Synopsis of the Clinical Trial Report

Effects of selective serotonin re-uptake inhibition on MOrbidity, mOrtality and mood in Depressed Heart Failure patients

A double-blind, randomised, placebo-controlled, parallel group study to determine the effects of serotonin re-uptake inhibition with the SSRI escitalopram on morbidity, mortality and mood in depressed patients with chronic systolic heart failure

MOOD-HF

investigational product:	Escitalopram (10-20 mg/day)
Indication:	Chronic systolic heart failure, evidence of comorbidity with current episode of major depression
Phase of the clinical trial:	IV
EudraCT-No:	2007-006609-25
Trial Registration:	ISRCTN33128015

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Start of clinical trial:	11.03.2009
End of clinical trial:	02.09.2014

Report Signatures

With their signatures, the signing authors agree with the contents of presented report. The presented clinical trial was performed according to the principles of the Declaration of Helsinki, Good Clinical Practice and according the applicable legal requirements.

Legal representative of the sponsor and coordinating investigator:

Prof. Dr. med. Christiane Angermann

14. 9. 2015
Date

[redacted]
Signature

Table of Contents

1 Sponsor and authorized representative of the sponsor

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2 Name of Finished Product

Cipralex®

3 Name of Active Substance

Escitalopram

4 Individual Study Table

not applicable

5 Title of Study

Effects of selective serotonin re-uptake inhibition on MOrbidity, mOrtality and mood in Depressed Heart Failure patients - **MOOD-HF**

The version of the trial protocol final 1.5 (23.01.2009, incl. Amendment 01 final 1.1) was approved by the regulatory authority and positively evaluated by the lead ethics committee.

There have been 11 amendments to the clinical trial. A summary is find in the appendix (chapter 22.1).

6 Investigators and

7 Study centre(s)

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8 Publication (reference)

The trial was be registered at the online-register www.controlled-trials.com and has the register-No ISRCTN33128015.

Study design information was published on 2007:

Angermann CE, Gelbrich G, Störk S, Fallgatter A, Deckert J, Faller H, Ertl G; MOOD-HF Investigators.
Rationale and design of a randomised, controlled, multicenter trial investigating the effects of selective serotonin re-uptake inhibition on morbidity, mortality and mood in depressed heart failure patients (MOOD-HF). Eur J Heart Fail. 2007 Dec; 9(12):1212-22.

9 Studied period (years)

Date of first enrolment: 11.03.2009

Date of last completed: 02.09.2014

10 Phase of development.

The MOOD-HF was an investigator-initiated phase IV trial.

11 Objectives of the trial

Primary Objectives:

To investigate the effects of selective serotonin re-uptake inhibition with the SSRI escitalopram on morbidity and mortality in depressed patients with CHF. The primary endpoint is the time to a first clinical event, either death or unplanned hospitalisation, whichever occurs first, for any reasons.

Secondary Objectives:

Major secondary objectives:

- To estimate the reduction of depression attributable to *escitalopram* as measured by the PHQ-9 and MADRS scales.
- To check whether reduction of morbidity and mortality possibly found in the primary analysis is mediated by reduction of depression.

Further secondary objectives:

To investigate the effects of treatment with *escitalopram*, accounting for patient co-variables (sociodemographic, history, type and baseline severity of heart failure, other co-morbidity, history of vs. newly diagnosed depression), on the following secondary endpoints:

- Time alive out of hospital
- Cardiovascular morbidity and cardiovascular mortality
- General and disease-related quality of life as measured by the SF-36 and KCCQ scales, as well as anxiety as measured by the PHQ-GAD-7 scale
- Extent of cognitive dysfunction as assessed by the MMSE
- Clinical parameters of severity of CHF (e.g. New York Heart Association functional class, walk distance in the 6-minute walk test)
- Laboratory parameters of severity of CHF (e.g natriuretic peptides, troponins)
- Technical parameters of severity of CHF (e.g. left ventricular ejection fraction as determined by echocardiography)
- Adherence to study medication (pill count, *escitalopram* plasma levels)
- Adherence to CHF medication
- Safety and tolerability of study medication
- Frequency and severity of adverse events
- Function of the sympathetic nervous system (e.g. mean heart rate, heart rate variability, arrhythmias, plasma cortisol, circadian variation of cortisol in saliva, urine norepinephrine excretion, plasma aldosterone)

12 Clinical trial design / Methodology

MOOD-HF is a prospective randomized, double-blind, placebo-controlled, two-armed, parallel group multi-center Phase IV trial.

