2. SYNOPSIS

Name of Sponsors: **Serbia : I.R.I.S. 50 rue Carnot - 92284 Suresnes Cedex – France** **Russia : LLS 50 rue Carnot - 92284 Suresnes Cedex – France**		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Not applicable **Name of Active Ingredient:** Trimetazidine MR 80 mg (S 06795)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: Clinical acceptability of trimetazidine MR 80 mg *o.d.* compared to trimetazidine MR 35 mg *b.i.d.* in patients with chronic stable angina pectoris. An international, multicentre, randomised, double-blind, parallel-group study in patients treated for 12 weeks. **Protocol No: CL3-06795-008.** The description of the study protocol given hereafter includes the modifications of the substantial amendment No.1 to the protocol.		
International coordinator: [redacted]		
Study centres: In all, 15 centres included at least one patient: 12 centres in Russia and 3 centres in Serbia.		
Publication (reference): Not Applicable.		
Studied period: Initiation date: 31 January 2013 Completion date: 27 August 2013	**Phase of development of the study:** III	
Objective: The objective of this study was to compare the clinical acceptability of trimetazidine MR (Modified Release) 80 mg once daily with trimetazidine MR 35 mg twice daily in patients with chronic stable angina.		
Methodology: Phase III, international, multicentre, randomised, double-blind, parallel-groups study with a 12-week treatment period (trimetazidine MR 80 mg *o.d.* or trimetazidine MR 35 mg *b.i.d.*) conducted in patients with chronic stable angina pectoris of effort. Study treatment was given on top of both routine antianginal therapies and secondary prevention therapy. The randomization was balanced (non-adaptative) with stratification on the centre. This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.		
Number of patients: Planned: 150 included patients with 75 in each treatment group. Included: 165 included patients with 82 patients in trimetazidine MR 80 mg and 83 patients in the trimetazidine MR 35 mg groups.		
Diagnosis and main criteria for inclusion: Male or female patient, ≥ 21 years old, of any ethnic origin, with a prior diagnosis of stable angina pectoris of effort where: - The symptoms were classified according to the Canadian Cardiovascular Society (CCS) classification as being either class 1, 2 or 3. - Treatment included at least one regular antianginal medication. - The patient had been treated with trimetazidine for at least 1 month at the time of selection and the investigator wished to continue the treatment. Trimetazidine had been given for angina pectoris with satisfactory clinical effect and tolerance. - There was documented evidence of coronary heart disease. - Renal function measured during the run-in period showed the estimated creatinine clearance (eCrCl) to be ≥ 60 ml/min. - Compliance to study medication was to be ≥ 80% and ≤ 120% during run-in period.		
Test drug: Trimetazidine MR 80 mg: 1 capsule swallowed once daily in the morning with breakfast.		

Comparator (Reference product):
Trimetazidine MR 35 mg: 1 tablet swallowed twice daily in the morning with breakfast and in the evening with a meal.

Duration of treatment:
Run-in period: a 2-week period with trimetazidine MR 35 mg *b.i.d.*
Active treatment period: a 12-week period of trimetazidine MR 80 mg *o.d.* or trimetazidine MR 35 mg *b.i.d.*

Criteria for safety evaluation:
- Emergent adverse events (all visits).
- Laboratory examinations: biochemical and haematological parameters (at Inclusion and W12).
- Weight (at Inclusion and W12).
- Supine and standing blood pressure (all visits).
- 12-lead electrocardiogram (all visits).
- CCS classification of symptoms of angina pectoris (all visits).

No efficacy measurements were performed in the present study.

Statistical methods:
Safety analysis: Descriptive statistics were provided on the Safety Set (SS) by treatment group (and overall for adverse events).

SUMMARY - CONCLUSIONS
STUDY POPULATION AND OUTCOME

Disposition of patients

	Trimetazidine MR 80 mg *o.d.*	Trimetazidine MR 35 mg *b.i.d.*	All
Included	82	83	165
Withdrawn	-	-	-
Completed	82	83	165
Randomised Set	82	83	165
Safety Set*	82	83	165

**: all included patients having received at least one dose of study drug*

The distribution of the treatment groups was well balanced. Overall, 19 patients (11.5%) had at least one protocol deviation before or at inclusion mainly due to date of blood sample before W0 visit (10.3%). After inclusion, 11 patients (6.7%) had at least one protocol deviation due to blood sample not taken before last visit (3.6%) and/or creatinine clearance < 60 ml/min (3.0%). No relevant between-groups difference was observed regarding protocol deviations.

