</td></tr>
<tr><td colspan="2">6. Telephone:</td><td>7. Fax:</td></tr>
<tr><td colspan="3">8. Indicate by marking YES or NO if you, your spouse, or your dependent children hold financial interests as described below:
YES NO
☐ ☐ Any financial arrangement in relation with the Study entered into between you and the Sponsor of the Study, whereby the compensation to you for reviewing the Study could be influenced by the outcome of the Study. If so, please attach details to this form.
☐ ☐ Any proprietary interest in the product tested in the Study, including but not limited to, property, patents, trademarks, copyrights, or licensing agreements. If so, please attach details to this form.
☐ ☐ Any significant equity interest in the Sponsor of the Study, such as ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices, or any equity interest in Servier, Inc. that exceeds € 50,000 (Euros) in aggregate. If so, please attach details (e.g., the number of stock shares and current trading price) to this form.</td></tr>
<tr><td colspan="3">I declare the information that is provided on this form is, to the best of my knowledge and belief, true, correct, and complete. Furthermore, if my financial interests and arrangements, or those of my spouse and dependent children, change from the information provided above during the course of the Study, and within 1 year after the last patient has completed this Study as specified in the protocol, I will notify Servier with specific details immediately.</td></tr>
<tr><td colspan="2">9. Signature</td><td>10. Date</td></tr>
</table>

Appendix 6: DMC Members Signature Page

I have read the Data Monitoring Committee charter for the study CL3-06790-010 sponsored by IRIS and I agree to follow the procedures set forth therein in carrying out my responsibilities as a Member of this Committee.		
Prof. P-G. STEG *(Chairman)*	Date:	Signature:
Prof. J. BENICHOU *(Statistician)*	Date:	Signature:
Prof. C. RAPEZZI	Date:	Signature:
Prof. M. VOLTERRANI	Date:	Signature:

ATPCI Statistical Analysis Plan

Document title	**STATISTICAL ANALYSIS PLAN (SAP)**
Study title	**The efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention.** **An international, multicentre, randomised, double-blind, placebo-controlled study in patients treated for 2 to 4 years.**
Test drug code	**S 06790 (Trimetazidine MR 35 mg)**
Indication	**Angina pectoris**
Development phase	**Phase III**
Protocol code	**CL3-06790-010 (ATPCI study)**
EudraCT Number	**2010-022134-89**
Universal Trial Number	**Not applicable**
Sponsor	**I.R.I.S.**
Date of the document	**05/05/2020**
Version of the document	**Final Version V1.0**
	CONFIDENTIAL

Signatories

Prepared by:	Signature	Date
Flavie SIMON Biostatistician I.R.I.S. - FRANCE		
Approved by:	Signature	Date
Anne CORREGES Biostatistics Project Manager I.R.I.S. - FRANCE		
Jean-Pascal CHALLETON Senior Clinical Development Leader I.R.I.S. - FRANCE		

Due to the worldwide situation linked to COVID-19 at the time of finalisation of this document, an approval of the document will be done by email instead of paper signatures. Paper signatures will be collected as soon as the situation has stabilised.

Follow up of versions

Version	Release date (dd/mm/yyyy)	Key modifications (*)	Impact
V1.0	05/05/2020	The analysis of the major secondary endpoint in the SAP (defined in agreement with section 4.1.2.1 of the protocol) is detailed. Namely, a two-sided p-value is provided for the major secondary endpoint in case the primary analysis is statistically significant (applying a gatekeeping procedure).	No impact (precision from the protocol). Of note that the consideration of this endpoint as a major secondary endpoint does not trigger any inflation of the alpha risk thanks to the use of a gatekeeping procedure (Guideline on multiplicity issues in clinical trials, 2016).
		Endpoints referred to as "Components of the primary endpoint" in the protocol are considered on the same level as the other secondary endpoints in the SAP.	No impact (precision from the protocol).
		In agreement with Executive Committee, additional analyses sets are defined in the SAP (Efficacy Analysis Set and Safety Analysis Set) to exclude patients with a potential unblinding due to a technical error from the main efficacy and safety analyses.	No impact as: For primary composite and major secondary endpoint, supplementary analyses including the patients excluded will be carried out to ensure the robustness of results. The safety data of the patients excluded will be listed separately. For randomisation, no imbalance between groups expected due to the few number of patients excluded.
		The change from baseline planned in the protocol for all other efficacy endpoints is defined in the SAP only for the endpoints for which a baseline is available (*i.e.* Number of antianginal drugs taken by the patient, EuroQoL-5D-3L Questionnaire). When available, difference between groups in the changes from baseline are assessed using 95% confidence intervals (no p-value of superiority tests).	No impact (adaptation of the analysis to collected data and importance of the criteria).
		Only a listing is presented on level of cardiac troponin due to the few data available.	No impact (adaptation of the analysis to available data).
		For each type of emergent adverse events, the period of analysis is specified.	No impact (precision from the protocol).
		The incidence of Serious Treatment Emergent Adverse Events (serious TEAE) occurring during the treatment period is defined as the primary safety endpoint in agreement with section 4.1.1.2 of the protocol and the associated analysis is specified: 95% confidence interval is provided to assess the magnitude of the effect.	No impact (precision from the protocol).

(*) Main changes as compared to the statistical analyses planned in the protocol for the first SAP signed version (1.0). Main changes from the previous signed version for the other SAP signed version(s)

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List of abbreviations

%	:	percentage
AE	:	Adverse Event
ALAT	:	ALanine AminoTransferase
aPTT	:	activated Partial Thromboplastin Time
ASAT	:	ASpartate AminoTransferase
ATC	:	Anatomical Therapeutic Chemical
b.i.d.	:	bis in die (twice a day)
BMI	:	Body Mass Index
bpm	:	beats per minute (heart rate unit)
CCS	:	Canadian Cardiovascular Society
CI	:	Confidence Interval
DBP	:	Diastolic Blood Pressure
E	:	Estimate
EAE	:	Emergent Adverse Event
EI	:	Event of Interrest
ES_{ana}	:	Efficacy Analysis Set
eCrCl	:	Estimated Creatinine Clearance
eCRF	:	Electronic Case Report Form
eGFR	:	Estimated Glomerular Filtration Rate
HR	:	Hazard Ratio
IHD	:	Ischaemic Heart Disease
INR	:	International Normalized Ratio
IMP	:	Investigational Medicinal Product
IWRS	:	Interactive Web Response System
LVEF	:	Left Ventricular Ejection Fraction
MAR	:	Missing at Random
MCMC	:	Markov chain Monte Carlo
MI	:	Multiple Imputation
mmHg	:	millimetre of mercury
o.d.	:	omni die (once a day)
OR	:	Odd Ratio
PBO	:	Placebo
PCE	:	Primary Composite Endpoint
PCI	:	Percutaneous Coronary Intervention
PCSA	:	Potentially Clinically Significant Abnormal
PR	:	Prothrombin ratio
PT	:	Preferred Term
RS	:	Randomised Set
SAQ	:	Seatle Angina Questionnaire
SBP	:	Systolic Blood Pressure
SE	:	Standard Error
SOC	:	System Organ Class
SS	:	Safety Set
SS_{ana}	:	Safety Analysis Set
TEAE	:	Treatment Emergent Adverse Event
TLG	:	Tables, Listings and Graphs
TMZ	:	Trimetazidine

1. INTRODUCTION

This Statistical Analysis Plan details the planned analyses to be performed, in accordance with the main characteristics of the amended study protocol.

