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

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## Synopsis

<table>
<thead>
<tr>
<th>Title of Trial</th>
<th>Effects of selective serotonin re-uptake inhibition on MOOrbidity, mOrtality and mood in Depressed Heart Failure patients (MOOD-HF Study)</th>
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<tr>
<td>Acronym</td>
<td>MOOD-HF</td>
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<td>Indication</td>
<td>Chronic systolic heart failure, evidence of comorbidity with current episode of major depression</td>
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| Eligibility criteria - inclusion | - Age >18 years  
- Stable systolic chronic heart failure (CHF, NYHA II to IV) with left ventricular ejection fraction (LVEF) <45%  
- Current comorbid episode of major depression confirmed by structured clinical interview (SCID)  
- Written informed consent |
| Eligibility criteria - exclusion | - Current treatment with a selective serotonin re-uptake inhibitor (SSRI)  
- Previous treatment failure with escitalopram  
- Acute myocardial infarction (<3 months), acute cardiac decompensation, recent (<3 months) or planned (<12 months) cardiac surgery  
- Advanced renal failure (MDRD <30ml/min/1.73 m²)  
- Thyreotoxicosis  
- Reduced life expectancy due to other comorbidity (e.g. malignancy)  
- Moderate or severe hepatic insufficiency (plasma levels of hepatic enzymes >threefold of the upper level of the normal range)  
- Known evidence of major psychiatric comorbidity: imminent risk for or history of attempted suicide, schizophrenia and spectrum disorders; bipolar affective disorder; current substance disorder; moderate and severe dementia; severe depressive episode with psychotic features  
- Other contraindications against therapy with escitalopram (according to product information) |
| Trial Design  | Prospective randomised, double-blind, placebo-controlled, 2-armed, parallel-group multicenter Phase IV trial |
| Primary Objectives | To investigate the effects of treatment with the SSRI escitalopram compared to placebo on morbidity and mortality in CHF patients with a current episode of major depression |
| Secondary Objectives | **Major:** To estimate the improvement of depression by escitalopram compared to placebo in depressed CHF patients. To assess whether possible reduction of morbidity and mortality (see primary objective) might be attributable to the improvement of depression.  
**Further:** To investigate the effects of treatment with escitalopram accounting for patient co-variables, on the following: time alive out of hospital, cardiovascular morbidity and mortality, state of mood (degree of depression and anxiety and cognitive function), quality of life, clinical (e.g. NYHA class, 6-minute walk test), and laboratory parameters (natriuretic peptides, troponins) of CHF severity, imaging parameters of CHF severity (LVEF by echocardiography), adherence to study and CHF medication, safety and tolerability of |
| Therapy/Interventions | **Experimental intervention:**  
|                       | • Cardiological care + escitalopram 10-20 mg/day p.o.  
|                       | **Control intervention:**  
|                       | • Cardiological care + placebo 10-20 mg/day p.o.  
| Primary endpoints / outcome(s) | **Primary efficacy endpoint:**  
|                       | Time to first event of death or hospitalisation  
| Secondary endpoints / outcome(s) | **Key secondary endpoint(s):**  
|                       | Major secondary: Reduction of degree of depression as assessed by PHQ-9 / MADRS  
|                       | • Degree of depression as assessed by the Patient Health Questionnaire (PHQ-9) Scale and the Montgomery Asberg Depression Scale (MADRS)  
|                       | Further secondary:  
|                       | • Days alive out of hospital  
|                       | • PHQ-GAD-7 (General Anxiety Disorder) Scale  
|                       | • MMSE (mini mental state examination), assessment of cognitive dysfunction  
|                       | • Quality of life as assessed by the Short Form Health Survey-36 (SF-36), and the Kansas City Cardiomyopathy Questionnaire (KCCQ)  
|                       | • Cardiovascular mortality  
|                       | • Cardiovascular morbidity  
|                       | • Health economy  
|                       | • Adherence to HF and study medication  
|                       | • CHF severity  
|                       | • Parameters of inflammation  
|                       | • Sympathetic nervous system function  
|                       | • Escitalopram plasma levels  
|                       | • Platelet function / coagulation (substudy)  
|                       | • Vasoreactivity / arterial stiffness / wave reflection (substudy)  
|                       | • Pharmacogenetics, -genomics (substudy)  
| Sample size | **To be assessed for eligibility**  
|                       | • SCID testing for n = 420 from HFNC database plus 1200 from first screening in hospitals (with initial PHQ-9 >11)  
|                       | **To be allocated to trial**  
|                       | • n = 700 (alive, depression confirmed by SCID, fulfil inclusion criteria, no exclusion criteria, willing to be randomised.  
|                       | **To be analysed**  
|                       | • n = 700, 350 per study arm (drop-out cases to be included into survival analysis)  

study medication, frequency and severity of adverse events, parameters of sympathetic nervous system function, parameters of systemic inflammation and parameters of platelet function, vasoreactivity, arterial stiffness and arterial wave reflection. To investigate the effect of optimized cardiological care alone on these endpoints (comparison of baseline and follow-up assessments in the placebo-arm).
### Biometry

**Primary endpoint:** Kaplan-Meier estimates of event-free survival with logrank test.

**Major secondary analysis:** Analysis of covariance for reduction of mood. Cox regression with factor "treatment" and time-dependent covariable "mood" for the role of mood as intermediate variable.

**Time alive out of hospital:** extended (multi-state) Kaplan-Meier.

**Other secondary endpoints:** Analysis of covariance, stepwise multiple regression, Cox regression.

### Trial duration

**First patient in to last patient out:**
24 months per centre, 26 months over all centres

**Duration of intervention per patient:**
minimum 12 months, maximum 24 months, down titration 1 month

**Duration of the entire trial:**
36 months (first patient in to final report)

**Duration of recruitment:**
12 months per centre, 14 months over all centres

**Anticipated study start (Recruitment):**
01/2009

**Anticipated study end (first report / final report):**
01/2009 + 32/36 months
Study Flow

**Screening**

Double-blind treatment

Escitalopram + optimal cardiovascular pharmacotherapy

Placebo + optimal cardiovascular pharmacotherapy

Randomisation

SCID

PHQ-9, QoL, PHQ-GAD-7, MADRS, MMSE

Month 012361812915242125457810111314161719202223

Visit 0123456789

Up-titration

After 12 months, any visit, scheduled or unscheduled, may become the final visit

Time interval between PHQ-9 test and SCID: ≥14d

Time interval between SCID and randomisation ≤14d

Down-titration

Post-study visit to psychiatrist

Telephone Monitoring

weekly in uptitration phase, bimonthly thereafter
## Schedule of Assessments and Procedures

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>Scr</th>
<th>BASE</th>
<th>DOUBLE-BLIND TREATMENT PERIOD</th>
<th>DOWN- TITRA- TION</th>
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</thead>
<tbody>
<tr>
<td>Time, month</td>
<td>-1</td>
<td>0,5</td>
<td>0,75</td>
<td>1,5</td>
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<tr>
<td>Assessment/procedure</td>
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<td>In-/exclusion criteria</td>
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<tr>
<td>Informed consent</td>
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<tr>
<td>Randomization</td>
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<tr>
<td>Medical history</td>
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<tr>
<td>Adverse Events</td>
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<tr>
<td>General medication</td>
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<tr>
<td>Heart failure related medication</td>
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<td>Physical examination</td>
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<td>NYHA class, blood pressure, heart rate, body weight</td>
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<td>Echocardio- graphy</td>
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<tr>
<td>24h ECG (heart rate variability, arrhythmia)</td>
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<td>6 minute walk test</td>
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<td>MADRS</td>
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<td>MMSE</td>
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<td>Quality of Life (SF-36, KCCQ)</td>
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<td>Health economics</td>
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<td>Dispense of double-blind medication</td>
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<td>Drug accountability</td>
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<td>Lab</td>
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<td>Routine biochemistry incl. SSRI safety markers and natriuretic peptides</td>
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<td>24h urine norepinephrine excretion</td>
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<td>Escitalopram levels</td>
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<td>VASO-MOOD</td>
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</table>

* because not all patients will participate for 24 month in the trial, any visit after 12 months may become the final visit before downtitration

- Indicates psychometric testing tools
- Indicates that these samples are proceed and labelled on site, stored in aliquote and sent to Core Lab Würzburg three-monthly
1 RATIONALE

1.1 Medical Background

(Literature included until June, 06; for update on more recent publications see the study design paper of MOOD-HF: Angermann CE, Gelbrich G, Störk S, Fallgatter A, Deckert J, Faller H, Ertl G, on behalf of the MOOD-HF Investigators. Rationale and design of a randomized 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 Failure 2007;12:1212-1222)

1.1.1 Pathophysiological and Prognostic Relevance of Depression in Cardiovascular Disease

Depression (DEP) is common and clinically and economically highly relevant with an estimated prevalence of >4 million patients in Germany. In several studies, the prevalence of DEP in cardiovascular disease was 20-40\%\textsuperscript{1,12} even rates as high as 77.5\% were reported\textsuperscript{3}. An overview on the clinical importance of DEP in chronic heart failure (CHF) is given in\textsuperscript{4}. DEP is four to five times more common in CHF than in the general population\textsuperscript{5}. Recent evidence from the large COACH management trial in CHF patients suggested a gender-difference with a significantly higher prevalence in women\textsuperscript{6}. In an international population-based study DEP increased the risk of developing cardiovascular disease and of cardiovascular death in subjects without previously known cardiac disease\textsuperscript{7}. Recently published baseline characteristics of participants of the MIND-IT trial indicated that after a myocardial infarction the prevalence and severity of DEP correlated with the severity of left ventricular dysfunction and the prevalence of CHF\textsuperscript{8}. Own results\textsuperscript{9} (see figure) and data from the literature\textsuperscript{4} show higher rates of mortality and hospital admission in patients with established CHF and DEP as a co-morbidity. DEP predicts adverse outcomes regarding health-related quality of life, subjective suffering, mortality, morbidity and health care expenditure\textsuperscript{4,10}. Hospitalization costs were 26–29\% higher in patients with DEP compared to those without DEP in a recent 3-year retrospective study of a health maintenance organization on more than 10,000 patients with CHF\textsuperscript{10}. In this study, the excess expenses were due to increased in- and outpatient utilization for CHF and not due to increased mental health utilization.

The adverse effects of DEP on outcome in cardiovascular patients may be mediated by pathways which are common for both diseases. Dysregulation of autonomic nervous control represents one of the most plausible mechanisms\textsuperscript{11,12}. Reduced parasympathetic and increased
sympathetic nervous system (SNS) activation can lower the threshold for myocardial ischemia, ventricular tachycardia, ventricular fibrillation and sudden cardiac death in patients with cardiovascular diseases. Several studies on autonomic regulation in DEP consistently found a higher resting heart rate and decreased heart rate variability and an increased norepinephrine excretion, all well described risk factors for serious cardiac events even in the general population. High levels of circulating catecholamines may contribute to recurrent endothelial injury. They may also induce a procoagulant state by potentiating platelet activation through direct agonist effects. Patients with DEP exhibited substantial platelet activation and procoagulant properties compared to healthy controls. Catecholamines also increase hemodynamic stress on the vascular wall and inhibit vascular synthesis of protective eicosanoids. Further, increased sympathetic tone is associated with increased levels of plasma cortisol, serotonin, renin, aldosterone, angiotensin and free radicals. Several studies implicate that the immune system is also involved in the relationship between DEP and the development or progression of cardiovascular disease (reviewed in ). The main outflow pathways by which the central nervous system affects the immune system are the hypothalamic-pituitary-adrenal system and the autonomous nervous system. In DEP, corticotrophin-releasing hormone is elevated and acts as the main regulatory hormone including the release of pro-inflammatory cytokines and other immune system responses. A decreased inhibition of macrophage activation in DEP via the cholinergic anti-inflammatory pathway may also contribute to the elevation of pro-inflammatory markers as CRP, IL-1β, IL-6 and TNF-α. Inflammation appears, thus, as another risk factor. Finally, depressed patients often have an unhealthy lifestyle and fail to comply with treatment recommendations. E.g., patients with DEP are less likely to exercise regularly and to take their medication after a myocardial infarction or to quit smoking after a cardiovascular event. Although there are no studies testing the impact of poor treatment adherence on outcome, it is likely that non-adherence to treatment also contributes to the increased cardiovascular risk in DEP.

1.1.2 Possible Bidirectionality of the Relation of Depression and Psychobiological Pathways

The central nervous system may control the immune system but, vice versa, inflammatory processes may also affect the central nervous system via humoral and neural pathways. Alterations of the central nervous system are associated with symptoms of DEP. Pro-inflammatory cytokines relevant to cardiovascular disease (e.g. TNF-α) administered to healthy volunteers result in elevated extracellular serotonin levels, depressed mood, sleep disorders and general malaise. Such observations suggest that DEP symptoms may be mutually related to immune system parameters. However, most clinical studies were case-
controlled or cross-sectional and did not control for behavioural mediators as poor treatment compliance. Thus, up to date, a possible causal relation between DEP and inflammation is not established. It seems possible that DEP exacerbates inflammation in patients with cardiovascular disease thus increasing the risk of subsequent events. Conversely, inflammation itself may trigger DEP which, in this scenario, would then only reflect the elevated inflammatory state known to be associated with the higher risk of cardiac events. Prospective studies are warranted considering clinical parameters and biomarkers and testing interventions to further elucidate a potential bidirectional relation of depression and psychobiological pathways which may be of paramount therapeutic importance.

1.1.3 Treatment Trials in Depressed Patients with Cardiovascular Disease

The recognition of the prognostic importance of DEP in patients with cardiovascular disease has increased the need for treatment guidelines based on well-designed clinical trials in this population. Although large patient numbers have been involved in randomized clinical trials of antidepressants, physical comorbidity has often been an exclusion criterion. Tricyclic antidepressants may induce conduction disturbances and postural hypotension rendering their administration problematic in patients with cardiovascular disease. There is little evidence available for the treatment of DEP in patients with cardiovascular disease and maybe multiple other comorbidities.

To date, only two major multicenter randomized outcome trials of DEP treatment in patients with cardiovascular disease have been published. The SADHART trial proved that selective serotonin reuptake inhibition (SSRI) is safe and efficacious in depressed patients with cardiovascular disease (CVD) but was underpowered to detect a survival benefit. In the ENRICHD trial, cognitive behavioural therapy and optional additional SSRI treatment was also effective in CVD patients regarding improvement of DEP but did not result in a survival benefit. A recent post-hoc re-analysis of ENRICHD revealed, however, that the risk of cardiovascular death or recurrent myocardial infarction as well as the risk of all-cause-mortality was significantly lower in patients on SSRI compared with those who did not use SSRIs. The ongoing CREATE trial in patients with chronic CVD is another placebo-controlled trial comparing the effect of the SSRI citalopram and two forms of short term structured psychotherapy on improvement of DEP in a 2-by-2 factorial design in patients with chronic coronary artery disease. Both SSRIs and structured psychotherapy have demonstrated efficacy for relieving major depression symptoms in patients without comorbid cardiovascular disease. The largest outcome trial so far undertaken in patients with DEP and cardiovascular disease is the ongoing Dutch MIND-IT-trial which will include more than 2000 patients after an acute myocardial infarction and compare antidepressive pharmacotherapy with mirtazepin or citalopram with care-as-usual.
The study aims to clarify whether psycho pharmacotherapy of DEP with these agents can improve cardiac prognosis after an acute myocardial infarction.

1.1.4 Chronic Heart Failure and the Treatment of Depression

In industrialized countries, CHF in its various manifestations represents the number one cause of death. Its prognosis is comparable to that of common malignancies. With the ongoing sociodemographic changes in our ageing industrial societies and increasing immediate success rates of interventional procedures in cardiovascular diseases, its prevalence will continue to increase. Comorbidity with DEP is frequent but remains unrecognized and untreated in the majority of cases. A two- to three-fold increase in mortality and rehospitalisation risk has been demonstrated in CHF patients with DEP compared to those without DEP. While cardiologists are familiar with the pathogenetic role of various lifestyle behaviours in cardiovascular disease and used to manage features as overeating, physical inactivity and smoking, they rarely assess and treat psychosocial risk factors. This is not only due to a limited familiarity with possibly effective management strategies but also to the fact that evidence for treatment-related improved morbidity and mortality in cardiovascular disease justifying either psychopharmacotherapy or psychotherapy is lacking. In case DEP is recognized in clinical practice, the choice of treatment for depressed patients with CVD will largely depend on the clinician’s preference and experience with pharmacological and non-pharmacological treatment options. Neither the German nor the European Guidelines for the treatment of CHF provide specific handling directives for the patient with CHF suffering from DEP as a comorbidity.

Thus, a prospective randomized multicenter trial is urgently needed to clarify whether and by which mechanism(s) therapy of comorbidity with DEP in CHF will influence the outcome.

1.2 Hypothesis and Novel Aspects of the Trial

1.2.1 Rationale and Hypothesis of the Proposed Study

In depressed CHF patients, no efficacy data regarding hard clinical endpoints are available for any treatment modality for DEP. Considering i) the very large population at risk who will qualify for treatment in case of a positive study outcome, ii) the physical incapacity of most elderly individuals or patients with advanced CHF precluding repeat visits to a specialist, and iii) the frequency of cognitive impairment in CHF, we propose to evaluate psychopharmacotherapy rather than psychotherapy vs. placebo added on top of standardized optimal CHF care according to current treatment guidelines for all patients. Careful frequent monitoring of treat-
ment effects of cardiological as well as study medication and of treatment safety will be complemented by expert psychiatric support wherever considered necessary.