Main baseline* characteristics in the Randomised Set

			Trimetazidine MR 80 mg *o.d.* (N = 82)	Trimetazidine MR 35 mg *b.i.d.* (N = 83)	All (N = 165)
		n	82	83	165
Age (years)		Mean ± SD	63.3 ± 6.9	64.3 ± 8.3	63.8 ± 7.6
		Min ; Max	45 ; 78	37 ; 81	37 ; 81
	< 65	n (%)	45 (54.9)	36 (43.4)	81 (49.1)
	[65 - 75[	n (%)	33 (40.2)	37 (44.6)	70 (42.4)
	≥75	n (%)	4 (4.9)	10 (12.1)	14 (8.5)
Sex	Men	n (%)	56 (68.3)	57 (68.7)	113 (68.5)
	Women	n (%)	26 (31.7)	26 (31.3)	52 (1.5)
Ethnic group	Caucasian	n (%)	82 (100)	83 (100)	165 (100)
Weight (kg)		Mean ± SD	84.5 ± 13.2	81.9 ± 10.9	83.2 ± 12.1
		Min ; Max	55.5 ; 115.0	49.0 ; 112.0	49.0 ; 115.0
Blood pressure	SBP	Mean ± SD	129.7 ± 14.4	132.0 ± 13.7	130.9 ± 14.1
(mmHg)		Min ; Max	100 ; 180	100 ; 170	100 ; 180
	DBP	Mean ± SD	78.0 ± 7.5	78.7 ± 7.7	78.3 ± 7.6
		Min ; Max	60 ; 100	60 ; 95	60 ; 100
Orthostatic hypotension		Yes	3 (3.7)	7 (8.4)	10 (6.1)
Heart rate (bpm)		Mean ± SD	64.7 ± 9.8	63.3 ± 9.4	64.0 ± 9.6
		Min ; Max	47 ; 95	46 ; 85	46 ; 95

n: Number of affected patients
** assessed either at selection and/or inclusion visit at the latest.*
%: (n/N) x 100 (N: number of patients by treatment group).

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME (Cont'd)

No relevant difference between groups was observed regarding demographic characteristics, except a lower rate of patients ≥ 75 years old and higher rate of patients < 65 years old in the trimetazidine MR 80 mg group (4.9% and 54.9%, respectively) than in the trimetazidine MR 35 mg group (12.1% and 43.4%, respectively): no relevant between-group difference was observed regarding the mean age.

No relevant difference between groups was observed regarding blood pressure, heart rate, height and weight except a slightly lower rate of patients with orthostatic hypotension at baseline in the trimetazidine MR 80 mg group (3 patients, 3.7%) compared to the trimetazidine MR 35 mg group (7 patients, 8.4%).

Main characteristics* of coronary artery disease in the Randomised Set

		Trimetazidine MR 80 mg *o.d.* (N = 82)	Trimetazidine MR 35 mg *b.i.d.* (N = 83)	All (N = 165)
Stable angina pectoris duration	n	82	83	165
(years)	Mean ± SD	5.75 ± 5.39	6.93 ± 5.27	6.34 ± 5.35
	Median	3.80	6.20	4.30
	Min ; Max	0.1 ; 27.0	0.2 ; 23.2	0.1 ; 27.0
CCS** Classification				
Class I	n (%)	22 (26.83)	14 (16.87)	36 (21.82)
Class II	n (%)	49 (59.76)	63 (75.90)	112 (67.88)
Class III	n (%)	11 (13.41)	6 (7.23)	17 (10.30)
Medical history of CAD	**n (%)**	**82 (100)**	**83 (100)**	**165 (100)**
Angina pectoris	n (%)	82 (100)	83 (100)	165 (100)
Myocardial infarction	n (%)	61 (74.4)	60 (72.3)	121 (73.3)
Angina unstable	n (%)	13 (15.9)	12 (14.5)	25 (15.2)
Arteriosclerosis coronary artery	n (%)	2 (2.4)	1 (1.2)	3 (1.8)
Coronary artery stenosis	n (%)	1 (1.2)	2 (2.4)	3 (1.8)
Acute coronary syndrome	n (%)	1 (1.2)	-	1 (0.6)
Myocardial ischaemia	n (%)	-	1 (1.2)	1 (0.6)
Family history of CAD	**n (%)**	**35 (42.68)**	**24 (28.92)**	**59 (35.76)**
Affected parents	n (%)	33 (94.3)	23 (95.8)	56 (94.9)
Affected brother and/or sisters	n (%)	5 (14.3)	1 (4.2)	6 (10.2)

n: Number of affected patients - %: (n/N) x 100 (N: number of patients by treatment group).
** assessed at selection (and at inclusion visit for the CCS class).*
*** Canadian Cardiovascular Society (CCS) classification.*

The mean duration (± SD) of the stable angina pectoris was lower in the trimetazidine MR 80 mg (5.8 ± 5.4 years, median = 3.8 years) than in the trimetazidine MR 35 mg group (6.9 ± 5.3 years, median = 6.2 years).