The templates for Tables, Listings and Graphs (TLG) are described in a separate document.

1.1. Study objectives

The purpose of this study is 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).

Primary objectives: 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.

Secondary objectives: to evaluate the effect of trimetazidine on the other efficacy endpoints as well as the other safety parameters, clinical and biological.

1.2. Study design

The study CL3-06790-010 is a phase III, international, multicentre, double-blind, placebo-controlled study randomised in 2 parallel and balanced arms (trimetazidine 35 mg b.i.d.* and placebo) on top of post-PCI recommended treatment for Ischaemic Heart Disease (IHD), both secondary prevention and regular antianginal therapies as per current guidelines.
Note: *o.d. for patients with moderate renal failure.

1.2.1. Study plan

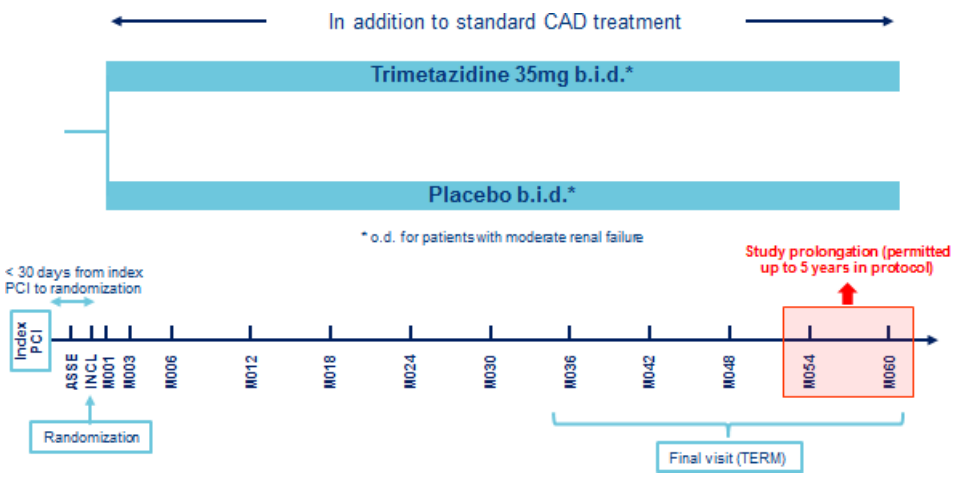
The study is divided into the following periods:

- At selection (ASSE): Selection of patients as soon as possible after PCI (during the hospitalisation for the PCI, or shortly after discharge); of note, this PCI is called index PCI.
- At inclusion: Inclusion of patients as soon as their antianginal treatment, if any, is stable (no later than 30 days following the index PCI procedure). Patients are then randomised in double-blind conditions to one of the two treatment groups: trimetazidine or placebo.
- Double-blind period: from 3 to 5 years (of note, the study duration was increased from 4 to 5 years in order to reach the number of events required, as was allowed by the initial study protocol).

Investigational Medicinal Products (IMPs) are supplied as one tablet swallowed twice daily (once daily for patients with moderate renal failure), at mealtimes in the morning and evening. The first dose of IMP intake takes place on the day after the inclusion visit in the morning at mealtime and then the second dose takes place in the evening at mealtime.

The study plan is shown in Figure (1.2.1) 1.

Figure (1.2.1) 1 - Study plan



Visits M054 and M060 were added after study prolongation

1.2.2. Type of randomisation

The characteristics of the randomisation are:

- Centralised using an Interactive Web Response System (IWRS) procedure,
- Balanced between the two treatment groups (trimetazidine and placebo), using permuted blocks,
- Non-adaptive,
- Stratified on country and nature of index PCI (elective or urgent).

1.3. Determination of sample size

According to the protocol, the sample size calculation was based on the primary efficacy endpoint. For 85% power and 5% type I error rate (2-sided), 1 363 events were necessary to show a treatment effect of trimetazidine of 15% relative risk reduction compared to placebo. Assuming an annual incidence rate of the primary efficacy endpoint of 10% in the placebo group, a mean follow-up duration of 3 years (2 to 4 years) and an annual withdrawal rate (non-cardiac deaths and consent withdrawals) of 2% in all groups, 5 800 patients were required. Of note that, the hypotheses above led to an expected annual incidence rate for the primary efficacy endpoint of 9.28%.

The protocol planned that if, during the study, it was estimated that the number of events required for the primary efficacy endpoint was not reached at the scheduled end of study, the sample size and/or the duration of follow-up (up to 5 years) would be adjusted in order to maintain the power. In that respect, blinded estimates of the annual incidence rate for the primary efficacy endpoint were routinely run (no inflation of type I error expected (Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry, 2019)). After the end of the recruitment period, the blinded estimate of the primary efficacy endpoint annual incidence rate was lower than expected (*i.e.* < 9.28% / year). At this time of the study, only an increase of the duration of follow-up was possible because the recruitment had already been stopped. Therefore, a method to predict the end of the study based on blinded observed results was set up (from simulations based on a Bayesian model). According to those predictions, the study was prolonged up to 5 years, as permitted by the protocol.

2. ANALYSIS SETS / TREATMENT GROUPS

2.1. Analysis sets

- **Randomised Set** (RS):

All included patients with a randomization number allocated.

- **Efficacy Analysis Set** (ES_{ana}):

All patients of the Randomised Set, except patients with a potential unblinding due to a technical error.

- **Safety Set** (SS):

All patients having taken at least one dose of IMP.

- **Safety Analysis Set** (SS_{ana}):

All patients of the Safety Set, except patients with a potential unblinding due to a technical error.

