2. SYNOPSIS

Study Title	Mildronate – Efficacy And Safety In Treatment For Chronic Coronary Heart Disease (Stable Angina Study - **SAS I**)
Identification No.	GRMSS-04-07
EudraCT No.	2007-005179-32
Sponsor	JSC "Grindeks", Krustpils Street 53, Riga, LV-1057, Latvia
Name of Finished Product	Mildronate (Meldonium)
Name of Active Ingredient	Meldonium [3-(2,2,2-trimethyl hydrazine) propionate dihydrate]
Test Product	Mildronate (Meldonium) Batch numbers: Mildronate 50: 010604; 8461206; 1900108; 280108; 8271008 Mildronate 150: 10604; 8471206; 1910108; 290108; 8281008 Mildronate 500: 1310403; 8240906; 1920408; 300108; 8291008
Reference Product	Placebo Batch numbers: 10131724; 8481206; 1990108; 310108; 8301008
Dose and mode of administration	Oral application either: 1) 2 x 50 mg/day Mildronate or Placebo; 2) 2 x 150 mg/day Mildronate or Placebo; 3) 2 x 500 mg/day Mildronate or Placebo; 4) 2 x 1500 mg/day Mildronate or Placebo
Indication	Chronic Coronary Heart Disease (Stable Angina)
Study Design	A prospective, randomized, double- blind, placebo controlled phase II study with five treatment groups. Follow-up time of 17 weeks: 4 weeks run-in period + 12 weeks randomized therapy + 1 week post-study follow-up.
Treatment duration	Twelve (12) weeks of double blind treatment
Study Phase	II
Investigators	For the list of the investigators, please refer to Appendix 16.1.4.

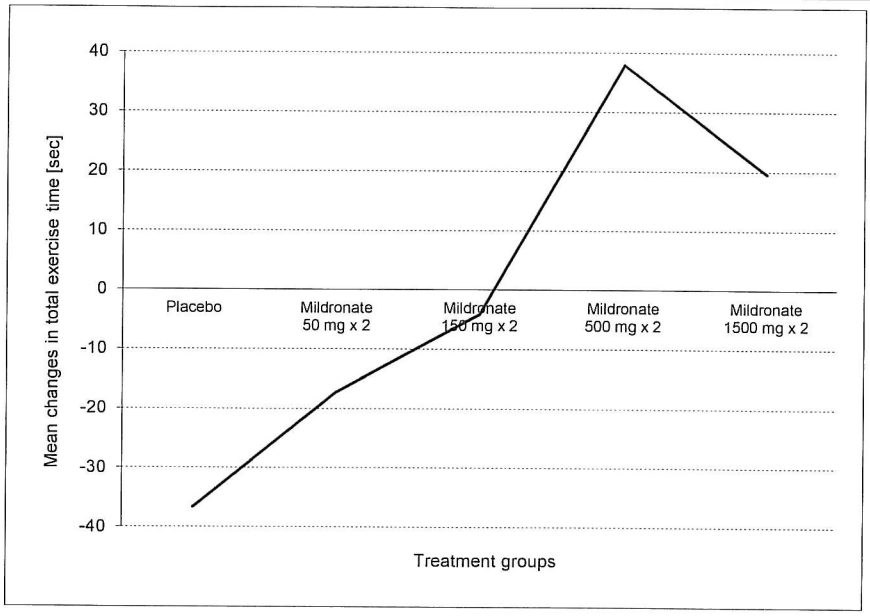
Total number of study sites	72 study sites initiated: Latvia – 8 sites, Georgia – 14 sites, Russia – 42 sites, Ukraine – 8 sites.
Countries involved	Latvia, Georgia, Russia, Ukraine
Publication (reference)	None
Study period	Date of first enrolment: 06-Apr-2006 Date of last enrolment: 22-May-2009 Last Subject Completed: 25-Sep-2009
Objective and aim of the study	***The objective*** of the study was to assess the efficacy and safety of the treatment with Mildronate in combination with standard therapy for the exercise tolerance of patients with stable angina pectoris. ***The aim*** of the study was to assess the efficacy of different various doses of Mildronate upon the symptoms of CHD, using the indices of physical exercise of patients with stable angina pectoris.
Number of patients (planned and analyzed)	Planned: 465 Screened for randomization and randomized: 564 Safety population: 563 ITT population: 524 TPP population: 486
Inclusion criteria	1. Written informed consent. 2. Age over 18 years. 3. At least 3 months prior to the study history of stable effort angina II-III functional class according to classification of CCS verified either by: • previous myocardial infarction, or; • coronary angiography, or; • percutaneous coronary angioplasty, or; • coronary artery by-pass surgery, or; • exercise test with typical findings of myocardial ischemia. 4. Myocardial ischemia with typical ST-changes (horizontal or down sloping ST-depression ≥ 1mm) as the limiting factor of exercise in bicycle ergometry at least on visits 3 and 4. 5. Willingness to comply with the standard antianginal therapy

