Medizinische Hochschule Hannover

DIGIT-HF

STUDY PROTOCOL

Study Title:

A multicenter, randomized, double-blind, placebo-controlled study to demonstrate that digitoxin reduces a composite of overall mortality and hospitalization for worsening heart failure in patients with chronic heart failure and reduced ejection fraction

Short title/term:	DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure/ DIGIT-HF
EudraCT number:	2013-005326-38
Study design:	Multicenter, randomized, double-blind, parallel-group, placebo-controlled, phase IV trial
Sponsor:	Hannover Medical School, Carl-Neuberg-Str. 1 30625 Hannover
Coordinating investigator/representative head of the clinical study according to German drug law (LKP):	Prof. Dr. med. Udo Bavendiek
Study chair:	Prof. Dr. med. Johann Bauersachs
Protocol code:	DIGIT-HF
Protocol version:	4.1
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Including the following amendment(s):	3.0

PROTOCOL SIGNATURES

This clinical study protocol has been approved by the following persons. The following signatures document their approval.

Sponsor Hannover Medical School represented by Prof. Dr. Christopher Baum	Date
Prof. Dr. Udo Bavendiek Coordinating Investigator/LKP	Date
Prof. Dr. Johann Bauersachs Study chair and investigator	Date
Prof. Dr. Armin Koch Trial statistician	Date
Prof. Dr. Dirk O. Stichtenoth Pharmacovigilance and SAE-reporting	Date

By my signature, I agree to personally supervise the conduct of the study and to ensure its conduct in compliance with the protocol, national drug law, ICH GCP and the applicable national and European regulations covering the conduct of clinical studies.

Name of study center

Printed name of investigator

Signature of investigator

Date

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE	Angiotensin-converting enzyme
AE	Adverse event
ARB	Angiotensin-Receptor-Blocker
ARNI	Angiotensin Receptor-Neprilysin-Inhibitor
AT1	Angiotensin II receptor, type 1
AV	Atrioventricular
BMBF	German Federal Ministry of Education and Research
CEAC	Clinical Event Adjudication Committee
CHF	Chronic heart failure
CRF	Case report form
CRT	Cardiac resynchronization device therapy
DBP	Diastolic blood pressure
DCC	Direct current cardioversion
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EF	Ejection fraction
EOT	End of treatment
ESC	European Society of Cardiology
GCP	Good Clinical Practice
ICD	Implantable cardioverter-defibrillator
ICH	International Conference of Harmonisation
IEC	Independent ethics committee
iDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product
LKP	Representative head of the clinical study according to German drug law
LV	Left ventricular
mg/die	Milligram per day
MRA	Mineralocorticoid receptor antagonist
NCA	National competent authority
NYHA	New York Heart Association
p.o.	Per oral
SA	Sinoatrial
SAE	Serious adverse event

SBP	Systolic blood pressure
SmPC	Summary of product characteristics, Fachinformation
SOC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TIF	Trial investigator file
TSC	Trial steering committee

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STUDY SYNOPSIS

Title of Study	A multicenter, randomized, double-blind, placebo-controlled study to demonstrate that digitoxin reduces a composite of overall mortality and hospitalization for worsening heart failure in patients with chronic heart failure and reduced ejection fraction.
Short Title/Term	DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure/ DIGIT-HF
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Sponsor	Hannover Medical School Carl-Neuberg-Str. 1 D-30625 Hannover, Germany
Coordinating investigator/LKP	Prof. Dr. Udo Bavendiek Hannover Medical School Department of Cardiology & Angiology Carl-Neuberg-Straße 1 D-30625 Hannover, Germany
Study Chair and Investigator	Prof. Dr. Johann Bauersachs Hannover Medical School Department of Cardiology & Angiology Carl-Neuberg-Straße 1 D-30625 Hannover, Germany
Study Design	Multicenter, randomized, double blind, parallel-group, placebo-controlled, phase IV trial
Patient Population	Patients with advanced systolic chronic heart failure NYHA class III-IV and EF ≤ 40% or NYHA class II and EF ≤ 30%
Participating Centers	Approximately 50 study centers
Sample Size	To be allocated to trial: n = 2190 (1095 per group) To be analysed: n = 2190 (1095 per group) Interim analysis: after 367 adjudicated primary endpoint events
Objectives	To demonstrate in a large and simple clinical trial-approach that digitoxin (target serum concentrations preferably 8 - 18 ng/ml (10.5 – 23.6 nmol/l)) on top of standard of care is superior in reducing a composite of all-cause mortality and hospitalization for worsening heart failure (whichever occurs first) in patients with

	advanced systolic chronic heart failure (NYHA class III-IV and EF ≤ 40% or NYHA class II and ≤ 30%) to a greater extent compared to standard care plus placebo.
Inclusion and Exclusion Criteria	Inclusion criteria: 1. Signed written informed consent and willingness to comply with treatment and follow-up 2. Male or female patients age ≥ 18 years at day of inclusion 3. Patients capable of understanding the investigational nature, potential risks and benefits of the clinical trial 4. Patients with chronic heart failure NYHA class III-IV and a ventricular ejection fraction of EF ≤ 40%* **or** patients with heart failure NYHA class II and EF ≤ 30 %* * determined at screening by echocardiography or cardiac magnetic resonance tomography or within 8 weeks prior to study inclusion by left-ventricular angiography, echocardiography, radionuclide ventriculography, cardiac magnetic resonance tomography AND an evidence based heart failure therapy at least for six months upon discretion of the treating physician 5. Women without childbearing potential defined as one or more of following: • Women at least 6 weeks after surgical sterilization by bilateral tubal ligation or bilateral oophorectomy with or without hysterectomy at the day of inclusion • Women ≥ 50 years of age at the day of inclusion who have been postmenopausal since at least 1 year • Women < 50 years and in postmenopausal state ≥ 1 year with serum FSH > 40 IU/l (proved by a second laboratory assessment after 4 weeks) OR Women of childbearing potential who have a negative hCG pregnancy test and agree to meet one of the following criteria from the time of screening/baseline, during the study and for a period of 40 days following the last administration of study medication: • Correct use of reliable contraception methods. This includes hormonal contraceptive (oral contraceptives, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release) or an

intrauterine device (IUD/IUS) or a barrier method of contraception such as condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide (foam/gel/film/cream/suppository)
- True abstinence (periodic abstinence and withdrawal are not acceptable methods of contraception)
- Sexual relationship only with female partners and/or sterile male partners

OR

Men

Exclusion criteria:

1. Recent (< 2 months ago): myocardial infarction, coronary revascularization, surgery or catheter intervention for valvular heart disease, acute coronary syndrome, stroke or cerebral ischemia, start of heart failure device therapy potentially improving left ventricular ejection fraction or heart failure symptoms (e.g. cardiac resynchronization therapy (CRT), cardiac contractility modulation (CCM), baroreflex-activation therapy (BAT))
2. Scheduled surgery or catheter intervention for valvular heart disease or scheduled coronary revascularization
3. Active myocarditis
4. Complex congenital heart disease; this does not include: mild-moderate valve disease, uncomplicated shunts (isolated patent foramen ovale, small atrial or ventricular septum defects without associated lesions), repaired secundum or sinus venosus atrial septal defects or ventricular septal defects without residua, previously ligated or occluded ductus arteriosus
5. High-urgency listing for heart transplantation or scheduled therapy with left ventricular assist device (LVAD)
6. Heart rate < 60 b.p.m. (except if functional CRT in place)
7. SA-/AV-block > I°, sick sinus syndrome or carotis sinus syndrome (except if pace-maker protected)
8. Proven or suspected accessory, atrio-ventricular pathways (e.g. WPW-syndrome)
9. History of symptomatic or sustained (≥ 30 s) ventricular arrhythmia unless a cardioverter/defibrillator implanted
10. Current ventricular tachycardia or fibrillation (this means

	patients presenting with a running ventricular tachycardia or fibrillation. If ventricular arrhythmias are terminated and a cardioverter/defibrillator is implanted inclusion is allowed according to point 9.) 11. Hypertrophic obstructive cardiomyopathy (idiopathic subaortic stenosis) 12. Cor pulmonale 13. Constrictive pericarditis 14. Thoracic aortic aneurysm (defined as diameter ≥ 45 mm) 15. Concomitant severe liver and renal disease 16. Persistent hypokalaemia (< 3.2 mM) 17. Hypercalcemia or hypomagnesemia, if clinically suspected and verified by laboratory testing (e. g. hyperparathyroidism, neoplasia induced hypercalcemia, signs of neuromuscular hyperexcitability) 18. Present (within 6 weeks before baseline/day 0 visit) and continuous treatment with Amiodarone (Single or short-term (up to 3 days), not continuous administration of amiodarone immediately before or during study treatment are acceptable) 19. Scheduled direct current cardioversion (DCC) in the next 24 h (e. g. patients not on cardiac glycosides with new onset of atrial fibrillation. Patients already included and on treatment with IMP can continue IMP and study when scheduled for DCC) 20. Presence of both treatment with cardiac glycosides and atrial fibrillation 21. Simultaneous intravenous treatment with calcium salts 22. Evidence of cardiac glycosides intolerance or known hypersensitivity to any component of investigational medicinal products 23. Suspected intoxication with cardiac glycosides 24. Unlikely compliance with protocol requirements 25. Pregnant and lactating women 26. Use of other investigational drugs or devices at the time of enrollment, or within 30 days prior to enrollment or 5 half-lives for investigational drugs, whichever is longer 27. Life expectancy < 12 month (e.g. due to active cancer)

Interventions	All patients receive standard of care (SOC) as recommended by expert guidelines of European Society of Cardiology (ESC) comprising of the following elements: beta-blocker, ACE-inhibitor/AT1-receptor-blocker, mineralocorticoid receptor antagonist (MRA), as well as, if indicated, angiotension receptor-neprilysin-inhibitor (ARNI), ivabradine, cardiac resynchronization device therapy (CRT) and implantable cardioverter-defibrillators upon discretion of the treating physician. Control intervention: Standard of care (SOC) + placebo p.o. (corresponding to 0.05, 0.07 or 0.1 mg digitoxin tablets) Experimental intervention: Standard of care (SOC) + digitoxin p.o. (0.05, 0.07, or 0.1 mg/die) Dose adjustment at week 6, and, if indicated, at week 12 after start of treatment. Target serum concentration of digitoxin 8 - 18 ng/ml (10.5 – 23.6 nmol/l) Follow-up visits per patient: At week 6, at week 12 (only if at week 6 dose has been up-titrated) & 6 months after start of treatment and thereafter every 6 months. All patients will be followed up until the end of the study. The duration of the follow-up period is event-driven (but at least 13 months after inclusion of the last patient) until the required number of 734 adjudicated primary events is recorded. Duration of IMP treatment per patient: Until the end of the study End of treatment (EOT) visit per patient: 40 days after last IMP treatment
Investigational Medicinal Products (Dose, Route of Administration and Frequency)	Digitoxin: 0.05 mg/die, 0.07 mg/die or 0.1 mg/die titrated to arrive at a target serum concentration of digitoxin of 8 - 18 ng/ml (10.5 – 23.6 nmol/l), as one single tablet p.o. Placebo: One single tablet daily p.o. with random up- and down- titration to blind the trial
Trial Duration	Recruitment: Approx. 72 months Duration of the entire trial (first patient in to last patient out):

	The duration of the follow up period is event driven, until the required number of 734 adjudicated primary events is recorded, but at least 13 months per patient. All patients will be followed up until the end of the study.
Blinding and Randomization	This is a randomized, placebo-controlled, double-blind clinical trial. Randomization will be performed centrally and will be stratified by center, gender, NYHA class (II, III or IV), atrial fibrillation and treatment with cardiac glycosides at baseline.
Endpoints/Outcomes	<u>Primary endpoint:</u> Composite endpoint of all-cause mortality and hospital admission for worsening heart failure (whatever occurs first) Admission for worsening heart failure is defined by presence of the following points together: 1.) Worsening of heart failure based on clinical judgment (presence of heart failure symptoms) by the treating physician. 2.) hospital stay overnight 3.) i.v.-treatment with diuretics or vasoactive substances (e. g. nitroglycerine) or inotropes (e. g. dobutamine). <u>Key secondary endpoints:</u> All-cause mortality, hospital admission for worsening heart failure, (recurrent) hospital admission for worsening heart failure <u>Secondary endpoints:</u> cardiovascular mortality, death from heart failure, any non-cardiovascular death, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, any cardiovascular hospitalization, hospital admission for any cause, implantation of a cardioverter-defibrillator, implantation of a cardiac-resynchronisation device, implantation of a pacemaker, sudden cardiac death, change in functional capacity assessed by NYHA class. <u>Assessment of safety:</u> Adverse events (AEs), serious adverse events (SAEs) and laboratory abnormalities will be compared between the treatment groups.
Statistical Analysis	Efficacy: The study-wise error rate is set to 5% (two-sided).

	Description of the primary efficacy analysis and population: The primary analysis is conducted on the intention-to-treat (ITT) population. This is a study of digitoxin, and placebo on top of standard of care. The aim of the study is to prove superiority of digitoxin over placebo. The primary endpoint is a composite endpoint of all-cause-mortality and hospital admission for worsening heart failure (whichever occurs first). Digitoxin will be compared to placebo with a Cox regression model including treatment (digitoxin vs. placebo), center, gender, NYHA class (II, III or IV) and atrial fibrillation and treatment with cardiac glycosides at baseline as independent variables and time to death or hospital admission for worsening heart failure, whichever occurs first as the dependent variable. An interim analysis will be done after 50% (367) of the adjudicated primary endpoint events have been observed. If digitoxin is superior to placebo with a two-sided *p*-value < 0.01, the study stops for proven efficacy. In case the study continues superiority will be concluded if the two-sided *p*-value in the final analysis is less than 0.045 (O'Brian & Fleming plan with one interim and one final analysis). Secondary endpoints: The type I error is set to 5% (two-sided). As soon as the primary hypothesis is rejected, a confirmatory assessment of non-inferiority of digitoxin against placebo concerning all-cause mortality with a margin of 1.303 for the hazard ratio will be conducted to exclude detrimental effects on mortality. All secondary analyses will be conducted on the ITT and follow the analysis strategy of the primary analysis. For each gender, NYHA class (II, III or IV) and atrial fibrillation and treatment with cardiac glycosides at baseline a subgroup analysis in line with the primary analysis will be done. All secondary analyses will be explorative. Safety: Adverse events, serious adverse events and laboratory abnormalities will be compared between treatment groups with a chi-square test and other appropriate tests. P-values will be assessed descriptively.

1 BACKGROUND AND STUDY RATIONALE

1.1 Overview of Medical Indication

Heart failure remains a major cause of mortality and morbidity in industrial countries representing the most frequent reason for hospitalization in Germany[1-4]. It is responsible for 1% to 2% of direct health costs in the Western industrialized nations, and for around 1.1% in Germany. The combination of demographic developments and medical progress - leading to falling mortality rates from ischemic heart events - means that the prevalence and incidence of heart failure will continue to increase and lead to a further rise in public health costs. In addition, the course of this disease is characterized by repeated hospital admissions at relatively short intervals and a limited prognosis for survival. Thus, heart failure places a heavy medical and economic burden on society[5]. Despite treatment progress has markedly improved prognosis after hospital admission in recent years, heart failure remains a disabling disorder that severely affects patients´ quality of life; and the prognosis of patients suffering from heart failure remains poor[6]. Therefore, it is crucial to identify additional therapeutic strategies to improve the prognosis and morbidity of heart failure patients.