- **Subgroup:**

Nature of PCI procedure before selection (*i.e.* index PCI): elective or urgent index PCI, according to investigator's opinion.

The size of each analysis set and sub-group will be described. Reasons for exclusion of each analysis set will also be described. Moreover, listing of patients in each analysis set and subgroup as well as listing of patients of RS (resp. SS) excluded from ES_{ana} (resp. SS_{ana}) with reasons for exclusion will be provided.

2.2. Treatment groups

Treatment groups considered are:

- Trimetazidine,
- Placebo.

The treatment group considered for all analyses (disposition and baseline characteristics, efficacy and safety) will be the randomised treatment (*i.e.* allocated by the IWRS). Indeed, only few patients may have received at inclusion a treatment different from the randomised treatment. In case of patients having received the study treatment without randomisation, they will be counted in the treatment group corresponding to the therapeutic unit received at inclusion.

Main safety and IMP administration data of patients with erroneous treatment intake at inclusion or treatment switch after inclusion will be listed.

3. STATISTICAL METHODS

3.1. General considerations

Details concerning definitions of derived variables are provided in a separate document (see "Specifications associated to the statistical analysis plan").

3.1.1. Descriptive statistics

For **qualitative data**, number of observed values, number and percentage of patients per class will be presented. Unless otherwise specified in the TLG, no class "Missing" is considered.

For **quantitative data**, number of observed values, mean, standard deviation, median, first and third quartiles, minimum and maximum will be presented.

For **events**: number of patients having experienced the event (n), number of events that occurred and number of patients at risk for the event (N) will be presented. Moreover, the patients-years at risk for the event (NPY) as well as the crude and annual incidence rates may be also provided. They will be calculated as follows:

- NPY = sum of patient exposure time in years (*i.e.* for efficacy analyses: time to first event or, if no event, time to censor; for safety analyses: to be consistent with the whole regulatory dossier (*Risk Management Plan Version 1.0)*, time to censor).
- Crude incidence rate (*i.e.* percentage): % = 100 x (n / N).
- Annual incidence rate (*i.e.* exposure-adjusted incidence rate): npy = 100 x (n / NPY). Of note that the annual incidence rate is interpreted as the number of events occurring per 100 patients-years.

3.1.2. General definitions

Unless specified otherwise in sections 3.2 to 3.6, the following definitions will be considered:

- **Analysable value** will be defined as any non-missing value.
- **Baseline value** will be defined as the last analysable value (among selection/inclusion) prior to the first IMP intake (*i.e.* before or the same day as the first IMP intake date).
  Note: In case of patient included and/or randomised but not treated (*i.e.* patients with treatment duration equal to 0): value at baseline is defined as the last analysable value prior or equal to date of inclusion visit.
- **Post-baseline value** will be defined as any value recorded at a given timepoint after baseline.
- **The last post baseline value** will be defined as the last non-missing value after baseline.
- **Change from baseline** will be defined as the arithmetic difference between a post-baseline value and the baseline value for a given variable at a given time point.
- A value is considered as occurring **during the treatment period** if the assessment date (after selection/inclusion) is between the first IMP intake date (included) and last IMP intake date + 2 days (included).
- **End of study date:** minimum date between: date of death (from adjudication), date of premature withdrawal, date of study completion.
- **End of theoretical termination period** corresponds to the 30th November 2019.

3.2. Disposition and baseline characteristics

Disposition of patients and baseline characteristics will be described by randomised treatment group, to assess their comparability, and overall.

3.2.1. Disposition of patients

Disposition of patients, including reasons for study/IMP premature discontinuation, will be summarized during the study, overall and by visit, in the RS and ES_{ana} as well as in the patients of the ES_{ana} with elective (resp. urgent) index PCI. Moreover, the vital status of patients with study premature discontinuation for non-medical reason will be described in the same analysis sets.

In order to assess the drop-out pattern between the treatment groups, the time to study/IMP premature discontinuation will be described, in the RS and ES_{ana}, using a Kaplan-Meier analysis.

The disposition of patients by country will also be presented, in the RS.

3.2.2. Protocol deviations

Protocol deviations before or at inclusion, as well as after inclusion, will be described in the RS and the ES_{ana}, by category of deviations (based on ICH E3 guideline and ICH E3 Q&A).

3.2.3. Demographic data and other baseline characteristics

Demographic data and other baseline characteristics will be described in the RS and the ES_{ana} as well as in the patients of the ES_{ana} with elective (resp. urgent) index PCI.

Demographic data and other baseline characteristics such as life habits, additional information on IHD, time between index PCI and randomisation as well as vital signs and clinical examination will be described.
The following continuous data will be described in classes:

- Age: < 55, [55 ; 60[, [60 ; 65[, [65 ; 70[, [70 ; 75[, [75 ; 80[and ≥ 80 years old,
- Disease duration: < 0.25, [0.25 ; 1[, [1 ; 5[, [5 ; 10[and ≥ 10 years,
- Supine systolic blood pressure (SBP): < 140 and ≥ 140 mmHg,
- Supine diastolic blood pressure (DBP): < 90 and ≥ 90 mmHg,
- Blood Pressure Control (yes / no): supine SBP < 140 mmHg and supine DBP < 90 mmHg,
- Supine heart rate: < 70 and ≥ 70 bpm
- BMI: < 18.5, [18.5 ; 25[, [25 ; 30[and ≥ 30 kg/m²,
- LVEF: < 40, [40 ; 50[and ≥ 50%,
- Time between index PCI and randomisation: ≤ 7,]7 ; 14] and > 14 days,
- Estimated creatinine clearance (eCrCl) or estimated Glomerular Filtration Rate (eGFR) (gathered): < 30, [30 ; 60[, [60 ; 90[and ≥ 90 mL/min or mL/min/1.73m².

Moreover, all previous treatments taken within the month before the index PCI will be described by ATC code and preferred name, as well as all medical history and surgical or medical procedures history (specific and non-specific), by primary System Organ Class (SOC) and Preferred Term (PT).

3.3. Treatments of patients

3.3.1. Extent of exposure and treatment compliance

Extent of exposure and treatment compliance (%) will be described by treatment group in the RS, the ES_{ana}, the SS and the SS_{ana} as well as in the patients of the ES_{ana} with elective (resp. urgent) index PCI. The following endpoints will be described:

- **Follow-up duration** and **treatment duration** (months): quantitative and by class (≤ 1 month,]1 ; 6],]6 ; 12];]12 ; 18],]18 ; 24],]24 ; 30],]30 ; 36],]36 ; 42],]42 ; 48],]48 ; 54] and > 54 months as well as cumulative classes),
- **Compliance** (%): quantitative and by class (< 70%, [70 ; 130] , > 130%).