Eligible patients were randomly assigned to receive either escitalopram (10 or 20 mg once daily) or matching placebo. The randomisation ratio was 1:1 using Pocock's minimization algorithm. Randomisation was stratified by Gender (male/female), Age (<70 / ≥70 years), depression severity (2 categories derived from PHQ-9 Score ≤16 / >16) and hospitalization within the past 4 weeks at the time of SCID (yes/no).

13 Number of patients (planned and analysed)

The planned sample size was 700 patients (350 patients per group), expecting an effect size of 27% versus 36% of cumulative events in patients receiving escitatopram or placebo, respectively, corresponded to a hazard ratio of 0.705. Accordingly, to achieve a power of 80% a total of 257 endpoint events confirmed by the independent endpoint committee were needed.

After recruitment of 240 patients a total of 115 primary outcome events had been recorded, and the Kaplan-Meier estimate of the overall annual event rate amounted to 60%, - 29.5% more than the anticipated average event rate of 31.5%. Taking into account the remaining time under observation and drop-out rate of the patients that were already recruited, it could be expected that these patients would contribute another 55 events. In accordance with the assumption (based on the rates observed so far) that 50% of newly recruited patients observed for 12 months would contribute a primary outcome event, we calculated that another 174 patients would be sufficient to achieve the remaining 87 events required to complete the MOOD-HF Study.

During the study, 11086 patients underwent PHQ-9 screening and of these 773 consented to a SCID interview. Of 508 patients with SCID-confirmed major depression 376 satisfied all in- and exclusion criteria and were randomized. Four patients withdrew their decision before receiving study medication. Thus, 372 patients (185 receiving escitalopram and 187 placebo) constituted the intention-to-treat population.

The corresponding CONSORT-Flowchart is found in the appendix (chapter 22.2).

14 Diagnosis and main criteria for inclusion

Patients must meet ALL of the following criteria:

- Age ≥18 years
- Chronic systolic heart failure of any etiology with
  - current NYHA class II-IV and
  - at least one measurement of LVEF <45% by echocardiography or laevocardiography or cardio-MRT within the preceding three months
- Diagnostic and Statistical Manual of Mental Disorders-IV diagnosis of current major DEP based on the Structured Clinical Interview for DSM-IV (SCID) performed by a certified psychiatric/psychosomatic specialist.
- Provision of written informed consent.

No inclusion was possible, if any of the following exclusion criteria was fulfilled:

- Recent history of acute myocardial infarction (<3 months)
- Acute cardiac decompensation
- Recent (<3 months) or planned major cardiac surgery (<12 months)
- Advanced renal failure (MDRD <30ml/min/1,73m²)

- Moderate or severe hepatic insufficiency (plasma level of serum transaminases > threefold of the upper level of the normal range) or manifest hepatic failure
- Thyreotoxicosis
- Other medical contraindication against treatment with SSRI
- Significantly reduced life expectancy due to other comorbidity (e.g. malignancy)
- Use of any antidepressants including SSRI, lithium or anticonvulsants for mood disorder in adequate dosage (according to evidence based recommendations for clinical effectiveness), with sufficiently long duration (at least 8 weeks) of antidepressive treatment and positive clinical outcome
- Currently undergoing any form of psychotherapy
- Absence of response to a previous adequate trial of escitalopram treatment
- Life time history of early termination (<8 weeks) of escitalopram treatment because of adverse events or side effects
- Life time history of early termination (<8 weeks) of other SSRI (e.g. sertraline, citalopram) treatment because of adverse events or side effects
- SCID documented bipolar affective disorder
- Severe depressive episode with psychotic features
- Evidence of substance abuse or dependency during the previous 12 months
- Moderate and severe dementia (MMSE <18)
- Serious risk of imminent suicide based on clinical judgment
- Participation in another clinical trial
- Inability to comply with PHQ-9 and/or SCID testing and/or telephone monitoring for mental or linguistic reasons or lack of access to telephone
- Pregnancy or nursing period
- Women with child bearing potential without effective contraception during the conduct of the trial
- Expected low compliance with the visit schedule or telephone monitoring (e.g., due to comorbidity or travel distance to the trial site)
- Patients with normal ventricular activation (no bundle branch block (total or incomplete) no other intraventricular conduction delay, and no pacemaker) and known QTc prolongation ≥ 500 ms **or** inborn long QT syndrome
- Patients with current treatment with drugs inducing QT prolongation, such as antiarrhythmic drugs class IA and III, anti-psychotics, tricyclic antidepressants

15 Test product, dose and mode of administration, batch number

Cipralex® contains escitalopram (10 mg) as active ingredient and was administrated once daily oral as a tablet.

