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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

1 Summary

Study title: ERASER – Effect of ranolazine in ischemic patients with indication of staged interventional therapy

Study phase: Phase II

EudraCT number: 2012-001584-77

Study code: MEIN/10/Ran-PCI/005

Competent authority: The study protocol, all protocol amendments and patient information leaflets were submitted for review to and approved by the following competent authority:

Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn

After the approval of the final protocol version (**12/09/2012**) no changes and no further study amendments were done.

Submission number: 4038378

Ethics committee The study protocol (**Final version 3.6 - 12/09/2012**) and patient information leaflets were submitted for review to and approved by the following ethics committee:

Ethikkommission der Universität Ulm
[redacted]

After the final approval of the final protocol version (**12/09/2012**) no further study amendment was submitted.

Transaction number: 204/ 12

Study type and design:	A randomized, double-blind, placebo-controlled, 2-parallel-group proof-of-concept study
Number and characteristics of patients:	Patient characteristics: patients diagnosed with ischemia at first study MRI evaluation after diagnostic coronary angiography with or without initial percutaneous coronary intervention (PCI) and indication of further interventional treatment. Planned total number: 20 patients
Study duration:	Total enrolment period: 12 months Treatment period: 5 weeks after initial magnetic resonance imaging (MRI) evaluation Follow-up period: none Total study duration: 13 months
Objectives:	Evaluation of the anti-ischemic effect of ranolazine during dobutamine stress and at rest in comparison to patients treated with placebo.
Main efficacy criteria:	Improvement of induced wall motion abnormalities in ischemic areas in patients after 5 weeks of ranolazine treatment compared to placebo.
Safety criteria:	Incidence of adverse events and serious adverse events.
Number of centres:	1
Country:	Germany
Sponsor statement:	This study was conducted according to the study protocol, Good Clinical Practice (GCP), the ICH guidelines, local laws and obligations and the World Medical Association Declaration of Helsinki.

2 Study Design

Study Rationale and Hypothesis

CAD patients are in need of innovative treatment strategies to relieve them from suffering myocardial ischemia and its consequences (arrhythmias, heart failure, and death). This proof-of-concept (PoC) study aimeds at evaluating the antiischemic effect of ranolazine based on changes of induced wall motion abnormalities and reversible perfusion deficits with cMRI during dobutamine stress and at rest compared to patients treated with placebo. The analysis of wall motion abnormalities via dobutamine stress MRI is superior to dobutamine stress echocardiography in terms of sensitivity and specificity, thus making it an adequate instrument for the detection of myocardial ischemia (20,22). Additionally, MRI-dobutamine stress testing is a suitable method for the evaluation of the myocardial contractile reserve (23). Late gadolinium enhancement measurement via cMRI is a reference standard for diagnosis of chronic and acute myocardial infarction. It is well established in the clinical routine for the identification and quantification of myocardial fibrotic areas and irreversibly scarred myocardial tissue (20).

Study Objectives

Primary Objectives

Primary objective of this study was to evaluate the efficacy of ranolazine treatment in terms of changes of wall motion abnormalities in ischemic areas in patients treated with ranolazine compared to patients treated with placebo at follow-up magnetic resonance examination after five weeks of ranolazine treatment.

Secondary Objectives

Evaluation of the heart's perfusion deficit, dynamic geometry and related variables:

- transmural extent of perfusion deficit
- hyperenhancement
- new hyperenhancement
- left ventricular ejection fraction (LVEF, %)
- left ventricular end-diastolic volume index (LVEDVI, mL/m^2)
- left ventricular end-systolic volume index (LVESVI, mL/m^2)
- stroke volume index (SVI, mL/m^2)
- left ventricular mass index (LVMI, g/m^2)
- left ventricular mass absolute (LV mass, g)

Evaluated Safety Issues

- Adverse events
- Serious adverse events

Study Population

Patients diagnosed with ischemia at first study MRI evaluation after diagnostic coronary angiography with or without initial percutaneous coronary intervention (PCI) and indication of further interventional treatment.