3.3.2. Concomitant treatments

All concomitant treatments (specific and non-specific) ongoing at inclusion, ongoing or stopped the day of inclusion, and after inclusion will be described in the RS and ES_{ana} as well as in the patients of the ES_{ana} with elective (resp. urgent) index PCI, by ATC code and preferred name.

3.4. Efficacy analysis

All efficacy analyses will be performed in the ES_{ana}. The randomised treatment will be considered for all analyses.

General definitions are provided in section 3.1.2.

3.4.1. Statistical hypotheses

Let $HR_{TMZ/Pbo}$ be the Hazard Ratio for trimetazidine versus placebo associated to the primary efficacy endpoint, the hypotheses to be tested are:

- H_0: $HR_{TMZ/Pbo}=1$ (The risk of having the endpoint is equal between the treatment groups),
- H_1: $HR_{TMZ/Pbo}\neq 1$ (The risk of having the endpoint is different between the treatment groups).

The type I error of the statistical tests will be set at 5% (2-sided test).

The null and alternative hypotheses for the secondary endpoints are the same as for the primary efficacy endpoint.

3.4.2. Primary efficacy endpoint

3.4.2.1. Primary analysis

Definitions:

- The **Primary Composite Endpoint** (PCE) is defined as the time to first event among:
  - Cardiac death (cardiac death and death from unknown cause),
  - Hospitalisation for a cardiac event (hospitalisation for acute myocardial infarction (MI), unstable angina (UA), heart failure, sustained ventricular tachycardia, resuscitated cardiac arrest or angina and/or ischemia 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 ischemia),
  - Recurrent or persistent angina leading to performing a coronary angiography (angina alone or with documented ischemia).
- **Events contributing to the primary efficacy analysis**: all first events positively adjudicated and occurring during the **efficacy time-window**, *i.e.* after the randomisation date (included) and:
  - before the end of study date of the patient (included) if this date is before the end of theoretical termination period,
  - else, before the end of theoretical termination period (included).

  If no event is observed in the efficacy time-window described above, the data will be censored at the end of this efficacy time-window.
- Follow-up duration for efficacy analyses (days) is defined as event onset date or censoring date - Randomisation date + 1. This duration will be also calculated in months dividing by 30.44 and in years dividing by 365.25.

Primary analysis:

The superiority of trimetazidine as compared to placebo will be tested on the PCE using a Cox's proportional hazards model (Collet, 1994) adjusted on treatment group as well as on the baseline covariates country and nature of index PCI (Guideline on adjustment for baseline covariates in clinical trials, 2015).

The assumptions underlying the model such as hazards proportionality in covariates will be checked.

Censorship handling: A non-informative censoring process will be considered.

Multiplicity issues: No adjustment for multiplicity is required for a single primary endpoint (Guideline on multiplicity issues in clinical trials, 2016).

Statistical elements:

The following elements will be provided in a summary table:

- Estimate of the treatment effect: Estimate (E) of the Hazard Ratio ($HR_{TMZ/PBO}$) between treatment groups; it should be noted that $E < 1$ will be in favour of trimetazidine, Standard Error (SE) of the log of the estimate, two-sided 95% confidence interval (CI) of the estimate and two-sided p-value (to be compared to 0.05).
- Descriptive analysis by treatment group (see section 3.1.1).

Moreover, a plot of Kaplan-Meier curves will be performed by treatment group. The number of patients at risk, the cumulative number of events and the cumulative frequency (calculated from the survival estimated by Kaplan-Meier) by treatment group at specific timepoints every 6 months will also be provided.

3.4.2.2. Sensitivity analyses

The following sensitivity analyses will be conducted to assess the robustness of the statistical model used for primary analysis:

- Cox's proportional hazards model only adjusted on treatment group,
- If proportional hazards assumption is not verified for the treatment group: logrank test on the treatment groups,
- If proportional hazards assumption is not verified for the country: Cox's proportional hazards model adjusted on the treatment group and the nature of index PCI, and stratified on the country,
- If proportional hazards assumption is not verified for the nature of index PCI: Cox's proportional hazards model adjusted on the treatment group and the country, and stratified on the nature of index PCI.

The same statistical elements to estimate the treatment effect as for primary analysis will be provided.

If necessary, sensitivity analyses other than those planned in the SAP could be carried out, in the framework of the validation of the assumptions underlying the model.

3.4.2.3. Supplementary analyses

Those analyses are conducted to provide additional insights into the understanding of the treatment effect assessed with the primary analysis and will be thus of descriptive nature. In that context, there is no multiplicity concern and no p-value will be provided.

The primary analysis will be repeated for the PCE in the RS.

Moreover, descriptive analysis of the components within the PCE will be performed by treatment group in the ES_{ana}. It should be noted that the sum of the first events within each component of the PCE will equal the total number of events of the PCE. A hierarchical rule is defined in section 3.3.1.4 of "Specifications associated to the statistical analysis plan" for events occurring the same day. The patients-years at risk for the PCE will be considered for the description of the components.

Details of hospitalisations for cardiac events will also be provided. No hierarchical rule is defined for hospitalisations for cardiac events, so that the sum of the sub-categories may exceed the total number of hospitalisations for cardiac events counted in the PCE. The patients-years at risk for the hospitalisations for cardiac events belonging to the PCE will be considered for the description of the hospitalisations.

3.4.3. Secondary efficacy endpoints

3.4.3.1. Major secondary endpoint

Definition:

- The **major secondary composite endpoint** is defined as the time to first event among:
  - Cardiac death (cardiac death and death from unknown cause),
  - Hospitalisation for a cardiac event (hospitalisation for acute myocardial infarction, unstable angina, heart failure, sustained ventricular tachycardia, resuscitated cardiac arrest or angina and/or ischemia 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 ischemia),
  - Recurrent or persistent angina leading to performing a coronary angiography (angina alone or with documented ischemia).
  - Evidence of ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
  - Evidence of ischemia (documented by Stress Imaging) leading to performing a coronary angiography.
- **Events contributing to the main analysis**: same definition as for the PCE.

Analysis:

The superiority of trimetazidine as compared to placebo will be tested on the major secondary composite endpoint using the same model as for the primary analysis of the PCE.

Censorship handling: Same as for the primary analysis of the PCE.

Multiplicity issues: Positive result on the major secondary endpoint can be interpreted only if the primary objective has been achieved (hierarchical procedure) (Guideline on multiplicity issues in clinical trials, 2016).