Published evidence suggests that SSRI may favourably influence the mortality risk not only by improving health behaviour but also via direct modulation of biological pathways (see 1.1.1 for details). While some markers reflecting these biological systems seem to co-vary with DEP severity, others may have an independent impact on prognosis. A platelet substudy performed within the SADHART trial demonstrated that treatment with the SSRI sertraline was associated with diminished platelet/endothelial activation despite co-administration of widespread antiplatelet regimens including aspirin and clopidogrel

The major hypothesis of the trial is that long-term therapy with the SSRI escitalopram in patients with symptomatic systolic CHF is safe and will improve outcome defined as a prolongation of the time to a first clinical event (death or hospitalisation). We further hypothesize that treatment with escitalopram will exert a favourable effect on DEP as assessed by serial testing with the Patient Health Questionnaire-9 (PHQ-9) and the MADRS-scale, on anxiety as assessed by the PHQ-GAD (General Anxiety Disorder)-7 questionnaire, on general quality of life as assessed by the Short Form Health Survey-36 (SF-36), and on disease-related as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), the German version of which has been validated by our group. Further, we test the hypothesis that escitalopram may increase the number of patient days spent alive out of hospital during the study period and reduce cardiovascular mortality and morbidity. We also hypothesize that by measuring prospectively a variety of clinical and biological factors known or assumed to be causally related to the increased cardiovascular risk in patients with cardiovascular disease and DEP (for details see 1.1.1 and 1.1.2) we will be able to generate and support new hypotheses by which biological mechanism(s) therapy of DEP with escitalopram may be capable of improving outcome in CHF patients. Finally we consider possible that optimized cardiological care alone will impact on the endpoints of this trial. This will be assessed by comparison of baseline and follow-up assessments in the placebo-arm.

Compared with survivors of an acute myocardial infarction or chronic coronary artery disease without CHF, the CHF population has a considerably higher disease-related mortality and morbidity risk. Thus, a prospective, randomized multicenter trial addressing the treatment of DEP in such a more vulnerable cohort CHF requires a dedicated interdisciplinary approach. Facilities for standardized CHF care as well as psychiatric and/or psychosomatic expertise and supervision are pivotal to ensure adequate study conduct including optimal CHF management. This is difficult to attain outside the setting of a university-based network of CHF specialists with access to psychiatric and/or psychosomatic facilities. In our view, it is highly advantageous that the current proposal utilizes established network structures within the framework of
the German Heart Failure Network of Competence (HFNC). Cardiologists initiate this investigator-driven trial with a study design tailored to the specific medical needs of CHF patients irrespective of commercial interests. Close cooperation with psychiatrists and/or psychosomatic specialists will, at the same time, ensure expert guidance and evaluation of psychopharmacotherapy and facilitate successful testing of the study hypotheses. For the first time, the current proposal addresses hard clinical endpoints rather than improvement of DEP in patients with CHF.

1.2.2 Rationale for the Use of Escitalopram

Escitalopram oxalate is the S-enantiomer of the racemic bicyclic phthaline derivative citalopram. The mechanism of its antidepressant action is presumed to be linked to enhanced serotonergic activity in the central nervous system, resulting from its inhibition of neuronal reuptake of serotonin. Escitalopram has very little effects on other receptors rendering it the most selective of all SSRIs. Escitalopram is >100 times more potent than the R-enantiomer; its plasma concentration is approximately 1/3 of the total citalopram concentration with the implication that the other 2/3 of the total citalopram concentration is biologically inactive as an antidepressant.

We postulate that the superior antidepressant efficacy of escitalopram compared with other SSRI will be complemented by an equally stronger positive effect on the risk of cardiovascular events. The rationale for using the SSRI escitalopram in this trial is its superior efficacy in conjunction with a favourable side-effect profile in general, lack of significant cardiovascular side effects in particular, and the relative lack of toxicity in overdose. Also, its low potential for drug-drug interactions renders escitalopram particularly attractive in CHF patients who usually take multiple cardiac and other medications. The safety of escitalopram corresponds to that of citalopram. Regarding the relative lack of cardiac side effects, e.g., on conduction/repolarization during either long- or short term treatment both substances are comparable, while the antidepressant efficacy of escitalopram is superior. Clinical studies with escitalopram for the treatment of major DEP have been conducted and provide further evidence of the compounds’ efficacy and potency. A fixed dose placebo-controlled trial of escitalopram compared with citalopram and placebo showed that 10 mg of escitalopram were at least as efficacious as 40 mg of citalopram while having an overall rate of side effects comparable to placebo. A further potential benefit is a more rapid onset of action. Escitalopram compared with placebo was statistically superior to placebo as early as one week after initiation of treatment, while citalopram did not significantly discriminate form placebo until week six. In a meta-analysis of more than 2000 patients treated with different antidepressants escitalopram was superior to all comparators in overall treatment effect on DEP including all other SSRIs.
The antiplatelet activity of the SSRI sertraline and paroxetine is well known\textsuperscript{34,44}. In vitro experiments in human platelets show that escitalopram also selectively inhibits human platelets\textsuperscript{45}. However, the comparative antiplatelet activity of escitalopram in the clinical setting is not known and requires prospective testing in patients.

In summary, we have chosen to use escitalopram for the following reasons:

- Superior antidepressant potency and efficacy compared with other SSRIs. It may, thus, be speculated that unfavourable biological factors co-varying with DEP will also improve more via the more effective improvement of DEP.

- Favourable side-effect profile, relative lack of significant cardiovascular side effects, relative lack of overdose toxicity, and relative lack of potential for drug-drug interaction rendering this antidepressant much more suitable for cardiovascular patients compared with other compounds (e.g., tricyclic antidepressants).

- In vitro evidence for favourable effects of escitalopram on platelet function as observed also for other SSRIs. The modulation of platelet activity has been suggested as one potential mechanism responsible for the strong trend toward reduction of cardiovascular events in major DEP after treatment with the SSRI sertraline\textsuperscript{26}. It may be postulated that escitalopram will exert an at least equal or even superior effect on platelet activity, which may potentially prove one relevant factor for improvement of prognosis.

1.2.3 Rationale for the Use of Placebo

Participants with a SCID-confirmed episode of major DEP will be prospectively randomized 1:1 into the intervention and control arm. The placebo-controlled design is chosen, because all previous studies have not changed the fact that there is no established reference treatment for patients with cardiovascular disease in general and CHF in particular, who suffer from DEP as comorbidity. It still remains to be demonstrated that the efficacy and tolerability of escitalopram are superior to treatment with a pill-placebo in this group of patients who usually is elderly and multimorbid, has some degree of renal failure, may suffer from diabetes, and are expected to use numerous other medications. In such a chronically ill patient population it is unclear to what extent optimal CHF therapy according to guidelines by itself will improve DEP besides improving overall prognosis\textsuperscript{27}. As there is no established reference treatment for DEP in patients with cardiovascular disease, only the use of a pill-placebo against a background of optimized CHF care will be able to demonstrate the putative superiority of escitalopram regarding the reduction of the cardiovascular event rate and improvement of DEP.
The MOOD-HF protocol has several built-in safeguards to assure the well-being of patients in both arms of the trial. (a) Selection of patients for study participation and randomization will in every case involve certified psychiatric/psychosomatic specialists who will assess subjects to be randomised on an individual basis at the occasion of SCID-testing. Personalised certification for this responsibility will be carried out by members of the psychiatric Core Laboratory (Head: Prof. Dr. J. Deckert) for each of the participating centres. It will be assured that SCID-testing will be carried out exclusively by certified psychiatric/psychosomatic specialists, who will take care that patients with SCID documented bipolar disorder, current episode of co-morbid major DEP with psychotic features, moderate or severe dementia or serious risk of imminent suicide based on clinical judgment will not be included (see also 4.2, exclusion criteria, p. 31-32). (b) Study medication will be given on the background of CHF therapy according to treatment guidelines and will be delivered by cardiologists rather than general practitioners. Regarding cardiac management this represents a regimen which would presently be considered as optimal. The access to such a management programme is not generally available for patients with CHF outside a clinical or health care research trial. (c) Further, MOOD-HF will involve repeat assessments of psychic well-being besides clinical and technical cardiac assessments. Weekly telephone monitoring of cardiac status as well as mental state during up-titration of cardiac medication and study drug followed by two-weekly telephone monitoring thereafter will, together with repeat cardiac and DEP assessment at defined intervals during the entire course of the trial, ensure timely recognition of DEP as well as CHF worsening also in patients on placebo. Diagnosis of DEP worsening will primarily be based on the results of PHQ-9, MADRS- and PHQ-2-testing (telephone) which is performed at the occasion of all patient contacts. However, to ensure recognition of psychic deterioration even further, cardiologists as well as CHF specialist nurses involved in clinical and telephone monitoring will receive a standardised training regarding evaluation of DEP by MADRS or PHQ and recognition and diagnosis of suicidal ideas. The required contents and quality of this training will primarily be communicated at the occasion of the pre-scheduled standardisation session for psychiatric testing to be performed by members of the Psychiatric Core Lab prior to study initiation. Psychiatric/psychosomatic specialists of each participating center will serve as multipliers for this training at their own study sites. Further, all patients will be re-evaluated by a certified psychiatrist/psychosomatic specialist (certification procedure see above) 6 months after randomization and at the end of the trial. Suspected suicidality or significant worsening of DEP as well as lack of significant improvement after up titration of moderate to severe DEP will at any time during the study immediately induce a patient contact with the responsible certified psychiatric/psychosomatic specialist for assessment and put into practice further pre-specified supportive strategies including the option of additional open treatment according to patient needs. At each study site the joint expertise of at least one certified psychiatric or psychosomatic physi-
cian will be available for decision about the necessity of premature termination of study in each individual case. Algorithms for interaction between nurses, cardiologists and psychiatric or psychosomatic specialists will be established at the occasion of the pre-scheduled standardisation session for psychiatric testing to be performed by members of the Psychiatric Core Lab during the Kick-Off-Meeting.

Although SSRIs appear safe and effective regarding DEP from a limited number of previous trials\textsuperscript{26,29,30}, evidence for subsequent reduction of morbidity and mortality is still lacking. Only a large-scale placebo-controlled trial which will at the same time elucidate the seemingly more complex biological mechanisms of SSRI action in depressed CVD patients is suited to confirm the safety of SSRIs also for the CHF population. If positive, the study will exert a major impact on CHF management practice guidelines thus providing a rationale for routine DEP screening and for more evidence-based management strategies in the large CHF population.

1.3 Risk-Benefit Consideration

\textit{Escitalopram} 10–20 mg/d represents a well-tolerated and effective treatment option for major depressive disorders and various anxiety disorders including panic disorders. Head-to-head comparisons with other antidepressants have been published; pooled analyses of studies using \textit{citalopram} as the active comparator suggest an advantage of \textit{escitalopram} with respect to efficacy. The drug shows a highly selective serotonergic effect and represents a potent SSRI with a straightforward pharmacokinetic profile and very little effect on hepatic metabolism. Thus, \textit{escitalopram} may be considered as a therapy of choice for the management of major DEP and also anxiety within, but also outside a clinical trial with beneficial effects on both psychiatric disorders in the majority of patients.

\textit{Escitalopram} may not be used in conjunction with some other psychopharmacologic drugs (e.g., non-selective MAO-inhibitors) or in patients with severely depressed renal function. Relative contraindications, which require careful supervision of treatment, include paradoxical anxiety symptoms, manic disorders, suicidal thoughts, convulsions, diabetes mellitus, significant liver disease as cirrhosis, hyponatremia, hemorrhage, comedication with anticoagulants or thrombocyte inhibitors, comedication with electroconvulsive therapy, comedication with reversible selective MAO-A-Inhibitors and comedication with medical products causing a serotonergic syndromes. Further comedications requiring special caution are selegilin, serotonergic drugs (e.g. antimigraine drugs), drugs decreasing convulsion threshold, lithium, tryptophan, St. John’s Wort, drugs that are metabolized via the CYP2D6 enzyme system as flecainid, propafenon and metoprolol, and drugs that may inhibit the CYP2C19 system as omeprazol (see product information). \textit{Escitalopram} may further not be used during pregnancy and nursing
and with a history of early termination of escitalopram or other SSRIs due to adverse or side effects. Due to limited clinical experience caution is recommended in cardiovascular diseases.

The following side effects of escitalopram may occur: Reduced appetite, reduced libido, orgasm disorders, ejaculation disorders, impotence, sleeping disorders, dizziness, vertigo, nausea, vomiting, diarrhoea or constipation, increased sweating, fever and tiredness, dry mouth, anorexia, increased liver enzymes, anaphylactic reactions, arthralgia, myalgia, tremor, apraxia, cerebral convulsions, serotonin syndrome, manic disorder, hallucinations, galactorrhea, eczema, ecchymosis, pruritus, angioedema, increased perspiration.

Although in clinical practice escitalopram is very well tolerated and safe if contraindications are respected, safety issues have been carefully reflected in the design of MOOD-HF by

- Rigorous exclusion of patients with any of the exclusion criteria listed under 4.2, including in particular any unstable cardiac state, severe renal failure, psychiatric comorbidity including SCID documented bipolar disorder, major DEP with psychotic features or the risk of imminent suicide, evidence of substance abuse or dependency during the previous 12 months, moderate or severe dementia and known intolerability of escitalopram.
- Guideline-adjusted CHF therapy delivered by cardiological specialists.
- Stepwise up-titration of the study medication.
- Weekly telephone monitoring of patient well being in the up-titration-phase and two-monthly monitoring thereafter.
- Availability of immediate psychiatric or psychosomatic specialist contact if necessary

For reasons given under 1.2.2 we consider it ethically justified not to offer escitalopram to a control population of CHF patients with DEP. Conversely, for the reasons outlined in 1.2.1 no significant adverse cardiovascular effects of escitalopram need to be anticipated. Should any side effects occur, these are expected to be reversible and not life threatening. Also, they will be discovered and dealt with early due to close monitoring. Thus, the risks of study participation are amply outweighed by the expected treatment benefit.

All study participants will benefit from optimized CHF care and close monitoring of well being. CHF treatment according to guidelines as delivered to all patients in MOOD-HF is associated with a proven survival benefit compared with the low guideline adherence often observed in CHF patients in every day clinical practice\(^ {46,47}\). This constitutes an additional ethical justification for the trial. For patients in whom repeat DEP screening as implemented in the study protocol indicates significant worsening of DEP as well as lack of significant improvement after up titration of moderate to severe DEP the study schedule implicates immediate individualized
support by psychiatric/ psychosomatic specialists which will be offered to participants of both study arms.

Apart from the favourable risk-to-benefit-ratio for individual study participants there is also a positive risk-to-benefit-ratio regarding the future management of the CHF population as a whole. Whereas today, DEP is infrequently diagnosed and even less frequently treated in these patients, the proposed placebo-controlled outcome study has the potential to impact significantly on CHF management practice guidelines by (i) proving safety and antidepressant efficacy of escitalopram in the CHF population and (ii) by elucidating relevant pathophysiological links between DEP and cardiovascular disease thus potentially promoting improved evidence-based management for patients suffering from both conditions.
2 OBJECTIVES

2.1 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.

2.2 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),
• Parameters of systemic inflammation (e.g., CRP, fibrinogen, uric acid, IL-6, IL-10, TNF-α, CD 40L, sICAM)

We also plan to investigate the effect of optimized cardiological care alone on the endpoints of MOOD-HF (by comparison of baseline and follow-up assessments in the placebo-arm).

We further plan to analyse cost-effectiveness of treatment with escitalopram in depressed patients with CHF in all patients using the available demographic data, information on mortality, morbidity and treatment, the SF-36 (Profile Instrument) and the EuroQol Questionnaire (Utility Index Instrument). Additionally we will determine the prevalence and positive predictive value of PHQ-9 sum >11 in patients with systolic CHF of NYHA class ≥II and to describe the correlation of PHQ-9 sum and its positive predictive value with patients gender, age and NYHA class.(SCREEN-MOOD). Also, we plan to perform a substudy (THROMBO-MOOD) in 60-80 patients, which will assess the effects of escitalopram on parameters of platelet function and coagulation, and a further substudy in 60 patients (VASO-MOOD) on arterial stiffness and endothelial function using pulse wave velocity, augmentation index, forearm blood flow and vasoreactivity as target parameters. Patients involved in this substudy will be recruited from the study site of the University of Würzburg). A further substudy (GENE-MOOD) aims to investigate for candidate gene polymorphisms that predispose to depression in CHF, as well as for polymorphisms that determine the therapeutic response to escitalopram. Finally, OSMO-MOOD will investigate the effects of antidepressant medication on osmoregulation and sodium-homeostasis (urine osmolality, serum and urine sodium, fractional excretion of uric acid). For more details of these sub-studies see chapter 10.
3 TRIAL DESIGN AND DESCRIPTION

3.1 Trial Design

- We propose a phase IV clinical trial, using an authorised drug, the SSRI escitalopram, for an indication covered by the authorisation. Although authorisation is backed by considerable data showing efficacy, safety and tolerability in otherwise healthy subjects with DEP, data in patients with physical comorbidities as CHF are more scarce and the results less explicit. We thus intend to test treatment safety and efficacy of escitalopram with respect to mortality, morbidity and surrogate endpoints (biological markers) known or presumed to possess clinical relevance in depressed CHF patients.

- The trial will be a 2-armed, parallel group, randomised (with stratification), controlled, double-blinded multicenter trial

- The arrangement of screening, randomization, treatment and follow-up is illustrated by the flow chart on p. 11.

3.2 Requirements for Participating Investigators and Trial Sites

Participating centers must be recognised clinical institutions with special interest in and facilities for management and clinical research in patients with cardiovascular disease. At the same time, institutions need to have the possibility of and previous experience in close cooperation with psychiatric or psychosomatic specialists with proven expertise in screening for DEP as well as in diagnosing and treating DEP. Basic requirements are

- In- and outpatient facilities, from which patients fulfilling the inclusion criteria may be recruited, and outpatient logistics facilitating implementation of the study protocol. Capacity, experience and willingness by cardiologists and psychiatric and psychosomatic to cooperate in MOOD-HF regarding inclusion of patients and performance of the study according to the German AMG and international GCP regulations.