Patients start with a dose of 5 mg once daily and are uptitrated after 3 weeks to 10 mg once daily. After further three weeks patients up to 65 years old are uptitrated to 20 mg/day. Slower up-titration was permitted for tolerability reasons. Twelve weeks after study start the final dosage of study drug must be reached.

Manufacturer: H.Lundbeck A/S, Ottiliavej 9, DK-2500 Kopenhagen-Valby, Danmark

Labelled by: Haupt Pharma Wülfing GmbH, Bethelner Landstr. 18, D-31028 Gronau/Leine, Germany

Batch No (Customer, Escipalopram Placebo): 2116115, 2174029, 2224637, 2278492

Batch No (Customer, Escipalopram 10mg): 2118528, 2180023, 2223101, 2276562, 2354584

16 Duration of treatment

Maximum individual study and treatment duration was 24 months, followed by a one month down-titration phase. After last patient in, the next scheduled appointment constituted the final study visit in patients still in the study. Thus, the minimum treatment duration was 6 months, followed by a one month down-titration phase.

17 Reference therapy, dose and mode of administration, batch number

Not applicable

18 Criteria for evaluation: Efficacy, Safety

The primary efficacy outcome was time to a first event of the composite of all-cause death or hospitalization. Planned hospital admissions for non-cardiac causes were not considered an outcome event. Pre-specified secondary outcomes included changes from baseline to 12 weeks in the MADRS sum-score[23], subgroup and component analyses of the primary outcome, time to cardiovascular death or hospitalization for heart failure, escitalopram serum levels, changes in heart failure pharmacotherapy, and variables describing heart failure severity, cardiac status and safety. Adjudication of time-to-event outcomes was carried out by an independent endpoint adjudication committee according to prespecified criteria.

The safety was judged by tolerability of study drug, frequency and severity of adverse events and the need for additional psychiatric intervention.

19 Statistical methods

Analyses were performed according to the intention-to-treat (ITT) principle, which included all subjects who took at least one dose of study medication. For the primary outcome and changes in the MADRS score we also performed a pre-specified exploratory analysis of patients on study medication (OSM), where individuals were censored when they stopped and did not re-start taking study medication.

Time-to-event endpoints were analyzed by Cox regression. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). Analyses were performed for ITT and OSM data sets for each endpoint, once unadjusted and once adjusting for randomization strata. The pre-specified primary hypothesis test was the adjusted ITT analysis of all-cause death and hospitalization. Time-to-event curves were generated using the Kaplan-Meier method.

Changes in the MADRS sum-scores between baseline and 12 weeks were assessed by analysis of covariance. Generalized estimating equations were used for repeated measurement analyses of all consecutive MADRS assessments.

Analysis of covariance and ordinal or binary logistic regression models were used to analyze other quantitative ordinal and binary outcomes as appropriate. Analyses of frequencies of serious adverse events were adjusted for time alive and under observation in the study.

IBM SPSS version 22.0 software (Armonk, NY) was employed.

20 Summary – Conclusions: Efficacy Results, Safety Results, Conclusion

20.1 Patients

Groups were balanced regarding baseline characteristics (Table 1). Patients were elderly and predominantly male. LVEF was impaired and cavity size enlarged. On average, depression

severity was moderate[1]. Most patients were receiving guideline-recommended heart failure pharmacotherapy[2]. Only 12% had a history of depression.

	Escitalopram (N=185)	Placebo (N=187)
Demographics		
Age – years (means±SD)	62.2±12.0	62.3±11.9
Female sex – no. (%)	45 (24)	46 (25)
Heart failure characteristics		
NYHA class III-IV – no. (%)	88 (48)	108 (58)
LV ejection fraction – % (means±SD)	34.9±8.5	34.7±8.2
LV end-systolic diameter – mm (means±SD)	47.0±12.8	47.1±10.6
NT-proBNP – pg/mL, median (quartiles)	837 (289-2512)	781 (313-1935)
Six-minute walk distance – m (means±SD)	356±125	342±125
Variables determined from the ECG		
Heart rate – bpm (means±SD)	69.3±12.9	69.8±13.3
QTc-time (Bazett) – ms (means±SD)	443.0±54.3	448.9±49.9
QTc-time (Bazett) >450 ms – no. (%)	77 (42)	92 (51)
QRS duration – ms (means±SD)	121.9±34.1	124.8±37.6
Atrial fibrillation – no. (%)	38 (21)	33 (18)
Depression characteristics		
History of depression – no. (%)	23 (12)	23 (12)
PHQ-9 sum score at screening (means±SD)	14.7±3.8	14.6±3.5
MADRS sum score at randomization (means±SD)	20.2±8.6	22.0±8.8