Planned total number: 20 patients

Inclusion criteria

- Male and female patients (females of childbearing potential must have a negative urine pregnancy test and must be using adequate contraceptive precautions, see also study protocol 17.4)
- Performed coronary angiography with or without initial PCI more than 24 hours before MRI
- Remaining ≥70% stenosis of a coronary artery bigger than 2 mm in diameter (not corrected by PCI)
- Indication of further interventional treatment
- Wall motion abnormalities in at least one segment; if segment 17 was affected, additional segments had to show wall motion abnormalities
- History of chronic angina pectoris
- Age ≥ 18 years
- Normal blood pressure < 140/90 mmHg and heart rate < 70 bpm and ≥ 50 bpm at rest
- Sinus rhythm
- Standard therapy: beta-blocker and/or calcium channel blocker (stable for 4 weeks)
- Signed informed consent

Study medication

Ranolazine (Ranexa®) 500 mg batch no.: 13012

Ranolazine (Ranexa®) 750 mg batch no.: 94003

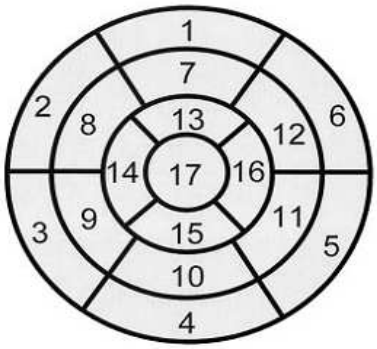
or matching placebo tablets

Assessment of Efficacy

The patients were examined in a 1.5T whole body MRI scanner (Intera, Philips Medical Systems, Best, The Netherlands) using a 32-element cardiac phased-array receiver coil. The MRI was performed according to Figure 3.

All MRI images were evaluated by two experienced and blinded readers together in consensus.

The MRI cine rest and dobutamine stress sequences were divided into 17 myocardial segments, according to the American Heart Association guidelines (24).



1. basal anterior	7. mid anterior	13. apical anterior
2. basal anteroseptal	8. mid anteroseptal	14. apical septal
3. basal inferoseptal	9. mid inferoseptal	15. apical inferior
4. basal inferior	10. mid inferior	16. apical lateral
5. basal inferolateral	11. mid inferolateral	17. apex
6. basal anterolateral	12. mid anterolateral	

Figure 1 Polar plot of the 17 myocardial segments and nomenclature for tomographic imaging of the heart (24)

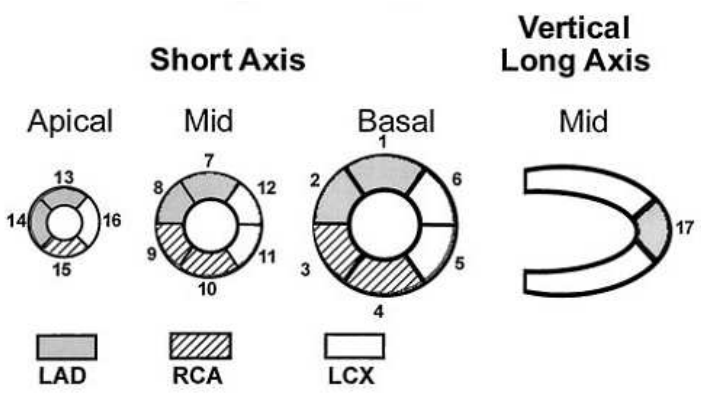


Figure 2 Assignment of the 17 myocardial segments to the territories of the left anterior descending (LAD), right coronary artery (RCA), and left circumflex coronary artery (LCX)

Wall motion of each segment was assessed at rest and at each dobutamine dosage level and was graded as (adapted from (25)):

1 = normal

2 = hypokinesia

3 = akinesia

4 = dyskinesia

An overall wall motion score was calculated as the sum of the scoring in all 17 segments. Inducible ischemia was defined as an overall wall motion score difference of one or more points during maximum stress achieved compared to the overall wall motion score at rest. An improvement of inducible myocardial ischemia at follow-up (V4) was defined as a decrease of the overall wall motion score (calculated as the difference between the wall motion at rest and during stress) of at least 1 point when compared to V0.