- Qualification for and experience in establishing the diagnosis of a current major depressive episode based on a Diagnostic and Statistical Manual-IV diagnosis using the Structured Clinical Interview for Depression and to follow the course of DEP using the MADRS scale. To assure standardised administration of the SCID and MADRS instruments, psychiatric/psychosomatic specialists from each study site will have to participate in a standardised SCID training program and cardiolo-
gists will have to participate in a standardised MADRS training program prior to study initiation. The training will be provided by members of the MOOD-HF Psychometric Core Lab at the University of Würzburg (Head: Prof. Dr. med. Jürgen Deckert, Director of the Clinic and Policlinic for Psychiatry, Psychosomatics and Psychotherapy, Prof. Dr. med. Andreas Fallgatter, Consultant Psychiatrist at the Clinic and Policlinic for Psychiatry, Prof. Dr. med. Dipl. Psych. Dr. Hermann Faller, Head, Institute of Medical Psychology and Psychotherapy). Participation in the training program and subsequent certification by the Directors of the Core Lab are prerequisites for the study initiation visit at each study site. To ensure high standardisation and SCID quality throughout the entire study, a test video containing two SCID and two MADRS interviews with representative cases (CHF patients with or without a current episode of major DEP) will be provided by the Directors of the Core Lab after 50% of each centers’ recruitment time. In case of incorrect DEP assessment in these cases further training is indicated and will be provided by the Core Lab. The standardised training program will also include directives regarding the training of cardiologists and CHF specialist nurses involved in the MOOD-HF study regarding the timely recognition of DEP worsening and the development of suicidal ideas as well as algorithms for visits by the psychiatric/psychosomatic specialists.

- Equipment for performance of the following technical/laboratory examinations according to current diagnostic quality standards: High quality two-dimensional echocardiographic examination including quantitative assessment of LV function, wall thickness, diameters and quantitative assessment of LV filling characteristics by Doppler echocardiography (including Doppler flow measurements plus tissue velocity imaging); 12-lead electrocardiography (ECG); 24-hour-ECG recording facility with capacity for determination of mean heart rate and quantitative assessment of type and frequency of arrhythmias and for determination of heart rate variability; facilities for performance of 6-minute walk test; laboratory facilities for routine testing including assessment of natriuretic peptides (BNP or NT-proBNP) for rapid assessment of CHF severity.

- Internet access with PC equipped with MS Internet Explorer 6 or similar (allowing connection to the trial database).

- -80°C freezer capacities for onsite storage of blood cell, plasma and serum samples until further processing.
3.3 Trial sites and number of trial subjects

3.3.1 Selection of Trial Sites

Nine clinical trial sites with dedicated in- and outpatient facilities for patients with cardiovascular diseases will be involved in the study (see list in the Appendix to the Clinical Study Protocol). At most sites, cardiological investigators involved in MOOD-HF are also established Project Leaders in the German Heart Failure Network of Competence (HFNC), which guarantees on one side the required excellence in CHF management and research ability as well as experience in the conduct of large clinical multicenter CHF trials and, on the other hand, optimal cooperation within the established network structures. Through the central facilities of the HFNC, scientists at all participating trial sites have already gained experience in mutual support of their individual scientific projects. Project Leader meetings as held at three to six months intervals within the HFNC have served as a platform to successfully develop and submit the Outline Trials Application for MOOD-HF and will continue to provide a platform for regular dialogue and exchange for the participating investigators. The Saarland University Hospital, Homburg was in addition selected as a study site because of its long-standing experience in the performance of large clinical trials and availability of large cohorts of potentially suited patients.

3.3.2 Number of Trial Subjects and Recruitment Capacity

700 patients need to be recruited for the trial (for discussion of sample size see chapter 9). On average, each center will identify 70-100 patients fulfilling the inclusion and exclusion criteria and willing to be randomized.

We consider this recruitment goal realistic for the following reasons:

- We have obtained permission to use the HFNC database. Based on the hitherto recruitment process, we expect that about 7000 subjects will be included by 12/2006. PHQ-9 screening for depression is part of the HFNC baseline documentation. All centres participating in MOOD-HF have contributed patients to the central HFNC database with different non-pharmacological (diagnostic, genetic, epidemiological) CHF trials. According to an estimate of the KKSL based upon the HFNC Basic Clinical Dataset, about 2200 of the patients recruited by the prospective MOOD-HF trial sites into the HFNC until 12/2006 will fulfil the cardiological inclusion/exclusion criteria (see 4.1 and 4.2). In subjects so far included into the HFNC and matching these criteria screening of the database reveals a prevalence of PHQ-9 score ≥9 of about 40%, so we expect to
have over 800 "prequalified" patients to be included into the screening process (see 4.3). If MOOD-HF is funded it will be possible to select at the Coordinating Centre for Clinical Trials (KKSL) the patient IDs of all potentially suited subjects. Using this information, each study site will be able to identify and contact their respective patients for PHQ-9 re-evaluation. Since the results of the 1st PHQ-9 screening were not communicated to including HFNC centres, it is expected that – according to usual practice in CHF – HFNC patients will since only rarely have received any pharmacotherapy targeting depression which would preclude study participation. Taking also into consideration the cumulative mortality until re-screening we estimate that 600 will receive written invitations from their respective site for repeat PHQ-9 evaluation. With a response rate of 70%, about 420 will be re-screened. If patients respond and have a 2nd PHQ-9 score of >11, they will be invited for SCID-testing at this trial site. Assuming a baseline prevalence of major depression of 20%, the prevalence among positively "pre-screened" patients should be about 55% (according to the data presented in Diagnostic & Statistical Manual of Mental Disorders, DSM-IV\(^{48}\)), yielding about 230 patients with depression in the rescreened group. Since rescreening with a cut-off of 11 points has sensitivity=0.98, and the willingness to participate is perhaps high among those who responded to the rescreening invitation, we estimate that about 200 depressive patients of this cohort will be included into the trial (besides about 50 non-depressive patients who will undergo SCID due to false positive PHQ-9).

- Additional participants will in parallel be recruited amongst outpatients and hospitalized CHF patients attending the 9 study sites during the recruitment period of MOOD-HF. In this unselected population (estimated number of screened patients in step 1: n = 4000, corresponding to 600–800 patients per center) the prevalence of a PHQ-9 score >11 will be about 30% at 1st testing \(^{49}\), confirmed by own data \(^{9}\). Screening will, thus, yield 1200 patients to be included into the SCID procedure. Again, with a PPV of 55%, we can assume that 660 patients will be eligible. At an inclusion rate of 75%, we estimate this will yield about 500 depressed patients for the trial.

Patient inclusion, psychiatric testing, psychopharmacotherapy and cardiological care will be accomplished as interdisciplinary task at each site. Based on the above assumptions we anticipate that by both strategies 700 patients will be recruited within 12 months even if we take into consideration that up to 25% of patients may refuse participation, and that up to 30% may not respond to the rescreening invitation.
3.4 Expected duration of trial / Timelines


Documents for submission to authorities prepared: 30/01/2008.

End of decision process of authorities: 27/05/2008.

Starting centre initiation, first centre recruiting: 01/2009 + 6 months.

All centres open: 01/2009 + 9 months.

Duration of recruitment: 12 months per centre.

Duration of follow-up: 24/12 months for the first/last patient recruited.

First/last centre close-out: 01/2009 + 30/32 months.

Cleaning of data finished: 01/2009 + 35 months.

First results presented: 01/2009 + 36 months.

Final report sent to authorities: 11/2008 + 42 months.

Duration of recruitment: 15 months. 700 subjects need to be recruited in 9 centers, i.e., on average 78 subjects per center.

3.5 Premature termination

3.5.1 Premature closure of a trial site

Premature closure of a trial site is to be considered if:

- The site does not meet the technical requirements of the protocol throughout the study period,
- the trial site fails to include sufficient patient numbers and does not provide evidence of respective endeavours thus justifying further study participation,
- the conduct of the study is not compliant with the trial protocol, or
- the quality of data delivered by the study site is not sufficient to warrant trial performance according to the German AMG and international GCP regulations.

The premature closure of a study site will be decided by the principal and coordinating investigator after consultation with the responsible biometrician, the Steering Committee and the Independent Advisory Board.
Individual investigators and/or whole trial sites deciding not to participate in the trial any longer have to inform the coordinating investigator immediately in writing. The decision letter should be well-founded and detail the reasons for premature termination of study participation. Details regarding the further treatment and follow-up of patients participating in the study at the time of premature study termination will have to be discussed and regulated together with the coordinating investigator.

3.5.2 Premature termination of the trial

In case of the following situations, a premature termination of the trial has to be considered:

- Serious adverse drug reactions / unexpected not justifiable toxicity
- Substantial changes in risk-benefit considerations
- New insights from other trials
- Insufficient recruitment rate of all study sites
- Unsustainable trial organization

The Data Monitoring and Safety Committee (DMC) will – based on interim reports generated by the KKSL (small reports every 6 months plus more detailed annual reports) - monitor the study conduct and all safety aspects of the trial and will give recommendations to the Steering Committee as well as the Independent Advisory Committee whether to stop the trial or to change the trial protocol. Care will be taken that members of the DMC will be in every possible respect independent of the study to guarantee unbiased advice and recommendations. Decisions regarding premature termination of the trial will jointly be taken by the Steering Committee and the Independent Advisory Committee after consultation with the funding organisations, the DMC, and the senior biometrician.

According to the German drug law, the trial may be also suspended or prematurely terminated by decision of the competent federal authority (Bundesinstitut für Arzneimittel und Medizinprodukte – BfArM).
4 SELECTION OF TRIAL SUBJECTS

4.1 Inclusion Criteria

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 laevocardiology 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 (SCID48) performed by a certified psychiatric/psychosomatic specialist (see 1.2.3, p. 19-21)*.
- Provision of written informed consent.

* It is recognised that co-morbid depressive symptoms which, according to standardized test criteria (developed in patients suffering from depression as a primary psychiatric disorder), meet the diagnosis ‘current major depression’ are not strictly comparable to ‘current major depression’ in a patient with depression as a primary disorder with regard to pathogenesis and treatment requirements. However, as the distinction between these disease entities (co-morbid depression versus primary depression) cannot be achieved by psychometric testing, it is the responsibility of the certified psychiatric/psychosomatic specialist to decide on the eligibility of patients suffering from co-morbid depressive symptoms proposed for randomization by the cardiologist on the basis of the inclusion and exclusion criteria for treatment with escitalopram or placebo (see below). Below, the term ‘current major depression’ will be used under these premises.

4.2 Exclusion Criteria

Patients will be excluded for ANY ONE of the following reasons:

- 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 levels of hepatic enzymes >threefold of the upper level of the normal range)

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

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)
4.3 Screening Process

Step 1: PHQ-9 screening for suspected DEP

Patients are screened for possible DEP with the PHQ-9\textsuperscript{35} if they

- are aged $\geq$ 18 years
- have systolic CHF as described by the inclusion criteria
- are not obviously non-eligible by the exclusion criteria due to
  - psychiatric disorder or drug treatment for psychiatric disorder
  - psychiatric diagnoses representing exclusion criteria
  - contraindication for SSRI

A PHQ-9 sum of $>11$ is considered a positive test, qualifying for step 2 of the screening process.

Patients temporarily excluded (e.g., participating in another trial) may become eligible later and may, therefore, be included into the screening process.

However, if temporary exclusion is due to an acute cardiac condition, it must be considered that a positive PHQ-9 test at this moment may probably result from a transient depressive episode not representing major DEP. Avoid superfluous inclusion into step 2 of cases who are likely to be false positive. Thus, PHQ-9 screening should not be performed during an acute cardiac condition, or a positive PHQ-9 result obtained in such condition should be repeated after this condition is resolved before entering step 2.

It is also recommended that patients with PHQ-9 sums of $\geq9$, not yet qualified for step 2, undergo repeat PHQ-9 screening at the next opportunity.

Step 2: Diagnostics of major DEP and assessment of eligibility

Patients having a PHQ-9 sum score of $>11$ are suspected of suffering from a current episode of co-morbid major DEP. They will undergo the SCID\textsuperscript{48} diagnostics for major DEP $\geq14$ days after the PHQ-9 result has been obtained. The final decision about eligibility for randomization to escitalopram or placebo with respect to the psychological situation will be made by the testing psychiatric or psychosomatic specialist \textit{on an individual basis} at the occasion of SCID testing.

The PHQ-9 thresholds for entering step 2 or repeated step 1 of the screening procedure may be shifted during the study by an amendment if this would be considered reasonable.
4.4 Participation in Several Clinical Trials

The examination of a concurrent participation of patients in other interventional clinical trials according to German drug law (AMG) is part of the careful examination of the inclusion and exclusion criteria. If this should be the case, no study inclusion takes place. Additionally the patient confirms by the signing of the informed consent that he participates not at the same time in other clinical examinations.

4.5 Explanation for the Inclusion of Dependent Persons

In the scope of the patient inclusion the investigator examines by questioning whether the potential study participants could be dependent on the investigator, coordinating investigator or sponsor in any way. If dependence should be assumed, no study inclusion takes place.

4.6 Gender Distribution

We expect the study sample to consist of about 30% women (n=210) and 70% men (n=490). These data are based on our experiences with the PHQ-9 in over 3500 patients of the KNHI. Thus we can assume that these rates are in concordance with the ‘real world’ population of depressed patients with systolic CHF.

Assuming that half of the patients will be included into the verum arm, there will be a power of over 90% to detect an absolute 20% gender difference of the rates of successful SSRI treatment (in the sense of resolution / improvement of DEP).

The biometrician is responsible to monitor the rates of women and men included into the trial. When recruitment data show a tendency suggesting that women might become significantly underrepresented, appropriate measures will be taken by the steering committee in order to increase the rate of women included into the trial.
5 INVESTIGATIONAL PRODUCT

5.1 Study Medication

Cipralex® contains escitalopram (10 mg) as active ingredient. Cipralex® represents a commercially available and approved medication. Cipralex® will be administrated oral as a tablet. The white tablets are of identical appearance, film-coated, oval, convex, scored and with a single break line on both sides.

Generic name: Escitalopram
Commercial name: Cipralex®
Manufacturer: H.Lundbeck A/S, Ottiliavej 9, DK-2500 Kopenhagen-Valby, Danmark
Provided by: Manufacturer
Packed/labelled by: Wülfing Pharma
Form: Tablets, 10 mg escitalopram or Placebo per tablet
Packing size: Wallet card with Blisters containing 14 tablets each.

Medication kits (1 per patient) containing 104 wallet cards each. One kit is sufficient for 2 years
Storage: At 30°C maximum
Expiry: After (time)
Incompatibilities: Incompatible with non-selective MAO inhibitors;
Caution when co-administering serotonergic drugs;
Further: see 5.4.3
Placebo: Identical tablets without pharmaceutic agent

5.2 Packing and Labelling

Study drug will be packed in walled cards with blisters, each blister contains 14 tablets. Each medication kit will contain 104 walled cards. This allows study medication dispensal for a period of 24 months and additional 8 weeks (±2 weeks for visits allowed). Identical matching placebo will be provided by H. Lundbeck A/S. Packaging of study drug (escitalopram, matching placebo) and labelling of study drug (escitalopram, placebo) will be done by Wülfing Pharma. Production, packaging and labelling of study medication will follow AMG and GMP regulations.
Study medication will be labelled according to the regulations of §5 GCP-V and ICH-GCP Guideline E6. Study medication will be labelled in German.

### 5.3 Drug Accountability

**Delivery of medication kits to the study sites:**

Study medication will be dispensed by Wülfing Pharma.

Current status and location of all medication kits will be stored in the randomization database at the KKSL. Based on this information Wülfing Pharma will receive instructions from the KKSL which kits should be sent to which trial site whenever delivery is necessary. Wülfing Pharma will send packages with the requested sets of kits to the study sites. The study sites will notify receipt on the form coming along with the medication and fax this form to the KKSL. The KKSL staff will register the confirmation of receipt in the randomization database. When this information is not entered 3 days after generation of the medication request, a tracking procedure will be started to clarify were the circle has been interrupted.

Note that medication will not be requested for each patient individually. A number of kits of each treatment arm will be stored at each site. After randomization of a certain number of patients, a new request will be generated in order to fill up the buffer.

**Storage and use of study medication at the trial sites:**
The kits should be stored in a manner that protects study medication from unauthorised use. Unused kits, kits being in use (assigned to a patient who is currently treated in the study), and kits after use containing empty blisters and rests of medication (assigned to a patient who has already finished the study) should be stored separately from each other. A card with the patient’s name and date of birth should be attached to each kit being in use, and should be removed after the patient has finished the study.

Study medication should be used only for randomised patients. After the trial, unused medication kits and rests of used kits will be destroyed by H. Lundbeck A/S. Wait for instructions from the KKSL how to proceed; do not send back or destroy any kits without prior instruction. This applies also when the trial would be stopped prematurely.

It is the responsibility of the principle investigator for the conductance of the trial at each individual study site to ensure that a current record of investigational product disposition is maintained at each study site where the investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area
- Amount currently in storage area
- Label ID number or batch number
- Dates and initials of person responsible for each investigational product inventory entry/movement
- Amount dispensed to and returned by each subject, including unique subject identifiers
- Amount transferred to another area for dispensing or storage
- None-study disposition (e.g., lost, wasted, broken)
- Amount returned to sender (H. Lundbeck A/S)

The investigator or his/her designee must agree not to dispense any study product to any person, except patients included in the study.

The sponsor together with KKSL will provide forms to facilitate inventory control if staff at the investigational site does not have an established system that meets these requirements.
5.4 Administration of Study Drug

5.4.1 Application Schedule

The study drug is administered once daily by oral intake in the morning.

At the beginning, patients start with a dose of 5 or 10 mg/day (=1/2 or 1 tablet) according to the recommendation of the consulting psychiatrist. The process of uptitration is also done in close cooperation with the consulting psychiatrist. Patients are uptitrated after 3 weeks to 10 mg/day (=1 tablet/day) if indicated, or maintained on 10 mg/day (=1 tablet/day) for another 3 weeks. After further three weeks patients are uptitrated to 20 mg/day (=2 tablets/day), if the study drug has been well tolerated. If the study drug has not been well tolerated (e.g., due to side effects not infrequently observed in the initial treatment phase, refer to 5.4.4), the patient is maintained at the initial dose (5 mg or 10 mg) until the next visit. Then uptitration is reconsidered. If again not feasible, the dosage is maintained at the tolerated level (5 mg or 10 mg). If after uptitration the higher dosage is not well tolerated, the dosage may also be transiently reduced followed by another attempt of uptitration later on. Twelve weeks after study start the final dosage of study drug must be reached in all patients.