Table 1: Baseline characteristics of study participants, according to study group

20.2 Efficacy Results

The primary end point occurred in 116 (63%) and 119 (64%) of the participants on escitalopram or placebo, respectively, HR for escitalopram 0.99, CI 0.76-1.27, P=0.92 (Figure 1A). When only events on study medication were considered the HR was 1.03, CI 0.79-1.34, P=0.85 (Figure 1B). All-cause death occurred in 18 (10%) and 14 (7%), respectively, HR 1.39, CI 0.69-2.79, P=0.36. No significant between-group differences were found for any time-to-event outcomes (Table 2). Neither adjustment for randomization strata nor analysis of OSM events only yielded materially different results.

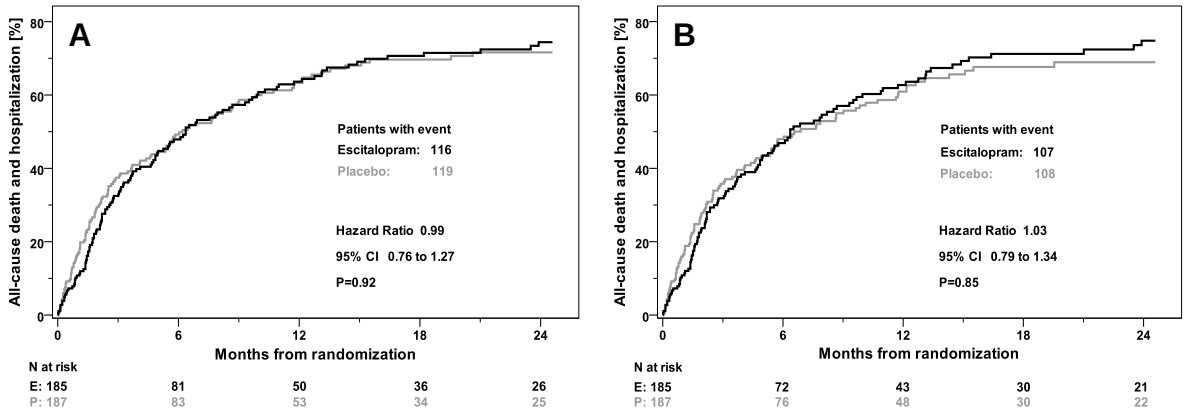


Figure 1: Kaplan-Meier Estimates for Primary End Point Events.
Panel A shows the Kaplan-Meier curves for the primary composite outcome of death or hospitalization from any cause according to an intention-to-treat analysis. Panel B shows the Kaplan-Meier curves for a pre-specified exploratory analysis of the population on study medication, where patients were censored at the time they stopped and did not re-start taking the study drug.

Mean baseline MADRS scores were 20.2+8.5 in the escitalopram and 21.4+8.5 in the placebo arm. At 12 weeks, patients took comparable dosages of study medication (15.8+6.4mg and

14.9+7.6mg). MADRS scores had decreased to 11.2+8.1 and 12.5+7.6, respectively, both P<0.001, and the estimated escitalopram effect was–0.9 (CI –2.6-+0.7, P=0.26. Figure 2A displays the trajectory of MADRS improvement across the treatment phase. The overall escitalopram effect did also not differ from that of placebo. The OSM analysis yielded comparable results (Figure 2B).