Statistical elements: Same as for the primary analysis of the PCE. The p-value will be provided if superiority of trimetazidine over placebo is demonstrated on the PCE.

The same sensitivity and supplementary analyses as for the PCE will be performed.

3.4.3.2. Other secondary endpoints

3.4.3.2.1. First events

Definitions:

- The following secondary endpoints will be expressed in terms of time to first event:
  - 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 ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
  - Evidence of ischemia (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 UA, hospitalisation for angina (other than MI or UA) 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 revascularization,
  - Repeat coronary revascularization in response to angina.

Note: for cardiac death and hospitalisation for a cardiac event, see definition in section 3.4.2.1.

- **Events contributing to the analysis**: same definition as for the PCE.

Analysis:

The effect of trimetazidine compared with placebo will be assessed using the same model as for the primary analysis of the PCE.

Censorship handling: Same as for the PCE

Multiplicity issues: These analyses are provided for descriptive purposes and there will be no adjustment for multiplicity.

Statistical elements: The same statistical elements as for the primary analysis of the PCE will be provided, except the p-value. The two-sided 95% confidence interval (CI) of the estimate will be given to assess the magnitude of the treatment effect.

3.4.3.2.2. Recurrent events

Definitions:

- Recurrent events analysed: the recurrence of each component of the PCE, of each component of the major secondary composite endpoint as well as of each other secondary endpoint, except endpoints including death.
- Events contributing to the analysis: all events (first or not) occurring in the efficacy time-window (see section 3.4.2.1 for definition).
- Classes of recurrence: none, 1, 2, 3, 4, ≥ 5 events.

Analysis: A descriptive analysis will be performed by treatment group (endpoint expressed as quantitative and by class).

3.4.4. Other efficacy endpoints

3.4.4.1. CCS classification of angina severity

Descriptive analysis will be provided by treatment group at each visit and at the last visit. Of note, the pre-IMP value is measured before index PCI and will not be considered as a baseline for IMP.

3.4.4.2. Number of angina episodes per week

Descriptive analysis (quantitative and by class: 0,]0-7], > 7 attacks per week) will be provided by treatment group at each visit and at the last visit. Of note, there is no baseline for this endpoint.

3.4.4.3. Short acting nitrates consumption per week

Descriptive analysis (quantitative and by class: 0,]0-7], > 7 short acting nitrates per week) will be provided by treatment group at each visit and at the last visit. Of note, there is no baseline for this endpoint.

3.4.4.4. Number of antianginal drugs

Definition: Any (evidence-based) antianginal drug identified in concomitant treatments and ongoing at inclusion for the analysis at baseline, or the day before a visit for the post-baseline analyses, is considered. Trimetazidine taken as IMP will not count as one antianginal drug but open-label trimetazidine taken as concomitant treatment will count as one antianginal drug (whatever the treatment group).

The antianginal drugs (evidence-based therapies) will be classified in seven categories:

- Beta-blockers,
- Long-acting nitrates and molsidomine,
- Calcium Channel Blockers (CCB) (dihydropyridine derivatives),
- Calcium Channel Blockers (CCB) (Heart-rate-lowering CCB),
- Trimetazidine, ranolazine and perhexiline,
- Nicorandil,
- Ivabradine.

The number of antianginal drugs is defined as the number of categories of treatment taken by a patient, ranging from 0 to 7.

Analysis: Descriptive analysis will be provided by treatment group, at baseline, at each post-baseline visit and at the last post-baseline visit as well as change from baseline to each post-baseline visit and last post-baseline visit. A shift table between value at baseline and value at the M012 visit will also be presented by treatement group. Moreover, the effect of trimetazidine on the number of antianginal drugs at M012 as compared to placebo will be assessed using an ordinal logistic regression analysis adjusted on treatment group and baseline number of antianginal drugs (see appendix 5.2.4).

Statistical elements:

- Estimate of the treatment effect: Estimate (E) of the odds ratio between treatment groups ($OR_{TMZ/PBO}$) on the number of antianginal drugs at M012; it should be noted that E > 1 will be in favour of trimetazidine, standard error (SE) of the log of the estimate, two-sided 95% confidence interval (CI) of the estimate.
- Descriptive analysis by treatment group (see section 3.1.1).

3.4.4.5. Seattle Angina Questionnaire

Definition: The Seattle Angina Questionnaire (SAQ) will be analysed according to the 5 following dimensions: physical limitation, anginal stability, anginal frequency, treatment satisfaction and disease perception.

Analysis:

- The SAQ has been already validated (John A Spertus *et al*, 1994; John A Spertus *et al*, 1995). The psychometric properties will be checked separately.
- Descriptive analysis will be provided by treatment group, at each post-baseline visit for each SAQ dimension.

3.4.4.6. EuroQoL- 5D-3L Questionnaire

Definition: The EuroQoL – 5D-3L questionnaire (EQ-5D) will be analysed according to the descriptive system composed of 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and the Visual Analog Scale (VAS). The EQ-5D index score, a single score based on the descriptive system, will also be analysed.

Analysis:

- The EuroQoL – 5D-3L questionnaire has been already validated (Matthew TD Dyer *et al*, 2010). The psychometric properties will be checked separately.
- Descriptive analysis will be provided by treatment group, at baseline, at each post-baseline visit for each EQ-5D dimension as well as change from baseline to each post-baseline visit for EQ-5D index score and EQ-5D Visual Analog Scale.
  The effect of trimetazidine as compared to placebo will be assessed on the change from baseline to M012 of EQ-5D index score (resp. EQ-5D VAS) using an ANalysis of COVAriance (ANCOVA) model adjusted on treatment group and baseline. This analysis will be restricted on patients having a baseline EQ-5D index score (resp. EQ-5D VAS) and at least one post-baseline EQ-5D index score (resp. EQ-5D VAS).

Missing data handling:
In case of missing EQ-5D index score (resp. EQ-5D VAS) at M012, the following imputation rules will be applied (for ANCOVA model only):

- In case of death, the EQ-5D index score (resp. EQ-5D VAS) will be set to 0 for all visits following the death,
- Otherwise, the EQ-5D index score (resp. EQ-5D VAS) will be imputed using the multiple imputation approach (MI) considering a monotone missing pattern (see appendix 5.2.5).

Statistical elements:

- Estimate of the treatment effect:
  - Estimate (E) of the difference between treatment groups of the change from baseline to M012,
  - Standard error (SE) of the estimate,
  - Two-sided 95% confidence interval (CI) of the estimate.
- Descriptive analysis by treatment group (see section 3.1.1).