The dose level reached in the up titration phase at 12 weeks will then be maintained until the final follow-up.

At the end of the study period, DEP is assessed by MADRS, and down titration is accomplished as follows:

- Patients on 2 tablets/day (20 mg of study medication) will be advised to take 1 tablet/day for the following 14 days. If they are still depressive (i.e. MADRS >21), they will take additionally 10 mg escitalopram open label. Thus, there will be a two-week double-blind downtapering period; after this period, patients will no longer receive placebo or study product:

- Patients on 1 tablet/day who are still depressive (i.e. MADRS > 21), will discontinue study medication and will receive 10 mg escitalopram open label. Thus, there will be a two-week double-blind downtapering period; after this period, patients will no longer receive placebo or study product.

- In both cases the dosage may be reduced to 5 mg escitalopram open label if 10 mg escitalopram open label are not well tolerated.

After this downtapering period, open label treatment of each patient will be guided by a psychiatrist/psychosomatic specialist unrelated to the trial, who will treat the patient according to his/her individual needs.
5.4.2 Compliance

At every visit, the patients will receive study drug in advance, in sufficient quantity to cover periods between study visits. At every visit, empty blisters and unconsumed tablets are to be returned to the investigator. The study staff will register the returned medication and document this in the CRF.

In addition, the physician/nurse will document a subjective assessment of the patient’s compliance with both the heart failure medication as well as the study medication in a standardised fashion in the CRF.

In the verum group, *escitalopram* plasma levels will be an additional correlate of intake of the medication allowing to conclude about (but not determine) compliance. However, in order not to unblind the study, the blood samples will be analysed in a Core Lab for *escitalopram* plasma levels only after the study has been terminated and unblinded.

5.4.3 Contraindication/ Forbidden Concomitant Medication

<table>
<thead>
<tr>
<th>Medication (Generic)</th>
<th>Disallowed from time before screening and during the study</th>
<th>Restrictions for use during the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any investigational drugs</td>
<td>30 days</td>
<td>X</td>
</tr>
<tr>
<td>IMAO, RIMA, SSRI (except fluoxetine), TCA, SNRI</td>
<td>2 weeks</td>
<td>X</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>5 weeks</td>
<td>X</td>
</tr>
<tr>
<td>St-John’s Wort, S-adenosymethionine (SAMe), kava kava, valerian, gingko biloba</td>
<td>2 weeks</td>
<td>X</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>2 weeks</td>
<td>X</td>
</tr>
<tr>
<td>Lithium</td>
<td>2 weeks</td>
<td>X</td>
</tr>
<tr>
<td>Anti-convulsants / anti-epileptics / antimanic / mood stabilisers (including lamotrigine, valproic acid, gabapentine, carbamazepine, phenytoin)</td>
<td>2 weeks</td>
<td>X</td>
</tr>
<tr>
<td>Any other antidepressant</td>
<td>2 weeks</td>
<td>X</td>
</tr>
<tr>
<td>Oral anti-psychotics</td>
<td>2 weeks</td>
<td>X</td>
</tr>
<tr>
<td>Depot anti-psychotics</td>
<td>6 months</td>
<td>X</td>
</tr>
<tr>
<td>Benzodiazepines at equivalence doses higher than 10 mg diazepam*</td>
<td>See footnote</td>
<td>X</td>
</tr>
<tr>
<td>Dopamine antagonists (e.g. metoclopramide)</td>
<td>2 weeks</td>
<td>X</td>
</tr>
<tr>
<td>Serotonergic agonists (e.g. triptans)</td>
<td>2 weeks</td>
<td>X</td>
</tr>
</tbody>
</table>
Medication (Generic) | Disallowed from time before screening and during the study | Restrictions for use during the study
---|---|---
Any other drugs with potential psychotropic effects | 2 weeks | X
Products that are mainly metabolised by CYP2D6 (e.g. metoprolol) | 2 weeks | X
Drugs with serotonin-reuptake inhibiting properties (e.g. tramadol) | 2 weeks | X

*Benzodiazepines and GABA-A receptor hypnics (zopiclone, zolpidem, zaleplon) are allowed if the equivalence dose does not exceed 10 mg of diazepam. A listing with substances and equivalence doses will be distributed to study centers via the handling guidelines. Recommended are temazepam, oxazepam and zolpidem. In addition to the medications listed above, electroconvulsive therapy (ECT) is disallowed for 6 months prior to screening and at any time during the study.

5.4.4 Known Adverse Drug Reactions (ADR)

Type of ADR (observed rate / excess compared to placebo rate) occurring in >5% of patients in four short-term trials

- nausea (15.0/7.6)
- ejaculation disorder (9.3/9.3)
- insomnia (9.2/5.3)
- diarrhea (8.0/2.8)
- somnolence (6.9/4.7)
- dizziness (6.0/2.5)
- influenza-like symptoms (5.0/0.9).

It appears from a long-term trial that rates of rhinitis, back pain and influenza-like symptoms might be increased.

**Timing**: Most of the adverse reactions probably attributable to the active agent (causing the excess rate in comparison with placebo) seem to appear during the first two weeks of treatment.

Rare events which have been reported and should be considered possible:

- Alteration of glycemic control in diabetic patients is reported to be rare (<1 per million)
- Anxiety symptoms may be increased in patients with panic disorder at the onset of treatment
- Hyponatremia, especially in elderly women, probably due to inappropriate antidiuretic hormone secretion
- Slight but clinically unimportant lowering of the heart rate is possible
- Seizures
- Manic reactions
- Cutaneous bleeding abnormalities.

5.4.5 Handling of known ADR

In case of known ADR proceed as follows:

- Reduce dose step by step until symptoms vanish
- Symptomatic treatment if appropriate
- If necessary, interrupt study medication
- If appropriate, try uptitration again. However, do not force uptitration if the patient might become incompliant by reoccurrence of ADR symptoms. Better a low dose of study medication is given than no medication
- In case of reoccurrence of symptoms after uptitration, reduce dose again to the level tolerated. Do not uptitrate any further
- In event of seizures, discontinue the drug and terminate study participation.

5.4.6 Overdose Symptoms

At 10-30 times the normal clinically used doses, nausea, dizziness, tachycardia, tremor, drowsiness and somnolence MAY occur. At still higher doses, convulsions and ECG changes may occur. A few fatalities have been reported, mostly in conjunction with other drugs.

5.4.7 Overdose Treatment

No specific antidot is available.

Proceed as follows:

- oral ingestion
- gastric lavage
- symptomatic supportive treatment
- monitoring of cardiac and vital signs

Haemodialysis is pointless (only 1% of escitalopram is removed).
In case of suspected drug-drug interactions contact the local toxicology center and proceed according to established individual guidelines.

5.4.8 Treatment of SUSARs

Proceed like in event of overdose. See chapter 8 for reporting.

5.5 Blinding and Unblinding

The trial medication is blind. Each medication kit is identified by a code. The assignment of verum or placebo to the codes is known only to the biometrician generating the randomization list and to Wülfing Pharma responsible for labelling the trial medication.

Unblinding information is contained in sealed envelopes contained in the medication kits. The conditions for unblinding and the procedures for documentation and reporting are explained by a guideline (see investigator site file). The emergency envelopes must not be opened except for the conditions described in the guideline, even not after the patient has finished the study.

Check of intactness of the seals, or of the documentation when the seal has been broken, is subject to monitoring (mandatory for all medication kits).
6 INDIVIDUAL TRIAL PROCEDURES

6.1 Screening

The KKSL will screen the HFNC data base for patients included by the prospective nine MOOD-HF trial centers, who satisfy the cardiological inclusion/exclusion criteria and have a PHQ-9 score >11. The KKSL will produce lists of the respective patient IDs for each center. Using this information, each study site will be able to identify and contact their patients for PHQ-9 re-evaluation. Patients responding to the invitation to participate in the second PHQ-9 screening will qualify a patient for a screening visit at the respective center if repeat PHQ-9 produces again a score >11.

At the same time participating trial centers will screen all consecutive outpatients and inpatients that fulfill the cardiological inclusion/exclusion criteria CHF NYHA II-IV and LVEF \(<45\%\) with a first PHQ-9. Patients not recruited into the HFNC who have undergone a previous PHQ-9 screening, for other reasons also need to undergo a second PHQ-9 screening, if the first screening was performed \(>4\) weeks ago. Screening may be repeated at the next opportunity when the PHQ-9 sum was \(\geq9\) but not \(>11\).

For all patients with a score of \(>11\) at a PHQ-9 screening, which triggers an invitation for SCID at the study site, a screening log for documentation of these patients is mandatory and will be supplied by KKSL. All patients will be documented in the screening log and assigned a screening number. If a patient will subsequently not be entered into the trial after SCID-testing, the reasons need to be indicated in the screening list (e.g. absence of current episode of major depression according to DSM-IV, no informed consent).

In patients invited to participate in a SCID which will be performed at the respective study site, the following will be performed during this visit (visit 0):

1) Establishment of the diagnosis of a current episode of co-morbid major depression according to the Diagnostic & Statistical Manual of Mental Disorders (DSM-IV\textsuperscript{46}). The SCID will be performed by a certified expert (see 3.2), who will take responsibility for the eligibility of the patient to participate in the MOOD-HF-study with respect to all psychological/psychiatric aspects. Care should be taken to avoid unnecessary commuting of the study participant between cardiologist and psychiatrist/psychosomatic specialist. Whenever possible, the psychiatrist/psychosomatic specialist should visit the patient and conduct the interview on the premises of the recruiting site. Importantly, if the psychiatrist/psychosomatic specialist suspect moderate or severe dementia in a patient screened for study participation, he/she will conduct the MMSE interview immediately after the SCID. Subjects with a MMSE \(<18\) should not enter the
study, in subjects with a MMSE between 18 and 24 the psychiatric/psychosomatic specialist should check the ability to give informed consent. If the MMSE falls below 18 during the study, it is at the discretion of the study investigator to discontinue the double-blind treatment in an individual patient. However, as in other circumstances, an attempt should be made to follow-up these subjects throughout the entire duration of the study.

2) If the psychiatric inclusion criterion (SCID positive) is fulfilled, the psychiatric exclusion criteria are checked including the eligibility for escitalopram or placebo treatment.

3) The psychiatrist/psychologist informs the cardiologist about the SCID test result. The cardiologist completes the inclusion/exclusion criteria list.

4) If the patient satisfies all inclusion/exclusion criteria, inform the patient about the possibility to participate in MOOD-HF. At this time, the investigator will explain to each trial subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail to each trial subject. Each potential trial subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship to the treating physician. The patient will be provided with enough time (at least 24 hours) to think about the participation in the study and have the opportunity to ask questions about the study at repeat occasions.

6.2 Patient Information and Informed Consent

Informed Consent will be asked for at the earliest on the next day after the information about MOOD-HF has taken place (see 6.1). The Informed Consent needs to be given by means of a standard written statement, written in non-technical language. The trial subject will have the opportunity to read the statement and consider his/her decision before signing and dating the document, and will be given a copy of the signed document. If written consent is not possible, oral consent can be obtained if witnessed by a signed statement from one or more persons not involved in the study, mentioning why the patient was unable to sign the form.

No patient will be able to enter the study before his/her Informed Consent has been obtained. The Informed Consent form will be found in the Investigator Site File. The signed Informed Consent form will be duplicated to provide one version to the participant and one for the trial site which will be filed in the Investigator Site file. The Informed Consent form signed by the patient will also refer specifically to the assessment and processing of data on the patients’
health. The patient will be informed explicitly on the purpose and extent of the assessment and the use of his/her personal data, especially the health-related data.

Written informed consent for long-term storage of the patients' biomaterials (blood cells, serum, plasma) in the biomaterial bank of the HFNC (including DNA) as well as at the study site of the Principal Investigator at the Würzburg University Cardiovascular Center will be obtained separately. The patient may not consent to the latter, but still be included into MOOD-HF. See Appendix for further information.

Written informed consent will be obtained prior to any study related procedures. No change in pre-existing medical therapy apart from subsequent implementation of optimal CHF therapy, which will take pace during the up-titration-phase of the study, will be required by the study protocol.

6.2.1 Withdrawal of Informed Consent

Patients will be informed that they may withdraw their consent to participate at any time of the trial without giving the reason for it. Nevertheless, the patient should be asked for the reason of the premature termination but he/she should also be aware, that he/she needs not to answer this question. The patient will be informed that choosing not to participate or to withdraw the consent will not affect his/her subsequent medical treatment or relationship to the treating physician.

Date of enrolment and date of and reason for withdrawal will be documented in any case. The patient will be informed that in case of revocation of his/her consent the stored data may be used further, as may be necessary:

- to assess effects of the study drug to be tested
- to guarantee that the interests of the patient are not impaired
- to comply with the regulatory requirements.

6.3 Enrolment and Randomization

Eligibility of enrolment will be confirmed, and randomization will be done at visit 1 (week 0 of the study).

During the enrolment and randomization visit, the following procedures will be performed:

1) Confirm subject satisfies inclusion and exclusion criteria. Specifically, check that laboratory tests are within the required ranges (e.g., renal and hepatic function)
2) Obtain vital signs and perform physical examination. Obtain the NYHA class, record body weight and waist-to-hip ratio

3) Record concomitant non-cardiac medication

4) Record cardiac medication (including ACE-inhibitors, angiotensin-receptor-blockers, β-blockers, diuretics, glycosides, aldosterone antagonists, statins and platelet inhibitors /anticoagulants)

5) Obtain a 12-lead ECG

6) Obtain a 24-hour long-term-ECG (measurement of heart rate variability, arrhythmia)

7) Obtain blood and morning spot urine for safety laboratory parameters

8) Obtain blood for assessment of CHF severity based on natriuretic peptides

9) Instruct patient about harvesting of morning and evening saliva for determination of cortisol levels and about 24-hour-collection of urine for determination of norepinephrine-excretion, dispense appropriate sampling vessels and prepaid dispatch sets for the samples which will be sent to the endocrinological core lab

10) Obtain blood for the Central Laboratory Core Lab at Würzburg University and for GENE-MOOD substudy following the blood taking guideline. Ensure appropriate further processing of the blood at the study site and storage of aliquots at –80°C Celsius until transport

11) Obtain systolic and diastolic function by echocardiography. Patients may be enrolled if the LVEF is <45% and is in NYHA functional class II–IV irrespective of diastolic function parameters

12) Perform a 6-minute walk test

13) Assess quality of life using the SF-36 and KCCQ self assessment questionnaires

14) Assess depression using the PHQ-9 self assessment and MADRS questionnaires

15) Assess general anxiety using the PHQ-GAD-7 and cognitive function using the MMSE

16) Assess health economy

17) Obtain blood for THROMBO-MOOD substudy (trial site Würzburg)

18) Obtain quantitative vascular ultrasound (trial site Würzburg), measure pulse wave velocity and augmentation index for VASO-MOOD substudy (trial sites Würzburg and Lübeck).
Randomization procedure

If a patient has signed the *Informed Consent* form and is eligible for the trial (according to visit 0 and 1) the investigator will proceed as follows:

1) **Assignment of a Patient-ID:** In the centre patient list (CP, see investigator site file), fill in the patient personal data at the first free position of the list. The Patient ID printed in the list at this position is assigned to the patient and will be used throughout the study as a synonym for the patient (cf. data protection, chapter 15).

2) **Before randomization,** make sure that age, gender and the result from SCID diagnostics of the patient are available.

Login at the site

http://www.knhi.de/Forschung/AP-MOOD-HF/Dateneingabe.jsp

preferably via the MS Internet Explorer 6. The user will be asked for the Patient ID, for check of eligibility criteria, presence of informed consent in writing, age, sex and SCID result (classification as moderate or more severe depression). Enter these items. Then click the randomization button. The system will return to you the code of the medication kit assigned to the patient.

Write the medication code into the CP list.

3) **Complete the baseline documentation** (all B sheets of the CRF)

4) **Provide subjects with study medication for a period of 3 weeks** (one or two wallet cards with 14 tablets, respectively, depending on the scheduled dose of 5 or 10 mg/d)

5) **Instruct subjects regarding the following items for visit 2:**

   - Start of study medication with ½ tablet (1 tablet) per day and continue this dosage until visit 2
   - Explain weekly telephone monitoring of patients’ well-being during up-titration including also monitoring of tolerability of study medication
   - Date and time of the next visit (3 weeks ± 2 days)
   - All other concomitant medications must be taken as usual until the second visit
   - Optimisation of CHF medication according to current CHF treatment guidelines is required. This will follow the current version of the ESC Guidelines for the Diagnosis and Treatment of CHF. See Appendix for further details.

Violation of eligibility criteria
If a patient has been included into the study and it turns out that he/she violated the eligibility criteria, proceed as follows: In case the patient has not been randomised, stop his/her participation in the trial entirely. Since a patient ID code has been already assigned to the patient, notify in the patient list (CP) that the patient has been withdrawn. Do not use this ID code for any other patient.

If the patient has already been randomised, contact the KKSL data management and the coordinating investigator/the sponsor immediately. Only stop the treatment immediately in case the violated criteria represent an additional risk for the patient or in case the patient has been randomised by error without his/her consent. In all other cases, proceed per protocol and wait for instructions. The principal/coordinating investigators and the senior biometrician of MOOD-HF will in each individual case discuss with the investigator if further treatment within the MOOD-HF-study is indicated. Documentation of the patient’s clinical data will be continued throughout the entire trial.