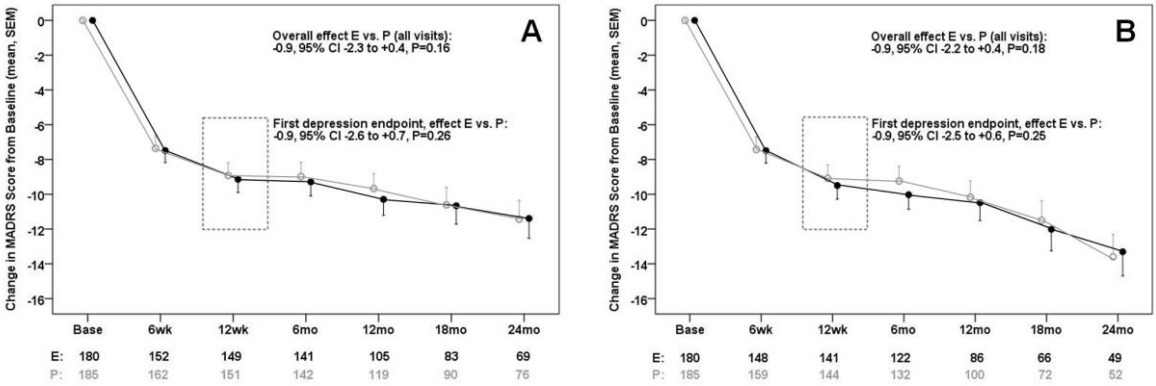


Figure 2: Kaplan-Meier Estimates for Serial Changes from Baseline in the Score of MADRS
Panel A shows the Kaplan-Meier curves for the changes in MADRS score according to intention-to-treat analysis in the escitalopram (E) versus the placebo (P) arm. Panel B shows the Kaplan-Meier curves for prespecified exploratory analysis of the population on study medication, where patients were censored at the time they stopped and did not re-start taking the study drug. ☐ marks assessment at 12 weeks (secondary outcome).

20.3 Safety Results

After 6 and 12 weeks the proportion of patients withdrawn from treatment was 11 and 15% (21/185 and 25/185 patients) under escitalopram as compared to 5 and 7% (10/187 and 14/187 patients) under placebo, P=0.04 and 0.02, respectively. Across the entire study, participation was comparable, and HR for study withdrawal, discontinuation of study medication and open antidepressant therapy did not differ in escitalopram- and placebo-treated patients. Furthermore, there were no between-group differences in safety parameters and rates of serious adverse events except for worsening depression, which occurred more often under placebo (see Table 2).

	Escitalopram	Placebo	P-value
QTc (Bazett) [ms]			
Patients with follow-up measurements – no. (%)	140 (76)	149 (80)	0.38
Maximum increase* from baseline – mean (SD)	25 (58)	15 (46)	0.06
Categories of maximum increase – no. (% of available)			
No increase	46 (33)	47 (32)	
>0 - 50 ms	58 (42)	73 (49)	
>50-100 ms	25 (18)	26 (18)	
Estimated GFR [mL/min/1.73m^2]			
Patients with follow-up measurements – no. (%)	164 (89)	170 (91)	0.50
Number of follow-up measurements – mean (SD)	5.3 (1.7)	5.4 (1.7)	0.48
Maximum decrease* from baseline – mean (SD)	13 (16)	13 (12)	0.63
Heart rate from the electrocardiogram [bpm]			
Patients with follow-up measurements – no. (%)	141 (76)	150 (80)	0.38
Number of follow-up measurements – mean (SD)	2.3 (0.8)	2.3 (0.7)	0.51
Maximum decrease* from baseline – mean (SD)	6.0 (12.8)	6.6 (12.0)	0.77
Serious adverse event (SAE)			
Total number of events, any SAE	272	312	0.59
Total number of cardiovascular events	130	148	0.63
Number of patients with event, any SAE	106 (57)	112 (60)	0.71
Number of patients with cardiovascular event	68 (37)	73 (39)	0.73

	Escitalopram	Placebo	P-value
Worsening heart failure	37 (20)	43 (23)	0.47
Arrhythmia	22 (12)	16 (9)	0.24
Cerebrovascular event	7 (4)	3 (2)	0.20
Peripheral vascular event	2 (1)	6 (3)	0.19
Other cardiovascular event	21 (11)	27 (14)	0.44
Medical SAE other than cardiovascular	24 (13)	25 (13)	>0.99
Renal failure	6 (3)	6 (3)	0.96
Gastrointestinal event	11 (6)	10 (5)	0.72
Other medical event	8 (4)	15 (8)	0.16
Psychiatric SAE	15 (8)	23 (12)	0.20
Worsening depression	9 (5)	21 (11)	0.03
Other	8 (4)	2 (1)	0.08
Trauma/injury	14 (8)	9 (5)	0.26
Other surgery	6 (3)	11 (6)	0.27
Infection	19 (10)	21 (11)	0.80
Tumor	8 (4)	5 (3)	0.37
Bleeding	10 (5)	8 (4)	0.66
Other	22 (12)	18 (10)	0.41

Table 2: Changes in safety parameters

* Maximum increase/decrease refers to the largest change from baseline observed at any follow-up visit

20.4 Conclusions

In the multisite randomized MOOD-HF study involving 372 patients with stable systolic heart failure and depression escitalopram did not decrease the elevated mortality and morbidity risk associated with this comorbidity. The overall incidence of severe cardiovascular events, the gold standard for safety, was comparable between escitalopram and placebo.