For the assessment of perfusion, the transmural extent of perfusion deficit (calculated as the difference between the transmural perfusion at rest and during stress) was evaluated and graded as (26):

0 = no defect

1 = 1% - 25%

2 = 26% - 50%

3 =51% - 75%

4 = 76% - 100%

According to the same scale, the transmural extent of late gadolinium enhancement was graded. A reversible perfusion deficit was defined as a difference of 1 or more points between perfusion score and late gadolinium enhancement score. An improvement of the reversible perfusion deficit at follow-up (V4) was defined as a decrease of the difference between perfusion score (calculated as the difference between the transmural perfusion at rest and during stress) and late gadolinium enhancement of at least 1 point in comparison to V0.

Assessment of Safety

Safety-Relevant Parameters

The incidence of adverse events and serious adverse events was assessed and evaluated. Therefore, at each visit patients were asked for adverse events experienced.

Physical Examination

A physical examination was performed by a physician during visit 0 (screening visit, day -2 to 0) and visit 4 (last visit, day 35). This physical examination covered the following organ systems: cardiovascular, respiratory and abdominal.

Laboratory Examinations

The following laboratory values were assessed from two tubes (15 mL total) of venous blood (EDTA and serum):

Haematology

- Haemoglobin
- Haematocrit
- Red blood cells
- White blood cells and formula
- Platelet count
- Mean platelet volume (MPV)

Biochemistry

- Transaminases (AST, ALT)
- γ-GT
- Total bilirubin
- Serum electrolytes (Na^+, K^+, Mg^{2+}, Ca^{2+})
- Creatinine
- GFR (calculated from serum-creatinine using the Modification of Diet in Renal Disease (MDRD) formula)

Blood samples were transferred for analysis to the on-site routine laboratories within two hours after blood sample collection.

Women of childbearing potential were requested to provide a urine sample for pregnancy testing.

Study procedures and planned visits

Each patient was asked to present for 5 visits in the study centre (visit 0 – visit 4).

Visit 0/ 1

During visit 0 a MRI stress-test was performed to diagnose abnormalities in the motility of the myocardial wall in patients that had agreed to participate in the study by signing the informed consent. Only patients with existing abnormalities were included in the study and at visit 1 received ranolazine or placebo, respectively.

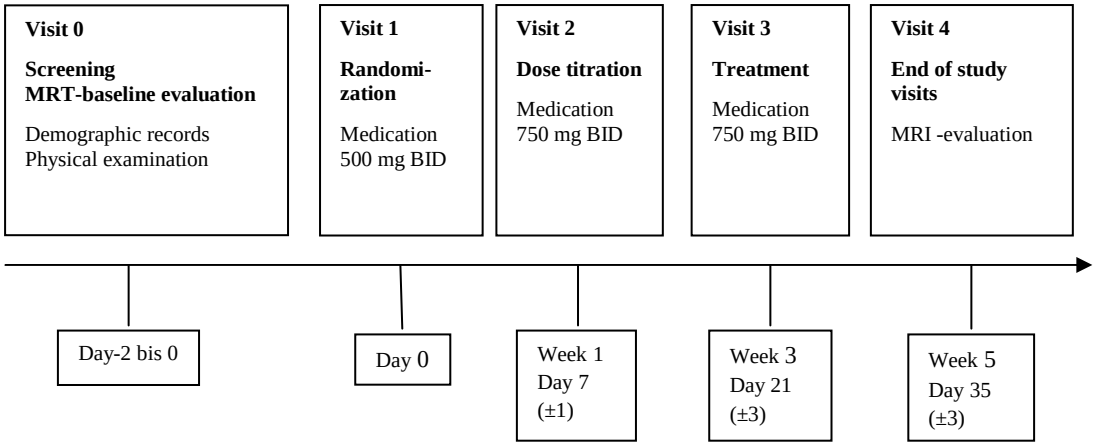
	Cardiovascular risk factors such as lipid status, hypertension or smoking habits were recorded to evaluate the cardiovascular risk profile in accordance with the Framingham Risk Score. In addition, a blood sample was collected for haematology/biochemistry and cholesterol. In case of participating women of childbearing potential in the study a standard pregnancy test was planned at this visit.
Visit 2/ 3	During visit 2 (after one week) and visit 3 (after approximately 3 weeks) assesment of vital signs was performed. In addition, the patient was asked to return unused study medication with which patient compliance was evaluated. At these visits, the patient was also given the opportunity to report adverse events that had occurred in the meantime.
Visit 4	At visit 4 another MRI stress test was performed as well as a blood withdrawal for laboratory parameters In addition, for women of childbearing potential another standard pregnancy test was planned for this visit.