6.4 Treatment of Trial Subjects

Uptitratinon: Visit 2 to 3 (week 3 and week 6 post randomization ± 2 days):

1) Obtain NYHA class and body weight and perform limited physical examination including vital signs with the recording of clinically relevant changes since last visit as an AE with date and time of onset

2) Obtain blood samples for safety parameters (natriuretic peptides, potassium, sodium, and creatinine) and also blood for the Central Laboratory Core Lab at Würzburg University (only Visit 3)

3) Assess AE since last visit

4) Assess morbidity (number and days of hospitalisations since last visit)

5) Record concomitant CHF medication taken since last visit (enquire about type and dosage/day of individual drugs, refer to visit 1 for classes of medication to be checked)

6) Uptitrate CHF medication or/and add new CHF medication if indicated according to treatment guidelines considering also contraindications to specific drugs in individual patients

7) Assess compliance with study medication (pill count; check of pill calendar)

8) Determine if patient has tolerated the level of study medication. If yes, instruct patient to continue to take study medication once daily and increase study medication, if the target dosage of 20 mg/day has not yet been reached
9) Assess depression using Short version of Patient Health Questionnaire (the first 2 PHQ-9 questions + the last PHQ-9 question regarding suicidality)

10) Assess necessity to arrange a visit of the patient to psychiatrist/psychosomatic specialist from result of PHQ-2 and suicidal testing. Worsening of co-morbid major depression or de novo suspected suicidality will trigger involvement of the responsible psychiatrist/psychosomatic specialist.

11) Document all data and information obtained in the patients’ Case Report Form

12) At visit 2, instruct subjects regarding the following items for visit 3:
   - Date and time of the next visit (at 6 weeks + 2 days)
   - Continue study medication as prescribed until visit 3
   - All other concomitant medications must be taken as usual until the visit, unless
   - Further optimization of CHF medication according to current CHF treatment guidelines is required. See Appendix for further details

13) At visit 3, instruct subjects regarding the following items for visit 4:
   - Date and time of the next visit (3 months + 1 week)
   - Continue study medication as prescribed including an attempt to further uptitrate to 20 mg/day, if this target dose has not yet been reached. Tolerability of study medication will be monitored by the weekly prescheduled telephone calls
   - All other concomitant medications must be taken as usual until visit 4, unless further optimization of CHF medication according to current CHF treatment guidelines is required. See Appendix for further details

14) At visit 3, also obtain blood for routine biochemistry including SSRI safety markers and for plasma levels of natriuretic peptides

15) At visit 3, provide subjects with study medication for a period of 7 weeks (4 wallet cards with 14 tablets).

End of uptitration: Visit 4 (3 months post randomization ± 1 week):

1) Obtain NYHA class and body weight and perform limited physical examination including vital signs with the recording of clinically relevant changes since last visit as an AE with date and time of onset. Obtain blood samples for safety parameters including SSRI safety markers and for plasma levels of natriuretic peptides
2) Obtain blood for the Central Laboratory Core Lab at Würzburg University for escitalopram plasma levels, endocrinology, and inflammation markers following the blood taking guideline. Ensure appropriate further processing of the blood at the study site and storage of aliquots at – 80°C Celsius until transport.

3) Assess AE since last visit.

4) Assess morbidity (number and days of hospitalisations since last visit).

5) Record concomitant CHF medication taken since last visit (enquire about type and dosage/day of individual drugs, refer to visit 1 for classes of medication to be checked).

6) Inform patient that up-titration of study drug and CHF medication is completed.

7) Confirm that patient has tolerated the level of study medication.

8) Assess compliance with study medication (pill count; check of pill calendar).

9) Assess quality of life using the SF-36 and KCCQ self assessment questionnaires.

10) Assess general anxiety using the PHQ-GAD-7 and cognitive function using the MMSE.

11) Assess health economy.

12) Assess depression using the PHQ-9 self assessment and MADRS questionnaires. With respect to the MADRS assessment, the following applies: if a patient is below a score of 22 at follow-up, no action from the cardiologist is needed. However, if the cardiologist feels uncertain about a possible deterioration (e.g., jump from 14 at baseline to 20 at follow-up), he/she may always contact the psychiatrist/psychosomatic specialist and ask for guidance. If a patient scored 22 and higher at baseline and the score at follow-up is unchanged (“change” is defined as +/- 15%) or worsened, then the help of the psychiatrist/psychosomatic specialist needs to be sought. If a patient scored 22 and higher at baseline and the score at follow-up is improved (defined as drop >15%) but still above 21, then no psychiatric action is forced, but as with scores of lower than 22 the cardiologist may always contact the psychiatrist/psychosomatic specialist and ask for guidance. See the following examples:

<table>
<thead>
<tr>
<th>MADRS Score</th>
<th>Action by cardiologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit X</td>
<td>Visit X+1</td>
</tr>
<tr>
<td>&lt; 22</td>
<td>&lt; 22</td>
</tr>
<tr>
<td>&lt; 22</td>
<td>≥ 22</td>
</tr>
<tr>
<td>≥ 22</td>
<td>≥ 22</td>
</tr>
<tr>
<td>≥ 22</td>
<td>&lt; 22</td>
</tr>
</tbody>
</table>

See the following examples:
13) Assess necessity to arrange a visit of the patient to psychiatrist/psychosomatic specialist from result of PHQ-9 and MADRS testing (no change or worsening of co-morbid major depression or de novo suspected suicidality will trigger involvement of the responsible psychiatrist)

14) Instruct subjects regarding the following items for visit 5:
   - Date and time of the next visit (at 6 months ± 2 days)
   - Continue study medication at maximum tolerated dose (up to 20 mg per day)
   - Change of frequency of telephone monitoring to every two months
   - All other concomitant medications must be taken as usual until the visit
   - Continue optimized cardiac medication according to current CHF treatment guidelines and non-cardiac medication as usual

15) Document all data and information obtained in the patients’ Case Report Form

16) Provide subjects with allocated study medication for a period of 3 months (14 wallet cards with 14 tablets).

Maintenance phase: Visit 5 (6 months post randomization ± 2 weeks):

1) Obtain NYHA class and body weight and perform limited physical examination including vital signs with the recording of clinically relevant changes since last visit as an AE with date and time of onset

2) Obtain blood samples for safety parameters including SSRI safety markers and for plasma levels of natriuretic peptides

3) Obtain blood for the Central Laboratory Core Lab at Würzburg University for escitalopram plasma levels, endocrinology and inflammation following the blood taking guideline. Ensure appropriate further processing of the blood at the study site and storage of aliquots at – 80°C Celsius until transport

4) Assess AE since last visit

5) Assess morbidity (number and days of hospitalisations since last visit)

6) Record concomitant CHF medication taken since last visit (enquire about type and dosage/day of individual drugs, refer to visit 1 for classes of medication to be checked)

7) Assess compliance with study medication (pill count; check of pill calendar)

8) Record concomitant non-cardiac medication
9) Contact central randomization system to confirm that the visit has taken place and to confirm the subject’s latest dose level

10) Obtain a 12-lead ECG

11) Obtain a 24-hour long-term-ECG (measurement of heart rate variability, arrhythmia)

12) Assess quality of life using the SF-36 and KCCQ self assessment questionnaires

13) Assess depression using the PHQ-9 self assessment and MADRS questionnaires

14) Assess general anxiety using the PHQ-GAD-7 and cognitive function using the MMSE

15) Arrange a visit of the patient to psychiatrist/psychosomatic specialist regardless of the result of PHQ-9 and MADRS testing in order to assess that blinded treatment in this patient is still medically safe and ethically justifiable

16) Obtain systolic and diastolic function by echocardiography

17) Perform a 6-minute walk test

18) Instruct patient about harvesting of morning and evening saliva for determination of cortisol levels and about 24-hour-collection of urine for determination of norepinephrine excretion, dispense appropriate sampling vessels and pre-paid dispatch sets for the samples, which will be sent to the endocrinological core lab

19) Obtain blood for THROMBO-MOOD substudy (trial site Würzburg)

20) Obtain quantitative vascular ultrasound (trial site Würzburg), measure pulse wave velocity and augmentation index for VASO-MOOD substudy (trial sites Würzburg/Lübeck)

21) Instruct subjects regarding the following items for visit 6:
   - Date and time of the next visit (at 12 months ± 2 days)
   - Continue study medication at maximum tolerated dose (up to 20 mg per day)
   - All concomitant medications must be taken as usual until the visit
   - Continue optimised cardiac medication according to current CHF treatment guidelines and non-cardiac medication as usual

22) Document all data and information obtained in the patients’ Case Report Form

23) Provide subjects with allocated study medication for a period of 6 months (28 wallet cards with 14 tablets).

**Maintenance phase: Visit 6 (12 months post randomization ± 2 weeks):**
1) Obtain NYHA class, body weight and waist-to-hip ratio and perform limited physical examination including vital signs with the recording of clinically relevant changes since last visit as an AE with date and time of onset

2) Obtain the waist-to-hip-ratio

3) Obtain blood samples for safety parameters including SSRI safety markers and for plasma levels of natriuretic peptides

4) Obtain blood for the Central Laboratory Core Lab at Würzburg University for endocrinology and inflammation following the blood taking guideline. Ensure appropriate further processing of the blood at the study site and storage of aliquots at –80°C Celsius until transport

5) Assess AE since last visit

6) Assess morbidity (number and days of hospitalisations since last visit)

7) Record concomitant CHF medication taken since last visit (enquire about type and dosage/day of individual drugs, refer to visit 1 for classes of medication to be checked)

8) Assess compliance with study medication (pill count; check of pill calendar)

9) Record concomitant non-cardiac medication

10) Contact central randomization system to confirm that the visit has taken place and to confirm the subject’s latest dose level

11) Obtain a 12-lead ECG

12) Obtain a 24-hour long-term-ECG (measurement of heart rate variability, arrhythmia)

13) Assess quality of life using the SF-36 and KCCQ self assessment questionnaires

14) Assess depression using the PHQ-9 self assessment and MADRS questionnaires

15) Assess general anxiety using the PHQ-GAD-7 and cognitive function using the MMSE

16) Assess necessity to arrange a visit of the patient to psychiatrist / psychosomatic specialist from result of PHQ-9 and MADRS testing. No change or worsening of co-morbid major depression or de novo suspected suicidality will trigger involvement of the responsible psychiatric/psychosomatic specialist.

17) Obtain systolic and diastolic function by echocardiography

18) Obtain health economy

19) Instruct subjects regarding the following items for visit 7:

- Date and time of the next visit (at 12 months ± 2 days)
- Continue study medication at maximum tolerated dose (up to 20 mg per day)
- All concomitant medications must be taken as usual until the visit
- Continue optimized cardiac medication according to current CHF treatment guidelines and non-cardiac medication as usual

20) Document all data and information obtained in the patients' Case Report Form
21) Provide subjects with allocated study medication for a period of 6 months (28 wallet cards with 14 tablets).

**Maintenance phase: Visit 7 (18 months post randomization ± 2 weeks):**

1) Obtain NYHA class and body weight and perform limited physical examination including vital signs with the recording of clinically relevant changes since last visit as an AE with date and time of onset
2) Obtain blood samples for safety parameters including SSRI safety markers and for plasma levels of natriuretic peptides
3) Assess AE since last visit
4) Assess morbidity (number and days of hospitalisations since last visit)
5) Record concomitant CHF medication taken since last visit (enquire about type and dosage/day of individual drugs, refer to visit 1 for classes of medication to be checked)
6) Assess compliance with study medication (pill count; check of pill calendar)
7) Record concomitant non-cardiac medication
8) Contact central randomization system to confirm that the visit has taken place and to confirm the subject’s latest dose level
9) Assess depression using the PHQ-9 self assessment and MADRS questionnaires
10) Assess general anxiety using the PHQ-GAD-7 and cognitive function using the MMSE
11) Assess necessity to arrange a visit of the patient to psychiatric/psychosomatic specialist from result of PHQ-9 and MADRS testing. No change or worsening of co-morbid major depression or de novo suspected suicidality will trigger involvement of the responsible psychiatric/psychosomatic specialist.
12) Instruct subjects regarding the following items for visit 8/final visit:
    - Date and time of the next visit (at 12 months + 2 days)
- Continue study medication at maximum tolerated dose (up to 20 mg per day)
- All concomitant medications must be taken as usual until the visit
- Continue optimized cardiac medication according to current CHF treatment guidelines and non-cardiac medication as usual

13) Document all data and information obtained in the patients’ Case Report Form

14) Provide subjects with allocated study medication for a period of 6 months (28 wallet cards with 14 tablets).

**Maintenance phase: Visit 8 (24 months post randomization ± 2 weeks) – final study visit:**

1) Obtain NYHA class and body weight and perform limited physical examination including vital signs with the recording of clinically relevant changes since last visit as an AE with date and time of onset

2) Obtain blood samples for safety parameters including SSRI safety markers and for plasma levels of natriuretic peptides

3) Obtain blood for the Central Laboratory Core Lab at Würzburg University for escitalopram plasma levels, endocrinology and inflammation following the blood taking guideline. Ensure appropriate further processing of the blood at the study site and storage of aliquots at – 80° Celsius until transport

4) Assess AE since last visit

5) Assess morbidity (number and days of hospitalisations since last visit)

6) Record concomitant CHF medication taken since last visit (enquire about type and dosage/day of individual drugs, refer to visit 1 for classes of medication to be checked)

7) Assess compliance with study medication (pill count; check of pill calendar)

8) Record concomitant non-cardiac medication

9) Contact central randomization system to confirm that the visit has taken place and to confirm the subject’s latest dose level

10) Obtain a 12-lead ECG

11) Obtain a 24-hour long-term-ECG (measurement of heart rate variability, arrhythmia)

12) Assess quality of life using the SF-36 and KCCQ self assessment questionnaires

13) Assess depression using the PHQ-9 self assessment and MADRS questionnaires
14) Assess general anxiety using the PHQ-GAD-7 and cognitive function using the MMSE
15) Obtain systolic and diastolic function by echocardiography
16) Perform a 6-minute walk test
17) Obtain health economy

18) Instruct subjects regarding the following items for post study visit (together with psychiatric/psychosomatic specialist):
   - Date and time of the next visit (final visit +14 ± 2 days)
   - Continue study medication at 50% of last dose, if last dose was 20 mg/day
   - Discontinue study medication, if last dose was 5 or 10 mg/day
   - Take open label escitalopram at 10 mg/day in both cases provided MADRS demonstrates current moderate or severe episode of major DEP (i.e. MADRS >21)
   - All other concomitant medications must be taken as usual until the visit
   - Continue optimized cardiac medication according to current CHF treatment guidelines
   - Advise about necessity of appointment with psychiatric/psychosomatic specialist for further care after termination of study and arrange this appointment
   - Recommend regular visits to cardiologist after termination of study, offer support in obtaining an appointment

19) Document all data and information obtained in the patients’ Case Report Form
20) Advise patients previously taking 20 mg/d of study medication to use 10 mg/d of medication from the last remaining box of their previous quantity of study medication for the next two weeks and leave this box with the patients. Obtain all other boxes from the patients. Obtain all boxes with remaining study medication from patients previously taking 10 mg/d.

**Down Titration / Post study Visit (14±2 days after final study visit):**

1) Obtain NYHA class and body weight and perform limited physical examination including vital signs with the recording of clinically relevant changes since last visit as an AE with date and time of onset
3) Assess AE since last visit
4) Assess morbidity (number and days of hospitalisations since last visit)
5) Assess compliance with study medication (pill count; check of pill calendar)

6) Instruct subjects regarding the following items:

- Assure date and time of visit to psychiatric/psychosomatic specialist organizing further care for the patient (must take place within 14 days after down titration visit)
- Discontinue study medication if still taken
- Continue to take open *escitalopram* at 100% of last dose (e.g., 20 mg per day, if last dose of study medication was 20 mg per day), provided the MADRS demonstrated current moderate or severe episode of DEP at final study visit (i.e. MADRS > 21)
- Recommend to continue all other concomitant medications as usual including optimised cardiac medication according to current CHF treatment guidelines
- Provide patient with referral letter to psychiatric/psychosomatic specialist containing information about last MADRS result and also a prepaid envelop with a documentation sheet for AE, asking the psychiatric/psychosomatic specialist to fill in this documentation sheet covering the first 4 weeks after study termination and send it to the KKSL.

**Telefone Monitoring During Uptitration (1 week to 3 months post randomization):**

Telefone monitoring will be performed by a trained study nurse at weekly intervals in a standardized fashion. The nurse will cover and document in writing the following items:

1) Patients' subjective well being

2) Short version of Patient Health Questionnaire (the first 2 PHQ-9 questions + the last PHQ-9 question regarding suicidality). With respect of suicidality, an algorithm gives detailed advice on actions to performed depending on the severity of suicidal tendencies. The nurse will contact the cardiologist whenever in doubt. The cardiologist will then handle the telephone assessment and decide on further actions.

3) Ask about potential side effects of *escitalopram* and cardiac medication as prescribed at the last study visit

4) Strengthen patients' compliance by asking him/her to continue with study medication according to the study protocol and with CHF medication.

The following general remarks also apply: Nurses may discuss results of structured telephone interviews with the cardiologist in charge at the respective study site. In case of intolerable side effects or worsening or lack of improvement of depression or suspected active suicidal tendencies the responsible psychiatric/psychosomatic specialist will be contacted and reas-
sess the patient by telephone on the same day. Confirmed suspected suicidal tendencies or significant worsening or lack of improvement of severe depression will immediately induce pre-specified supportive strategies including psychiatric/psychosomatic involvement and open treatment according to patient needs, if necessary. The decision about whether individual premature study termination is required will be a joint responsibility of the psychiatric/psychosomatic specialist and the cardiologist in charge. In all these instances, the cardiological and psychiatric hot lines of the core labs may be used.

For treatment of AE refer to 8.1.

**Telefone Monitoring During Maintenance (3 to 24 months post randomization):**

Telefone monitoring will be performed and documented by a trained study nurse at 2-monthly intervals in a standardized fashion, as described above.

### 6.5 Follow-up

For a period of four weeks after the last intake of study drugs, all AEs and SAEs need to be documented. Usually, the responsible psychiatrist/psychosomatic specialist will complete respective forms. In addition, a final telephone call of the study nurse will be placed to ensure the patient well-being and provide guidance should need arise.