We obtained a neutral result while investigating for the first time the composite of all-cause mortality and hospitalization in a heart failure population. This result was based on a sizable number of adjudicated outcome events. Moreover, since the CI of the observed HR did not comprise the HR underlying our sample size calculation, the study hypothesis was significantly rejected.

In line with SADHART-CHF[3], escitalopram did not reduce MADRS scores more than placebo. This is contrary to evidence from patients with coronary disease[12-16] including a meta-analysis[9], where SSRI therapy was associated with significantly greater improvement of depressive symptoms. Since escitalopram levels were in the therapeutic range[10] in MOOD-HF, our results indicate true absence of antidepressant efficacy supporting the concept of alternative pathophysiological mechanisms for depression in somatic illnesses, which result in symptoms less or, as in heart failure, unresponsive to antidepressants. Placebo-controlled trials for marketing authorization of antidepressants tend to exclude such patients. Our observations indicate that their efficacy results are not necessarily transferable to populations, in whom these drugs may then be prescribed.

Multiple factors may be responsible for the improvement of depression in both groups. Placebo effects play a major role in depression[11]. Multidisciplinary management involving up-titration of heart failure medication, interactions with the multidisciplinary team and motivation for better adherence and self-care might thus have also ameliorated depression. Furthermore, participants were recruited when seeking advice for cardiac problems. Most were unaware of their depression before screening, which was on average less severe than that of patients typically enrolled in antidepressant trials[12]. Improvement of heart failure as evidenced by higher LVEF and lower NT-proBNP levels might have also improved overlapping depressive symptoms as e.g. fatigue in such patients.

LVEF and NT-proBNP levels are accepted outcome markers, and their improvement predicts better survival[2,13,14]. In MOOD-HF, mortality rates were low in both groups, particularly when

compared to those reported from SADHART-CHF[3], and rather in the range reported from The Heart Failure- A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study or the Patient-Centered Disease Management for Heart Failure (PCDM) trial, which enrolled unselected patients with or without depression[15.16]. In contrast, rehospitalization rates were high. Both findings might result from comprehensive therapy and surveillance. Comparable effects were obviously not attainable by psychosocial support in SADHART-CHF[3].

Side effects involved with initiation of SSRI therapy[4] led to higher early withdrawal rates in escitalopram-treated patients, but across the entire study tolerability was comparable between groups. There were no differences in various additional safety parameters including heart rate, blood pressure, renal function and QTc-interval. However, a non-significant trend toward a greater risk of primary outcome events was observed in escitalopram-treated patients who were older, or had more severe heart failure, depressive symptoms or cognitive impairment. Furthermore, NT-proBNP levels decreased more slowly under escitalopram, and cavity size did not decrease as in placebo-treated subjects. Interpretation of these secondary findings demands great caution, but the possibility of unfavorable long-term effects of escitalopram on cardiac status must be considered.

A chief limitation of MOOD-HF is its lack of generalizability. Numerous patients were not randomized because of contraindications. Therefore, our results cannot be extended beyond the patients examined in MOOD-HF. Excellent compliance with the study drug in escitalopram-treated subjects suggests that they were perhaps also particularly motivated to follow other treatment recommendations. MOOD-HF did not assess escitalopram alone, and beneficial effects of study participation per se could have blunted possible escitalopram effects. Nevertheless, considering the paucity of prognostic benefit and potential side effects of antidepressant pharmacotherapy our results suggest multidisciplinary treatment including comprehensive heart failure management as a primary care model.

Presently, multidisciplinary care models are not reimbursed outside clinical trials in most countries. Therefore, further research addressing prospectively the efficacy and cost-effectiveness of such treatment approaches in depressed patients with heart failure is urgently needed.

In conclusion, MOOD-HF found that adding escitalopram to multidisciplinary care in patients with stable systolic heart failure and depression neither reduced the composite primary outcome of all-cause death or hospitalization, nor depression. Although the overall incidence of severe cardiovascular events was comparable in both groups, unfavorable long-term effects of escitalopram on cardiac status cannot be fully excluded.