Study Schedule

Table 1 Schedule of Assessments

	Visit 0 Day -2 - 0	**Visit 1** Day 0	**Visit 2** Day 7 (± 1)	**Visit 3** Day 21 (± 3)	**Visit 4** Day 35 (± 3)
Informed consent	x				
Inclusion/ exclusion criteria	x	x			
Demography	x				
Vital signs (heart rate, blood pressure)	x	x	x	x	x
Physical examination	x				x
Medical history	x				
Number of AP attacks/ week	x				
Cardiovascular risk factors	x				
Concomitant medication	x	x	x	x	x
MRI stress test	x				x
ECG	x				x
Haematology, biochemistry, cholesterol	x				x
Urine pregnancy test					
Randomisation		x			
Dispense of study drug		x	x	x	
Return of study drug and compliance assessment			x	x	x
Adverse events	x	x	x	x	x

Study flow chart



Procedure of MRI Stress Test

Patients who received beta-blockers within 24 hours prior to the scheduled MRI were not eligible for MRI analysis. These patients were offered an alternative appointment for MRI within the next 3 days.

The patients were examined in a 1.5T whole body MRI scanner (Intera, Philips Medical Systems, Best, The Netherlands) using a 32-element cardiac phased-array receiver coil. The MRI was performed according to Figure 3. A vector ECG was used for ECG trigger. ECG abnormalities such as ST elevation or ST depression (measured in mV) were recorded in the patient's CRF. When required, MRI images were acquired in end-expirational breath-hold.

The survey was performed in transversal, coronal and sagittal views to allow for optimal planning of the following sequences. Afterwards steady-state free-precession cine images in contiguous short axis and in 4-chamber, 3-chamber and 2-chamber views were performed at rest followed by the dobutamine stress test.

Dobutamine was infused intravenously in 3 min-stages starting at the dose of 10 µg/kg/min body weight and continuing in 10 µg/kg/min steps up to a maximum dose of 40 µg/kg/min (10, 20, 30, 40 µg/kg/min) until the target heart rate (defined as (220-age) × 0.85/min) was reached. If the target heart rate could not be achieved by this procedure, atropine was administered in 0.25 mg increments up to a maximal dose of 1.0 mg. The stress test was discontinued when the target heart rate was reached or a discontinuation criterion occurs. In case of MRI discontinuation, the heart rate reached until discontinuation of the MRI