Exclusion criteria	after visit 1. 1. Known intolerance of Mildronate preparation or its ingredients. 2. Inability to perform bicycle ergometry test. 3. Over 20 % difference in the exercise time between the last two exercise tests of the run-in period. 4. Exercise time less than 3 or more than 13 minutes in bicycle ergometry at visit 4. 5. Extreme obesity (body mass index > 35 kg/m^2). 6. Myocardial infarction, stroke or unstable angina within 3 months prior to the study and during the screening period. 7. Coronary revascularization within 3 months prior to the study. 8. Congestive heart failure class III-IV according to classification of NYHA. 9. Hemodynamically significant valvular heart disease. 10. Hemodynamically significant congenital heart disease. 11. Acute myocarditis. 12. Unischemic cardiomiopathia. 13. Pericarditis. 14. *Cor pulmonale*. 15. Planned cardiac surgery during the forthcoming 12 months. 16. Heart rate < 50 or > 100 bpm at rest. 17. Serious changes of ECG, making impossible correct interpretation of bicycle ergometry results including: • second or third degree atrioventricular (AV)-block, • sick sinus syndrome, • Wolff-Parkinson-White (WPW)-syndrome, • left bundle branch block (LBBB). 18. Sustained ventricular tachycardia, supraventricular tachycardia, ventricular flutter or fibrillation within 3 months prior the study. 19. Systolic blood pressure (sBP) < 100 mmHg or > 180 mmHg or diastolic blood pressure (dBP) < 70 mmHg or > 110 mmHg. 20. Any medical condition making the patient unsuitable for the study including: • severe chronic obstructive pulmonary disease,

	• severe bronchial asthma, • uncontrolled arterial hypertension, • anemia (Hb < 110 g/l), • severe hepatic failure, • renal dysfunction as evidenced by serum creatinine over 200 μmol/L, • diabetes mellitus Type I. 21. Treatment with group I C antiarrhythmic drugs or digoxin within 3 months prior to the study. 22. Treatment with L-thyroxine, trimethazidine, L-carnitine, Q10 coenzyme or ranolazine within 3 months prior to the study. 23. Treatment with Mildronate within 6 months prior to the study. 24. Use of ophtalmic beta-blockers. 25. Narcotic and alcohol misuse. 26. Premenopausal females not using a medically accepted method of birth control. 27. Pregnant or breastfeeding women. 28. Administration of any investigational drug within the preceding 3 months. An investigational drug is defined as any agent (placebo or drug) dispensed as part of any other clinical research study. 29. Expected poor compliance (for example, planned long business trips etc.).
Primary endpoint	The change in exercise time in bicycle ergometry from baseline after 12 weeks treatment with Mildronate or placebo (at through drug concentrations) in comparison with the baseline data. The baseline was defined as the mean exercise time of the last two measurements (visit 3 and visit 4) of the run-in period. The exercise time after 12 weeks treatment was defined as the mean of the measurements at visit 6 and visit 7.
Secondary endpoints	• presence of anginal symptoms during the study as measured by Seattle angina questionnaire (SAQ), • use of short-acting nitrates during the double-blind treatment, • change in functional class of angina pectoris according to Canadian cardiovascular society classification (CCS) during the double-blind treatment,