3.4.4.7. Cardiac troponin

Definition: For each post-baseline elective PCI, cardiac troponin will be considered as **analysable** if there is:

- a non-missing result of troponin I before and after PCI,
- or a non-missing result of troponin T before and after PCI.

Analysis: Considering the few number of data available, only a listing of analysable cardiac troponin results will be provided.

3.4.5. Subgroup analysis

The analysis of primary and secondary efficacy endpoints will be run in the patients of the ES_{ana} with elective (resp. urgent) index PCI.

The effect of trimetazidine compared with placebo will be assessed using the same model as for the primary analysis of the PCE.

Censorship handling: Same as for the PCE.

Multiplicity issues: These analyses are provided for descriptive purposes and there will be no adjustment for multiplicity.

Statistical elements: The same statistical elements as for the primary analysis of the PCE will be provided, except the p-value. The two-sided 95% confidence interval (CI) of the estimate will be given to assess the magnitude of the treatment effect.

3.5. Exploratory analysis

Not applicable.

3.6. Safety analysis

All safety analyses will be performed in the SS_{ana} by treatment group. Moreover, safety data of patients of the SS excluded from SS_{ana} will be listed separately.

3.6.1. Primary safety endpoint: serious adverse events

Definition:

- The primary safety endpoint is the incidence of **Serious Treatment Emergent Adverse Events** (serious TEAE) according to the investigator or sponsor opinion occurring during the treatment period (see section 3.6.2.1 for the definition).
- **Events contributing to the primary safety analysis**: all first events (*i.e.* serious TEAE) occurring during the treatment period.

Analysis:

The difference between trimetazidine and placebo will be assessed on the annual incidence rate during the treatment period and the associated confidence interval will be calculated using a normal approximation (see Liu GF *et al* (2006) and appendix 5.2.6).

Multiplicity issues: This analysis is provided for descriptive purposes and there will be no adjustment for multiplicity.

Statistical elements:

The following elements will be provided in a summary table:

- Estimate of the difference between groups: Estimate (E) of the difference between treatment groups (TMZ-PBO), Standard Error (SE) of the estimate and two-sided 95% confidence interval (CI) of the estimate.
- Descriptive analysis by treatment group: number of serious TEAE as well as number, percentage and annual incidence rate of patients experiencing at least one serious TEAE.

3.6.2. Adverse events

3.6.2.1. Emergent Adverse Events

Definition:

- **Emergent Adverse Events** (EAE) (*i.e.* emergent during the study) are defined as all adverse events:
  - which occur from the first IMP intake date (included),

or

  - which occur before the first IMP intake date and which worsen (in terms of intensity) or become serious according to the investigator's opinion from the first IMP intake date (included).

  Of note, in case of multiple information for the same event before the first IMP intake date, the information nearest to the first IMP intake date is taken into account.

- **Treatment Emergent Adverse Events** (TEAE) (*i.e.* emergent during the treatment period) are defined as all adverse events:
  - which occur between the first IMP intake date (included) and the last IMP intake date + 2 days (included),

or

  - which occur before the first IMP intake date and which worsen (in terms of intensity) or become serious according to the investigator opinion between the first IMP intake date (included) and the last IMP intake date + 2 days (included).

  Of note, in case of multiple information for the same event before the first IMP intake date, the information nearest to the first IMP intake date is taken into account.

- The **seriousness** and the **relationship with the IMP** of the adverse event are based on investigator opinion and sponsor decision to upgrade seriousness and/or relation to IMP (see TLG for details).

Analysis:

Number of events as well as number, percentage and annual incidence rate of patients experiencing at least one event, presented by primary SOC and/or PT (depending on the analysis), will be provided for:

- TEAE, TEAE leading to IMP withdrawal, TEAE requiring new treatment or increase of on-going treatment, TEAE requiring surgical or medical procedure, TEAE related to IMP, serious TEAE, severe TEAE, non-serious TEAEduring the treatment period.
- EAE, serious EAE, EAE related to IMP during the study.

TEAE will be 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.

3.6.2.2. Adverse Events of Interest

Definition:

Adverse Events of Interest (AEI), according to adjudicator's opinion (resp. to investigator's opinion by selection of specific MedDRA codes) during the treatment period (see section 3.6.2.1 for the definition):

- Neurological symptoms*,
- Coagulation disorders and/or non-traumatic haemorrhages**,
- Trombocytopenia,
- Agranulocytosis,
- Falls,
- Arterial hypotension***,
- Serious skin disorders,
- Hepatic disorders.

Note: For AEI according to adjudicator's opinion the following sub-categories will be also defined: * = Parkinson's syndrome, disorientation, hallucination, convulsion, ** = major bleedings (*i.e.* grade 2), coagulation disorders, *** = hypotension (supine position), orthostatic hypotension.

Analysis:

Analyses according to adjudicator's opinion:

- Estimate of the difference between groups and descriptive analysis: same analysis as primary safety endpoint (see section 3.6.1) for each AEI. Note: for the difference between treatment groups, if the annual incidence rate is below a pre-defined threshold in each group*, only the estimate (E) will be provided.
  * Threshold = npy ≤ 0.001 in one group and ≤ 0.025 in the other group (see appendix 5.2.6).
- Descriptive analysis of AEI adjudication forms will be provided.

Analyses according to investigator's opinion:

- Descriptive analysis by treatment group: Number of events, as well as number, percentage and annual incidence rate of patients experiencing at least one event, presented by primary SOC and PT will be provided for each AEI.

3.6.3. Events of Interest not reported as Adverse Events

Definition:

Events of Interest (EI) not reported as Adverse Events according to adjudicator's opinion during the treatment period (see section 3.6.2.1 for the definition of EAE):

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

Those EI not reported as Adverse Events have been detected through post-baseline biological/clinical values reported in the eCRF and then adjudicated.

Analysis:

- Estimate of the difference between groups and descriptive analysis: same analysis as AEI according to adjudicator's opinion (see section 3.6.2.2). EI reported as AE and not reported as AE are cumulated for this analysis.
- Descriptive analysis of EI adjudication forms will be provided. Note: Several causes, diagnoses and outcomes can be counted by patient. For others items, the worst modality will be considered.

3.6.4. Clinical laboratory evaluation

Definition:

- A laboratory value is considered as **analysable** if non-missing and not flagged in the ClinTrial database as "not analysable". In addition, fasting blood level of glucose value is considered as analysable if the patient is in fasting state.
  Note: Values flagged in the ClinTrial database as "not analysable" (depending on fasting state, specimen condition, etc.) are identified by the sponsor before breaking the blind.