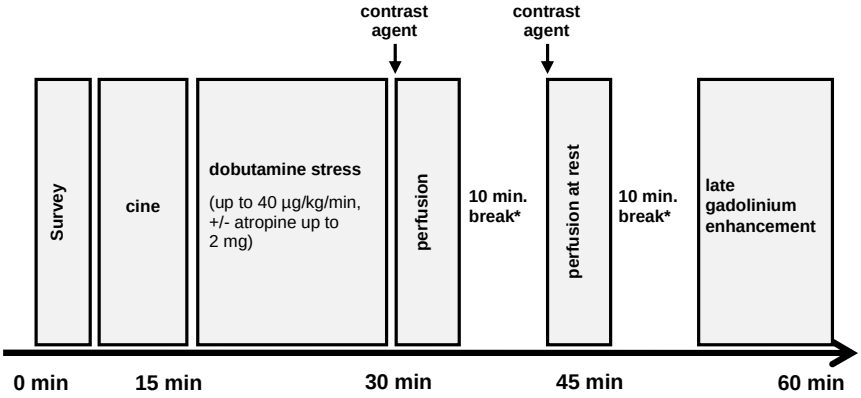
investigation was defined as the maximum stress level (MSL) achieved for this patient.

For evaluation of ventricular volumes, global and regional function, a standard steady-state free-precession sequence in contiguous short and long axis geometry covering the entire left ventricle were acquired.

First-pass of a gadolinium-based contrast agent (0.1 mmol/kg) were visualized using a steady-state free-precession sequence in three short axis (apical, midventricular and basal). Ten minutes later, rest-perfusion using the same sequence was acquired using a second contrast bolus (0.1 mmol/kg).

After another ten minutes, a 3D inversion-recovery sequence (late gadolinium enhancement) covering the entire left ventricle was acquired for visualization and quantification of myocardial necrosis and microvascular obstruction.

If necessary, metoprolol was administered during the ten minutes breaks to reduce the heart rate.



* if necessary, metoprolol will be administered to reduce the heart rate

Figure 3 Procedure of MRI Stress Test

Dosing regimen

Dosing of Ranolazine: Titration 500 mg BID (visit 1) for one week to 750 mg BID at day 7 (visit 2) for 4 weeks

Dosing of the matching placebo: Same regimen as Ranolazine

Route of administration: oral for both Ranolazine and matching placebo.

Primary objective

Primary objective of this study was to evaluate the efficacy of ranolazine treatment in terms of changes of wall motion abnormalities in ischemic areas in patients treated with ranolazine compared to patients treated with placebo at follow-up magnetic resonance examination after five weeks of ranolazine treatment.

Secondary objective

Evaluation of the heart's perfusion deficit, dynamic geometry and related variables:

- Transmural extent of perfusion deficit
- Hyperenhancement
- New hyperenhancements
- Left ventricular ejection fraction (LVEF, %)
- Left ventricular end-diastolic volume index (LVEDVI, ml/m^2)
- Left ventricular end-systolic volume index (LVESVI, ml/m^2)
- Stroke volume index (SVI, ml/m^2)
- Left ventricular mass index (LVMI, g/m^2)
- Left ventricular mass absolute (LV mass, g)

3 Results

Premature termination of the study

The study was terminated prematurely on 28-Jun-2013 because it could not be completed within a reasonable time frame due to low recruitment rate.

Between November 2012 and June 2013 only one patient could be enrolled. Five other patients signed the informed consent form but after the screening examinations were not eligible for participation according to the study protocol, i.e. did not fulfil inclusion criteria or met exclusion criteria, respectively.

Modifications of inclusion criteria were discussed extensively, however a feasibility analysis showed, that even with modified inclusion criteria it would have been unlikely that a sufficient number of patients could be identified within an adequate period of time.

Also the participation of an additional Screening Centre did not yield better results.

Apparently the remaining stenoses after a coronary angiography do not cause relevant wall motion abnormalities to meet inclusion criterion 5.

First patient in: 15. Nov. 2012

Last patient completed: 19. Dec. 2012

Study population (summary)

In total, six patients signed the informed consent.

One patient (pat. 101) completed the study according protocol.

Four further patients (pat. no. 103,104, 105 and 106) were screening failures and did not receive any study medication.