Methodology, including Safety Assessments	• the difference in the number of cardiovascular and cerebrovascular events between the treatment groups. These events include: all deaths independently of cause, stroke and all cases of myocardial infarction (with or without thrombolytic treatment), sudden death (resuscitated), hospitalization for myocardial ischemia (acute coronary syndrome) and revascularizations (PTCA or by-pass surgery), • the change in the time to ST segment depression of 1 mm in bicycle ergometry from baseline after 12 weeks of treatment, • global assessment of therapy results using CGI-C (Clinician's Global Impression of Change) scale. • Canadian Cardiovascular Society angina classification (CCS) • Electrocardiography (ECG) at rest • Bicycle ergometry • Recording of cardiovascular and cerebrovascular events • Presence of anginal symptoms during the study (Seattle Angina Questionnaire – SAQ) • Global assessment of the therapy results (patient's condition) by means of Clinician`s Global Impression of Change (CGI-C) scale. • Safety laboratory • AE/SAE recording/reporting
Statistical methods	The primary efficacy analysis was performed on the intention-to-treat population (ITT) and treated per protocol population (TPP). The hypothesis behind the study was that there is a dose-related improvement of exercise capacity in coronary heart disease (CHD) patients treated with Mildronate. The hypothesis of superiority in the change in the exercise time in VEM (bicycle ergometry) was to be tested. The hypothesis was tested by non-parametric Mann-Whitney test. In addition, the subgroup analysis of the primary variable was performed on the ITT population for the observed cases. The "treated-per-protocol" (TPP) group is a subset of the ITT group (FAS - Full Analysis Set) in this study. The TPP subset of the study includes subjects who are more compliant with the protocol. All analyses of secondary efficacy variables were based on the ITT population, analysis for the observed cases using data from all

	available visits was conducted. The change from baseline in maximum achieved load and change from baseline in maximum deviation of ST-segment from isoline were analyzed using the same models as with the primary efficacy variable. Other secondary variables: the time to onset of angina, time to deviation of ST-segment to 1 mm at least, cardiovascular and cerebrovascular events, SAQ, use of short-acting nitrates, CCS class, CGI-C were investigated using descriptive statistics and suitable statistical tests, in terms of treatment differences (Mildronate 50 mg and Placebo groups, Mildronate 150 mg and Placebo groups, Mildronate 500 mg and Placebo groups, Mildronate 1500 mg and Placebo groups) in the ITT population. Safety analyses were performed on the safety population. Incidence rates and type of adverse events were descriptively analysed. For laboratory parameters descriptive statistics were calculated.
Summary/Conclusions **Primary Endpoint**	At the baseline patients of all five treatment groups were comparable with respect to demographic data, disease anamnesis, medical history data, use of concomitant medication, smoking habits. In the ITT population the mean change in the total exercise time from the baseline to week 12 was -17.24 (± 105.39) seconds in Mildronate 50 mg group, -4.12 (± 67.59) seconds in Mildronate 150 mg group, 37.95 (± 74.13) seconds in Mildronate 500 mg group, 19.63 (± 87.52) seconds in Mildronate 1500 mg group and -36.62 (± 74.93) seconds in Placebo group. Therefore the maximum improvement in the total exercise time comparing the baseline and week 12 was achieved in Mildronate 500 mg group. Hereto the difference between Mildronate 500 mg group and Placebo group was highly significant (p-value < 0.001). The difference between Mildronate 50 mg and Placebo groups was statistical significant (p-value = 0.014), but differences between Mildronate 150 mg and Placebo groups and between Mildronate 1500 mg and Placebo groups also were highly statistically significant (p-value < 0.001). The mean changes in total exercise time [seconds] from the baseline to week 12 by treatment groups for the ITT population are presented in the graph below.



In the TPP population the mean value of the change in the total exercise time in Mildronate 50 mg group was -13.87 ± 106.29 seconds, in Mildronate 150 mg group it was -4.65 ± 67.92 seconds, in Mildronate 500 mg group it was 34.83 ± 73.99 seconds, in Mildronate 1500 mg group it was 24.06 ± 87.51 seconds, but Placebo patients had mean value -34.13 ± 72.84 seconds. The differences between all Mildronate groups and Placebo group were significant: for differences between Mildronate 50 mg and Placebo groups p-value = 0.012, between Mildronate 150 mg and Placebo groups p-value = 0.001, between Mildronate 500 mg and Placebo groups p-value < 0.001, and also between Mildronate 1500 mg and Placebo groups p-value < 0.001.