### 6.6 Premature Termination of Therapy or Follow-up

#### 6.6.1 Planned Termination at the End of the Study

Treatment and study visits will end for all patients when the first patient included and not dropped out completed 24 months treatment AND the last patient included and not dropped out completed 12 months treatment. Each patient should then undergo the final visit. The KKSL biometry and data management monitoring the progress of the study visits in all patients will anticipate the approximate date when this will happen. In agreement with the coordinating investigator, the KKSL will send out information to the centres at the appropriate time that patients should be scheduled for final study visit within a prescribed time frame.

#### 6.6.2 Other premature termination

Each other premature termination of the trial therapy as well as every premature termination of follow-up has to be documented by the responsible investigator. If possible, date, circum-
stances of and reason for the termination should be documented in detail, and communicated to the KKSL / Data Management. Use the X form of the CRF for the first communication to the KKSL of premature termination or the intent thereof. Depending upon reason and circumstances, the KKSL will confirm termination and/or give advices as to how to proceed further.

6.6.3 Premature Termination of Trial Therapy

If necessary, study therapy should be reduced or interrupted, but not stopped completely, if this can be avoided. Try to restart drug therapy after any interruption. The only reasons for termination of study treatment should be the following:

- Suicidality or no change/worsening of depression requiring specific psychopharmacological (other antidepressant or antipsychotic) or psychological (e.g. CBT, IPT) interventions. Allowed are benzodiazepines as specified above and problem-oriented supportive interventions by psychiatrists/psychosomatic specialists or other health professionals.
- Serious adverse drug reactions or SUSARs representing contraindications for continued application of escitalopram, or withdrawal of consent by the patient.

In case of a premature termination of therapy, reasons/circumstances and if applicable the final status have to be documented. If the patient does not withdraw the consent for further follow-up, he or she should be followed-up as planned throughout the entire duration of the trial.

6.6.4 Premature Termination of Follow-up

In case the patient misses the scheduled visits, the investigator should contact the patient directly, in order to motivate him/her for further follow-up. Withdrawal of consent, inability to attend the study visits or obvious incompliance with further visits are reasons to stop clinical follow-up. In these cases, whenever possible, telephone follow-up should be attempted. In case of a premature termination of therapy, reasons/circumstances and if applicable the final status have to be documented. A concept for further treatment of the patients after termination of the trial is given in 6.5.
# METHODS OF DIAGNOSTICS AND DATA SAMPLING

## Assessment of secondary outcomes: domains, instruments, characteristics and targets

<table>
<thead>
<tr>
<th>Domain</th>
<th>Instrument</th>
<th>Characteristics</th>
<th>Target</th>
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<tbody>
<tr>
<td>Symptoms</td>
<td>SF-36</td>
<td>SQ*, 36 items</td>
<td>Health related quality of life</td>
</tr>
<tr>
<td></td>
<td>KCCQ</td>
<td>SQ*; 23 items</td>
<td>Disease-related quality of life</td>
</tr>
<tr>
<td></td>
<td>PHQ-9</td>
<td>SQ*; 9 items</td>
<td>Vital exhaustion, depressive symptoms</td>
</tr>
<tr>
<td></td>
<td>PHQ-GAD-7</td>
<td>SQ*, 7 items</td>
<td>Generalized anxiety symptoms</td>
</tr>
<tr>
<td></td>
<td>MMSE</td>
<td>Therapist administered; 10 items</td>
<td>Cognitive function</td>
</tr>
<tr>
<td></td>
<td>MADRS</td>
<td>Therapist administered, 10 items</td>
<td>Severity of depression</td>
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<tr>
<td></td>
<td>SCID</td>
<td>Standardised interview</td>
<td>DSM-IV diagnosis of depression</td>
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<td></td>
<td>Telefon questions</td>
<td>Study nurse administered</td>
<td>Monitoring of general and emotional health, side effect and compliance</td>
</tr>
</tbody>
</table>

| Health economy          | EuroQoL with SF-36          | SQ*; 5 items & SQ*, 36 items             | Health care utilisation                     |

<p>| Somatic variables       | Clinical examination        | Blood pressure, BMI, waist-hip ratio     | Classical risk factors                     |
|                         |                             | NYHA class                                | Heart failure severity                     |
|                         | 6-minute walk test          | Walking distance                          | Physical capacity                           |
|                         | Echocardiography            | Left ventricular dimensions &amp; function   | Heart failure etiology &amp; severity          |
|                         | ECG &amp; 24h ECG (MTM)        | Basal heart rate, heart rate variability, arrhythmia | Autonomic dysfunction                      |
| Blood sample            | Total-, LDL-, HDL-cholesterol, triglycerides, fibrinogen | Classical risk factors                   |
|                         | Natriuretic peptides, Troponins | Heart failure severity                   |
|                         | Liver and renal profile, glucose, electrolytes | Study drug safety parameters             |
| Urine sample            | Albumin/creatinin ratio    | Classical risk assessment                 |                                            |
|                         | Osmolality, uric acid      | Osmoregulation                            |                                            |
|                         | 24h urine sample           | Norepinephrine excretion                  | Neuroendocrinological function             |
| Saliva sample           | Cortisol                   | Neuroendocrinological function            |                                            |</p>
<table>
<thead>
<tr>
<th>Domain</th>
<th>Instrument</th>
<th>Characteristics</th>
<th>Target</th>
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<tbody>
<tr>
<td>Study drug compliance</td>
<td>Pill count</td>
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<td>Compliance with study drug</td>
</tr>
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<td></td>
<td>Blood sample</td>
<td><em>Escitalopram</em> plasma levels</td>
<td>Compliance with study drug</td>
</tr>
<tr>
<td>Heart failure medication</td>
<td>CRF based questions</td>
<td>Compliance assessment</td>
<td>Optimization of heart failure pharmacotherapy</td>
</tr>
<tr>
<td>THROMBO-MOOD substudy (n=60)</td>
<td>Blood sample</td>
<td>Platelet surface: expression of P-selectin and CD40 ligand, binding of fibrinogen to activated GP IIb/IIIa; circulating platelet/leucocyte &amp; platelet/monocyte aggregates</td>
<td>Platelet function</td>
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<tr>
<td>VASO-MOOD substudy (n=150)</td>
<td>High-resolution ultrasound, oscillometric blood pressure and pulse wave recording</td>
<td>Brachial artery vasoreactivity, pulse wave velocity and augmentation index</td>
<td>Arterial endothelial function, arterial stiffness and pulse wave reflection</td>
</tr>
<tr>
<td>GENE-MOOD substudy (all participants)</td>
<td>Blood sample with following DNA extraction</td>
<td>PCR and MALDI-TOF</td>
<td>Determination of candidate gene polymorphisms for disease and drug response</td>
</tr>
<tr>
<td>OSMO-MOOD substudy</td>
<td>Urine and blood sample</td>
<td>Serum sodium, urine electrolytes and osmolality, fraction excretion of uric acid, copeptin</td>
<td>Volume and sodium homeostasis</td>
</tr>
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*SQ= Standardised self-rating questionnaire; further abbreviations are listed on page 15.
8  ADVERSE EVENTS (AE/SAE)

8.1  Adverse Event (AE)

8.1.1  Definition

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investiga-
tion subject administered a pharmaceutical or medical product and which does not necessarily
have a causal relationship with this treatment. An AE can therefore be any unfavourable and
unintended sign (including abnormal laboratory finding for example), symptom, or disease
temporally associated with the use of a medicinal (investigational) or medical product, whether
or not it is considered to be related to the medicinal (investigational) product. (ICH-Guideline
E2A)

An unexpected AE is an AE, the nature or severity of which is not consistent with the applica-
ble product information.

The separation expected/unexpected must be decided from the perspective of previously de-
scribed untoward reactions, not on the basis of what might be anticipated from pharmacologi-
cal properties of a medicinal product.

8.1.2  Documentation and Reporting

Each AE has to be documented on the AE form. Please provide information regarding:
start/stop date, type of AE, classification as SAE (yes or no), severity, causality, treatment and
result. For the type of AE, use the code for expected AE listed on the back of the AE sheet,
and ICD-10 coding or verbal description otherwise.

In case of SAE, please fill out the SAE form (see below) in addition to the row on the AE form.

Several AE may be documented on one AE sheet. Enumerate AE sheets and adverse events
consecutively. There may be a single cause for several symptoms occurring at the same time.
However, use a separate row in the AE table for each of the symptoms. Use the comments
field if you want to indicate possible correlation of several AE.

Fast reporting is necessary only for SAE (see below). Usual AE reports should be provided in
the same manner like the standard documentation.
8.1.3 Concomitant Diseases

Note that significant worsening of concomitant diseases represents an AE. However, details of heart failure recorded elsewhere on the CRF (like worsening of NYHA class) do not require an extra AE report.

8.2 Serious adverse event (SAE)

8.2.1 Definition

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
  
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect or
- other medical important condition (see below)

  NOTE: Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. (see ICH guideline E2A, section IIB)

The following potential complications, even the death of the patient, are typical symptoms or consequences of the underlying disease (i.e., heart failure) and will, thus, not be regarded as serious adverse events according to the definition given above:

- Death on the strength of chronic heart failure or one of the following co-morbidity (already existing at the begin of the study):
  
  — Any cardiovascular disease (myocardial infarction, acute cardiac decompensation,
renal failure, arrhythmias leading to sudden cardiac death, pulmonary congestion leading to infectious complications, cardiac interventions or operations

— cerebrovascular disease (stroke, PRIND, TIA, hypertensive crisis)
— COPD

NOTE: As an exception, hospitalisation or prolonged hospitalisation will not be regarded as a serious adverse event according to the definition given above, if it may be regarded a consequence of the severity of heart failure or one of the co-morbidities listed below (already existing at the begin of the study):

- any cardiovascular disease or associated complications or comorbidities (myocardial infarction, acute cardiac decompensation, arrhythmias leading to cardiac decompensation, cardiac interventions or operations, implantation/explantation/replacement of pacemaker or ICD or biventricular device, ICD discharge [adequate or inadequate], device electrode dislocation or malfunction, renal failure, anemia, pulmonary congestion resulting in infectious complications)
- cerebrovascular disease (stroke, PRIND, TIA, hypertensive crisis)
- COPD

8.2.2 Documentation and reporting

Every SAE, except of the above-named SAE, must be documented by the investigator on the SAE page of the CRF. The Serious Adverse Event Report Form must be completed, signed and sent to the KKSL drug safety immediately. All outstanding data must be provided in written as soon as it becomes available. The above-named reasons for death or hospitalisations were contemporary documented by the investigator on the study sheet for death or hospitalisation.

If the SAE was a SUSAR (see below) and/or resulted in death or was life-threatening, the investigator must fax the filled-in form immediately to the KKSL Drug safety. The KKSL will forward the information to the sponsor. If part of the information is not yet available, a preliminary version should be provided, and complete information should be sent later.

In all other situations, provide the SAE documentation in the same manner as standard documentation.

If an SAE resulted in death, additionally fill in form D.
In case of the death of a patient, the investigator has to forward to the leading ethics committee, in multi-centre trials to all involved ethics committees, as well as to the competent regulatory authorities (BfArM) and to the Coordinating investigator all additional information required.

The immediate and follow-up reports should identify subjects by the Study Patient ID Codes assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses.

Occurrence of ANY of the following SAE:

- Death, irrespective of cause and relationship to study medication
- Other SAE which are not certainly or likely explained by a reason not related to the study medication

has to be notified immediately (within 24 h), at latest the next working day, at the corresponding address (see below):

**KKSL / Drug safety**
University of Leipzig,
Coordination Centre for Clinical Trials Leipzig
Härtelstr. 16-18, 04107 Leipzig
Phone: +49/341/97-16 129
Fax: +49/341/97-16 278
E-mail: Pharmacovigilance@kksl.uni-leipzig.de

After check of completeness the SAE-CRF will be sent by fax to the investigators:

PD Dr. S. Störk, PhD and Dr. J. Baulmann
Med. Klinik und Poliklinik I
University of Würzburg
Klinikstr. 6-8
97070 Würzburg
Fax-No.: +49/931/201-70380

The coordinating investigator of the clinical trials makes the medical secondary evaluation of each SAE regarding causal relationship to trial drug and the decision expect/unexpected according to the criteria described in chapter 8.5. This will be documented on the Assessment Sheet and this will be sent by fax together with the SAE-CRF within 2 days after receipt back to the KKSL (department of drug safety).

The data input of the SAE-CRF and the Assessment sheet take place immediately as well as coding with MEDRA.
8.2.3 Periodic Reports

The sponsor writes an annual (or upon request) safety report (following the "detailed guidance on the collection, verification and presentation of adverse events reports arising from clinical trials on medicinal products for human use"). This report comprises a detailed risk-benefit-analysis, a list of all documented SARs – serious adverse reactions (see below) – as well as a summary table containing all documented SARs in the course of the trial. The sponsor submits this report detailing the safety of the tested medicinal products to the leading ethics committee as well as to the competent regulatory authority (BfArM) and the data monitoring and safety committee (DMC).

Up to the time of writing of the annual safety report all SAEs, also those, which are to be announced not immediately (expected SAR and illness-referred SAE), must be documented and forwarded to the KKSL.

Deadline for the writing is the date of the first permission of the clinical examination by the BfArM. From this time the ASR has to be finished and submitted within 60 days.

The ASR will be written by the coordinating investigator in cooperation with the project manager and the biometrician of the KKSL.

Every six months a short safety report will be sent to the members of the DMC.

8.3 Suspected Unexpected Serious Adverse Drug Reactions (SUSAR)

8.3.1 Definition

Suspected Unexpected Serious Adverse Drug Reactions (SUSARs) are side effects (probably or definitely connected with the administration of the investigational product), the nature or severity of which are inconsistent with the information available about the product. Information about the trial product are contained in the SmPC (Summary of medicinal Product Characteristics) should be used to verify if the adverse reaction has been previously described.

8.3.2 Documentation and Reporting

The KKSL, on behalf of the sponsor, submits all information available about a SUSAR immediately, latest within 15 days after the event becomes known, to the leading ethics committee, the competent regulatory authority (BfArM), and to all participating investigators.
In the case of death caused by a SUSAR the leading ethics committee, the competent regulatory authority (BfArM), and all participating investigators must be informed by the KKSL, on behalf of the sponsor within 7 days after the event becomes known. Additional information have to be given within further 8 days. The KKSL on behalf of the sponsor submits yearly or on request a list of all SARs documented, together with an extensive safety report on the investigational product to the competent regulatory authority (BfArM) and to the leading ethics committee.

The principle investigator informs all other investigators of his study centre about the occurrence of the SUSAR.

The competent regulatory authority receives an electronic SUSAR-message. The responsible ethics committee and all principle investigators are informed paper-based by means of CIOMS-I-form about the SUSAR.

8.4 Therapeutic Procedures

AEs requiring therapy must be treated with recognized standards of medical care to protect the health and well being of the subject. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

The action taken by the Investigator must be documented:

a) in general
   • None
   • drug therapy started
   • test performed (e.g. laboratory)
   • unknown
   • not applicable

b) on the investigational product
   • treatment stopped
   • dose reduced
   • dose increased
   • dose not changed
   • unknown
   • not applicable
8.5 Classification of the adverse event

8.5.1 Severity
The severity of an adverse event will be estimated according to definitions in chapter 8.1 and 8.2.

8.5.2 Intensity
Assessment of severity according to CTCAE V3.0.

a) Adverse event (AE):

Mild Adverse Event:
- No special medical treatment necessary
- All laboratory parameters or x-ray diagnoses without clinical symptoms
- Low medical relevance

Moderate Adverse Event:
- minimal or local medical treatment necessary
- exclusively non-invasive treatment (e. g. bandages) necessary

Severe and undesirable Adverse Event:
- significant symptoms (including suicidality), leading to in-patient treatment or invasive therapy
- e. g. transfusions, elective interventional radiology treatment, therapeutic endoscopy or surgery

b) Severe adverse event (SAE):

Severe and undesirable Adverse Event:
- significant symptoms (including suicidality), leading to in-patient treatment or invasive therapy
- e. g. transfusions, elective interventional radiology treatment, therapeutic endoscopy or surgery

Life-threatening or disabling Adverse Event:
- exacerbated by acute life-threatening complications affecting the metabolism or circulation, e. g. break down of the circulation, hemorrhage, sepsis
- life-threatening physiological consequences
- necessity of intensive care, immediate invasive, interventional or radiotherapy, therapeutic endoscopy or surgery
- suicide attempt

Death related to Adverse Event:
• Death caused by the AE

8.5.3 Causal Relationship

The investigator must judge whether or not, in his opinion, the Adverse Event was connected with the administration of the investigational product according to the classification given below. Each Adverse Event has to be reported, even if the investigator feels that it is not connected with the administration of study drug.

• Not possible
• Possible

A connection with the investigational product is possible if:

• feasible temporal connection and no explanation by concomitant disease or other products, and positive reaction on stop taking pills, and known pharmacological or phenomenological reaction, and positive reuptake of investigational drug, if necessary

• substantiated temporal connection, and explanation by concomitant disease or other products implausible, and positive reaction on stop taking pills

• substantiated temporal connection, but explanation by other products or concomitant disease possible, informations about stop taking pills are incomplete or indistinctly

• more informations are necessary to evaluate exactly
• evaluation not possible because informations are insufficient or contradictorily

A connection will be evaluated as not possible, if the following aspect according to WHO-UMC is fulfilled:

• causal connection is implausibly because of temporal connection, and a plausible explanation is given by other products or basic disease

8.5.4 Expected/Unexpected

An Unexpected AE is an AE, the nature or severity of which is not consistent with the applicable product information (IB/SmPC). The separation expected/unexpected must be decided from the perspective of previously described untoward reactions, not on the basis of what might be anticipated from pharmacological properties of a medicinal product.
8.5.5 Outcome

The outcome of an AE has to be classified as follows:

- recovered/resolved
- recovered/resolved with sequelae
- not recovered/not resolved
- fatal*
- unknown

*NOTE: A subject's death per se is not an event, but an outcome. The event which resulted into subject's death must be fully documented and reported, even in case the death occurs within four weeks after test drug treatment end, and without respect of being considered treatment-related or not.