- **Haematology parameters**:
  - Haemoglobin,
  - Haematocrit,
  - Red blood cell,
  - White blood cell,
  - Neutrophils,
  - Eosinophils,
  - Basophils,
  - Lymphocytes,
  - Monocytes
  - Platelet counts.
- **Biochemical parameters (fasting condition)**:
  - Sodium,
  - Potassium,
  - Creatinine,
  - ALanine AminoTransferase (ALAT),
  - ASpartate AminoTransferase (ASAT),
  - Fasting blood level of glucose,
  - Total cholesterol,
  - HDL-cholesterol,
  - LDL-cholesterol,
  - Triglycerides,
  - International Normalized Ratio (INR) or Prothrombin ratio (PR) or Prothrombin Time (PT),
    Note: If at a given visit a patient has an analysable value for several parameters (*e.g.* INR and PT), his/her value will be considered in the analysis of each parameter.
  - activated Partial Thromboplastin Time (aPTT),
  - activated Partial Thromboplastin ratio,
  - estimated Creatinine Clearance (eCrCl) or estimated Glomerular Filtration Rate (eGFR).

Analysis:

For each haematological parameter, descriptive statistics on value at baseline, on value at each post-baseline visit under treatment, on last post-baseline value under treatment and on change from baseline to each post-baseline visit under treatment and to last post-baseline value under treatment will be provided. Of note that, for those analyses, in case of multiple samples for a same visit, only the first analysable will be taken into account.

For each biochemical and haematological parameter, the following analyses will be performed:

- Number and percentage of patients with at least one high/low emergent abnormal value under treatment, according to the laboratory reference ranges and to the cut-offs for Potentially Clinically Significant Abnormal (PCSA) values.
- Laboratory parameters classified (number and percentage of patients in each class) according to these reference ranges and cut-offs, and using shift tables from baseline to the worst (high and/or low) values under treatment.

Moreover, eCrCL or eGFR will be described by class (< 30, [30; 60[, [60; 90[and ≥ 90 mL/min or mL/min/1.73m²).

Listings of patients with out-of-range or PCSA analysable values emergent under treatment and of non-analysable values excluded from analyses will be provided.

3.6.5. Vital signs, clinical examination and other observations related to safety

3.6.5.1. Vital signs and clinical examination

Definition:

- **Vital signs and clinical examination parameters**:
  - Weight (kg),
  - BMI (kg/m²),
  - Supine and standing (at 1 and 3 min) SBP and DBP (mmHg),
  - Supine and standing (at 1 and 3 min) HR (bpm).

Analysis:

For each parameter, descriptive statistics on value at baseline, on value at each post-baseline visit under treatment, on last post-baseline value under treatment and on change from baseline to each post-baseline visit under treatment and to last post-baseline value under treatment will be provided.

3.6.5.2. Electrocardiogram

Not applicable.

4. INTERIM ANALYSIS

During the study, the safety was periodically reviewed by a DMC (partial unblind). Those analyses are not covered by the present Statistical Analysis Plan.

5. APPENDICES

5.1. Analytic definitions and data handling conventions

See "Specifications associated to the statistical analysis plan".

5.2. Statistical methods details

5.2.1. Cox proportional hazards model

MODEL

The Cox proportional hazard model is specified as follows:

$$h(t, X_1, ...X_p) = h_0(t) \exp\left(\sum_{j=1}^{p} \beta_j X_j\right)$$

where:

- $h(t, X_1, ..., X_p)$ is the hazard function at time t
- $h_0(t)$ is an arbitrary baseline hazard function depending only on time
- $X_1, ...X_p$ are p explanatory variables (including treatment)
- $\beta_1, ...\beta_p$ are the p regression coefficients to be estimated

ESTIMATES

The effect of a variable X_i over the hazard function can be expressed in terms of Hazard Ratio: $\hat{HR} = \exp(\hat{\beta}_i)$. By coding the trimetazidine as 1 and the placebo as 0 in the treatment covariable β_1, $\exp(\hat{\beta}_1)$ represents the change in risk in the trimetazidine group compared to the placebo group. A value of hazard ratio inferior to 1 will indicate a decrease in risk in the trimetazidine group compared to the placebo group.

The estimated $(1-\alpha)$-confidence interval of the hazard ratio can be calculated as:

$$CI_{1-\alpha}(HR) = \left[\exp(\hat{\beta}_i - z_{1-\alpha/2} \times SE(\hat{\beta}_i)); \exp(\hat{\beta}_i + z_{1-\alpha/2} \times SE(\hat{\beta}_i))\right]$$

Where:

- $SE(\hat{\beta}_i)$ is the estimated standard error of $\hat{\beta}_i$
- $z_{1-\alpha/2}$ is the $100(1-\alpha/2)^{th}$ percentile of the standard normal distribution.

Note:

The exact method will be used for handling ties in the time to occurrence of event/censor.

STATISTICAL TEST

The Wald test will be used to test the nullity of a parameter β_i associated to an explanatory variable X_i: the test statistics follows a χ^2 distribution with 1 degree of freedom under the null hypothesis H_0: $\beta_i = 0$ (equivalent to H_0: $HR_i = 1$)

$$\frac{\hat{\beta}_i^2}{V(\hat{\beta}_i)} \sim \chi^2_1$$

where:

- $\hat{\beta}_i$ is the parameter associated to the variable X_i
- V ($\hat{\beta}_i$) is the variance associated to the parameter $\hat{\beta}_i$

VALIDATION OF HYPOTHESIS

Hazards proportionality

The hazards proportionality will be assessed for all (categorical) explanatory variables included in the cox model of the primary analysis, from:

- The graph of the log cumulative hazard estimated from the main Cox model according to the time, for each class of the variables (for variables with more than 2 classes, all classes will be represented in pairs with a same class chosen as reference). The curves should be approximately parallel.
- The graph of the cumulative hazard estimated from the main Cox model of one class according to the cumulative hazard of another class (for variables with more than 2 classes, all classes will be represented against a same class chosen as reference). The curve should be approximately a line.
- The Wald test of the interaction between each variable and the time/the log of the time, added to the main model. Non-significance is expected.
- The graph of Schoenfeld residuals according to the time, for each parameter estimated in the main Cox model, and the test of the correlation between the Schoenfeld residuals and the rank of time. The curve should be approximately horizontal around 0 and the test should be non-significant (for each variable).

Other checks may be performed if deemed necessary, based on the results of the checks described above.

Censoring process

The assumption of random censoring process will be assessed from the following analyses performed by treatment group:

- Kaplan-Meier estimates taking into account censored data as events and events as censors
- Description of nature of censors.