The ITT (Full Analysis set) and TPP sets demonstrated similar results of the primary study parameter.

Summary/Conclusions

Secondary Endpoints

In the ITT population the mean value of the change in maximum achieved load in Mildronate 50 mg group was -1.82 (± 17.42) W, in Mildronate 150 mg group it was a slightly higher: 0 (± 11.61) W, in Mildronate 500 mg group it was more higher: 6.02 (± 12.73) W, but in Mildronate 1500 mg group it was: 3.18 (± 15.41) W, while Placebo patients had the mean value -3.33 (± 14.21) W. The differences between Mildronate 50 mg and Placebo, between Mildronate 150 mg and Placebo groups were non-significant. The difference between Mildronate 500 mg and Placebo groups was statistically highly significant (p-value < 0.001). Also the difference between Mildronate 1500 mg and Placebo groups was statistically significant (p-value = 0.002).

	At week 12 the mean time to deviation of ST-segment to 1 mm at least decreased in Mildronate 50 mg group from 371.58 (± 130.65) sec at the baseline to 369.07 (± 134.13) sec and in Placebo group from 371.33 (± 127.83) sec at the baseline to 348.21 (± 131.68) sec. Whereas, the increase of the time to deviation of ST-segment to 1 mm at least were observed in Mildronate 150 mg group from 373.87 (± 140.28) sec at the baseline to 385.43 (± 139.02) sec, in Mildronate 500 mg group from 339.99 (± 125.02) sec at the baseline to 388.34 ± 134.33 sec and in Mildronate 1500 mg group from 360.72 (± 124.39) sec at the baseline to 383.62 (± 127.01) sec. At week 12 only the difference of time to deviation of ST-segment to 1 mm at least between Mildronate 500 mg group and Placebo group was marked as statistically significant (p=0.036). The differences between Mildronate 50 mg and Placebo groups, Mildronate 150 mg and Placebo groups, Mildronate 1500 mg and Placebo groups at week 12 were non-significant. The mean time to onset of angina increased at the week 12 in Mildronate 500 mg group from 371.24 (± 118.83) sec at the baseline to 374.97 (± 156.75) sec and in Mildronate 1500 mg group from 374.99 (± 127.03) sec at the baseline to 380.39 (±167.21) sec, but decreased in Mildronate 50 mg group from 392.00 (± 133.03) sec at the baseline to 372.46 (± 147.62) sec, in Mildronate 150 mg group from 384.92 (± 135.23) sec at the baseline to 372.12 (± 169.32) sec and in Placebo group from 394.87 (± 129.88) sec at the baseline to 349.14 (± 152.60) sec. The differences of time to onset of angina between Mildronate 50 mg and Placebo groups, Mildronate 150 mg and Placebo groups, Mildronate 500 mg and Placebo groups, Mildronate 1500 mg and Placebo groups at the week 12 were non-significant.
Safety results **Conclusion**	No statistically significant difference between the treatment groups was observed for the safety parameters. Please see list of central laboratories in Section 6. Totally 629 adverse events were observed in the study, 526 from them were considered as treatment emergent adverse events and 103 – as baseline symptoms. Please see Table 12.1 for the AE and SAE distributions. During the treatment period, a total number of 221 patients in the safety population had 526 treatment-emergent adverse events. 117 treatment-emergent adverse events occurred in 49 patients of the Mildronate 50 mg group, 85 events occurred in 44 patients of the Mildronate 150 mg group, 92 events occurred in 39 patients of the Mildronate 500 mg group, 95 events occurred in 40 patients of the Mildronate 1500 mg group and 137 events occurred in 49 Placebo patients.

	Safety conclusion: summarizing observed adverse events in all treatment groups mildronate has demonstrated good tolerance and safety having favourable safety profile.