1.2 Evidence

Cardiac glycosides (digitalis) have been used for the treatment of chronic heart failure since two centuries. However, sufficient prospective trials investigating the impact of digitalis on all-cause mortality and morbidity are very limited and have entirely been performed with digoxin[7-9]. These trials demonstrated, that digoxin has no impact on mortality in the overall trial population[7] but significantly reduced hospitalizations due to worsening of heart failure and improved exercise capacity and quality of life[7-9]. Post hoc analysis of the DIG-trial population indicated, that heart failure patients (NYHA class II-IV) treated with digoxin at serum concentrations of 0.5-0.9 ng/l (lower range of the current therapeutic range of 0.8-2.0 ng/ml) had a statistically significant 19-23% reduction in all-cause mortality (RR 0.77-0.81) compared to placebo[10,11]. In contrast, patients treated with digoxin at serum concentrations > 1.2 ng/ml had a significant increase in overall mortality [10, 12]. Especially in women, there seems to be a stronger interaction with increasing digoxin serum concentrations and mortality than in men[10,13]. This might explain the increased mortality of women observed in a post-hoc-analysis of gender subgroups of the overall trial population[14].

Despite this evidence, prospective randomized trials investigating potential effects of cardiac glycosides on mortality or cardiovascular endpoints at serum concentrations in the lower therapeutic range in man and women have not been performed, yet. One reason might be a lacking commercial interest of the pharmaceutical industry due to generic availability of digitalis drugs. Prescription rates of digitalis are steadily falling[15] possibly relating to concerns about digitalis toxicity and the increasing availability of proven mortality-reducing drugs such as ACE-inhibitor/AT1-receptor blocker, beta-blocker, mineralocorticoid receptor antagonists (MRA) and angiotension receptor-neprilysin-inhibitor (ARNI) in patients with chronic systolic heart failure. Overall, the reduced prescription rates of cardiac glycosides ignore the substantial benefit in morbidity seen with digoxin (number needed to treat for 3 years to avoid one costly heart failure hospitalization = 10–12)[7, 10, 12, 16]. Moreover, the large randomized trials showing the benefits of ACE-inhibitors, beta-blockers, MRAs, ARNI, ivabradine and cardiac resynchronization therapy (CRT) have been performed with a background therapy of

digitalis in 25-90% of the study populations[1, 4, 16]. Although these therapeutic interventions may exert their benefits independently of any interaction with digitalis treatment, the reduced mortality in these trials might substantially depend on co-treatment with digitalis. Furthermore, a post hoc analysis of the US Carvedilol Trial's data demonstrated that digoxin use appeared to be even more effective to reduce the combined endpoint of death or hospitalization from all causes in patients receiving (relative risk 0.64, 95% CI 0.52–0.79) than not receiving (relative risk 0.82, 95% CI 0.71–0.99) carvedilol[17]. In the RALES trial, the survival benefit of spironolactone, an MRA, was only significant in patients receiving digoxin[18]. In addition, a recent retrospective analysis of the DIG-trial looking at the primary composite endpoint used in the SHIFT-trial (cardiovascular death or hospital admission for worsening heart failure) indicated a remarkably similar risk reduction in the composite outcome and in its components among patients receiving digoxin or ivabradine[19]. Apparently heart-rate reduction by digoxin was discussed as a potential underlying cause. Importantly, cardiac glycosides, especially in combination with beta-blocker therapy, also effectively reduce heart rate in patients with atrial fibrillation, who cannot be treated with ivabradine for heart rate reduction based on its selective mode of action depending on sinus rhythm. Therefore, digitalis treatment in combination with a beta-blocker might demonstrate its beneficial impact on risk reduction especially in patients with atrial fibrillation, which is very frequent in patients with advanced heart failure. In this context it is important to note, that heart failure patients with atrial fibrillation experience no benefit from cardiac resynchronization therapy[20] or have been excluded from these trials[21]. Besides its negative chronotropic and dromotropic action digitalis is the only inotropic agent that does not increase mortality and improves the neurohormonal profile in heart failure. Larger controlled trials even demonstrated a significant increase of the left ventricular ejection fraction with digoxin[22, 23]. Based on its pharmacodynamics an important advantage of digitalis treatment is the lack of blood pressure reduction, which often limits the treatment with beta-blocker and ACE-inhibitors in heart failure patients.

Digitoxin represents the other cardiac glycoside mainly used for heart failure therapy. Digitoxin exerts the same pharmacodynamic effects as digoxin, but has a more stable pharmacokinetic profile. It does not accumulate in presence of renal or hepatic dysfunction (avoiding dose adjustment at these conditions), and is associated with a lower incidence of side effects compared to digoxin[24]. As it is the pharmacologically more stable cardiac glycoside, the favourable effects in clinical heart failure trials observed with digoxin (e. g. DIG-trial)[7] are likely to be even more pronounced with digitoxin. Furthermore, we observed effects of digitoxin but not digoxin in endothelial cells[25], which might improve endothelial dysfunction in heart failure patients and thereby impact prognosis[26]. Compared to digoxin, treatment with digitoxin achieves stable target serum levels much better than treatment with digoxin. Especially in patients with renal and hepatic dysfunction, this avoids regular measurements of serum concentrations and dose-adjustments.

Toxicology

For detailed information on Digitoxin toxicology refer to the corresponding summary of product characteristics (SmPCs) in its actual version.

1.3 Study and Dose Rationale

In the *post hoc* analysis of the DIG trial, digoxin treatment, at serum concentrations in the lower therapeutic range, was accompanied with a reduction in mortality but also in hospitalization for heart failure of ~20-25% and ~40% in patients with chronic systolic heart failure (NYHA class II-IV), respectively. This is even expected to be exceeded by digitoxin treatment because of its higher pharmacological stability. Therefore, digitoxin might have substantial impact on survival, severity of disease, quality of life and relieving the burden of disease in patients with advanced systolic heart failure. However, clinical trials prospectively proving a beneficial effect of cardiac glycosides, in particular digitoxin, on all-cause mortality and morbidity in heart failure patients are still lacking. This persistent uncertainty (since the DIG-trial 1997) also mirrors in the recommendations for the treatment with cardiac glycosides in the heart failure guidelines of the European Society of Cardiology (ESC)[2], potentially causing under prescription of a possibly life-saving and/or disease-relieving drug in heart failure patients. Therefore, this trial is needed now. For clinical practice, the proposed trial will provide important evidence that cardiac glycosides, in particular digitoxin, reduce all-cause mortality or hospitalization for worsening heart failure in patients with advanced chronic heart failure treated with standard of care for chronic systolic heart failure including ACE-inhibitor/AT1-receptor-blocker, beta-blocker, MRA as well as, if indicated, ARNIs, ivabradine and CRT-device therapy. As heart failure patients with atrial fibrillation cannot be treated with ivabradine and have no proven benefit from CRT device therapy, especially this patient population included in this trial might benefit from treatment with digitoxin in clinical practice.
As heart failure places a heavy medical and economic burden on society, reduction in mortality and morbidity in patients with chronic systolic heart failure by digitoxin treatment will have enormous socio-economic impact. This will be even enhanced due to the very low treatment costs with digitoxin compared to other treatments (especially device therapy).
Overall, DIGIT-HF would answer the important open question in a prospective, multicenter, randomized, double blind, parallel-group, placebo-controlled, phase IV trial: Do cardiac glycosides, in particular digitoxin, reduce all-cause mortality or hospitalization for worsening heart failure in patients with heart failure on contemporary drug and device therapy?

Dose, mode and scheme of intervention

In contrast to digoxin, clinical trials investigating the effect of digitoxin on clinical relevant cardiovascular endpoints in heart failure patients have not been performed at all.
In patients with chronic heart failure (NYHA II-III) daily administration of 0.07 mg digitoxin caused a significant decrease in endsystolic diameters and a significant increase in posterior wall motion amplitude, stroke volume, shortening fraction and early diastolic left ventricular filling speed[27]. For a mean digitoxin dose of 0.06-0.07 mg/day even in patients with impaired renal function digitoxin serum concentrations of 6.4 – 9.4 ng/ml (8.5 – 12.2 nM) have been described[28]. In line, concentrations of digitoxin in a range of 8-18 ng/ml increased parameters of systolic function in dose-response analyses in man equivalent to digoxin concentrations of 0.5-0.9 ng/ml [29], the latter have been shown to be associated with a reduced overall-mortality in heart failure with reduced ejection fraction (HFrEF) in the DIG-trial. Furthermore, our own studies demonstrated that treatment of endothelial cells with digitoxin at concentrations of 10 nM up to 30 nM (7.65 ng – 22.95 ng/ml) effectively inhibits activity of the Na^+/K^+-ATPase (unpublished data), cytokine-induced proinflammatory processes (e. g. expression of MCP-1, VCAM-1, monocyte adhesion), production of reactive oxygen species and apoptosis but

increased the expression and activation of the endothelial NO-synthase[25]. Based on these studies, concentrations of digitoxin ≥ 8 ng/ml seem to be necessary for improving myocardial function as well as a potential improvement of endothelial dysfunction in patients with advanced systolic chronic heart failure. Therefore, we choose a digitoxin target serum concentration of 8 – 18 ng/ml (10.5 – 23.6 nmol/l) in the DIGIT-HF-trial.

Based on pharmacokinetic data[24, 29] 0.05 mg – 0.1 mg of digitoxin will be chosen to achieve digitoxin serum concentrations of ***8 - 18 ng/ml*** (10.5 – 23.6 nmol/l). In addition, well established commercially available formulations for digitoxin (Digimerck®) will be used providing stable pharmacokinetics in 3 available doses (digitoxin: 0.05/0.07/0.1 mg).The use of these 3 doses provides easy dose adjustment without necessity of tablet splitting, which also might affect pharmacokinetics and therefore serum levels. In addition, pharmacokinetics of digitoxin (elimination mainly entero-hepatic) should avoid high concentrations of digitoxin with the dose regimen chosen even in patients with advanced kidney disease. To simplify treatment and avoid adverse, especially pro-arrhythmogenic actions, starting doses of digitoxin will be 0.07 mg/die without an initial loading dose.

Due to its pharmakokinetic profile, stable serum concentrations of digitoxin will be reached by this treatment after 3-4 weeks. Therefore, serum concentrations of digitoxin will be determined at 6 weeks after baseline (Visit V1) and necessary dose adjustments are performed to achieve target serum concentrations. If the dose of digitoxin is up-titrated at 6 weeks, a dose reduction will be performed at 12 weeks (Visit V1x) for patients whose serum concentrations are higher than the target range. Otherwise, the present dose of digitoxin will be maintained. The Institute for Biostatistics will blind the dose adjustment.

As we expect stable digitoxin serum concentrations and to keep simplicity of the trial, which will be crucial for adherence of patients and centres, further measurements of digitoxin serum concentrations will only be performed during the entire trial if digitoxin toxicity or adverse reactions potentially due to digitoxin are suspected or treatment with cardiac glycosides has to be started for medical reasons (for details s. chapter 5.1, 5.2 & 5.3).

There was concern that early deterioration and withdrawal of patients previously on cardiac glycoside treatment who would be randomized to placebo would lead to increased dropouts and consequent loss of statistical power. Therefore, at the beginning of the trial patients already on treatment with cardiac glycosides have been excluded from trial participation. However, in the ongoing trial it must be realized, that treatment with cardiac glycosides is the main reason for exclusion of a majority of patients otherwise applicable for trial participation inevitably endangering sufficient enrolment of patients. Therefore, the decision to exclude patients on treatment with cardiac glycosides at baseline was re-evaluated in light of the fact that these patients had been included into the DIG-trial.

44% in the placebo and digoxin group of the DIG-trial, respectively, were treated with digoxin before enrolment[7]. There are no known inconsistencies between patients pretreated with cardiac glycosides in the DIG trial. In the primary result publication no differential effects are reported. One subgroup analysis of these patients is presented in the main publication, showing consistent effects on the occurrence of death due to worsening heart failure or hospitalization due to worsening heart failure[7] (hazard ratio for Digoxin/Placebo in patients with previous use of digoxin: 0.74, 95%confidence interval: [0.66;0.83], hazard ratio for Digoxin/Placebo in patients without previous use of digoxin: 0.77, 95%confidence interval: [0.68;0.86], interaction p-value: p=0.60). Based on this result, it seems unlikely that patients are endangered if pretreatment with cardiac glycosides is terminated before start of IMP

treatment and if randomized to placebo. Furthermore, patients are regularly monitored within the study visits for adverse events and side effects to ensure patient safety. Since the efficacy of Digitalis is unproven (which is the aim of this trial), there are no ethical issues when switching patients from previous treatment with cardiac glycosides to placebo.
Overall, this argues against exclusion of patients with previous treatment of cardiac glycosides from participation in DIGIT-HF. In addition, there is another even more important reason for inclusion of patients pretreated with cardiac glycosides. As recently demonstrated, there is a clear bias to preferably treat sicker patients with cardiac glycosides[30]. As a result patients on treatment with cardiac glycosides suffer from significantly more comorbidities. Exclusion of these patients may lead to selection of a “healthier” patient population with a lower event rate, affecting statistical power and generalizability of the study results. Based on these considerations, for the ongoing trial only patients with atrial fibrillation presently treated with cardiac glycosides have to be excluded from trial participation, because termination of cardiac glycoside therapy might affect sufficient rate control in these patients. Other patients treated with cardiac glycosides applicable for study participation can be enrolled.
Because of the known preference to treat sicker patients with cardiac glycosides, treatment with cardiac glycosides at baseline must be considered a prognostic factor. It has been reported that these patients have an increased mortality[30]. Therefore treatment with cardiac glycosides at baseline will be incorporated as a stratification variable for randomization and the primary analysis will be adjusted for treatment with cardiac glycosides at baseline.
Due to the treatment protocol, needing 3-4 weeks to achieve stable serum concentrations of digitoxin, no washout of cardiac glycosides is necessary before start of the study medication. If pretreatment with digoxin and randomization to digitoxin, washout of digoxin will occur before achievement of relevant digitoxin concentrations due to the short half-life of digoxin (1-2 days). If pretreatment with digitoxin and randomization to digitoxin, serum concentrations of digitoxin will reach a stable equilibrium until determination at 6 weeks (visit V1) after start of study medication. If randomized to placebo, washout of digoxin or digitoxin will be sufficient until visit V1 at 6 weeks with blinded determination of digitoxin serum concentrations. Therefore, enrolment of patients pretreated with cardiac glycosides will not complicate the study protocol and will not affect patient compliance.

Based on the evidence described, the hypothesized impact of digitoxin treatment on all-cause mortality and hospitalization for worsening heart failure (whichever occurs first) in patients with advanced systolic chronic heart failure (NYHA class II-IV) in addition to treatment with ACE-inhibitor/AT1 blocker, beta-blocker and MRA would be comparable to treatment effects observed with ivabradine and CRT. However, these treatments, in particular CRT, are much more cost-intensive and invasive compared to treatment with digitoxin.