8.5.6 Pregnancy

The Investigator has to report every pregnancy, emerging during study conduct, to drug safety department of the KKSL.

**KKSL / Drug safety**

University of Leipzig,
Coordination Centre for Clinical Trials Leipzig
Härtelstr. 16-18, 04107 Leipzig

Phone: +49/341/97-16268
Fax: +49/341/97-16259
E-mail: Pharmacovigilance@kksl.uni-leipzig.de

Every pregnancy must be documented by the investigator on the CRF "Pregnancy". Serious adverse events during pregnancy must be documented on the SAE-CRF.

The result of the pregnancy has to be documented on the CRF "Pregnancy".
9 BIOMETRICAL ASPECTS

9.1 Randomization Algorithm

Randomization will be 1:1 for either escitalopram or placebo.

Stratification will be done by the following factors:

- Gender (male/female)
- Age (<70 / ≥70 years)
- Severity of depression (2 categories derived from PHQ-9 Score ≤16 / >16)
- Hospitalization within the past 4 weeks at the time of SCID (yes/no)
- Centre

The randomization routine will use Pocock’s minimisation algorithm.

9.2 Endpoints

9.2.1 Primary Endpoint

The primary endpoint is the time from randomization until death or hospitalisation for any reason, whatever occurs first.

As an exception, elective hospitalisation for clearly non-cardiac reason is considered to be censoring, not an event. In contrast to this, emergency hospitalisation for seemingly non-cardiac reason is considered an event because circumstances causing the emergency situation might be related to some cardiac condition. As well, elective hospitalisation for seemingly non-cardiac reason which, however, might be related to cardiac condition, is considered to be an event.

In order to avoid bias when using this endpoint, the blinded independent Endpoint Committee (members: see Appendix to Clinical Study Protocol) will classify each hospitalisation to be or not to be an event.

9.2.2 Major Secondary Endpoints

Degree of depression: Scores of PHQ-9 and MADRS.
9.2.3 Further Secondary Endpoints

- Time alive out of hospital: A function defined for each day d after randomization, taking the value 1 when the patient is alive and out of hospital on day d, 0 when the patient is hospitalised or dead on day d, and „unknown“ when the patient is not observable from day d on.

- Cardiovascular morbidity and mortality: time to cardiovascular hospitalisation or death or either of both; count of cardiovascular events; time free of cardiovascular events (like time alive out of hospital, not counting days with hospitalisation for other causes)

- Quality of life, anxiety and cognitive function: Scores of KCCQ, SF-36, anxiety (degree of generalized anxiety): Score of PHQ-GAD-7, cognitive function (Score of MMSE)

- Clinical parameters of severity of CHF (e.g. New York Heart Association functional class, six-minute walk test), laboratory parameters of severity of CHF (e.g. natriuretic peptides) and technical parameters of severity of CHF (e.g. left ventricular ejection fraction as determined by echocardiography)

- Function of the sympathetic nervous system / related endocrinological changes (e.g. mean heart rate, heart rate variability, arrhythmias, plasma cortisol, circadian variation of cortisol in saliva, urine norepinephrine excretion, plasma aldosterone).

- Parameters of systemic inflammation / endothelial function (e.g. CRP, fibrinogen, uric acid, IL-6, IL-10, TNF-α, CD 40L, sICAM)

- Adherence to study medication: putative intake according to pill count and estimated percentage of intake of study medication (subjective assessment by the physician)

- Adherence to heart failure medication: degree of intake (estimated percentage) of beta-blockers, AT1 antagonists, ACE inhibitors, and diuretics according to subjective assessment by the physician

- Occurrence of adverse events (as far as not covered by the other variables mentioned here)

- Severity of adverse events: each event rated as mild, moderate or severe

- Laboratory parameters: NT-proBNP, CRP, fibrinogen, platelet function parameters, electrolytes, 24 hour catecholamine excretion, cortisol diurnal rhythm (saliva), escitalopram plasma levels

- Cost (overall and components)
9.3 Statistical Formulation of the Primary Objective

9.3.1 Primary Statistical Hypothesis

The null hypothesis is that the survival functions in terms of the primary endpoint are the same for escitalopram and placebo treatment. The test will be two-sided since a putative advantage of treatment with escitalopram as well as possible harm by adverse reactions should both be discoverable and presentable by a significant result.

9.3.2 Statistical Error Levels

The type I error level for the test is set at 0.05. A power of 0.8 should be achieved.

9.4 Statistical Methods

9.4.1 Planned Methods for Analysis

- For primary analysis, Kaplan-Meier estimates of event-free survival rates depending on time will be computed for both treatment groups. The log rank test will be used to test the primary null hypothesis.

- In addition, parametric effect estimates (hazard ratios) with confidence intervals will be computed by Cox regression. In case of non-proportional hazard, an appropriate description of the change of the hazard ratio depending on time is desired.

- Major secondary, effect on mood (degree of DEP): To assess the treatment effect on mood, analysis of covariance will be used. Short and long term follow-up values of the DEP scales will be considered the outcomes, treatment is the factor and the baseline values of the DEP scales are covariates. Separate analyses for PHQ and MADRS scales to be carried out.

- Major secondary, intermediate role of mood: To check whether possible reduction of morbidity and mortality might be mediated by reduction of DEP, Cox regression will be carried out, using the primary endpoint as outcome, treatment as factor, and the DEP scales as time-dependent covariates. Clearly, we can not prove causality (as reduction of DEP and reduction of morbidity / mortality might both be correlated to drug compliance and plasma levels, but the correlations may be due to different mechanisms). However, if reduction of DEP would be causal for, and thus entirely explain reduction of cardiac morbidity and mortality, we can expect that the degree of DEP will predict the
outcome (in particular, degree of DEP during follow-up; the baseline severity of DE can naturally be expected to be predictive even without treatment). At the same time the independent explanatory value of treatment should markedly lower or even vanish if the treatment information is entirely represented by the course of DEP. As before, separate analyses with the PHQ-9 and MADRS scales will be carried out. This might also allow checking whether either of the scales is more informative than the other for this purpose.

- Time alive and out of hospital will be assessed using extended (multi-state) Kaplan-Meier analysis. Different variants of this analysis will be computed, considering hospitalisation as reversible state (“currently hospitalised”), irreversible state (“ever hospitalised”) or multiple states (counting the number of hospitalisations). As well, we will try to find out which endpoint (time to first event or time alive and out of hospital) is more powerful to detect treatment effects and other predictors of event-free survival.

- As well, confidence estimates for differences of means (for quantitative variables) or frequencies (indicator variables) will be computed for the other secondary endpoints. In case of repeatedly measured quantitative variables (like quality of life, lab values), follow-up measurements will be considered endpoints. Analysis of covariance will be carried out for these endpoints depending on the factor “treatment”, possibly some other factors (like gender) if appropriate, and the baseline values of the respective quantity as covariate.

- The relevance of the endpoints for the patient’s quality of life will be examined by correlation and simple regression analysis.

- Multivariate regression analyses will be used to identify predictors of the endpoints, and to compute adjusted estimates of the effect of the study drug (if applicable).

Except for the primary test, parameter estimates with confidence intervals will be considered more essential than P-values. Frequencies of missing values will be analysed and discussed for possible informative dropout. A detailed plan of analysis will be established before starting the final analysis.

### 9.4.2 Analysis Population

Primary analysis will be carried out according to the intention-to-treat principle. This means that patients will be analysed as randomised. As the primary method is Kaplan-Meier, all patients who were randomised will be included into the analysis, possibly with censored observation times. Censoring is triggered only by loss to observation, not by interruption of intake of
the study medication. As well, the first line analysis of secondary endpoints is intention-to-treat. Note that missing values are possible when the respective method can not handle censored information.

Per-protocol analysis is secondary. A patient is considered per protocol if he/she was treated as randomised, compliance data suggest intake of the study medication as prescribed on more than 90% of the days, and the timing of study visits was within the limits defined by the protocol. If appropriate, several levels between intention-to-treat and per-protocol may be defined later. Per-protocol analyses shall serve to discuss the possible bias of the intention-to-treat effect estimates, not to perform primary hypothesis tests.

All efforts will be taken to prevent missing values in subjects who are alive. Whenever there is the possibility of significant bias due to missing data, additional analyses using imputation techniques are required.

9.4.3 Interim Analysis

Confidential safety analyses and reports to the independent DSMB will be provided half-yearly. No further interim analysis will be performed.

9.4.4 Subgroup Analyses

Subgroup analyses will be carried out for the factors NYHA class (II vs. III+IV) and gender. However, the sample size is not calculated for interaction effects, thus the power to achieve evidence in the sense of significance may be not satisfactory. Therefore Bayesian methods will be applied in addition to conventional analysis.

9.5 Effect Size

Clinical experience suggests an annual event rate of 45% in the normal clinical course. We assume a relative reduction by 20% due to more intense observation in the trial; this yields 36% for the control group. Since depressed patients have a hazard twice as high as non-depressive patients, an absolute of 18% of events can be assumed to be associated with depression. We aim to reduce the event rate attributable to depression by relative 50%, this is by absolute 9%. This yields an event rate of 27% for the intervention group.

9.6 Observation Time and Drop-out

The first patient will be observed for 24 months while the last patient will be observed for 12
months (scheduled observation times). The rate of recruitment is assumed to be constant. The annual drop-out rate is expected to be about 15%.

9.7 Sample Size Discussion

9.7.1 Sample Size Calculation

With the hypothesis, method, error rates, observation times and drop-out rate specified above, 700 patients need to be randomised for the study. About 100 of them will drop out, being evaluable for time-to-event analysis but not available for the evaluation of changes from base line to the one-year follow-up examination.

9.7.2 Power Analysis

Regarding clinical situation: assume the rough scenarios of improving / persisting / worsening clinical state of 5 / 55 / 40 percent of the patients in the control group and 10 / 60 / 30 percent in the intervention group, respectively. With 700 patients overall, the power to detect this difference is 0.91; in case of 100 patients dropping out the power is still 0.86.

Regarding quality of life: The SF-36 physical functioning score has a cross-sectional SD of 23 points and a serial correlation of 0.6 (data from clinical experience). With 700 patients overall, the power to detect a 6 (5) point difference in the change of this score is 0.93 (0.82). With 600 patients overall, the power is still 0.89 (0.76).
10 CONCOMITANT SCIENTIFIC PROJECTS

10.1 SCREEN-MOOD

**Coordinated by:** Dr. Dr. Götz Gelbrich, KKSL, Härtelstraße 16-18, 04107 Leipzig

**Objective:** To determine the prevalence and positive predictive value of PHQ-9 sum >11 in patients with systolic CHF of NYHA class ≥II in a large cohort. To describe the correlation of PHQ-9 sum and its positive predictive value with patients gender, age and NYHA class

**Patients:** All subjects entering screening step 1 (see 4.3)

**Additional data required:** Age, gender, NYHA class and PHQ-9 of all patients entering screening step 1

**Data privacy:** Data of patients not included into screening step 2 will be transmitted entirely anonymously. There will be no code allowing to trace the identity of such patients. Patients entering step 2 of the screening will be informed that their data will be stored using an ID code which represents a pseudonyme. Written informed consent is obtained from these patients for processing their data

**Analysis:** A separate plan of statistical analysis will be written prior to analysis of the data.

10.2 THROMBO-MOOD

**Coordinated by:** Prof. Dr. Johann Bauersachs, Dr. A. Schäfer, Med. Klinik I, Klinikstraße 6-8, Universität Würzburg

**Objective:** To determine the effect of the SSRI escitalopram on platelet activation in depressed patients with CHF

**Patients:** Consecutive subjects entering screening step 1 at the Center of Würzburg (expected number: n= 60)

**Additional data required:** Markers of platelet activation comprise platelet surface expression of P-selectin and CD40 ligand, binding of fibrinogen to activated glycoprotein IIb/IIIa on the platelet surface, and measurement of circulating platelet/leucocyte and platelet/monocyte aggregates. Whole blood will be sampled at baseline and after 6 months of therapy, immediately incubated with the respective antibodies and fixed. Flow cytometry will be performed within the next hours on the same day. Further, soluble P-selectin, soluble CD40 ligand and thromboglobulin will be determined in plasma
Analysis: A separate plan of statistical analysis will be written prior to analysis of the data.

10.3 VASO-MOOD

Coordinated by: Dr. J Baulmann and PD Dr. Stefan Störk, PhD, Med. Klinik und Poliklinik I, Klinikstraße 6-8, Universität Würzburg

Objective: Vasoreactivity of large vessels is an accepted surrogate to monitor favourable and detrimental effects of pharmacotherapy on the atherosclerosis risk profile. We aim to determine the effect of the SSRI escitalopram on endothelium-dependent and -independent vasoreactivity, large artery stiffness and pulse wave reflection in depressed patients with CHF and to investigate concurrent changes with markers of inflammation (see substudy THROMBO-MOOD) and heart failure severity

Patients: All subjects entering screening step 1 at the Center of Würzburg and Lübeck (expected number: n=150)

Additional data required: Assessment of endothelium-dependent (flow-mediated dilatation) and endothelium-independent (nitroglycerin-induced) vasoreactivity of the right brachial artery before study start and after 6 months. Measurement of pulse wave velocity as a direct marker for arterial stiffness and augmentation index as a direct marker for pulse wave reflection

Analysis: A separate plan of statistical analysis will be written prior to analysis of the data.

10.4 GENE-MOOD

Coordinated by: PD Dr. Andreas Reif, M.D, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Universität Würzburg, and Prof. Dr. Christiane Angermann, Medizinische Klinik und Poliklinik I, Klinikstraße 6-8, Universität Würzburg

Objectives: a) to determine whether selected polymorphisms in candidate genes are associated with an increased risk for depression in CHF. Emphasis will be placed on candidate genes which have already been linked to depression and CHF (e.g., ACE or NOS3). b) to investigate whether polymorphisms in candidate genes affect plasma levels of escitalopram (pharmacogenomics, -kinetics). c) to test whether polymorphisms in candidate genes impact on the therapeutic response towards escitalopram (pharmacogenomics, -dynamics). The panel of candidate genes focuses on functional polymorphisms in the serotonergic system (e.g., the serotonin transporter 5HTT, 5HT2a, and p11)

Patients: All subjects (n= 700)

Additional data required: DNA specimens (extracted from blood at the Center of Würzburg).
Subsequently, candidate gene polymorphisms are determined by PCR and MALDI-TOF techniques. Hypothesis-free whole-genome association studies are performed in a later step.

**Analysis:** A separate plan of statistical analysis will be written prior to analysis of the data.

### 10.5 OSMO-MOOD

**Coordinated by:** PD Dr. Stefan Störk, M.D, PhD, Med. Klinik und Poliklinik I and Prof. Dr. Bruno Allolio, Medizinische Klinik und Poliklinik I, Klinikstraße 6-8, Universität Würzburg

**Objectives:** a) to examine whether antidepressant medication with *escitalopram* modifies the water and sodium homeostasis in subjects with heart failure and comorbid depression along the trial, and to estimate the prognostic utility of markers involved in the osmo- and volume regulation as serum sodium, urine osmolality, fractional excretion of sodium and uric acid, copeptin; b) to examine associations between severity of depression and anxiety (MADRS, PHQ-9, GAD-7), severity of heart failure (NYHA functional classe, NT-proBNP levels) and the above described panel of markers of water and sodium homeostasis

**Patients:** All subjects (n= 700)

**Additional data required:** Copeptin measurement (determined from samples stored at the Center of Würzburg).
11 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

All trial participants consider conducting the study in accordance with local laws and ICH guidelines for Good Clinical Practice (GCP) issued in July 2002 and CPMP/ICH/135/95 from September 1997, taking into account the Declaration of Helsinki and all its revisions.

11.1 Initial submission

11.1.1 Qualification of Investigators and Trial Sites

Prior to the initial submission to the ethics committees (EC) each centre that wants to participate in the trial must submit proof of qualification and experience of trial personnel and appropriateness of the trial site according to §7(2) and §8(5) German GCP-laws (GCP-V). To this purpose, the principal investigator has to make available to the sponsor the following documents:

Investigator:

1. Dated and signed CV including: Name, address of service facility, recent job title, professional development, additional qualifications, track records of former clinical trials (number, phases, indication)
2. If available: publication list, certificates of qualifications
3. Confirmation of knowledge of ICH-GCP Guideline, requirements AMG and GCP-V (knowledge of protocol, information about the investigational product, definitions of AE/SAE, notification requirement, archiving, requirements regarding monitoring, audits and inspections etc.)
4. If available, results of monitoring, audits and inspections already done
5. Dated and signed financial disclosure.

Trial sites:

Information about personnel available: Number of staff, function and qualification (education, experiences in clinical trials, training) thereof, description of trial related tasks delegated

1. Appropriateness and certificate of qualification
   - Results of pre-study visits
   - Main focus of treatment in the trial site
   - Number of patients (e.g. per year) of the required indication
• Information about competing trials

2. Infrastructure: description of the facility

• Finances and technical devices required for the trial conduct
• Availability and experiences/qualification in emergency care
• Availability and connection to emergency unit of a hospital (e.g. medical practice).

11.1.2 Submission to the Leading Ethics Committee and Competent Federal Authority

Prior to submission of the trial related documents to the leading ethics committee and the competent federal authority the sponsor is responsible to enter the trial into the European database of clinical trials (EudraCT). After the web based entry the sponsor will be issued a EudraCT number which must be submitted with all future documents.

Afterwards, the protocol and all other associated documents according to GCP-V §7 will be submitted to the leading ethics committee responsible for the coordinating investigator for approval. In addition to the required documents from each investigator the coordinating investigator must provide evidence of at least two years experience in clinical trials.

Parallel to the submission to the leading ethics committee each participating EC also receives a copy of all submitted documents including information about trial sites and investigators (see above) in their field of responsibility. This documentation should be used by the EC for evaluation of the appropriateness of the trial site.

At the same time the study documents will be submitted to the competent federal authority (BfArM) according to the requirements of GCP-V §7.