According the CCS classification, there was a higher rate of patients in classes I and III in the trimetazidine MR 80 mg group (26.8% and 13.4%, respectively) than in the trimetazidine MR 35 mg group (16.9% and 7.2%, respectively). In addition to angina pectoris, the most frequent medical histories related to CAD were myocardial infarction (73.3%) and angina unstable (15.2%). No relevant difference between groups was observed regarding CAD medical and/or surgical histories.

The rate of patients with family history of CAD was higher in the trimetazidine MR 80 mg group (42.7%) than in the trimetazidine MR 35 mg group (28.9%).

As expected according to the protocol, all patients were previously treated with trimetazidine on the day of selection (complementary analysis). Before treatment period, all of them received a specific treatment for CAD (complementary analysis) without relevant difference between groups. More specifically, all patients received anti-anginal therapy (complementary analysis), mainly beta-blocking agents (87.9% of the patients), vasodilatators used in cardiac disease (47.3%) and calcium channel blockers (33.9%) without relevant difference between groups. Similar data were observed at inclusion

The most frequent medical histories other than CAD were related to Vascular disorders (95.2% of the patients) mainly hypertension (86.1%), Metabolism and nutrition disorders (70.9%) mainly dyslipidaemia (29.7%) and type 2 diabetes mellitus (21.8%), and Cardiac disorders (67.3%) mainly chronic cardiac failure (47.9%).

Few differences between groups were observed regarding medical histories other than CAD: aortic arteriosclerosis were slightly less reported in the trimetazidine MR 80 mg group than in the trimetazidine MR 35 mg group (7 patients, 8.5% *versus* 15 patients, 18.1%, respectively); conversely, there was a trend to a slightly greater rate of patients with obesity and renal cyst in the trimetazidine MR 80 mg group (13 patients, 15.9% and 9 patients, 11.0%, respectively) than in the trimetazidine MR 35 mg group (7 patients, 8.4% and 3 patients, 3.6%, respectively).

SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Overall, 47.9% of the patients received a non-specific treatment before treatment period (complementary analysis) without relevant difference between groups. They were mainly diuretics (20.0% of the patients) and drugs used in diabetes (18.2% of the patients). Similar data was observed at inclusion.

During the treatment period, concomitant treatments were very similar to that reported before treatment period.

The global compliance during the run-in and the treatment periods were very satisfactory: on average more than 99.0% in both groups.

EFFICACY RESULTS

Not applicable.

SAFETY RESULTS

Overall summary for adverse events in the Safety Set (N = 165)

		Trimetazidine 80 mg *o.d.* (N = 82)	**Trimetazidine MR 35 mg *b.i.d.* (N = 83)**
Patients having reported			
at least one emergent adverse event	n (%)	14 (17.1)	19 (22.9)
at least one treatment-related emergent adverse event	n (%)	1 (1.2)	-
Patients having experienced			
at least one serious adverse event*	n (%)	3 (3.7)	3 (3.6)
at least one serious emergent event	n (%)	3 (3.7)	3 (3.6)
at least one treatment-related serious adverse event	n (%)	-	-
Patients with treatment withdrawal		-	-
Patients who died	n (%)	-	-

** In addition, 2 SAEs (angina pectoris and myocardial infarction) were reported during the run-in period by selected but not randomised patients.*

In the Safety Set, the rate of patients who experienced at least one EAE during the treatment period was slightly lower in the trimetazidine MR 80 mg group (17.1%) than in the trimetazidine MR 35 mg group (22.9%).

Among the most frequent system organ classes affected (at least 3 patients) in the trimetazidine MR 80 mg group, infections and infestations were more frequently reported in the trimetazidine MR 80 mg than in the trimetazidine MR 35 mg group (6.1% *versus* 1.2%, respectively), whereas no relevant between-groups difference was observed for investigations (4.9% *versus* 6.0%) and cardiac disorders (3.7% *versus* 6.0%). No clinically relevant difference between groups was observed regarding other SOCs except metabolism and nutrition disorders less common in the trimetazidine MR 80 mg group than in the trimetazidine MR 35 mg group (1.2% *versus* 7.2%).