5.2.2. Stratified Cox proportional hazards model

MODEL

The Cox proportional hazard model stratified on a variable is specified as follows:

$$h_s(t, X_1, ...X_p) = h_{0s}(t) \exp\left(\sum_{j=1}^{p} \beta_j X_j\right)$$

where:

- s is the strata
- $h_s(t, X_1, ...X_p)$ is the hazard function at time t in strata *s*
- $h_{0_s}(t)$ is an arbitrary baseline hazard function in strata *s* depending only on time
- $X_1, ...X_p$ are p explanatory variables (including treatment)
- $\beta_1, ...\beta_p$ are the p regression coefficients to be estimated, common to all strata

A variable on which the model is stratified is not subject to the proportional hazard assumption. However, the effect of this variable on the hazard is not estimated in this case.

5.2.3. Kaplan-Meier estimation

The Kaplan–Meier estimator is a non-parametric method based on conditional probabilities used to estimate a survival function *S(t)*.

A survival function *S(t)* is defined as the probability that a patient survives (*i.e.* has no event) at least up to a time t (included):

$$S(t) = Pr(T > t)$$

Where:

- *S(t)* denotes the survival distribution function
- *T* is the time of the event of a selected patient

The median time to event is the time *t* so that *Pr (T > t) = 0.5*

The Kaplan-Meier estimate of *S*(t) is

$$\hat{S}(t) = \prod_{i/t_i \le t} \frac{n_i - d_i}{n_i}$$

- t_i is a time when at least one event happened
- d_i is the number of events that happened at time t_i
- n_i is the number of patients at risk just before t_i (*i.e.* who have not yet had an event or have been censored up to time t_i)

5.2.4. Ordinal logistic regression model

The ordinal logistic regression model is specified as follows:

$$\log\left(\frac{P(Y \le k \mid X)}{P(Y > k \mid X)}\right) = \beta_{0,k} + \left(\sum_{j=1}^{p} \beta_j X_j\right), k = 1,..., K-1$$

where:

- Y is an ordinal variable with values denoted by 1,2,...,K
- $X_1,...X_p$ are p explanatory variables (including treatment)
- $\beta_{0,k}$ are the intercepts (one associated to each level k estimated)
- $\beta_1,...\beta_p$ are the p regression coefficients to be estimated (one per variable for all levels k estimated, thus assuming odds proportionality across all logits)

The outcome Y represents here the number of antianginal treatments at M012, ordered from 0 to 7.

ESTIMATES

The effect of a variable X_i over the logit function can be expressed in terms of Odds Ratio: $\hat{OR} = \exp(\hat{\beta}_i)$. By coding the trimetazidine as 1 and the placebo as 0 in the treatment covariable β_1, $\exp(\hat{\beta}_1)$ represents the change in odds of observing a lower number of treatments at M012 in the trimetazidine group compared to the placebo group. A value of odds ratio superior to 1 will indicate a higher chance to observe a lower number of treatments at M012 in the trimetazidine group compared to the placebo group.

The estimated $(1-\alpha)$-confidence interval of the odds ratio can be calculated as:

$$CI_{1-\alpha}(\hat{OR}) = \left[\exp(\hat{\beta}_i - z_{1-\alpha/2} \times SE(\hat{\beta}_i)); \exp(\hat{\beta}_i + z_{1-\alpha/2} \times SE(\hat{\beta}_i))\right]$$

Where:

- $SE(\hat{\beta}_i)$ is the estimated standard error of $\hat{\beta}_i$
- $z_{1-\alpha/2}$ is the $100(1-\alpha/2)^{th.}$ percentile of the standard normal distribution.

5.2.5. Multiple imputation considering a monotone missing pattern

Multiple Imputation (MI) considering a monotone missing pattern involves 3 consecutive phases:

- **Imputation step**: The missing pattern is supposed to be monotone, so the regression method will be used to impute missing data. It is of note that this imputation step might be preceded by one MI approach based on MCMC method, in case of arbitrary missing pattern. A total of 100 imputed complete data sets will be generated. This will be performed under "missing-at-random" (MAR) hypothesis taking into account the treatment group, baseline and post-baseline assessments of the studied endpoint.
- **Analysis step:** The defined model will be applied to each of the 100 complete data sets obtained.

- **Combination step:** Each imputed dataset will produce an estimate of the effect of trimetazidine as compared to placebo. The multiple imputation estimator of this difference is the average of the individual 100 estimators. The variance of the estimator is the combination of the between and within-imputation variability (Kenward MG and Carpenter J, 2007).

5.2.6. Confidence interval of the difference in annual incidence rates

Confidence intervals of the difference between two annual incidence rates will be calculated using Wald's method (*i.e.* normal approximation). The formula is given by:

$$\hat{\lambda}_1 - \hat{\lambda}_2 \pm Z_{\alpha/2}\hat{\sigma} \text{ with } \hat{\sigma} = \sqrt{n_1/T_1^2 + n_2/T_2^2}$$

Where $\hat{\lambda}_1$ (resp. $\hat{\lambda}_2$) is the estimated annual incidence rate in group 1 (resp. group 2) ; n_1 (resp. n_2) is the number of patients with the event in group 1 (resp. group 2) ; T_1 (resp. T_2) is the total exposure (*i.e.* time to censor) in group 1 (resp. group 2) ; and $Z_{\alpha/2}$ is the $\alpha/2$ quantile of the normal distribution.

Simulations were performed (following Liu GF *et al* (2006) methodology) to assess Wald's confidence interval probabilities of coverage when annual incidence rates are low in both groups. If the annual incidence rate is below or equal to 0.001 in one group and is below or equal to 0.025 in the other group, confidence interval will not be calculated.

5.3. Software and programming codes

Adjusted Cox model:

```
proc phreg data=inputTable ALPHA=0.05;
     class treatment(ref="Placebo") country indexPCI;
     model time_to_PCE*censor(1) = treatment country indexPCI
/ties=exact risklimits ;
     ods output ParameterEstimates=outputTable;
run;
```

Non-adjusted Cox model:

```
proc phreg data=inputTable ALPHA=0.05;
     class treatment(ref="Placebo");
     model time_to_PCE*censor(1) = treatment /ties=exact risklimits;
     ods output ParameterEstimates=outputTable;
run;
```

Stratified Cox model:

```
proc phreg data=inputTable ALPHA=0.05;
     class treatment(ref="Placebo") country indexPCI;
     model time_to_PCE*censor(1) = treatment indexPCI /ties=exact
risklimits;
     strata country;
     ods output ParameterEstimates=outputTable;
run;
```

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