One further patient withdrew his consent before any study-related measures or examinations had been performed (without pat. no.).

Demographics

Table 2 Demographic Data of the participating subjects (including screening failures)

Patient No.	Age [years]	Sex	Ethnicity	Informed consent signed on
101	68	Male	Caucasian	15-Nov-2012
103	54	Male	Caucasian	15-Jan-2013
104	54	Male	Caucasian	31-Jan-2013
105	49	Male	Caucasian	21-Feb-2013
106	73	Female	Caucasian	03-Jun-2013

Physical examination

None of the patients showed abnormalities during the cardiovascular, respiratory and abdominal examination.

Table 3 Results of the physical examination

Patient No.	Cardio-vascular	Respiratory	Abdominal	Neurological
101	Normal	Normal	Normal	Not done
103	Normal	Normal	Normal	Not done
104	Normal	Normal	Not done	Not done
105	Normal	Normal	Normal	Not done
106	Normal	Normal	Normal	Not done

Table 4 Results of the cardiovascular examination

Patient No.	Cardio-vascular Stenosis [%]	LVEF [%]	LVEDVI [ml/m^2]	LVESVI [ml/m^2]	SVI [ml/m^2]	LVMI [g/m^2]	LVMABS [g]
101	90	42	112.7	65.6	47.1	114.6	236
103	75	47	109	58	51	55.45	122
104	75	56	91	40	51	61.3	122
105	75	61	76.3	30.1	46.2	55.3	110
106	90	56	71	31	40	0.7	90

LVEF = Left ventricular ejection fraction
LVEDVI = Left ventricular end-diastolic volume index
LVESVI = Left ventricular end-systolic volume index
SVI = Stroke volume index
LVMI = Left ventricular mass index
LVMABS = Left ventricular mass absolute

Baseline data

Table 5 Results of the Dobutamine Stress Test for patient 101

Patient 101				
	WM Score	Heart Rate (min^{-1})	Systolic BP (mmHg) during the test	Diastolic BP (mmHg) during the test
Rest	30	70	140	85
Dobutamine 10 µg/kg/min	30	85	140	80
Dobutamine 20 µg/kg/min	29	95	120	70
Dobutamine 30 µg/kg/min	30	115	100	60
Dobutamine 40 µg/kg/min	30	125	110	50
Dobutamine 40 µg/kg/min + 0,25 mg atropine	-	-	-	-

WM Score = wall motility score; BP = Blood Pressure

Although the total SUM score remained 30, inclusion criterion 5 (wall motion abnormalities in at least one segment) was fulfilled. Wall motion abnormalities were seen in myocardial segment 15 (apical inferior). Wall motion abnormality in segment 6 (basal anterolateral) improved by 1 degree during the dobutamine stress test.

Efficacy data (Visit 4)

For patient (patient 101) comparative data of visit 1 and visit 4 were recorded.

The patient had received ranolazine at 500mg BID from 15-Nov-2012 until 21-Nov-2012 and ranolazine at 750mg BID from 21-Nov-2012 until 19-Dec-2012.

This patient´s medical history included:

- myocardial infarction,
- coronary heart disease,
- transient ischemic attacks (TIA),
- intrarenal abdominal aortic aneurism,
- renal impairment,
- allergy to penicillin,
- arterial hypertension,
- microcytic anemia and
- hyperlipoproteinemia.