21 Date of report

01.09.2015

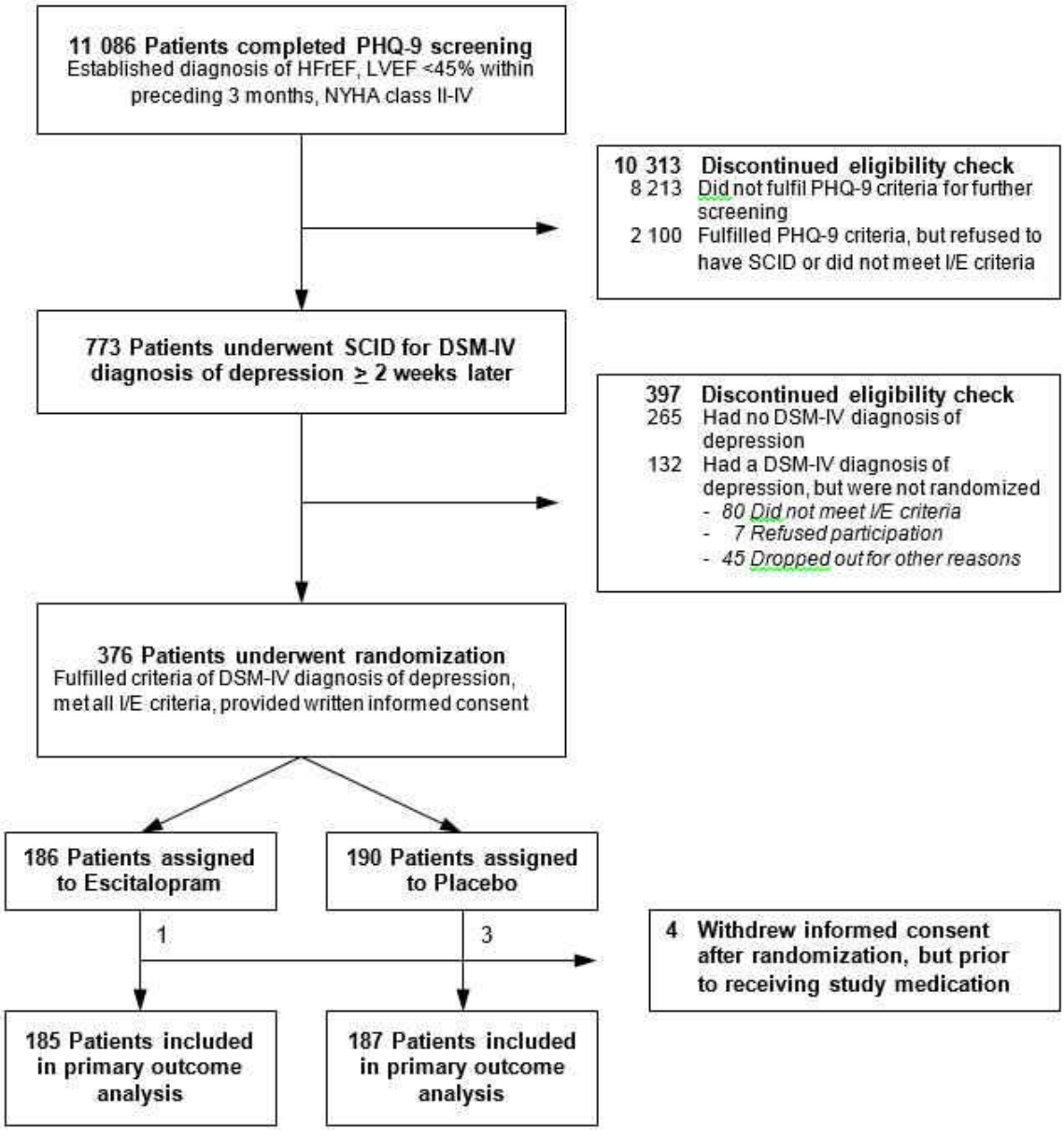
22 Appendices

22.1 Amendments of the MOOD-HF-Study

No.	Document/Version	Contents
01	Final 1.1 (23.01.2009)	Amendment in the course of the initial trial application: - Increase of the PHQ-9 sum Score from 11 to 12 as decision to perform the SCID-Interview (step 2 of the screening process) - Enrolment of the scientific Add-on project OSMO-MOOD - Study update (timelines, number of trial sites, assessment schedule, storage of biomaterial) - Corrections (IP adress of randomisation tool, study medication, exclusion criteria, stratification features) - Documentation and reporting of SAE
02	Final 3.1 (14.10.2009)	- Exclusion criterium (patients with insufficient dosage can be included) - Process of patient information - Addition of new trial centres (Leipzig, Rostock) - Closure of trial centre (Berlin Charité) - Notification of new investigators/departure of investigators in trial centres Würzburg, Essen, Lübeck, Marburg
03	Final 1.0 (22.06.2010)	- Addition of new trial centres (Magdeburg, Hamburg, Hannover) - Notification of new investigators/departure of investigators in trial centres Würzburg, Göttingen, Homburg, Lübeck, Mannheim, Marburg, Rostock
04	Subst. Amendment Form 02.12.2010	- Notification of new investigators in trial centres Würzburg
05	Final 1.0 (23.02.2011)	- Notification of new adress of the coordination investigator and trial centre Würzburg
06	Final 2.0 (10.05.2011)	- Decrease of the PHQ-9 sum Score from 12 to 9 as decision to perform the SCID-Interview (step 2 of the screening process) - Addition of the scientific Project Fe-MOOD - Addition of new trial centres (München, Düsseldorf, Bad Nauheim) - Closure of trial centre (Nürnberg, Rostock) - Notification of new investigators/departure of investigators in trial centres (Göttingen, Hamburg, Homburg, Hannover, Leipzig, Magdeburg, München, Würzburg)
07	Final 2.0 (25.08.2011)	- Exclusion criteria - Addition of new trial centres (Regensburg) - Notification of new investigators in trial centres (Hannover) - Updating the stuff of the Independent Advisory Board
08	Final 1.0 (29.02.2012)	- two new exclusion criteria (Pat. With QTc> 500 ms) - limiting the daily dose for patients over 65 years on 10 mg - ECG investigations at any study visit - message of PZ Bonn and Stuttgart, logoff PZ Essen, message and deregistration of other auditors - recalculation of the sample size (reduced from the planned 700 to about 414) - recording the collection of cost data (drugs, hospital stays, doctor visits) on the health insurance of the study patients