Only following a positive review by the leading ethics committee and approval from the competent federal authority the trial can start.

The written approval of the EC must be filed in the trial master file (TMF). Additionally, every participating centre must receive a copy of these documents to be filed in the investigator site file (ISF).

11.2 Submission of Protocol Amendments

According to GCP-V§10, the leading ethics committee and the competent federal authority are to be informed on any protocol amendments. In case of substantial changes, a new positive
review of the leading ethics committee and approval of the BfArM are required, before the changes become effective.

Changes that require approval and positive review by the ethics committee include:

- Changes that may have an effect on patient safety, e.g. essential changes in the therapeutic (dosage, guidelines for interruption/new onset or up/down titration of the study medication, concomitant medication, handling of adverse drug reactions) or diagnostic procedures (introduction of new procedures, change of follow-up schedule)
- Changes concerning the risk-benefit considerations
- Additional data collection or statistical evaluations that necessitate changes in the informed consent form
- New scientific data leading to changes in the rationale or the expected significance of the trial
- Significant changes concerning leadership or conduct of the trial
- Changes concerning the quality or the innocuousness of the investigational drug.
12 DATA HANDLING AND RECORD KEEPING

12.1 Case Report Forms (CRF)

The CRF will be provided by the KKSL in electronic form. Investigators will connect to the database via internet and input data directly into the eDE database. However, a paper version of the CRF will be available, so data can be documented in case of malfunction of the electronic system. The content of this paper version will then be entered to the database later. Each CRF page should be completed as soon as possible after the respective visit.

Each CRF page will be signed electronically. The signatures serve to attest that the information contained in the CRF is true and has not been falsified. In case of a major correction or missing data, the reason for it shall also be given. The investigator must assure completion, review and approval of all CRFs.

At all times the principal investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the CRF. Even if there are no changes from a previous examination the questions which are repeated in each section of the case report forms should be answered completely.

Printouts of the electronic data should be retained at the trial site. A new printout must be generated when changes are made.

12.1.1 Source Data

Source data in the sense of the ICH GCP guideline (E6) are the following:

- for clinical data: the patient file
- for clinical or demographic data recorded for the study which are not notified in the patient file: the print-out of the filled-in electronical CRF
- for echo data: the video recording
- for ECG: the print-out
- for 24h ECG: the electronic recording as stored by the 24h ECG core lab
- for questionnaire data: the questionnaire filled out by the patient.

In case the preliminary paper version of a CRF page has been filled out, this paper CRF will be source data instead of the print-out from the database (see above).
12.2 Data Management

For creation of the study database, the eResearch Technologies system will be used. The database will be validated according to the Standard Operating Procedures (SOPs) of the KKSL prior to data capture.

The information entered into the database by the investigators is systematically checked by routines implemented in the database, running every night. Error messages generated by these routines will be checked by the data management staff. Queries obviously not representing a true problem will be closed. Errors with an obvious solution will be corrected by the KKSL personnel immediately (self-evident correction).

All other queries will be passed to the investigator by the query management tool of the eResearch system. The principal investigator of the centre will receive notification of all queries concerning his/her centre. The KKSL staff will supervise the solution of the queries and remember the investigators if necessary. Corrected data will be checked by the automatic routines in the night after entry. In case a query can not be solved, the KKSL data management staff may force to close the query. This shall happen in agreement with the biometrician if the information addressed by the query seems to be relevant for the results.

An audit trail of all changes in the contents of the study database is automatically recorded.

Once the database has been declared complete and accurate, the database will be locked. Thereafter, any changes to the database are possible only by joint written agreement between the coordinating investigator, the biometrician and the data manager.

12.3 Archival Storage

The investigators have to arrange the retention of the subject identification codes for at least 15 years after the completion or termination of the trial. Patient files and other source data shall be kept for the maximum period of time permitted by the hospital.

The coordinating investigator or other owner of the data shall retain all other documentation pertaining to the trial for at least 10 years. These procedures shall include:

- the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product used
- standard operating procedures
- all written opinions on the protocol and procedures
- final report
- case report forms
- audit certificate(s), if available
- all other relevant documents of the trial master file, according to the ICH-GCP guideline.

Any change of data ownership shall be documented. All data shall be made available if requested by relevant authorities.
13 REFERENCE EVALUATIONS

13.1 Psychometric Core Lab

The Department for Psychiatry and Psychotherapy and the Institute for Psychotherapy and Medical Psychology of the University of Würzburg will act as the reference center for all aspects of psychometric assessment. The reference center will train and certify all physicians involved in SCID diagnostics and in performance of the MADRS. To assure standardized administration of the SCID, specialists from each study site will have to participate in a standardized SCID training program prior to study initiation. Cardiologists will be trained in standardized acquisition of the MADRS diagnostics. The training will be executed by members of the MOOD-HF Psychometric Core Lab. Participation in the training program and subsequent certification by the Directors of the Core Lab is prerequisite for the study initiation visit at each study site. After 50% of each centers’ recruitment time the Directors of the Core Lab will provide two SCID interviews and two MADRS interviews with representative cases (CHF patients with or without a current episode of major DEP) on video tape and reassess the qualification of investigators involved at each study site. Cardiologists will be trained in standardized acquisition of the MADRS diagnostics. The Psychometric Core Lab will also be responsible for quality control of all psychometric measurements. Original documentations of all tests performed during the trial will be screened by members of the Core Lab for completeness and quality of data within one week of testing. In case of quality problems, the reference center may ask the trial site to re-evaluate the patient in individual cases and educate the center, how to improve data quality in general. In addition, the psychometric core lab will provide advice to local psychiatric/psychosomatic specialists with regard to interventions in particular in situations where discontinuation of the study is considered for psychological reasons. The decision, though, will have to be made by the local psychiatrist/psychosomatic specialist in conjunction with the local cardiologist seeing the patient.

13.2 Core Lab Heart Rate Variability / Arrhythmia

The Division of Cardiology (Dr. Dr. med. Mathias Rauchhaus) at the Humboldt University Berlin, Charité, will act as the blinded reference center for all aspects of HRV/Arrhythmia diagnostics. All long-term ECGs will be recorded in a standardised manner by means of DMS300-3aA devices. After recording, the digital ECG-recordings will be sent to the Core Lab via satellite. The SOP for obtaining parameters of arrhythmia and of autonomic dysfunction and for transfer of these into the central data base of MOOD-HF at the KKSL will be released by the KKSL in
conjunction with the coordinating investigator and Dr. Rauchhaus. Trained, dedicated personnel blinded to the patients’ treatment will perform the data analyses.

13.3 Central Laboratory / Endocrinology / Escitalopram Plasma Levels / Genetic analyses

The blinded central laboratory facilities for MOOD-HF will be located at the University of Würzburg. Blood for the respective analyses shall be obtained, processed, labelled and stored until transport to the Central Core Laboratory according to respective guidelines, which will be issued by the KKSL in conjunction with the coordinating investigator and representatives of the Central Core Laboratory (Prof. Dr. B. Alloio for endocrinological parameters and for selected biomarkers, e.g. natriuretic peptides, (refer to 2.2) , Prof. Dr. U. Walter urine 24 hour norepinephrine excretion, CRP, uric acid and CRP, Prof. Dr. J. Bauersachs for markers of inflammation/endothelial function of these are not determined by Prof. B. Alloio and coworkers (refer to 2.2), PD Dr. Bruno Pfuhlmann and Prof. Dr. P. Riederer for determination of the plasma levels of escitalopram, and PD Dr. A. Reif for genetic analyses in cooperation with Prof. C. Angermann. Blood will be obtained at the time points indicated in the schedule of assessment.
14 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Direct Access to Source Data

According to ICH-GCP and to the applicable German laws, the principal investigator must permit all authorized third parties access to the trial site and insight into the medical records of the trial subjects (source data). This permission includes the clinical trial monitors, auditors and other authorized employees of the sponsor, as well as members of the local or federal authorities. All these persons are sworn to secrecy.

14.2 Monitoring

Monitoring will be performed by KKSL staff. The following monitoring visits will be scheduled for each of the centres.

<table>
<thead>
<tr>
<th>No.</th>
<th>Timing</th>
<th>Days</th>
<th>Purpose of monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>before recruitment</td>
<td>1</td>
<td>Presence of all materials and documents; Inspection of local facilities; Clarity about the study protocol, procedures and handling guidelines</td>
</tr>
<tr>
<td>2</td>
<td>after inclusion of 3-5 patients</td>
<td>1</td>
<td>Check of correctness of inclusion procedure, baseline examination and questionnaires</td>
</tr>
<tr>
<td>3</td>
<td>after 3-mo-visit of 3-5 patients</td>
<td>1</td>
<td>Check of correctness of medication handling and follow-up examination and questionnaires</td>
</tr>
<tr>
<td>4</td>
<td>after completing 3-5 patients</td>
<td>1</td>
<td>Check of correctness of complete follow-up</td>
</tr>
<tr>
<td>5</td>
<td>after completing 25% of patients</td>
<td>2</td>
<td>Data monitoring</td>
</tr>
<tr>
<td>5</td>
<td>after completing 50% of patients</td>
<td>2</td>
<td>Data monitoring</td>
</tr>
<tr>
<td>5</td>
<td>after completing 75% of patients</td>
<td>2</td>
<td>Data monitoring</td>
</tr>
<tr>
<td>5</td>
<td>after completing 100% of patients</td>
<td>2</td>
<td>Data monitoring</td>
</tr>
<tr>
<td>6</td>
<td>close-out at the end of the study</td>
<td>1</td>
<td>final solution of queries; completeness of trial documents</td>
</tr>
</tbody>
</table>

Additional visits may be scheduled when necessary.

The monitoring will include:
- check of completeness of the centre specific documents (e.g. presence of study protocol, copies of ethic votes, staff authorisation list etc.)

- presence of informed consent for all patients

- drug accountability for all medication kits

- source data verification (part of the data) according to a scheme to be specified by the coordinating investigator jointly with the biometrician; this will include 100% of key data and 10-20% of other data

- inspection of the local facilities

A monitoring guideline will be available. The monitor and the representative of the centre will confer about date and issues of monitoring prior to each visit. Please make sure that:

- access to all requested materials is guaranteed

- there is a person available to the monitor to answer all questions

- the monitor has a location for doing her/his work

14.3 Audits

In order to guarantee that the conduct of the study is in accordance with ICH-GCP and the national laws, the sponsor reserves the right to audit selected trial sites. The auditor will be independent from the staff involved in the proceedings of this clinical study.

The investigator agrees to give the auditor access to all relevant documents for review.

14.4 Inspections

According to the German drug law (AMG) and the corresponding GCP-ordinance (GCP-V), inspections of the trial sites may be performed by the local or federal authorities at any time during or after completion of the trial.

The investigator agrees to give the inspectors access to all relevant documents for review.
15 DATA PROTECTION

Within this study personal data of the trial subjects (name, date of birth, address) and data regarding the therapy and the course of disease (medical results, medication, putative covariates of the medical outcome) will be collected.

The trial subject will be informed that all data will be stored electronically and handled strictly confidential. Subjects will be identified throughout documentation and evaluation by the individual patient number only, whereas all subject names will be kept secret by the investigator. The subjects will be informed about the storage of their address and phone number for contact and must agree at the appropriate consent form in writing.

The investigators are obliged to keep all study data and information confidential and to use those data only in context with the persons involved in the trial conduct. Study material or information developed in this trial must not be available to third parties, except for official representatives of the sponsor or regulatory authorities.

Data will be processed in the KKSL, according to the written safety concept of this institution. In addition, personal data for central registration will be sent by the investigator to the Headquarter of the German Heart Failure Network (HFNC) and will be handled according to the safety and data privacy concept of the HFNC, approved by the German authorities for data protection. Access to the data will be strictly limited to authorized persons. Loss of data is excluded due to extensive back-up procedures. All legal requirements concerning data protection and confidentiality will be respected. All authorized persons are sworn to secrecy.

In the case of withdrawal of consent the stored data will be checked for further use. Data not necessary any longer are deleted immediately.

Collected personal data will be stored in an anonymous manner after reaching the study aim and finishing of all concomitant scientific projects 6 years at the latest, if there are no other regulatory or contractually archiving periods. Beyond this timeline, only the investigator will keep personal data in the files at the site were the patient was treated.

Declaration to data protection

During data entry, handling and analysis in the Koordinierungszentrum für Klinische Studien Leipzig (KKSL), Universität Leipzig, Härtelstr. 16-18, 04107 Leipzig, all requirements of the data protection act will be taken into account. Access to the data is strictly limited to authorized persons. Data are protected against unauthorized access.
16 ADMINISTRATIVE AGREEMENTS

16.1 Adherence to the Protocol

The clinical trial will be conducted in accordance with local laws and ICH guidelines for Good Clinical Practice (GCP) issued in June 1996 and CPMP/ICH/135/95 from September 1997, taking into account the Declaration of Helsinki and all its revisions.

Protocol violations are any deviations from the procedures outlined in this document:

- missed evaluations/ incorrect timing of evaluations
- non-compliance with study medications/ intake of prohibited medications

After a patient has been enrolled, it is the investigator's responsibility to make a reasonable effort to correct any protocol violation in order to keep the subject in the study.

Major protocol violations will be reported immediately to the coordinating investigator during the course of the study. The nature of these violations will be defined in the monitoring manual. All protocol violations will be listed and discussed with the coordinating investigator and biometrician prior to statistical analysis.

The investigator makes every effort to record data according to the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control of the investigator. All such deviations will be documented in the records, together with the reason for their occurrence, and where appropriate, detailed in the study report.

16.2 Protocol Amendments

In order to ensure most comparable conditions during all sessions of the trial and in the interests of valid statistical analysis, the investigators, the coordinating investigator or any other person involved in the trial conduct may not alter the study conditions agreed upon and set out in this protocol.

Amendments should be made only in exceptional cases and by mutual agreement within the steering committee. Any amendment must be set out in writing, at the same time giving the reasons, and signed by all parties concerned. The amendment then becomes part of the study protocol, and is to be filed in the Trial Master File (TMF).

Amendments which might have an impact on the well-being of the subject (major amendments) such as the use of additional invasive diagnostic procedures require an additional approval by the Ethics Committee (EC) and by the competent federal authority (BfArM). In addi-
tion, a further informed consent form is to be signed by all trial subjects enrolled in the trial who might be affected by the amendment. Minor changes will only be submitted to the Ethics Committee and the competent federal authority in a written form.

The investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to trial subjects without prior EC approval opinion. As soon as possible, the implemented deviation or change, the reason for it, and if appropriate, the proposed protocol amendment(s) should be submitted to the coordinating investigator for agreement.

16.3 Funding and Insurance

The sources of funding of this study are the following:

- Grant no. GFVT01024505 from the German Federal Ministry of Education and Research (BMBF)
- Financial support from H.Lundbeck A/S, Copenhagen, Denmark (see statement of commitment in the Appendices to the Trial Protocol)
- Study medication provided by H.Lundbeck A/S, Copenhagen, Denmark (see statement of commitment in the Appendices to the Trial Protocol)
- Support by Siemens Healthcare Diagnostics supplying up to 4000 Kits for the determination of plasma Brain Natriuretic Peptide (for offer see statement of the Appendices to the Trial Protocol).
- Patient insurance of this trial will be provided by Gerling Allgemeine Versicherung AG, Gerling Vertrieb Deutschland, Postfach 290216, 40529 Düsseldorf; Insurance Policy Number: 70-005673693-1

16.4 Notification to Local Authorities

Prior to enrolment of the first patients into the trial the sponsor, his legal representatives/contractors and all investigators are responsible for notification of his/her participation in the trial to the local regulatory authority, according to the German drug law (AMG §67 (1) and the requirements of the GCP-V §12).

According to §67 (3) AMG and §§ 12,13 GCP-V the sponsor, his legal representatives/contractors and all investigators are also responsible to notify amendments, premature terminations of trial arms or of the whole study and the regular trial finish of the trial to the local regulatory authority.
16.5 Publication Policy

The results of the study must be submitted for publication within one year after the end (last follow-up visit). It is aimed to publish the main results in high-ranked peer reviewed international journals.

In order to be able to publish the study in a high-ranked journal, it is registered prior to enrolment, at http://controlled-trials.com, ISRCTN33128015.

H. Lundbeck A/S and Siemens Diagnostics will not interfere in any respect with or impact on collection, storage, analysis interpretation and publication of the data collected in the MOOD-HF trial. When the Sponsor contemplates making any publication or public presentation of the outcome or any material relating to the Study, the Sponsor shall notify Lundbeck thereof to Lundbeck for the attention of Dr. Michael Friede no later than one (1) calendar month in advance of such planned publication/presentation.
17 REFERENCES

17.1 References General

1. Declaration of Helsinki: Guiding Physicians in Biomedical Research Involving Human Subjects. Adopted by the 18th World Medical Assembly, Helsinki (Finland), June 1964. Last amendment by the 48th General Assembly, Somerset West (Rep. of South Africa) 1996


17.2 References related to MOOD-HF


sant medication on morbidity and mortality in depressed patients after myocardial infarction. *Arch Gen Psychiatry*. 2005;62:792-8.


18 CONFIRMATION OF THE FINAL PROTOCOL

The signatories declare that they agree to conduct their responsibilities within this study in accordance with local law, the declaration of Helsinki, ICH-GCP and the study protocol as presented.

Coordinating investigator

02.12.2008

Date

Signature

Biometrician:

03.12.2008

Date

Signature
19 PROTOCOL AGREEMENT

The signatory declares

- that he/she agrees to conduct his/her responsibilities within this study in accordance with local law, the declaration of Helsinki, ICH-GCP and the study protocol as presented
- that he/she has acquainted his/herself with the results of the pharmacological and toxicological trials of the investigational product and the results of other studies carried out to date
- that he/she has read the study protocol and agrees to it in its entirety
- that he/she intends to adhere to the schedule as specified below.

Date: _________________________

Signature of the investigator: _________________________

Affiliation /address:

_________________________  
_________________________  
_________________________
20 APPENDICES TO THE TRIAL PROTOCOL

See separate document with separate index of contents.