The most frequently reported emergent adverse events (at least 2 patients) in the trimetazidine MR 80 mg group was influenza (2 patients, 2.4%), which was not reported in the trimetazidine MR 35 mg group. The most frequently reported emergent adverse events (at least 2 patients) in the trimetazidine MR 35 mg group were hyperglycaemia (4 patients, 4.8%) and atrial fibrillation (2 patients, 2.4%) which were not reported in the trimetazidine MR 80 mg group as well as hyperbilirubinaemia reported by 2 patients (2.4%) in the trimetazidine MR 35 mg group *versus* one patient (1.2%) in the trimetazidine MR 80 mg group.

Overall, 3 emergent adverse events (6.1%) were rated as severe; all reported the same day by a single patient in the trimetazidine MR 80 mg: cardiac failure acute, myocardial infarction and pulmonary oedema.

Only one patient (1.2%), in the trimetazidine MR 80 mg group, had experienced at least one emergent adverse event considered to be related to the treatment by the investigator: a polyuria, not serious. No emergent adverse event led to dose modification, drug withdrawal or temporarily interruption.

Overall, 6 patients in the safety Set, experienced 9 serious adverse events (all were emergent) during the study without relevant difference between groups: 3 patients (3.7%) reported 6 serious EAEs in the trimetazidine MR 80 mg group (cardiac failure acute, myocardial infarction, ventricular fibrillation, blood pressure increased, renal colic and pulmonary oedema) and 3 patients (3.6%) in the trimetazidine MR 35 mg reported 3 serious EAEs (2 atrial fibrillations and one ischaemic stroke).

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Regarding biochemical parameters, 8 emergent PCSA values were reported, sparse in both groups: one high GGT and low clearance creatinine in the trimetazidine MR 80 mg group and one high glucose and low HDL-cholesterol in the trimetazidine MR 35 mg group; to note 1 high PCSA value (1.3%) of triglycerides in the trimetazidine MR 80 mg dose group *versus* 3 (3.8%) in the trimetazidine MR 35 mg group.

Overall 2 patients had emergent haematological PCSA value: low platelets in the trimetazidine MR 80 mg group and high white blood cell count in the trimetazidine MR 35 mg group.

In the Safety Set, regarding weight and blood pressure, neither clinically relevant mean change from baseline to each post-baseline value (including last post-baseline value on treatment for blood pressure), nor difference between groups was observed over the study.

Emergent orthostatic hypotension on treatment was slightly more frequent in trimetazidine MR 80 mg group than in the trimetazidine MR 35 mg group (9 patients, 11% *versus* 6 patients, 7%, respectively). Except a sinusal tachycardia reported the same day as the orthostatic hypotension in the trimetazidne MR 35 mg group, no symptom was reported by the patients at the same time as the orthostatic hypotensions. In addition, all the patients had at least two concomitant treatments with anti-hypertensive action including beta-blocking agents.

Neither clinically relevant change from baseline to each post-baseline value and to last post-baseline value on treatment, nor relevant difference between groups over time was observed regarding ECG parameters.

Regarding clinically significant ECG abnormalities (reported as adverse events) during the treatment period, no relevant difference between groups was observed: 4.0% in the trimetazidine MR 80 mg group and 6.0%, in the trimetazidine MR 35 mg group. At last post-baseline assessment on treatment, one patient in each group had no more sinusal rhythm on ECG compared to baseline.

Regarding the CCS classification of symptoms of angina, no patient switched from a baseline value to a more severe last post-baseline class on treatment. Conversely, for 11 patients (13.4%) in the trimetazidine MR 80 mg group and 14 patients (16.9%) in the trimetazidine MR 35 mg group, the CCS classification was improved from baseline to last post-baseline assessment without relevant modifications of the concomitant anti-anginal therapy (to note, for one patient, treatment with dihydropyridine started about one month and a half before the improvement).

CONCLUSION

The objective of this phase III, international, multicentre, randomised, double-blind, parallel-group, 12-week study was to compare the clinical acceptability of trimetazidine MR 80 mg once daily with trimetazidine MR 35 mg twice daily in patients with chronic stable angina. Baseline characteristics of included patients were in accordance with the study's inclusion criteria. The safety profile of trimetazidine MR 80 mg o.d. was similar to that observed with trimetazidine MR 35 mg b.i.d. No unexpected adverse event was reported and the study showed no concern regarding the once daily intake of trimetazidine MR 80 mg.

Date of the report: 13 June 2014

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