1.4 Risk Benefit Evaluation

The rising life-expectancy of the population and progress in medical therapies of cardiovascular diseases (e. g. ischemic heart disease and myocardial infarction) steadily increase the prevalence and incidence of patients with heart failure. However, the prognosis of patients suffering from advanced heart failure still remains poor despite advances in medical treatment with high rates of mortality, morbidity and especially hospitalization due to worsening heart failure. Therefore, further therapies with proven evidence to reduce mortality

and morbidity of patients with advanced heart failure are of high medical and socio-economic impact and urgently needed.

The proposed trial will provide important evidence whether the cardiac glycoside digitoxin reduces all-cause mortality and hospitalization for worsening heart failure in patients with advanced systolic chronic heart failure treated with standard of care for chronic systolic heart failure including ACE-inhibitor/AT1-receptor-blocker, beta-blocker, MRA as well as, if indicated, ARNI, ivabradine and CRT/ICD. Importantly, heart failure patients with atrial fibrillation cannot be treated with ivabradine and have no proven benefit from CRT. Hence, especially this patient population included in this trial might benefit from the treatment with digitoxin in clinical practice.

Undesirable effects have been described after administration of the investigational medicinal product (IMP) digitoxin. For details on undesirable effects of the individual IMP described, please refer to the corresponding current SmPC.

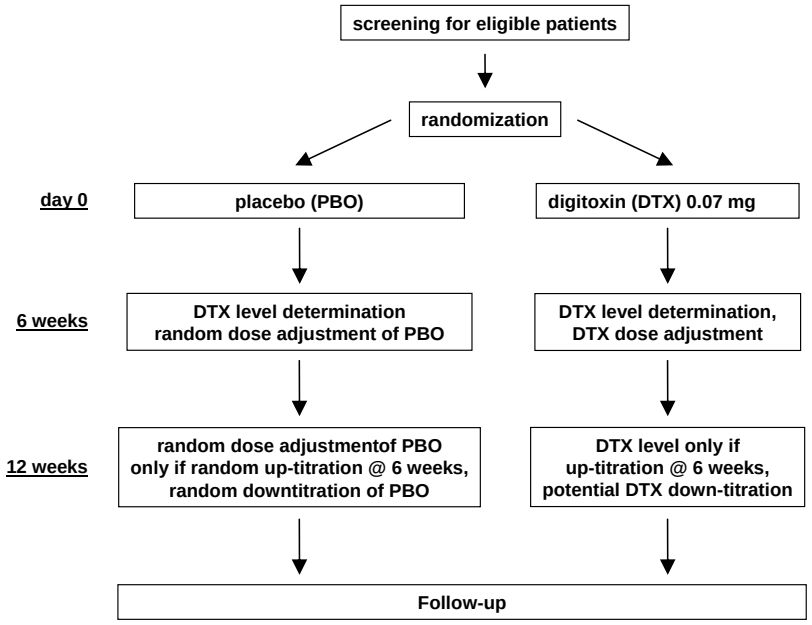
The most frequently reported undesirable effects of digitoxin are cardiac side effects such as supraventricular or ventricular arrhythmias and atrio-ventricular conduction disturbances. However, cardiac side effects mainly occur after overdosing of digitoxin. Furthermore, vegetative and neurologic symptoms such as abdominal pain, diarrhoea, vomiting, headache, fatigue and weakness are symptoms of digitoxin intoxication and only occur after excessive digitoxin overdosing. Overall, most side effects of digitoxin are reversible after the end of administration and are symptoms of digitoxin overdosing. Due to the study design including a target digitoxin serum concentration of 8 - 18 ng/ml (10.5 – 23.6 nmol/l), which represents the lower part of the currently therapeutic range used for treatment of patients, precautions are implemented that overdosing will not occur and adverse events will be identified, treated and documented. Therefore, the potential benefit of potentially increased therapeutic efficacy outweighs the potential risks for the patients.

For the group of patients pretreated with cardiac glycosides before inclusion no negative effects are expected if these patients are randomized to placebo, as described in section 1.3.

2 STUDY DESIGN AND OBJECTIVES

2.1 Study Design

This is a multicenter, randomized, double blind, parallel-group, placebo-controlled, phase IV trial that compares digitoxin to placebo in patients with advanced systolic chronic heart failure NYHA class III-IV and ejection fraction ≤ 40% or NYHA class II and ejection fraction ≤ 30%.
After the screening visit, patients applicable for study enrolment by fulfilling the given inclusion and exclusion criteria are randomized into two groups as follows:
Control intervention (placebo): standard of care (SOC) & one single dose placebo p.o./die.
Intervention group (digitoxin): standard of care (SOC) & one single dose digitoxin (0.05, 0.07 or 0.1 mg) p.o./die.



2.2 Study Objectives

To demonstrate in a large and simple clinical trial-approach that digitoxin (target serum concentrations preferably 8 - 18 ng/ml (10.5 – 23.6 nmol/l) on top of standard of care is superior in reducing a composite of all-cause mortality and hospitalization for worsening heart failure (whichever occurs first) in patients with advanced systolic chronic heart failure (NYHA class III-IV and EF ≤ 40% or NYHA class II and ≤ 30%) to a greater extent compared to standard care plus placebo.

2.3 Study Endpoints

Primary endpoint:

Composite endpoint of all-cause mortality and hospital admission for worsening heart failure (whatever occurs first)

Admission for worsening heart failure is defined by presence of the following points together:

1.) Worsening of heart failure based on clinical judgment (presence of heart failure symptoms) by the treating physician.

2.) hospital stay overnight

3.) i.v.-treatment with diuretics or vasoactive substances (e. g. nitroglycerine) or inotropes (e. g. dobutamine).

Key secondary endpoints:
All-cause mortality, hospital admission for worsening heart failure, (recurrent) hospital admission for worsening heart failure

Secondary endpoints:
cardiovascular mortality, death from heart failure, any non-cardiovascular death, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, any cardiovascular hospitalization, hospital admission for any cause, implantation of a cardioverter-defibrillator, implantation of a cardiac-resynchronisation device, implantation of a pacemaker, sudden cardiac death, change in functional capacity assessed by NYHA class.

Assessment of safety:
Adverse events (AEs), serious adverse events (SAEs) and laboratory abnormalities will be compared between the treatment groups.

2.4 Number of Patients / Centers

A total number of 2190 eligible patients in approximately 50 study centers will be included in this clinical trial (1095 per group).

2.5 Study Duration

Duration of the entire trial (first patient in to last patient out):
The overall study duration is event driven with a follow up period of a minimum of 13 months (last patient in), until the required number of 734 adjudicated primary events is recorded. All patients will be followed up until the end of the study.
An EOT visit will be conducted for each patient 40 days after last IMP treatment.

An interim analysis will be done after 50% (367) of the adjudicated primary endpoint events have been observed. If digitoxin is superior to placebo, the study stops at the interim for proven efficacy.

Duration of study per patient:
The study duration per patient will be at least 13 months for the last patient in. All patients will be followed up until the end of the study and will have an EOT visit. All patients will receive IMP treatment until the end of the study.

2.6 Blinding and Randomization

This is a double-blind clinical study and placebos matching the three dose strengths of digitoxin will be provided. Permuted block randomization will be used to randomize the blinded study medication.
Randomization will be stratified by center, gender, NYHA class (II, III or IV), atrial fibrillation and treatment with cardiac glycosides at baseline. Plasma levels of digitoxin are determined by a central laboratory and are provided to the Institute for Biostatistics, which will manage the dose adjustments including random placebo dose-titrations.

2.7 Emergency unblinding by investigators

Emergency unblinding should only be done where it is essential to know whether the patient was actually treated with digitoxin, especially if digitoxin toxicity is suspected (for details refer to chapter 5.2). Despite unblinding, patients will be further observed and will be analysed as randomized in the primary statistical analysis according to the intention-to-treat principle. A web-based system for unblinding will be provided. The responsibility for backup of unblinding if the web portal, e.g. for technical reasons is not available, is by the Department of Cardiology & Angiology. The needed information will be provided by the Institute for Biostatistics.
The reason, time and date of unblinding have to be documented in the electronic case report form (eCRF).

2.8 Premature Discontinuation of the Study

The sponsor has the right to terminate the study at any time for reasonable medical or administrative reasons. Also, an investigator can decide to terminate the study at the corresponding study center at any time for reasonable medical or administrative reasons.
If the study is prematurely terminated for any reason, the investigator has to ensure appropriate therapy and follow-up for study patients.

An independent Data Monitoring Committee (DMC) will be responsible for reviewing unblinded safety data at regular intervals during the study and may recommend stopping the trial because of harmful effects.

Non recruiting study centers will eventually be closed in due course; in all other situations all attempts will be made to improve recruitment in centers that have committed to participate in this trial.

2.9 Biobank

Biological material in the form of blood samples will be stored in coded form (pseudonymised) to enable analysis of future parameters in this valuable trial population (e. g. biomarker studies). The samples will be stored at the Hannover Medical School (MHH) in centralized, harmonized, unified biobank called Hannover Unified Biobank (HUB).

Biological material from the biobank will be stored after the end of the study for an unlimited period of time if the patient accepts this. At the screening visit, the patients will sign and date a study-specific informed consent regarding participation in the research biobank with additional scientific potential. Patients who are or not willing to participate in the additional biobank can still participate in the DIGIT-HF study.

2.10 Substudies

Substudies are welcome and will be designed with suitable centers (e. g. 6-minute walk test, assessment of quality of life etc.) and participating centers are encouraged to submit outlines for substudies of DIGIT-HF. These outlines will be carefully assessed by the trial steering committee regarding the feasibility of the project and the risk to unblind or endanger the integrity of the trial. Studies with a new research question in the same study population require a new protocol or an amendment to the positive assessed protocol.

Substudies will be included in the hierarchical test procedure of the trial after primary and key secondary analyses have been performed (see 9.3 and 9.5 for details).

3 STUDY POPULATION

3.1 Study Population/Condition

Patients with advanced systolic chronic heart failure NYHA class III-IV and ejection fraction ≤ 40 % or NYHA class II and ejection fraction ≤ 30% who are at least 18 years of age will be screened. They will be recruited from the clinics of the participating centers. A total of 2190 eligible patients will be enrolled. After signed written informed consent, patients fulfilling the inclusion/exclusion criteria will be randomized to either the digitoxin or placebo treatment arm at a ratio of 1:1 respectively.

3.2 Inclusion Criteria

1. Signed written informed consent and willingness to comply with treatment and follow-up
2. Male or female patients age ≥ 18 years at day of inclusion
3. Patients capable of understanding the investigational nature, potential risks and benefits of the clinical trial
4. Patients with chronic heart failure NYHA class III-IV and a ventricular ejection fraction of EF ≤ 40%* **or** patients with heart failure NYHA class II and EF ≤ 30 %*

   * determined at screening by echocardiography or cardiac magnetic resonance tomography or within 8 weeks prior to study inclusion by left-ventricular angiography, echocardiography, radionuclide ventriculography, cardiac magnetic resonance tomography

   AND

   an evidence based heart failure therapy at least for six months upon discretion of the treating physician
5. Women without childbearing potential defined as one or more of following:
   - Women at least 6 weeks after surgical sterilization by bilateral tubal ligation or bilateral oophorectomy with or without hysterectomy at the day of inclusion
   - Women ≥ 50 years of age at the day of inclusion who have been postmenopausal since at least 1 year
   - Women < 50 years and in postmenopausal state ≥ 1 year with serum FSH > 40 IU/l (proved by a second laboratory assessment after 4 weeks)

   OR

   Women of childbearing potential who have a negative hCG pregnancy test and agree to meet one or more of the following criteria from the time of screening/baseline, during the study and for a period of 40 days following the last administration of study medication:
   - Correct use of reliable contraception methods. This includes hormonal contraceptive (oral contraceptives, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release) or an intrauterine device (IUD/IUS) or a barrier method of contraception such as condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide (foam/gel/film/cream/suppository)

- True abstinence (periodic abstinence and withdrawal are not acceptable methods of contraception)
- Sexual relationship only with female partners and/or sterile male partners

OR

Men

3.3 Exclusion Criteria

1. Recent (< 2 months ago): myocardial infarction, coronary revascularization, surgery or catheter intervention for valvular heart disease, acute coronary syndrome, stroke or cerebral ischemia, start of heart failure device therapy potentially improving left ventricular ejection fraction or heart failure symptoms (e.g. cardiac resynchronization therapy (CRT), cardiac contractility modulation (CCM), baroreflex-activation therapy (BAT))
2. Scheduled surgery or catheter intervention for valvular heart disease or scheduled coronary revascularization
3. Active myocarditis
4. Complex congenital heart disease; this does not include: mild-moderate valve disease, uncomplicated shunts (isolated patent foramen ovale, small atrial or ventricular septum defects without associated lesions), repaired secundum or sinus venosus atrial septal defects or ventricular septal defects without residua, previously ligated or occluded ductus arteriosus
5. High-urgency listing for heart transplantation or scheduled therapy with left ventricular assist device (LVAD)
6. Heart rate < 60 b.p.m. (except if functional CRT in place)
7. SA-/AV-block > I°, sick sinus syndrome or carotis sinus syndrome (except if pace-maker protected)
8. Proven or suspected accessory, atrio-ventricular pathways (e.g. WPW-syndrome)
9. History of symptomatic or sustained (≥ 30 s) ventricular arrhythmia unless a cardioverter/defibrillator implanted
10. Current ventricular tachycardia or fibrillation (this means patients presenting with a running ventricular tachycardia or fibrillation. If ventricular arrhythmias are terminated and a cardioverter/defibrillator is implanted inclusion is allowed according to point 9.)
11. Hypertrophic obstructive cardiomyopathy (idiopathic subaortic stenosis)
12. Cor pulmonale
13. Constrictive pericarditis
14. Thoracic aortic aneurysm (defined as diameter ≥ 45 mm)
15. Concomitant severe liver and renal disease

16. Persistent hypokalaemia (< 3.2 mM)
17. Hypercalcemia or hypomagnesemia, if clinically suspected and verified by laboratory testing (e. g. hyperparathyroidism, neoplasia induced hypercalcemia, signs of neuromuscular hyperexcitability)
18. Present (within 6 weeks before baseline/day 0 visit) and continuous treatment with Amiodarone (Single or short-term (up to 3 days), not continuous administration of amiodarone immediately before or during study treatment are acceptable)
19. Scheduled direct current cardioversion (DCC) in the next 24 h (e. g. patients not on cardiac glycosides with new onset of atrial fibrillation. Patients already included and on treatment with IMP can continue IMP and study when scheduled for DCC)
20. Presence of both treatment with cardiac glycosides and atrial fibrillation
21. Simultaneous intravenous treatment with calcium salts
22. Evidence of cardiac glycosides intolerance or known hypersensitivity to any component of investigational medicinal products
23. Suspected intoxication with cardiac glycosides
24. Unlikely compliance with protocol requirements
25. Pregnant and lactating women
26. Use of other investigational drugs or devices at the time of enrollment, or within 30 days prior to enrollment or 5 half-lives for investigational drugs, whichever is longer
27. Life expectancy < 12 month (e.g. due to active cancer)

3.4 Premature Patient Discontinuation (Drop-Out)

Participation in this clinical study is voluntary. Patients have the right to withdraw consent and discontinue participation in the study at any time and for any reason and without prejudice to further treatment. These patients will be asked for their consent to be contacted for a final visit.
During the initial informed consent procedure patients will be informed that withdrawal from treatment does not necessarily mean withdrawal from all observations planned for and conducted within this trial (refer to chapter 5.2).