The patient had used the following drugs concomitantly:

Table 6 Concomitant medication of patient 101

Drug name	Posology	Indication	Start	End
ASS	100mg QD	Coronary Heart Disease	2012-09	Ongoing
Plavix	75mg QD	Stent Thrombosis	2012-09	Ongoing
Simvabeta	20mg QD	Hyperlipo-proteinemia	2012-09	Ongoing
Metohexal	47,5mg QD	Hypertension	2011-12	2012-11-15
Ramipril plus	2,5mg/12,5mg QD	Hypertension	2011-12	2012-11-15
Pantoprazol	40mg QD	Gastric Protection	2011-12	Ongoing
Marcumar	*	Plaque A ascendens	2010-09	Ongoing
Metoprolol	95mg BID	Hypertension	2012-11-16	Ongoing
Ramipril	5mg QD	Hypertension	2012-11-16	Ongoing
Hydrochloro-thiazid	25mg QD	Hypertension	2012-11-16	Ongoing

*according to INR value

Table 7 Comparison of Wall Motility Score, Heart Rate and Blood Pressure during the test (Baseline and at Visit 4) for patient 101

Patient 101								
	WM Score		Heart Rate (min^{-1})		Systolic BP (mmHg)		Diastolic BP (mmHg)	
Visit	**1**	**4**	**1**	**4**	**1**	**4**	**1**	**4**
Rest	30	29	70	75	140	163	85	96
Dobutamine 10 µg/kg/min	30	29	85	74	140	172	80	96
Dobutamine 20 µg/kg/min	29	29	95	86	120	164	70	77
Dobutamine 30 µg/kg/min	30	27	115	99	100	161	60	73
Dobutamine 40 µg/kg/min	30	28	125	112	110	157	50	68
Dobutamine 40 µg/kg/min + 0,25 mg atropine	-	29	-	129	-	152	-	75

WM Score = wall motility score; BP = Blood Pressure

Table 8 Comparison of Perfusion Deficit Grade, Heart Rate and Blood Pressure during the test (Baseline and at Visit 4) for patient 101

Patient 101				
	Perfusion Deficit grade Maximum stress level (MSL)			
	SUM Score	Heart Rate (bpm)	Systolic BP (mmHg)	Diastolic BP (mmHg)
Baseline	32	125	110	50
Visit 4	27	129	152	75
	Perfusion Deficit grade Rest			
	SUM Score	Heart Rate (bpm)	Systolic BP (mmHg)	Diastolic BP (mmHg)
Baseline	0	70	140	85
Visit 4	12	84	n.d.	n.d.
	Late Enhancement grade Rest			
	SUM Score	Heart Rate (bpm)	Systolic BP (mmHg)	Diastolic BP (mmHg)
Baseline	22	95	120	66
Visit 4	16	85	154	81

SUM Score = ; BP = Blood Pressure

Primary objective

Primary objective was the improvement of induced wall motility abnormalities in ischemic areas after 5 weeks of treatment with ranolazine compared to placebo treatment.

An improvement of inducible myocardial ischemia at follow-up (V4) was defined as a decrease of the overall wall motion score (calculated as the difference between the wall motion at rest and during stress) of at least 1 point when compared to V0.

Table 9 Effect of inducible ischemia at visit 4 compared to baseline for patient 101

Patient 101	
	Difference between WM-Score at rest and during maximum stress level (MSL)
Baseline	0
Visit 4	0

These data suggest no improvement of the condition of the patient.

Secondary objective

An improvement of the reversible perfusion deficit at follow-up (V4) was defined as a decrease of the difference between perfusion score (calculated as the difference between the transmural perfusion at rest and during stress) and late gadolinium enhancement of at least 1 point in comparison to V0.

Table 10 Difference between Perfusion Deficit grade (MSL) and Late Enhancement Baseline and Visit 4 for patient 101

Patient 101	
	Difference between Perfusion Deficit grade (MSL) and Late Enhancement
	SUM Score
Baseline	10
Visit 4	11

There was no improvement of the reversible perfusion deficit.

Safety data

Primary safety parameter was the incidence of adverse events and serious adverse events.

In the course of the study no serious or non-serious adverse events were reported.

Conclusion

The study was terminated prematurely due to a low recruitment rate. It is possible that after the initial coronary angiography (mostly with performed PCI), the remaining stenosis is not relevant enough to identify wall motion abnormalities in these patients.
The evaluation of the results of only one patient does not allow for generalisation or further interpretation.