09	Final 1.0 (23.10.2012)	- Change of Investigator (formerly PI) in the centers Hannover and Lübeck - Closure of trial centres (Hannover, Mannheim, München, Regensburg) - updating of contact data of the Biometrician

No.	Document/Version	Contents
10	Final 1.0 (22.06.2010)	- Change of Investigator (formerly PI) in the centers Lübeck and Marburg - Deregistration of trial sites Hannover, Mannheim, München, Regensburg - Notification of deputies in the centers Bad Nauheim, Bonn, Homburg, Leipzig
11	Final 1.0 (22.06.2010)	- updating of data for study duration and timelines of the study - change in the number Wallet Cards per medication code (reduction from 104 to 13 WC; sufficient for 3 months for patients to 65 years and 6 months for patients older than 65 years) - updapting of stuff and contact data the study team

22.2 CONSORT Flow Diagramm



22.3 Abbreviations

6MWT	six-minute walk testing
BMI	body mass index
BP	blood pressure
CHF	chronic heart failure
CI	confidence interval (95%)
DEP	depression
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
EF	ejection fraction
eGFR	estimated glomerular filtration rate
ENRICHD	Enhancing Recovery in Coronary Heart Disease trial
FPI	Firste Patient In
HF	Heart Failure
HFrEF	heart failure with reduced ejection fraction
ITT	Intention-to-treat
LPO	Last Patient Out
LV	left ventricular
LVEF	left ventricular ejection fraction
MADRS	Ten-item Montgomery–Åsberg Depression Rating Scale
MDRD	Modification of Diet in Renal Disease
MMSE	Mini-Mental States Examination
NT-proBNP	N-terminal cleavage product of pro B-type natriuretic peptide
NYHA	New York Heart Association
OSM	on study medication
QoL	quality of life
QTc (Bazett)	corrected QT time according to Bazett's formula
PCDM	Patient-Centered Disease Management for Heart Failure
PHQ-9	9 Item depression scale of the Patient Health Questionnaire
PHQ-GAD-7	7-item Patient Health Questionnaire for assessment of Generalized Anxiety Disorder
RR	blood pressure
SADHART-CHF	Sertraline Against Depression and Heart Disease in Chronic Heart Failure trial
SAE	serious adverse event
SCID	Structured Clinical Interview
SD	standard deviation
SF-36	36 Item Short Form Health Survey
SSRI	selective serotonin re-uptake inhibitor

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