In addition, the investigator has the right to withdraw a patient from the study if the patient's safety or wellbeing is compromised by further study participation or if the patient is not compliant. Concern for the interests of the patient must always prevail over the study interests.

If the study is prematurely terminated for any reason, the investigator has to ensure appropriate therapy and follow-up for study patients.

A final examination should be performed on all patients who discontinue the study participation.

4 INVESTIGATIONAL MEDICINAL PRODUCTS

4.1 Digitoxin Drug Information

In this trial Digimerck® tablets will be used. Three different doses of Digimerck® tablets are offered containing digitoxin and lactose and sucrose as supplements: Digimerck® pico 0.05 mg (0.05 mg digitoxin), Digimerck® minor 0.07 mg (0.07 mg digitoxin) and Digimerck® 0.1 mg tablets (0.1 mg digitoxin).
For a complete list of undesired effects and storage and handling see the current SmPC.

4.2 Placebo Drug Information

Placebo tablets have similar constituents as the active with the exception of digitoxin content.

4.3 Source of Drugs, Packaging and Labeling

All IMPs will be manufactured in accordance with EU Good Manufacturing Practice requirements. Placebo tablets will be manufactured and packed by NextPharma, Digimerck® tablets and placebo tablets will be labelled, and distributed to the study centers by Next Pharma.
Tablets, respective blister containing active IMP or placebo will be indistinguishable from each other in appearance, durability, packaging, labeling and instruction for use.

4.4 Accountability Procedures

After randomization, patients will receive IMP from their respective study center. The patients should be asked to return the IMP for accountability at every visit.
Patient should take between 50-110% of IMP to be compliant. The process for capturing the compliance information is the assessment by tablet counts at each study center. A record of all IMP movements including drug dispenses must be performed and documented by each study center.

5 TREATMENT

5.1 IMP Treatment and Dose Adjustment

All patients receive SOC as recommended by ESC comprising of the following elements: beta-blocker, ACE-inhibitor/AT1-receptor-blocker, MRA, as well as, if indicated, ARNI, ivabradine, CRT and implantable cardioverter-defibrillators upon discretion of the treating physician.

Patients on treatment with cardiac glycosides at baseline will be withdrawn from open label treatment with cardiac glycosides and immediately switched to double blind study medication. At the end of the study patient treatment is upon the discretion of the treating physician, who may request at this point in time un-blinding of the patient.

The IMP digitoxin or placebo will be given as continuous treatment until the end of the study on top of SOC (target digitoxin serum concentration of 8 - 18 ng/ml (10.5 – 23.6 nmol/l)).

Control intervention: SOC + placebo p.o. (corresponding to 0.05, 0.07 or 0.1 mg digitoxin tablets)

Experimental intervention: SOC + digitoxin p.o. (0.05, 0.07 or 0.1 mg/die)

Patients will be advised to take the IMP tablets unchewed once a day (in exceptional cases, every second day (please refer to following paragraphs)) in the evening with sufficient liquid after a meal. If a dose is missed, the subject should take the dose as soon as possible, but only if there are 12 or more hours remaining before the next dose is due. If the next dose is due in less than 12 hours, the subject should skip the missed dose and take the next dose as scheduled. If vomiting occurs after taking digitoxin, the subject should not take a replacement dose on that day. The subject should resume taking digitoxin at the next scheduled dose on the following day. If vomiting persists, the patient should be instructed to notify the investigator.

IMP treatment is started at day 0. The starting dose is 0.07 mg digitoxin p.o. daily or placebo p.o. At the first study visit (V1) 6 weeks after starting of IMP treatment serum concentrations of digitoxin will be determined in a central laboratory of the Institute for Clinical Chemistry, Hannover Medical School. Data from the analysis of digitoxin serum concentrations are provided to the Institute for Biometry to initiate dose adjustments. Dose adjustment will be supported by advice of an independent medical expert, if applicable. For the placebo-patients dose adjustment will be randomly assigned and for the digitoxin-group dose adjustment will be initiated employing a defined algorithm: If serum levels for digitoxin are lower/higher than the target serum concentration of 8 - 18 ng/ml (10.5 – 23.6 nmol/l), doses will be reduced or increased to 0.05 or 0.1 mg digitoxin, respectively. Otherwise, the present dose of digitoxin will be maintained. In patients the digitoxin dose was up-titrated another measurement of digitoxin serum concentrations will be performed 6 weeks after dose adjustment (12 weeks after randomization, visit V1x) in the central laboratory of the Institute for Clinical Chemistry to identify digitoxin serum concentrations higher than the target serum concentration. Again, for the placebo-patients dose adjustment will be randomly assigned and for the digitoxin-group defined dose adjustment will be initiated employing a defined algorithm: If determined digitoxin serum concentrations are higher than the preferred target range, the digitoxin dose will be reduced to the next lower dose (0.07 mg). Otherwise, the present dose of digitoxin will

be maintained. Data from the analysis of digitoxin serum concentrations are provided to the Institute for Biometry, which will make the potential dose adjustment available in the web based random tool, so that the investigator can allocate the next package/s (IMP-Label/s) appropriately at the next meeting.
If digitoxin serum levels determined at study visit V1 exceed a concentration of 25 ng/ml (33 nmol/l), which is the upper limit of the so called “therapeutic” range formerly used in clinical treatment, it is considered highly unlikely that the target range can be achieved with the above described dose adjustment. Therefore and for safety reasons patients with digitoxin serum levels > 25 ng/ml (33 nmol/l) should not continue digitoxin treatment with the proposed doses. An adapted dose adjustment will be performed as follows: If the measured digitoxin serum concentration is > 25 ng/ml (33 nmol/l) at study visit V1 (patients current dose = 0.07 mg/die), medication will be paused. After 6 weeks pause, medication will be started again with a dose of 0.05 mg taken every second day. As discussed in 1.3 no negative effects are expected due to this procedure.
In addition, if digitoxin serum levels determined at study visit V1x and V3 exceed a concentration of 25 ng/ml (33 nmol/l) patients should not continue digitoxin treatment for safety reasons. To keep simplicity of the trial and to avoid unblinding of these patients, their treatment will be switched to placebo. As discussed in 1.3 no negative effects are expected due to this procedure.
Due to the long half-life of digitoxin with slow decline of serum levels adverse events due to termination of IMP treatment are not expected. Therefore, IMP treatment can be stopped without special measures. After the end of the study the patient will continue to receive usual care at their treating physician with treatment and follow-up according to standard guidelines.

5.2 Premature IMP discontinuation

Patients who discontinue IMP for any reason will remain in the study to be evaluated for efficacy and safety endpoints and will be expected to continue study visits.

5.3 Management of Suspected Toxicity/Adverse Effects due to digitoxin and termination of study medication

If the patient or a physician suspects digitoxin toxicity or at occurrence of serious adverse effects consequences will follow as described below:

- If patients present with symptoms indicating digitoxin intoxication, study medication has to be stopped immediately, digitoxin serum concentrations have to be determined, and all necessary medical measures provided. Also, the study center of the patient has to be informed as soon as possible.
- If patients present with adverse reactions potentially due to digitoxin, study medication should be paused immediately. Only if medically indicated as judged by the treating physician, digitoxin serum concentrations should be determined immediately by the treating physician and all necessary measures should be performed; the study center has to be informed.
- If digitoxin serum concentrations do not have to be determined immediately as judged by the treating physician, first the study center has to be informed and the patient should present as soon as possible at her/his study center. There are two basic options for continuation:

1) The investigator confirms adverse reactions due to digitoxin (based on medical history, clinical examination and a 12-lead electrocardiogram). Consequently, the study medication has to be stopped and the treating physician has to be informed. Based on the investigator´s discretion, he/she has to decide whether the patient has to be unblinded. An immediate unblinding should be performed when the knowledge about the patient´s treatment has an impact on further therapy of the patient.

2) The investigator does not confirm adverse reactions due to digitoxin (based on medical history, clinical examination and a 12-lead electrocardiogram). Consequently, the study medication will be continued and the treating physician will be informed.

- If continuation of study treatment is not feasible for any reason, study medication will be stopped. This does not necessarily mean that the patient or the investigator has to be unblinded.
- If patients or their treating physician do not agree to continue study medication for any reason, study medication will be stopped. This does not necessarily mean that the patient or the study physician has to be unblinded.

5.4 Concomitant Therapy

Permitted medications

Study treatment is given on top of background cardiovascular therapy (SOC), which should be optimized in accordance with contemporary guideline recommendations[2]. Such therapy could include an ACE-inhibitor or an AT1 receptor blocker, a beta-blocker, a diuretic, an MRA, ARNI, ivabradine as well as treatment with pacemakers, implantable cardioverter defibrillators, and cardiac synchronization devices. Use of concomitant medications for other medical reasons/disease should be handled according to the current digitoxin SmPC.

Use with caution

Possible pharmacodynamic and pharmacokinetic drug-drug interactions between digitoxin and a variety of drugs should be taken into account[24]. However, this does not require exclusion from the trial or prohibition of use of all drugs with potential pharmacodynamic and pharmacokinetic interactions with digitoxin as well as exclusion of patients taking these drugs. Of course, drug-drug interactions causing serious side effects have to be avoided. Measures to avoid serious side effects will be determination of digitoxin serum levels during study visit V1/V1x/V3 after start of treatment as well as screening for signs of toxicity during all study visits by medical history, clinical examination and a 12-lead electrocardiogram. Furthermore, the treating physician will be informed to be aware of drugs having potential interactions with digitoxin according to the SmPC. If the patient, a treating physician or investigator suspect digitoxin toxicity or occurrence of adverse effects potentially due to digitoxin, treatment measures have to be performed as described above (section 5.2).

The following treatments are strongly discouraged during the study:

The use of non-dihydropyridine calcium channel blockers (e. g. diltiazem, verapamil), calcium i.v., colestyramine, colestipol.

If continuous treatment with amiodarone has to be started for medical reasons during the study treatment the study medication has to be terminated. This does not necessarily mean that the patient or the treating physician has to be unblinded. However, **single** or short-term (up to 3 days) but not continuous administration of amiodarone before or during study treatment is acceptable and does not lead to the termination/interruption of study medication.

Treatment of atrial fibrillation

The following treatment of atrial fibrillation is recommended during the trial based on the ESC-guidelines[2 31] for the treatment of heart failure:

New onset atrial fibrillation:

1. At the first occurrence of new onset of atrial fibrillation direct current cardioversion (DCC) is recommended for treatment to achieve rhythm control.
2. If new onset atrial fibrillation is recurrent and the patient is symptomatic, again first choice of treatment should be DCC; second choice of treatment should be ablation.
3. If new onset atrial fibrillation is recurrent and the patient is asymptomatic, the first choice should be rate-control as described below for the treatment of chronic atrial fibrillation.

Chronic atrial fibrillation:

For chronic atrial fibrillation rate-control should be performed.

1. First choice of treatment for rate-control should be the increase of beta-blocker therapy to the maximal tolerated dose.
2. If rate-control after increase of beta-blocker dose is not sufficient, cardiac glycosides should be added to beta-blocker therapy. In this case patients have to stop study medication and digitoxin concentrations have to be determined by the treating physician. This does not necessarily mean that the patient or the investigator have to be unblinded.
3. If rate-control remains not sufficient despite treatment with beta-blocker and cardiac glycosides, therapy with cardiac glycosides should be terminated and instead treatment with amiodarone in addition to beta-blocker therapy should be started. Also in this case patients or the investigator do not necessarily require unblinding.

6 STUDY EVALUATIONS/ASSESSMENT

The following chapter describes the detailed study evaluations which have to be performed at each study visit (see also study calendar).

Each blood withdrawal during the study will consist of approximately 40-50 ml blood.

6.1 Study Calendar

Study period	**Screening**	**Baseline[1]**	**Dose adjustment**		**Follow-up[2]**	**Follow-up[2]**	**Follow-up/ termination[2]**	**EOT [3]**
Visit	Screening	Baseline	V1	(V1x) [4]	V2	V3	V4, V5, V6, V7, V8, V9,…	EOT
Time	day -30 until 0	day 0	week 6 ± 5 days	week12 ± 5 days	month 6 ± 7 days	month 12 ± 7 days	Visit every 6 months ± 7 until the end of the study	40 days (+5 days) after last treatment
Informed consent form	X							
Informed consent form biobank	X							
Randomization		X						
Inclusion/Exclusion criteria	X							
Relevant medical history	X							
Prior CHF treatments	X							
Concomitant treatment		X			X	X	X	
LV ejection fraction (if not present [5])	X							
IMP Compliance [6]			X	X	X	X	X	
Allocation of IMP[6,7]		X	X	X	X	X	X	
Pregnancy test [8]	X	(X)	(X)	(X)	(X)	(X)	(X)	
Blood sample biobank (if applicable)		X				X		
Quality of Life (SF12)		X				X		
Clinical examination[9]		X			X	X	X	
Pre-specified events			X	X	X	X	X	
NYHA-class	X				X	X	X	
12 lead ECG and heart rate	X		X	X	X	X	X	
Adverse events[10]			X	X	X	X	X	X
Laboratory examinations[11]	X		X	X	X			
Digitoxin serum concentration[12]			X	X		X		

(1) Procedures conducted within 30 days prior to baseline as part of routine clinical management (e.g. imaging) and obtained prior to signing consent may be used for screening purposes if they are conducted as specified in the protocol.

(2) Telephone Follow-up for randomized participants who discontinued IMP treatment and cannot attend study visits is possible. In this case pre-specified events, adverse events (AE`S until EOT), concomitant medication, NYHA-class will be collected. If available also: information about clinical examinations, ECG and heart rate and lab examination.

(3) Determination of adverse events by telephone call.

(4) (V1x) will only be performed if digitoxin concentration was up-titrated at V1.

(5) By echocardiography or cardiac magnetic resonance tomography if no evaluation was determined in previous 8 weeks in the context of standard care by left-ventricular angiography, echocardiography, radionuclide ventriculography, cardiac magnetic resonance tomography

(6) Only as long as treated with IMP

(7) IMP allocation within 5 days after determination of the digitoxin serum concentration (V1 and V1x). IMP dispensation will be performed until the study is terminated.

(8) Pregnancy test will only be performed if clinically indicated.

(9) The physical status will be assessed including measurement of weight, height (only baseline), blood pressure (SBP, DBP), pulse status and heart rate, auscultation of heart and lungs, clinical signs of congestion and peripheral edema.

(10) AE documentation until 40 days after last IMP (EOT)

(11) Laboratory examinations: Screening Visit: haemoglobin, leucocytes, creatinine, GFR, urea, sodium, potassium, AST (GOT), ALT (GPT), γ-GT. At Visit 1, Visit V1x and Visit 2 only potassium will be determined.

(12) Blood samples must be obtained 8-24 h after the last intake of the IMP. Determination of serum digitoxin concentration only during IMP treatment.

6.2 Screening Evaluations

Each patient must be comprehensively informed about the clinical trial and must give her/his written consent before inclusion in the clinical trial.

The screening evaluations will be performed to determine the patient's eligibility for study participation. Procedures conducted within 30 days prior to baseline as part of routine clinical management (e.g. imaging) as well as obtained prior to signing consent may be used for screening purposes if they are conducted as specified in the protocol.

A screened patient is defined as follows: The patient was informed about the study, has received the study documents and signed/ not signed the consent form.

The following assessments/documentations will be performed:

- Informed consent form
- Informed consent form biobank
- Verification of inclusion and exclusion criteria
- Relevant medical history
- Prior chronic heart failure (CHF) treatments
- Left ventricular (LV) ejection fraction (if no evaluation determined in previous 8 weeks in the context of standard care)
- Pregnancy test (only for women of childbearing potential)
- Efficacy & safety measurements:
  - NYHA-class
  - 12-lead ECG and heart rate
  - Laboratory examinations

6.3 Baseline Evaluations

Evaluations will be performed for determination of the baseline status. IMP treatment starts with one tablet digitoxin (0.07 mg) or placebo/die at day 0. The following assessments/documentations will be performed at baseline visit:

- Randomization
- Concomitant treatment
- Allocation of IMP
- Blood sample biobank (if applicable)
- Quality of Life Questionnaire (SF12)
- Pregnancy test (if clinically indicated for women of childbearing potential)
- Efficacy & safety measurements:
  - Clinical examination

6.4 Dose Adjustment Visits

6 weeks (visit V1) after first treatment the digitoxin serum concentration will be determined for all subjects.
If dose adjustment (visit V1) is mandatory and if the dose of digitoxin was **up-titrated**, another measurement of digitoxin serum concentrations will be performed 6 weeks after dose adjustment (12 weeks after randomization, visit V1x).

If dose adjustment (visit V1) is mandatory due to digitoxin serum levels > 25 ng/ml (33 nmol/l), medication will be paused for 6 weeks and will be proceeded with 0.05 mg digitoxin every second day. At the following visits no additional measurement of digitoxin serum concentration will be performed for dose adjustment.

The following assessments/documentations will be performed at V1 and V1x:

- IMP compliance
- Allocation of IMP
- Pregnancy test (if clinically indicated for women of childbearing potential)
- Efficacy & safety measurements:
  - Pre-specified events
  - 12-lead ECG and heart rate
  - Adverse events
  - Laboratory examinations: only potassium
  - Digitoxin serum concentration

6.5 Follow-up Visits/Termination Visit

Follow-up visits will be performed 6 months after start of treatment and thereafter every 6 months until end of trial.
The following assessments/documentations will be performed at follow-up/termination visits (V2 until the end of the study):

- Concomitant treatment
- IMP compliance (only as long as treated with IMP)
- Allocation of IMP (only at follow-up visits and only as long as treated with IMP)
- Quality of Life questionnaire (only at V3)
- Blood sample biobank (if applicable, only at V3)
- Pregnancy test (if clinically indicated for women of childbearing potential)
- Digitoxin serum concentration for scientific and safety reasons (only at V3)
- Efficacy & safety measurements:
  - Clinical examination
  - Pre-specified events
  - NYHA-class
  - 12-lead ECG and heart rate
  - Adverse events
  - Laboratory examinations (only at V2): only potassium

For each patient, a termination visit according to assessments listed for visit 4 will be performed.

6.6 Telephone Follow-up for randomized participants who discontinued IMP treatment and cannot attend Follow-up study visits on site

If a participant who has discontinued IMP treatment becomes unwilling or unable to attend the study visits then study staff will telephone the participant at the time of each of her /his scheduled Follow-up appointments and following points will be queried:

- Pre-specified events
- Adverse events (until EOT)

- Concomitant medication
- NYHA class
- Clinical Examinations (if available from subject's doctor)
- 12-lead ECG and heart rate (if available from subject's doctor)
- Lab examinations (if available from subject's doctor)

If this is not possible, then study staff will attempt to check a participant's progress by direct correspondence with the participant's own doctors, and/or by reviewing available information about endpoints (location and period of hospitalization) from health insurance and the respective hospitals (see chapter 6.9, page 40).

6.7 End of Treatment Visit

The EOT visit will be performed by phone call 40 days after the last IMP treatment. Only AE`s will be recorded.

6.8 Unscheduled visit

Unscheduled visit is possible any time after screening on the opinion of the investigator and treating physician. The content of such visit is on the discretion of the investigator. The main issue for the unscheduled visit must be documented in the eCRF.

6.9 Assessments

Informed Consent

At the Screening visit (day -30 until 0), the patients will sign and date a study-specific informed consent form before any study procedures are performed.
At the Screening visit (day -30 until 0), the patient will sign and date a study-specific informed consent regarding participation in the research biobank with additional scientific potential. Patients who are not willing to participate in the additional research biobank can still participate in the DIGIT-HF study.

Relevant Medical History

A relevant medical history, including history of tobacco use, will be obtained from each patient.

Prior CHF treatments

A detailed list of prior chronic heart failure (CHF) treatments will be obtained from each patient.

Concomitant treatment

Information about usage of concomitant medication will be documented for each patient**.** Patients are allowed to take any form of concomitant medication during the study except non-dihydropyridine calcium channel blockers (e. g. diltiazem, verapamil), calcium i.v., colestyramine and colestipol.
For use of concomitant medication refer to chapter 5.4 and the current Digimerck® SmPC.

LV ejection fraction

LV ejection fraction will be determined only at screening by echocardiography or cardiac magnetic resonance tomography if not determined in the last 8 weeks in the context of standard care by left-ventricular angiography, echocardiography, radionuclide ventriculography, cardiac magnetic resonance tomography.

IMP Compliance
At every visit after baseline patients have to return the unused IMP for accountability and destruction of unused tablets according to section 4.4.

Allocation of IMP
IMP treatment starts with one tablet digitoxin (0.07 mg) or placebo/die at day 0. After determination of the digitoxin serum concentration (V1) the study medication (adapted concentration) will be provided to the patients (refer to chapter 5.1). IMP dispensation will not be performed at the termination visit.

Pregnancy test
Women of childbearing potential will be tested for pregnancy, verified by determination of beta-hCG in urine or blood samples at the screening visit. Women of childbearing potential will be asked for the date of their last menstruation at every visit. Only if clinically indicated a pregnancy test will be performed.

Biobank
Blood samples are to be obtained at Baseline and if applicable at V3 from all patients who agreed to biobank sampling. Following pre-processing and aliquoting, blood samples will be stored locally, at least at -20 °C but preferably at -80 °C prior to shipping to the HUB. Shipment to HUB will be performed by using a local courier and samples are to be sent on dry ice.

Quality of Life (SF12)
The Quality of Life assessment will be performed using the short form 12 questionnaire (Appendix A).

Clinical examination
The physical status will be assessed including measurement of weight, height (only at baseline), blood pressure (systolic blood pressure (SBP) and diastolic blood pressure (DBP)), pulse status and heart rate, auscultation of heart and lungs, clinical signs of congestion and peripheral edema.

Pre-specified events and adjudication
Pre-specified events described all events described as primary (Composite endpoint of all-cause mortality and hospital admission for worsening heart failure, whichever occurs first) and secondary (All-cause mortality, hospital admission for worsening heart failure, (recurrent) hospital admission for worsening heart failure, cardiovascular mortality, death from heart failure, any non-cardiovascular death, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, any cardiovascular hospitalization, hospital admission for any cause, implantation of a cardioverter-defibrillator, implantation of a cardiac-resynchronisation device, implantation of a

pacemaker, sudden cardiac death, death from worsening heart failure, change in functional capacity assessed by NYHA class) endpoints.

All of the following events will be reported by the investigator to HCTC: All death events and all hospital admissions for any cause. HCTC will provide the event documents for assessment to the Clinical Event Adjudication Committee (CEAC). The CEAC will be responsible for classifying all death events and hospitalizations for any cause according to the CEAC Charter in its current version and chapter 2.3.

NYHA-class
Classification will be performed according to the New York Heart Association (NYHA) Functional Classification scheme (Appendix B).

Heart rate/blood pressure
Resting heart rate will be determined in supine position by 12-lead ECG and blood pressure (systolic and diastolic) after a 5 min. period of rest.

Adverse Events
Documentation of all adverse events will be performed as described in chapter 7.3.

Laboratory examinations
Potassium serum concentrations will be measured at the local laboratory of the study sites. At screening, potassium level must be ≥ 3.2 mM (exclusion criteria).
If significant deviations in the course of the study occur, the treating physician has to be informed by the respective investigator.

Digitoxin serum concentration
The measurement of digitoxin serum concentrations will be performed at the central laboratory of the Institute for Clinical Chemistry, Hannover Medical School. Blood samples will be obtained 8-24 h after the last intake of the IMP at Visit 1 and if necessary at Visit 1x at the study sites. Samples are sent to the central laboratory via regular mail on the day samples are harvested, which is possible due to the high stability of digitoxin. Upon arrival, the samples are catalogued, prepared for measurement and immediately analyzed. The results of analysis will be transmitted to the Institute of Biometry immediately after digitoxin serum concentrations are determined. The investigators will be informed by the Institute of Biometry via email from the random tool within 5 days that the potential dose adjustment (i.e. the next package number) is available in the random tool (please refer to chapter 5.1)
Digitoxin serum concentrations will also be determined at visit 3 (V3) for scientific and safety reasons. No additional dose adjustment will be performed. To ensure patients safety, monitoring of digitoxin serum concentrations will be supported by advice of the independent medical expert, if applicable. Determination of serum digitoxin concentration will be performed only during IMP treatment.

Follow-up of randomized participants via individual data request to health insurances
Additional information about endpoints (location and period of hospitalization) will be sought from health insurances once a year, if applicable.

7 ADVERSE EVENT MONITORING AND REPORTING

7.1 Definitions

Adverse events (AE)
An adverse event (AE) as defined in this study is any untoward medical occurrence in a patient or clinical trial subject administered one of the investigational medicinal products. The event does not necessarily have to have a causal relationship with that treatment. AEs can be diseases, signs of disease or symptoms. Among others, adverse events include the following:

- All suspected medication adverse reactions.
- Apparently unrelated illnesses, including the worsening of a pre-existing illness, injury or accidents.
- Laboratory abnormalities that require clinical intervention.
- Accidents and complications from diagnostic interventions.

The following events do not fulfil the definition of an AE:

- An elective hospitalization during participation in a trial for an intervention or diagnostic procedure for a condition which was present before entering the trial.
- A pre-existing disease or condition which does not deteriorate during the participation in the trial.

Adverse reaction (AR)
An adverse reaction (AR) is any untoward and unintended response to the investigational product related to any dose administered. A response to the medicinal product is given when a causal relationship between the adverse event and one of the IMPs is at least a reasonable possibility.

Serious adverse events (SAE)
A serious adverse event (SAE) or reaction (SAR) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., in the opinion of the investigator, the subject is at immediate risk of death from the event)
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person’s ability to conduct normal life functions)
- Is a congenital anomaly/birth defect.

Additionally, important adverse events may be considered serious upon medical judgement by the investigator when they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

The following events do not fulfil the definition of an SAE:

- Events which might have resulted in a life-threatening situation but did not.
- Elective hospitalization during participation in a trial for an intervention or diagnostic procedure for a condition which was present before entering the trial.

Suspected unexpected serious adverse reaction (SUSAR)
A serious adverse reaction, the nature or severity of which is not consistent with the applicable reference document.

7.2 Reference document / Applicable product information

The applicable reference document for this trial is the summary of medicinal product characteristics (SmPC) for digitoxin (Digimerck®) in its version of May 2015 or its updates.

7.3 Documentation and reporting of adverse events by the investigator

Documentation Requirements

Adverse events (AE)
Adverse events will be collected by the investigator either based on the information provided spontaneously by the patient or evaluated by non-suggestive questions.
The following information is necessary:

- Type of AE (disease, symptoms).
- Seriousness (yes/no)
- Start and termination date of the AE.
- Causality to the study drug (yes/no)
- Measures taken with regard to study medication and treatment of the AE.
- Outcome of the AE.

The adverse event documentation period for this trial begins upon first administration of the IMP (after baseline visit) and ends 40 days after the last application of the IMP (EOT telephone visit). In case of continuation of any adverse event the documentation period will be prolonged until all adverse events are resolved or until the investigator assess the adverse events as “chronic” or “stable”.
Documentation of adverse events must be performed in a timely manner on the respective AE forms in the eCRF.

Serious adverse events (SAE)
The same documentation responsibilities as described for AEs apply to SAEs as well. In addition to entry into the eCRF, SAEs must be documented on the paper SAE-form and reported to the sponsor. Documentation of SAE must be as complete and detailed as possible. In case of death, an autopsy should be aimed for and the results should be forwarded to the principal investigator and the sponsor.

Reporting Requirements

Exceptions to the SAE reporting requirements
Serious adverse events that meet the definitions of primary or secondary endpoints have not to be reported by the investigator to the sponsor:

- all fatal SAEs
- (recurrent) hospital admission for worsening heart failure
- non-fatal myocardial infarction
- non-fatal stroke
- hospitalization for any cause
- implantation of a cardioverter-defibrillator
- implantation of a cardiac-resynchronisation device
- implantation of a pacemaker
- change in functional capacity assessed by NYHA class.

The documentation period of these events begin upon first administration of the IMP (after baseline visit) and ends at the end of the study.

The rationale for these exceptions is that DIGIT-HF is designed as a large double-blind trial with mortality/morbidity endpoints in which a high number of patients will reach those endpoints. Unblinding for regulatory purposes of SAEs that meet endpoint criteria would compromise the integrity of this double-blind trial. These events will be documented as endpoints of this trial and will be reported with the final study report. Moreover, the IMP has a longstanding safety record and new safety findings are unlikely to arise from this trial. Finally, a DMC will review safety data from this trial on a regularly basis. This is in accordance with the 'CT-3' guideline (Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use, chapter 7.11.1, 115.)

Serious Adverse Event reporting period by the investigator
The investigator has to report all SAEs that are not excluded from expedited reporting (see previous paragraph) by faxing or e-mail the SAE form immediately (within 24 hours after awareness) to the authorized representative of the sponsor:

Institute for Clinical Pharmacology
Hannover Medical School
Carl-Neuberg-Str. 1
D-30625 Hannover
Phone: +49-511-532-3959
Fax: +49-511-532-16-2794
E-Mail: sae-reporting@mh-hannover.de

Pregnancies
Any pregnancy occurring within the reporting period has to be reported to:

Institute for Clinical Pharmacology

Hannover Medical School
Carl-Neuberg-Str. 1
D-30625 Hannover
Phone: +49-511-532-3959
Fax: +49-511-532-16-2794
E-Mail: sae-reporting@mh-hannover.de

Events associated with pharmaceutical quality
Any findings or events that are encountered with the IMP that may be attributed to shortcomings of pharmaceutical quality must be reported informally to:

Institute for Clinical Pharmacology
Hannover Medical School
Carl-Neuberg-Str. 1
D-30625 Hannover
Phone: +49-511-532-3959
Fax: +49-511-532-16-2794
E-Mail: sae-reporting@mh-hannover.de

Overdosing
Significant overdosing must be reported as an SAE by the investigator to the sponsor.

7.4 SUSAR-Reporting by the Sponsor

In line with the German “GCP-Verordnung” (GCP-V) as well as international regulation, it is the responsibility of the sponsor to report all SUSARs that occur in this trial to all national competent authorities (NCAs), all leading Ethics Committees and to all investigators of the trial.
Fatal or life-threatening SUSARs must be reported within 7 days, all other SUSARs need to be reported within 15 days.
Also, all circumstances that require re-evaluation of the benefit-risk ratio of the investigational medicinal product have to be reported within 15 days in the same way as SUSARs. This includes:

- Case reports of expected serious adverse reactions (SARs) with an unexpected outcome.
- Increased incidence of SARs which is considered clinically relevant.
- Cases of suspected SUSARs which occurred in patients after completion of the trial participation.
- Occurrences in relationship to the trial or the investigational medicinal product which might affect the safety of the participants.

Details of the safety management in this trial will be set forth in a separate Safety Management Plan.

Unblinding for regulatory reporting purposes

Unblinding procedures that are necessary for regulatory reporting (7.4) and case exchange with the DMC will be described in detail in the Safety Management Plan.

7.5 Annual safety reports

In accordance with international regulations, the sponsor or his authorized representative will provide all NCAs and leading Ethics Committees with a written safety report on an annual basis throughout the duration of the entire clinical trial. The safety report's format will adhere to the ICH-guideline E2F (developmental safety update report, DSUR) which includes a cumulative summary tabulation of all SAEs, line listings of all suspected serious adverse reactions which have occurred during the reporting period as well as a general report of the subject's safety within this trial.

8 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be implemented to detect possible harms, assure continuous risk/benefit assessment, and allow for interim analysis in a blinded trial. The DMC will consist of at least two independent medical experts in the field of interest and one statistician. Details of the definition of DMC, its composition and its roles and responsibilities can be found in the separate DMC charter.
The DMC will receive unblinded data of all SAEs occurring in this trial on an ongoing basis. Furthermore, the DMC will be notified of other information that could affect patient safety or trial outcome (e.g. results from third-party clinical trials, “Dear investigator letters”). For interim analysis, the DMC will receive unblinded data on safety and critical efficacy endpoints aggregated by treatment groups. DMC reports will be prepared by the independent DMC statistician.

Based on this data, the DMC will give recommendations to the trial steering committee (TSC) whether to continue, modify, or stop the clinical trial.

9 STATISTICAL METHODS

9.1 Trial Objective and Hypotheses

The primary objective of this multicenter, randomized, double blind, parallel-group, placebo-controlled, phase IV trial is to demonstrate superiority of digitoxin over placebo on the top of standard of care in the treatment of patients with advanced chronic heart failure. Superiority will be concluded, if digitoxin (d) reduces the composite endpoint of all-cause-mortality and hospital admission for worsening heart failure (whichever occurs first) to a greater extent compared to placebo (p) in a time to event analysis. The statistical hypotheses for the trial are based on the hazard ratio (HR) and will be assessed in a Cox-Regression Model. The respective hypotheses are as follows:

H_o: $\lambda_d/\lambda_p = HR = 1.0$

H_1: $\lambda_d/\lambda_p = HR \neq 1.0$

As soon as the two-sided null-hypothesis is rejected, superiority will be concluded, if the median time to event is longer in the digitoxin treated patient group. The study will proceed with one interim and one final analysis.

Randomization will be performed centrally and will be stratified by center, gender, NYHA class (II, III or IV) and atrial fibrillation and treatment with cardiac glycosides at baseline.

9.2 Analyses Populations

The primary analysis will be conducted on the ITT-population including all patients that have been randomized and have taken at least one dose of the study drug. Patients will be analyzed as randomized independently of their actual treatment (digitoxin or placebo). All attempts will be undertaken to collect the information about the primary endpoint for patients that did drop-out from the study, or were withdrawn. Informed consent will already address the option to contact the patient for follow-up investigations after termination of the observational period of the initial clinical trial.

The per-protocol (PP)-population comprises of all patients that achieved the target plasma levels of digitoxin and were complying with the study-protocol until the end of the observational period and particularly remained in the treatment arm they were allocated to by randomization.

Safety population:

In the safety population, all patients are analyzed who received at least one dose of the study medication (active or placebo). Patients will be analyzed as treated.

9.3 Analyses of Variables

The primary analysis is based on the ITT population. The primary null hypothesis (as defined by 9.1) will be evaluated with a multivariate Cox-regression model including the time to death or hospitalization for worsening heart failure as a dependent variable and the variables treatment (digitoxin or placebo), center, gender, NYHA class (II, III or IV), atrial fibrillation and treatment with cardiac glycosides at baseline as independent factors. A lower hazard rate of the composite endpoint of all-cause-mortality and hospital admission for worsening heart failure (whichever occurs first) in the digitoxin group than in the placebo-group is proven if the corresponding p-value of the treatment effect estimated from the Cox-regression model is

less than the pre-specified two-sided type-I-error of 1% (at the interim analysis), or 4.5% in the final analysis, respectively (see section 9.6 regarding the particularities of the interim analysis).

As soon as the primary hypothesis is rejected, non-inferiority of digitoxin against placebo concerning all-cause mortality will be assessed as the first secondary analysis because European Medicines Agency guidance requires that detrimental effects on mortality must be excluded as soon as morbidity or a combined mortality endpoint is chosen as primary endpoint. Non-inferiority will be concluded if the upper bound of the one-sided 97,5%-confidence interval of the digitoxin/placebo hazard ratio is below 1.303, whereby the hazard ratio and the confidence interval are derived from a Cox-regression model as specified for the primary analysis (for justification of the non-inferiority boundary see 9.6). Superiority will be concluded, if there is a significant difference between digitoxin and placebo regarding overall survival in the respective Cox-Regression model as specified for the primary analysis (i.e. the upper bound of the one-sided 97,5%-confidence interval of the digitoxin/placebo hazard ratio is below 1).

If superiority of digitoxin over placebo regarding overall mortality is demonstrated, substudies will be tested at the significance level of 5%. The analysis of each substudy is described in the individual substudy synopsis. As in the course of the trial further substudies may be initiated, an appropriate approach to account for multiplicity issues (e.g. hierarchical ordering of the substudies or multiplicity correction for simultaneous testing) will be determined when all substudies are specified and before breaking the blind (at the blind data review).

To evaluate the robustness of the estimated treatment effects, the primary analysis will be repeated based on the PP population (sensitivity analyses).

The secondary endpoints hospital admission for worsening heart failure, cardiovascular mortality, non-fatal myocardial infarct and non-fatal stroke will be analyzed in line with the primary analysis strategy.
All secondary endpoints will be tested to a two-sided significance level of 5%. For all analyses estimates, their associated two-sided 95% confidence intervals and p-values will be provided and conducted on the ITT-population. For each gender, NYHA class (II, III or IV), atrial fibrillation and treatment with cardiac glycosides at baseline a subgroup analysis in line with the primary analysis will be done. Interaction P-values will be descriptively assessed, as derived from Cox-Regression Models as specified for the primary analysis additionally including the respective interaction term.

9.4 Data Handling Conventions/ Missing Values

Because a time-to-event analyses is done for the primary analyses missing values will not occur.

9.5 Discussion of Multiplicity Issues

First, confirmatory analyses will be performed for the primary hypothesis (digitoxin reduces all-cause-mortality or hospital admission for worsening heart failure to a greater extent

compared to placebo) at the interim analysis and at the end of the study. Multiplicity is accounted for by adapting the significance level to 1% and 4.5% (O'Brien & Fleming)[32] in the respective analyses. As soon as the primary hypothesis is rejected, non-inferiority of digitoxin against placebo concerning all-cause mortality will be assessed as the second confirmatory analysis. Because of the hierarchical testing strategy there is no multiplicity problem.
If the above described test procedure successfully demonstrated superiority of digitoxin over placebo regarding overall mortality, analysis of substudies will hierarchically follow at the significance level of 5%. An appropriate approach to preserve type-I-error-rate of 5% over all substudies will be determined before breaking the blind (at the blind data review).

9.6 Determination of Sample Size

The sample size estimation is based on the SHIFT-trial (ISRCTN70429960)[33]. In this study the effect of ivabradine was investigated on the primary composite endpoint (cardiovascular and hospital admission for worsening heart failure, whichever occurs first) compared to placebo. The primary endpoint was analyzed with a time-to-event analysis. The median follow up was about 24 months. 24% of the patients in the ivabradine group compared to 29% in the placebo group had an event with regard to the primary endpoint. Additionally, SHIFT reported 14% vs. 15% for cardiovascular mortality and 16% vs. 17% for all-cause mortality for patients treated with ivabradine vs. placebo, respectively. We thus assume that the proportion of events for the composite primary endpoint would be increased by 2% as well. Based on this, we assumed 26% and 31% for the proportion of events for the composite primary including all-cause mortality and hospitalization for worsening heart failure (whichever occurs first).
Taking into account that the population, which will be investigated in the DIGIT-HF trial, has a more severe heart disease compared to the population of the SHIFT-trial, we assumed that the treatment effect of digitoxin is in the same order (see event rates above) although some of the patients are treated with ivabradine as part of the treatment therapy.
Exponential survival is assumed for the sample size calculation. Additionally, it is assumed that the Cox regression model with treatment adjusted for NYHA class and center – as planned for the primary analysis – will increase the power. The primary analysis is conducted on the intention-to-treat (ITT) population. The Type-I-error is set to 0.05 (two-sided) and the power is set to 0.8.
An interim analysis (O'Brien-Fleming) is planned after 50% of the total number of required events (367) has been observed. The study can be successfully stopped at the interim (end of stage 1) if the primary null hypotheses can be rejected at the two-sided significance level of 0.01. In case the study continues, superiority for digitoxin will be proven if the respective null hypothesis can be rejected at the two-sided significance level of 0.045. 99% or 95.5% confidence intervals for the hazard ratio will be reported additionally.
Based on the significance levels, the power as described above and the results of the SHIFT study, the required sample size is estimated for an accrual period of 36 months and a maximum length of follow-up of 48 months. The event rates in the SHIFT trial of 26% (ivabradine) and 31% (placebo) were observed after 24 months. The hazard ratio is HR=0.811. Under these assumptions, a total of 2190 patients (1095 patients per group) with 734 events are required to prove superiority of digitoxin to placebo. The sample size calculation was made under the assumption that the accrual rate is constant. If the

recruitment of patients takes longer than expected, the follow-up period will be extended event-driven.
As soon as the primary hypothesis is rejected, non-inferiority of digitoxin against placebo concerning all-cause mortality will be assessed as a confirmatory analysis. According to the SHIFT-trial an all-cause mortality rate of 17% in the placebo group is assumed. In line with the proposed total sample size of 2190, a power of 80%, a type-1-error of 2,5% (one-sided) and the assumption that digitoxin has no effect on all-cause mortality (Hazard ratio of digitoxin and placebo is 1), the trial should be able to exclude detrimental effects on mortality with a margin of 1.303 (i.e. it should be possible to conclude non-inferiority with the upper bound of the one-sided 97,5%-confidence interval of the digitoxin/placebo hazard ratio being below 1.303).
The sample size has been calculated with AddPlan Version 6 (module “Group Sequential Plan Survival” with a delta of 0.14).

In the following, the size of potential interactions that can be detected with reasonable power at the final analysis is discussed based on the expected proportion of patients treated with cardiac glycosides at baseline.
In the SHIFT trial, 22% of the patients received digitalis at baseline. Assuming that 350 patients will be enrolled at the time when previous digitalis treatment is removed as an exlusion criterion, a total proportion of approximately 18.5% (=22%*(2190-350)/2190) of the included patients will be treated with digitalis at baseline. With the planned recruitment time of 36 months and a minimum follow up of 13 months, the mean observation time will be 30 months. With the planning assumption of a mean event rate of 28.5% after 24 months among both treatment arms (corresponding to 26% in the active and 31% in the control arm) and under the assumption of exponentially distributed survival times the expected event rate after a mean observation time of 30 months is 34.3%. According to the formulae provided by Schmoor et al. (2000), [34] with these event rates and a total sample size of 2190 an interaction between two factors corresponding to a hazard ratio of 1.7 can be detected at a significance level of 5% in a Cox regression model with a power of 80%. These calculations were performed using R 3.3.1.

9.7 Interim Analysis

An interim analysis (O’Brien-Fleming) is planned after 50% of the total number of required adjudicated primary endpoint events (367) has been observed. The study can be successfully stopped at the interim (end of stage 1) if the primary null hypothesis can be rejected at the two-sided significance level of 0.01.

10 DATA MANAGEMENT

All study data will be collected by the investigator and/or other study personnel. A validated clinical trial data base (electronic case report form) is provided in which the data are entered. Authorized and trained staff of the study centers will enter the data of the main DIGIT-HF study in the eCRF. Only SAEs will be additionally documented and reported on paper forms. Verification of the data in the eCRF occurs by risk-based monitoring as well as via range, validity, and consistency checks programmed in the system. Additionally, manual queries can be raised in the system if discrepancies are detected. Based on the queries, the investigator can review the data and resolve the discrepancy or justify the entered data directly in the system. All changes of data entered in the eCRF are documented in an audit trail.

A quality control will be performed before the database is closed. This procedure is documented. Finally, data transfer takes place for statistical evaluation.

11 MONITORING, AUDITS AND INSPECTIONS

Monitoring, audits, and inspections are performed for reasons of quality assurance and to verify that the study is conducted according to the protocol as well as to legal and regulatory requirements applicable for clinical trials, particularly the national drug law and ICH GCP.

11.1 Monitoring

The clinical study has to be initiated by the monitor at each study site before study subjects are enrolled. At regular monitoring visits, the monitor reviews the eCRF for completeness and clarity and performs source data verification in a risk-based monitoring approach. The monitor also reviews drug accountability records, reporting of SAEs and the trial investigator file (TIF). Furthermore, adherence to the protocol as well as to regulatory requirements is monitored. Problems will be discussed with the investigator. The monitor has to give due consideration to data protection and medical confidentiality. All original data should be readily available for review during scheduled monitoring visits and the investigator has to provide the monitor direct access to all study-related documents. Furthermore, the investigator assures the sponsor support at all times. After the last patient has completed the clinical study at a certain study center, the monitor performs a close-out visit at this study site.
The monitoring plan contains further details about the risk-based monitoring approach.

11.2 Audits and Inspections

Audits (by the sponsor) and inspections (by regulatory authorities) may be performed in order to verify that the clinical study is performed according to the study protocol as well as to the respective drug law, ICH-GCP, and other applicable regulatory requirements. The auditor or inspector is independent with regard to personnel involved in the conduct of this clinical trial. The investigator has to provide the auditor/inspector direct access to all study-related documents.

12 ETHICAL, REGULATORY AND ADMINISTRATIVE ASPECTS

12.1 Responsibilities

This study will be conducted in compliance with the national drug law, ICH GCP guidelines and other applicable national and European ethical and regulatory requirements.

Investigators must have sufficient time to conduct the clinical study in compliance with the study protocol. Furthermore, they have to accurately and completely enter study data in the eCRF. Investigators are responsible for obtaining informed consent of the patients as well as for the preparation and maintenance of adequate case histories in order to record observations and other data relevant for this clinical study. Furthermore, they have to file the study-related records in a TIF and have to maintain its actuality. They will permit study-related monitoring visits, audits by the sponsor or its representatives, as well as inspections by regulatory authorities. The investigator must provide direct access to the study site's facilities, to source documents, and to all other study documents.

12.2 Favorable Opinion of Independent Ethics Committee and Approval of National Competent Authority

Favorable opinion of the Independent Ethics Committee (IEC) and approval of national competent authority (NCA) must be available before the start of the study in the respective country.

12.3 Patient Information/Informed Consent and alert card

The investigator is responsible for obtaining patient's written informed consent after adequate explanation of the aim, study assessments, potential risks, benefits, and consequences of the study, as well as alternative treatment options. The patient information/informed consent form has to be signed in duplicate by the patient and the investigator. One document will be given to the patient, the other remains in the TIF at the trial site. No study procedures are allowed to be conducted until patient's written informed consent has been obtained.

The patient information/informed consent form has to be revised whenever important new information becomes available that may be relevant to the subject's consent. The patients have to be informed and asked to give their consent to continue study participation by signing the updated form.

Participation in this clinical trial is voluntary. Withdrawal from the trial at any time and for any reason is without any disadvantages to the patient's further treatment.

Each patient will receive an alert card after study inclusion.

12.4 Record Retention

The sponsor has to archive all relevant study-related documents for at least 10 years after termination or premature discontinuation of the clinical study.

The investigator agrees to keep the TIF, including the identity of all participating patients, all original signed informed consent forms, detailed records of treatment, all other applicable study related documents as well as source documents. The records should be retained by

the investigator for at least 10 years after termination or premature discontinuation of the clinical study. Source data have to be kept according to the national regulations.

12.5 Insurance

Every patient participating in the study will be insured according to national laws. All subjects will be informed about their rights and obligations with regard to insurance policies before participating in the study. A copy of the insurance policies will be handed out to each patient.

12.6 Data Protection

All study staff has to give due consideration to data protection and medical confidentiality. The collection, transfer, storage, and analysis of personal study-related data are performed pseudonymized according to national regulations. The declaration of data protection is contained within the patient information/informed consent form.

12.7 Financing

The study is supported by the German Federal Ministry of Education and Research (BMBF) under grant number: 01KG1303.

12.8 Amendments

Each amendment of essential study documents has to be approved and generated by the sponsor and Coordinating investigator/LKP. Favorable opinion of IEC and approval of the competent authority in the respective country is required for substantial amendments before implementation.

12.9 Publication

The data of the study will be published according to the publication guidelines. Publication of results from single centers is not allowed. Participating centers may publish data of substudies to be defined based on decision of the Trial Steering Committee.

The trial will be registered at a public study register according to current publication guidelines.

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14 APPENDICES

14.1 Appendix A:

Lebensqualität (SF12)

Wie würden Sie Ihren Gesundheitszustand im Allgemeinen beschreiben?	
ausgezeichnet	
sehr gut	
gut	
weniger gut	
schlecht	

Im Folgenden sind einige Tätigkeiten beschrieben, die Sie vielleicht an einem normalen Tag ausüben. Sind Sie durch Ihren derzeitigen Gesundheitszustand bei diesen Tätigkeiten eingeschränkt? Wenn ja, wie stark?			
	Ja, stark einge-schränkt	Ja, etwas einge-schränkt	Nein, überhaupt nicht einge-schränkt
mittelschwere Tätigkeiten, z.B. einen Tisch verschieben, staubsaugen, kegeln, Golf spielen			
mehrere Treppenabsätze steigen			

Hatten Sie in den vergangenen 4 Wochen <u>aufgrund Ihrer körperlichen Gesundheit</u> irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause?		
Ich habe weniger geschafft als ich wollte	ja	nein
Ich konnte nur bestimmte Dinge tun	ja	nein

Hatten Sie in den vergangenen 4 Wochen <u>aufgrund seelischer Probleme</u> irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause (z.B. weil Sie sich niedergeschlagen oder ängstlich fühlten?		
Ich habe weniger geschafft als ich wollte	ja	nein
Ich konnte nicht so sorgfältig wie üblich arbeiten	ja	nein

Inwieweit haben die Schmerzen Sie in den vergangenen vier Wochen bei der Ausübung Ihrer Alltagstätigkeiten zu Hause und im Beruf behindert?				
Überhaupt nicht	Ein bisschen	Mäßig	Ziemlich	Sehr

In diesen Fragen geht es darum, wie Sie sich fühlen und wie es Ihnen in den letzten 4 Wochen gegangen ist. Wie oft waren Sie in den vergangenen 4 Wochen ...						
	immer	meistens	ziemlich oft	manchmal	selten	nie
...ruhig und gelassen?						
...voller Energie?						
...entmutigt und traurig?						

Wie häufig haben Ihre körperliche Gesundheit oder seelische Probleme in den vergangenen 4 Wochen Ihre Kontakte zu anderen Menschen (Besuche bei Freunden, Verwandten usw.) beeinträchtigt?				
immer	meistens	manchmal	selten	nie

14.2 Appendix B:

Einteilung der Symptomatik nach der Klassifikation der New York Heart Association (zit. nach 1).

NYHA I	Herzerkrankung ohne körperliche Limitation. Alltägliche körperliche Belastung verursacht keine inadäquate Erschöpfung, Rhythmusstörungen, Luftnot oder Angina pectoris
NYHA II	Herzerkrankung mit leichter Einschränkung der körperlichen Leistungsfähigkeit. Keine Beschwerden in Ruhe. Alltägliche, stärkere körperliche Belastung verursacht Erschöpfung, Rhythmusstörungen, Luftnot oder Angina pectoris
NYHA III	Herzerkrankung mit höhergradiger Einschränkung der körperlichen Leistungsfähigkeit bei gewohnter Tätigkeit. Keine Beschwerden in Ruhe. Geringe körperliche Belastung verursacht Erschöpfung, Rhythmusstörungen, Luftnot oder Angina pectoris
NYHA IV	Herzerkrankung mit Beschwerden bei allen körperlichen Aktivitäten und in Ruhe. Bettlägerigkeit

14.3 Appendix C: Substudy: Endothelial Function

Study Protocol (DIGIT-HF-Substudy: endothelial function)

This is a substudy of DIGIT-HF. DIGIT-HF is an ongoing randomized, multicenter, double-blind, placebo controlled trial to demonstrate that digitoxin reduces a composite of all cause-mortality and hospitalization for worsening heart failure in patients with chronic heart failure and reduced ejection fraction. DIGIT-HF will randomize 2190 patients in approximately 40 centers to either Digitoxin or placebo in a 1:1 ratio.
The aim of this synopsis is to describe the goals and design of the above mentioned substudy as well as the interface with DIGIT-HF.

SUBSTUDY SYNOPSIS

RESPONSIBLE INVESTIGATOR / COORDINATING INVESTIGATOR SUBSTUDY	Prof. Dr. Udo Bavendiek Prof. Dr. Johann Bauersachs Medizinische Hochschule Hannover Klinik für Kardiologie und Angiologie Carl-Neuberg-Straße 1 D-30625 Hannover
STATISTICIAN (BIOSTATISTICAL SUPPORT FOR PLANNING AND ANALYSIS)	Lukas Aguirre Dávila Prof. Dr. Armin Koch Medizinische Hochschule Hannover Institut für Biometrie Carl-Neuberg-Straße 1 D-30625 Hannover
TITLE	DIGIT-HF-Substudy: The effect of digitoxin on endothelial function in heart failure with reduced ejection fraction
VERSIONSNO. /-DATE	1.3 / 06.02.2018
ADDITIONAL CONDITION	-
ADDITIONAL INCLUSION AND EXCLUSION CRITERIA	Inclusion criteria 1. Signed written informed consent of the substudy endothelial function Exclusion criteria 1. Patients with severe and/or hemodynamic relevant stenosis of upper limb arteries
OBJECTIVE(S)	1. To explore whether digitoxin has an effect on endothelial function 2. To explore potential relationships among demographic and clinical factors and biomarker on endothelial function in patients with chronic heart failure
ADDITIONAL INTERVENTIONS	• Measurement of endothelial function by EndoPAT® at baseline (V0) and at visit V2 (6 months after randomization) • Blood samples at baseline (V0) and at visit V2 for biomarker

	analyses
VARIABLES FROM MAIN TRIAL DIGIT-HF NEEDED FOR SUBSTUDY	The following variables are needed for the analyses of the substudy objectives: - Treatment arm (Placebo vs. Digitoxin) - stratification variables of the main trial - baseline variables (particularly demographic and clinical) - population definitions (protocol deviations) - Further variables may be needed to explore robustness of results
OUTCOME(S)	<u>Primary</u> Change of endothelial function from baseline to 6 months as measured by logarithmized reactive hyperemia peripheral arterial tonometry index (logRHI) (6 months - baseline). logRHI will be measured by EndoPAT®. <u>Secondary</u> - <u>Safety: see DIGIT-HF</u> See DIGIT-HF, measurement with EndoPAT® is non-invasive and therefore no additional safety evaluation is needed.
ADDITIONAL VARIABLES TO BE MEASURED	logRHI at baseline and after 6 months (for calculation of primary substudy endpoint)
STUDY TYPE	Substudy of the prospective randomized double blinded multicenter clinical trial DIGIT-HF
HYPOTHESES AND STATISTICAL ANALYSIS	<u>Primary analysis and population:</u> The primary analysis of the substudy will be conducted on the modified ITT population, consisting of all randomized patients who consented to the substudy and have taken at least one dose of the study drug and have available logRHI at baseline. Patients will be analyzed as randomized, irrespective of the treatment they actually received. The type I error is set to 5% (two-sided). The hypotheses are based on the difference of mean changes in logRHI (6 months - baseline) between digitoxin and placebo: H_0: $\mu_{Digitoxin}-\mu_{Placebo}=0$ H_1: $\mu_{Digitoxin}-\mu_{Placebo}\neq 0$ The change in endothelial function (logRHI 6 months - baseline) will be evaluated with a linear regression model adjusted for therapy (digitoxin / placebo), baseline logRHI and the stratification variables of the main trial DIGIT-HF (center (each center) if more than one center participates in the substudy, gender (female/male), NYHA classification (II/III/IV), atrial fibrillation (yes/no)). The null hypothesis of no effect of Digitoxin on endothelial function will be rejected if the 95%-confidence interval for the treatment effect estimate (Digitoxin-placebo) excludes 0. Since higher values of logRHI indicate a better endothelial function, a beneficial effect of Digitoxin will be hypothesized if the lower bound of the 95%-confidence interval for the treatment effect estimate is greater than 0. Missing values will be replaced by baseline observation carried forward (BOCF). Sensitivity analyses will be conducted on the (modified) PP population consisting of all randomized patients who consented to the

	substudy and had no major protocol violations until 6 months (V2) of study participation (major protocol deviations as defined for the main study). Secondary analysis: - Safety analyses: -
SAMPLE SIZE	n= at least 100 The maximal sample size is determined by the main trial DIGIT-HF. In order to be able to detect a difference in mean change of logRHI (6 months - baseline) with a power of 80% a sample size of 100 should be recruited. However a higher sample size is pursued to increase precision of estimates and to allow for exploration of prognostic factors for low endothelial function. Effect assumptions The required sample size is estimated based on the expected effect of Digitoxin compared to placebo. Estimates for the effect and the standard deviation are taken from Fujisue et al. (2015) where 362 patients with heart failure with reduced ejection fraction (EF≤50%) where observed for three years and associations of baseline logRHI with cardiovascular outcomes where evaluated. Baseline logRHI was reported separately for patients having a cardiovascular event (cardiovascular death or HF hospitalization) and for patients not having any of these events within the observational period as 0.42±0.18 and 0.54±0.21 respectively (mean±sd). Therefore an increase in logRHI of 0.12 (0.54-0.42) is considered clinically relevant. A common standard deviation of 0.21 is conservatively assumed. The patients in Fujisue at al. have a better condition than DIGIT-HF patients (NYHA class IV was excluded in Fujisue et al. and EF≤50% allowed). However, in another publication (Enomoto et al. 2011) where the effect of cardiac resynchronization therapy in HF patients with a more severe condition was studied a larger effect was reported (increase of RHI from 1.4 to 1.7 within 12 weeks corresponds to a change of 0.19 in logarithmized RHI). This trial only included 22 patients and was non-randomized, but nonetheless in its light the assumption of a clinically relevant and achievable effect of 0.12 is considered plausible. Sample size calculation The required sample size is calculated for a t-test for two independent groups. The type-I-error is set to 5% (two-sided). In order to be able to detect a difference of at least 0.12 in change of logRHI from baseline to 6 months with a common standard deviation of 0.21 with a power of 80% a sample size of n=50 patients per group is required. The main trial DIGIT-HF allocates patients to digitoxin and placebo in a 1:1 ratio, thus a total of n=100 patients is required for the substudy. A drop-out is not accounted for. The above calculations have been performed with nQuery Advisor 7.0.
FEASABILITY OF RECRUITMENT	DIGIT-HF is ongoing with stable recruitment in more than 30 centers (further centers will be initiated). MHH included 80 patients within approx. 2 years. Assuming constant accrual, 100 additional patients will be recruited at MHH within 2.5 years. It is expected that additional centers will participate in this substudy to increase accrual. The target sample size is considered feasible and all efforts will be taken to recruit as many patients as possible without compromising the main study. However, if the substudy fails to recruit the target sample size, the subsequent loss of power to generate hypotheses must be tolerated, as the main trial prevails over the substudy.
	The analysis will be performed when the main trial DIGIT-HF is being

TIMEPOINT OF ANALYSIS	analyzed (after breaking the blind).
RISK OF UNBLINDING	Data collection will be performed without knowledge of the treatment arm. The analysis will be performed when the main trial DIGIT-HF is being analyzed (after breaking the blind). Unblinding by individual EndoPAT® measures is not expected because the potential association between study treatment and endothelial function is unknown. It is the purpose of this substudy to investigate whether Digitoxin may influence endothelial function.
ADDITIONAL BURDEN FOR PATIENTS	EndoPAT®-measurements will be performed during the regular baseline visit and visit V2 and require ca. 30 min. additional time to these visits. Inflation of the blood pressure cuff during EndoPAT®-measurement causes some tension in the upper limb without clinical relevant impairment.
DATA MANAGEMENT	Data will be pseudonymously send to the MHH, after readability check centrally stored and entered in a validated CRF-system / database
MONITORING	Verification of informed consent forms. Random checking of the trial investigator file (TIF). No source data matching is carried out during the course of the study. At the end of the study, a random check of the source data and a comparison with the database will be carried out. The monitoring plan contains further details about monitoring details.
INSURANCE	The insurance of the main study is valid.
ADDITIONAL COSTS	Ca. 50 € for EndoPAT®-measurement, covered by investigator assigned institutional research funds
PARTICIPATING CENTERS	n = 1: Dept. of Cardiology & Angiology, MHH Further centres are encouraged to participate.

SIGNATURES

This substudy synopsis endothelial function Vs.1.3 has been approved by the following persons. The following signatures document their approval.

Prof. Dr. Udo Bavendiek (Responsible investigator, LKP of DIGIT-HF)	Date
Prof. Dr. Armin Koch (Trial statistician of the substudy and DIGIT-HF)	Date
Prof. Dr. Johann Bauersachs (Responsible investigator, Head of TSC DIGIT-HF study)	Date
Sponsor of the DIGIT-HF study represented by Prof. Dr. Christopher Baum	Date

By my signature, I agree to personally supervise the conduct of the substudy endothelial function Vs.1.3 and to ensure its conduct in compliance with the protocol, national drug law, ICH GCP and the applicable national and European regulations covering the conduct of clinical studies.

Name of study center

Printed name of investigator

Signature of investigator

Date

14.4 Appendix D: Substudy: Arrhythmielast

Studienprotokoll DIGIT-HF-Substudie: Effekt von Digitoxin auf die atriale und ventrikuläre Arrhythmielast

Anmerkung:
Bei der hier beschriebenen Studie handelt es sich um eine Substudie zu DIGIT-HF. Diese vom BMBF mit rund 3,2 Millionen Euro geförderte, prospektive, randomisierte und doppelblinde multizentrische Studie untersucht den Einfluss einer Therapie mit Digitoxin auf die Mortalität und Morbidität (Zeit bis Tod oder Rehospitalisierung wegen verschlechterter Herzinsuffizienz) von Patienten mit chronischer Herzinsuffizienz (2190 Patienten aus ca. 40 Zentren). Das Ziel der folgenden Synopse soll es sein, das Studiendesign der oben genannten Substudie und die Schnittstellen zur Hauptstudie zu beschreiben.

STUDIENSYNOPSE

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STUDIENTITEL	DIGIT-HF-Substudie: Der Effekt von Digitoxin auf die atriale und ventrikuläre Arrhythmielast
VERSIONSNR./-DATUM	1.4 / 06.02.2018
INDIKATION	Prophylaktische oder therapeutische Behandlung mit einem Herzschrittmacher und/oder Defibrillator (DDD-Schrittmacher (DDD-SM), Implantierbarer Cardioverter-Defibrillator (ICD), Schrittmacher für kardiale Resynchronisationstherapie (CRT) ohne oder mit ICD (CRT-P bzw. CRT-D)
ZUSÄTZLICHE EIN- UND AUSSCHLUSSKRITERIEN	Einschlusskriterien: 1. Unterschriebene Einwilligungserklärung zur Substudie Arrhythmielast 2. Zustand nach Implantation eines DDD-SM, DDD-ICD, CRT-P oder CRT-D (Implantation einer Vorhofelektrode) Ausschlusskriterien: Keine
STUDIENZIEL(E)	Es soll in dieser Substudie die Hypothese untersucht werden, dass eine Therapie mit Digitoxin keinen Einfluss auf das Auftreten von atrialen Tachyarrhythmien (AT) oder ventrikulären Tachyarrhythmien (VT) hat.
ZUSÄTZLIHCE ERHEBUNGEN/ INTERVENTIONEN	Komplette Abfrage des implantierten Devices halbjährlich im Rahmen der Studienvisiten • IEGM-Dokumentation der Vorhofflimmerepisoden (Beginn und Ende der Episode, atriale tachykardiale Zyklenlänge (TCL))

	• Dokumentation der ventrikulären Tachykardien (Beginn und Ende der Episode, ventrikuläre TCL, Therapie (ATP/Schock/keine Therapie))
BENÖTIGTE VARIABLEN AUS DER HAUPTSTUDIE	• Therapiegruppe (Placebo / Digitoxin) • Zeitpunkt (der ersten) Amiodaron-Therapie aufgrund von Kammertachykardien oder Vorhofflimmern • Zeitpunkt (der ersten) VT-Ablation • Zeitpunkt (der ersten) AF-Ablation • Kovariablen: o Demographisch o Anamnese ▪ Vorhofflimmern, Z.n. VT, Grunderkrankung ▪ Primär- vs. Sekundärprophylaktische ICD/CRTD Implantation o Begleitmedikation
ZIELPARAMETER	<u>Primär</u> 1. Veränderung der Vorhofflimmer-Last (change from baseline nach 12 Monaten: V2 - Baseline, Vorhofflimmer-Last: Quotient Zeit mit Vorhofflimmern / Zeit unter Beobachtung) in der Einheit Stunden / Tag (h/d) <u>Sekundär</u> 1. Veränderung der Vorhofflimmer-Last (change from Baseline) im Studienverlauf (alle 6 Monate) 2. Kammertachykardie-Häufigkeit 3. Zeit bis Beginn einer Amiodaron-Therapie/VT-Ablation zur Behandlung von Kammerarrhythmien 4. Zeit bis zur ersten dauerhaften Amiodaron-Therapie/AF-Ablation zur Behandlung von Vorhofflimmern 5. Progression von Vorhofflimmern (Neuauftreten, paroxysmal zu persistierend) Beurteilung der Sicherheit: siehe DIGIT-HF Da keine zusätzliche Intervention erforderlich ist, entstehen keine zusätzlichen Sicherheitsrisiken für teilnehmende Patienten. Die Devices werden zu allen Studienvisiten im 6-Monats-Rhythmus ausgelesen (V0, V2, V3, V4, …).
STUDIENTYP	Substudie DIGIT-HF: Prospektive, randomisierte, doppelblinde, multizentrische klinische Studie
STATISTISCHE ANALYSE	Beschreibung der primären Auswertung und Population: Die primäre Analyse der Substudie wird auf Basis der PP-Population (per protocol) durchgeführt, das heißt, es werden alle Substudienpatienten

	ohne schwerwiegende Protokollverletzungen analysiert. Die Veränderung der Vorhofflimmer-Last (change from baseline nach 12 Monaten: V2 - Baseline) wird anhand einer linearen Regression, stratifiziert für Therapie (Digitoxin / Placebo), Devicetherapie zu Baseline (prophylaktisch vs. therapeutisch), Vorhofflimmer-Last zu Baseline und den Stratifikationsvariablen der Hauptstudie (Zentrum, Geschlecht, NYHA-Klassifikation (II/III/IV) und Vorhofflimmern (ja/nein)) untersucht. Es wird geschlussfolgert, dass Digitoxin nicht die Arrhythmielast verschlechtert, wenn die obere Grenze des zweiseitigen 95%-Konfidenzintervalls für den Therapieeffekt (Digitoxin- Placebo) kleiner als 1.7 Stunden/Tag ist. <u>Auswertung der wichtigsten sekundären Endpunkte:</u> <u>Kammertachykardie-Frequenz</u> Die Kammertachykardie-Häufigkeit wird deskriptiv anhand einer negativ-Binomial-Regression (adjustiert für Therapie (Digitoxin/ Placebo), Devicetherapie zu Baseline (primär vs. sekundärprophylaktisch) und den Stratifikationsvariablen der Hauptstudie: Zentrum, Geschlecht, NYHA-Klassifikation, Indikation zur ICD Implantation, LVEF bei baseline und FU und Vorhofflimmern) untersucht. Es werden die Regressionskoeffizienten sowie zugehörige 95%-Konfidenzintervalle (zweiseitig) betrachtet. <u>Zeit bis zur ersten dauerhaften Amiodaron-Therapie zur Behandlung von Kammerarrhythmien</u> Die Zeit bis zur ersten dauerhaften Amiodaron-Therapie zur Behandlung von Kammerarrhythmien wird deskriptiv anhand einer Cox-Regression (adjustiert für Therapie (Digitoxin/ Placebo), Devicetherapie zu Baseline (primär- vs. sekundärprophylaktisch) und den Stratifikationsvariablen der Hauptstudie: Zentrum, Geschlecht, NYHA-Klassifikation, Indikation zur ICD Implantation, LVEF bei baseline und FU und Vorhofflimmern) untersucht. Es werden die Regressionskoeffizienten sowie zugehörige 95%-Konfidenzintervalle (zweiseitig) betrachtet. Übereinstimmungsanalyse: Da Werte sich zwischen den Begutachtern unterscheiden können, wird eine deskriptive Analyse der Übereinstimmungen mittels Bland-Altman-Diagrammen für stetige Variablen durchgeführt. <u>Sicherheitsanalysen:</u> Siehe DIGIT-HF, keine zusätzlichen Sicherheitsanalysen.
FALLZAHL	n= mindestens 220 Die maximal mögliche Gesamtfallzahl ist durch die Hauptstudie DIGIT-HF determiniert. Es sollen mindestens 220 Patienten in die Substudie eingeschlossen werden, um mit einer Power von 80% schadhafte Effekte von Digitoxin auf die Vorhofflimmer-Last auszuschließen. Eine höhere Fallzahl wird angestrebt, um auch für die sekundären Analysen die Präzision zu erhöhen.

	Annahmen für die mittlere Veränderung der Vorhofflimmer-Last, Standardabweichung und Nichtunterlegenheitsschranke. Die Annahmen stützen sich auf Gold 2009 (SAFARI-trial). In dieser randomisierten Studie wurde der Effekt einer präventiven Schrittmachertherapie bei 193 Patienten mit paroxysmalem Vorhofflimmern untersucht. Die Patienten in dieser Studie hatten eine mildere Herzinsuffizienz als die erwartete DIGIT-HF-Population (NYHA I/II; Einschlusskriterien für DIGIT-HF: NYHA II-IV). In der Experimentalgruppe wurde 6 Monate nach der Randomisierung eine mittlere Veränderung der Vorhofflimmer-Last (change from baseline) um - 0.73±4.50 Stunden/Tag (Mittelwert ± Standardabweichung) beobachtet. In der Kontrollgruppe wurde eine mittlere Veränderung der Vorhofflimmer-Last um 0.98±4.26 Stunden/Tag (Mittelwert ± Standardabweichung) beobachtet. Dies entspricht einem Unterschied der mittleren Veränderung der Vorhofflimmer-Last von -0.73-0.98=-1.71 Stunden/Tag zwischen den beiden Behandlungsgruppen. Für diese Substudie wird daher ein Unterschied von 1.7 Stunden/Tag in der mittleren Veränderung der Vorhofflimmer-Last als Nichtunterlegenheitsschranke gewählt, da mit diesem Unterschied in der SAFARI-Studie Überlegenheit gezeigt wurde. Es wird weiter angenommen, dass sich Digitoxin und Placebo bezüglich der Veränderung der Vorhofflimmer-Last nicht unterscheiden (erwartete Differenz = 0). Eine gemeinsame Standardabweichung von 4.5 Stunden/Tag in beiden Gruppen wird angenommen. Fallzahlberechnung: Die benötigte Fallzahl wird für einen Test auf Nichtunterlegenheit berechnet, da die Hypothese für diese Substudie ist, dass Digitoxin nicht zu einer Verschlechterung der Arrhythmielast führt. Um mit einer Power von 1-β = 80% und zum (einseitigen) Signifikanzniveau α=2.5% bei Annahme gleicher Veränderungen der Vorhofflimmer-Last und einer gemeinsamen Standardabweichung von 4.5 einen Unterschied in der mittleren Veränderung der Vorhofflimmer-Last von 1.7 Stunden/Tag mit einem t-Test auszuschließen, sind insgesamt 220 Patienten (110 pro Gruppe) erforderlich. Die Zuteilung zu den Behandlungsgruppen erfolgt in der Hauptstudie im Verhältnis 1:1. Ein Drop-Out wird nicht berücksichtigt. Die obigen Berechnungen wurden in nQuery Advisor 7.0 durchgeführt
MACHBARKEIT DER REKRUTIERUNG	Die Rekrutierung von mindestens 220 Patienten für die Substudie wird als machbar angesehen, da ein großer Anteil der Patienten über ein Device verfügt und alle DIGIT-HF-Studienzentren an der Substudie teilnehmen können.
ZEITPUNKT DER AUSWERTUNG	Die Auswertung erfolgt zum Zeitpunkt der Auswertung der Hauptstudie, nach Aufhebung der Verblindung.
ENTBLINDUNGSRISIKO	Die Datenerfassung erfolgt verblindet gegenüber der Therapiezuteilung. Die Auswertung erfolgt zum Zeitpunkt der Auswertung der Hauptstudie. Einzelne Deviceabfragen bedeuten kein zusätzliches individuelles

	Entblindungsrisiko, da der potentielle Zusammenhang zwischen Digitoxin und der Arrhythmielast nicht geklärt ist. Im Gegenteil ist es das Ziel dieser Substudie, den Einfluss von Digitoxin auf die Arrhythmielast zu messen.
ZUSATZBELASTUNG FÜR PATIENTEN	Das Auslesen der Devices erfolgt routinemäßig etwa halbjährlich und kann daher ohne Mehraufwand für die Patienten während der regulären Studien-Visiten erfolgen. Das Auslesen erfolgt elektronisch und ist für den Patienten nicht mit einem Eingriff verbunden.
DATENMANAGEMENT	Die Daten werden pseudonymisiert an die Medizinische Hochschule Hannover geschickt und dort zentral gespeichert. Bei Erhalt der Daten wird eine Lesbarkeitsprüfung durchgeführt. Vor der Auswertung werden die Daten in eine validierte Datenbank übertragen. Da Devices routinemäßig ausgelesen werden, werden von allen Patienten, die dem zustimmen, retrospektive Device-Daten verwendet. Der letzte Auslesezeitpunkt vor Studienstart wird als Baseline-Messung verwendet.
MONITORING	Überprüfung der Einwilligungserklärungen. Stichprobenartige Überprüfung des Prüfarztordners. Es wird im Verlauf der Studie kein Quelldatenabgleich durchgeführt. Am Ende der Studie erfolgt eine stichprobenartige Überprüfung der Quelldaten und ein Abgleich mit der Datenbank. Im Monitoringplan sind die Details des Überprüfungsprozesses dargestellt.
VERSICHERUNG	Die Patienten sind im Rahmen der Hauptstudie versichert.
TEILNEHMENDE ZENTREN	Alle Zentren der DIGIT-HF Studie können an der Substudie teilnehmen.

UNTERSCHRIFTEN

Dieser Substudien Synopse, Arrhythmielast Vs. 1.4, wurde von den folgenden Personen zugestimmt. Die folgenden Unterschriften belegen deren Zustimmung.

Prof. Dr. Christian Veltmann (Leiter der Substudie)	Datum
Prof. Dr. Udo Bavendiek (Leiter der Substudie, LKP der DIGIT-HF Studie)	Datum
Prof. Dr. Armin Koch (statistische Planung und Auswertung der Substudie und der DIGIT-HF Studie)	Datum
Prof. Dr. Johann Bauersachs (Leiter des Trial Steering Committees der DIGIT-HF Studie)	Datum
Prof. Dr. Christopher Baum (Sponsorvertreter der DIGIT-HF Studie)	Datum

Hiermit bestätige ich mit meiner Unterschrift, die Synopse gelesen und verstanden zu haben. Ich werde in Übereinstimmung mit der aktuellen Synopse Arrhythmielast Vs. 1.4, der nationalen Gesetzgebung sowie nach gültigen regulatorischen Bestimmungen, insbesondere den Grundsätzen von ICH-GCP und der Deklaration von Helsinki arbeiten.

Name des Prüfzentrums

Name des Prüfers

Unterschrift des Prüfers

Datum