# Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

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# DIGIT-HF End Point Definitions

All potential primary outcome events were adjudicated by an independent clinical event adjudication committee (CEAC), whose members were unaware of the trial-group assignments. Cause of hospitalizations and death were classified on the basis of documents that described the events (e.g. medical letters and discharge letters) as followed:

Definitions of hospitalizations:

1. **Definition of hospitalization for worsening of heart failure**
   Hospitalization for worsening heart failure is defined by presence of the following points together:
   - Worsening of heart failure based on clinical judgement (presence of heart failure symptoms) by the treating physician* and
   - hospital stay overnight or until death of patient occurs and
   - i.v.-treatment with diuretics or vasoactive substances (e. g. nitroglycerin) or inotropes (e. g. dobutamine).

* The CEAC also assessed clinical judgment of worsening heart failure. Unless the diagnosis is unequivocally not worsening of heart failure, it will be regarded as worsening heart failure.

2. **Definition of cardiovascular hospitalization**
   Unless an unequivocal non-cardiovascular cause was established, the reason for hospitalizations was considered as cardiovascular.

3. **Definition of non-cardiovascular hospitalization**
   Only if there is a clear non-cardiovascular reason for hospital admission it was classified as non-cardiovascular.

Definition of deaths:

1. **Definition of death due to worsening of heart failure**
   A cardiovascular death was classified as being due to heart failure if heart failure is considered a major cause/factor leading to death.

2. **Definition of death due to cardiovascular reasons**
   Unless an unequivocal non-cardiovascular cause is established, a death was considered as cardiovascular.

3. **Definition of death due to non-cardiovascular reasons**
   Death where an unequivocal non-cardiovascular cause is established was classified as non-cardiovascular.

# Extended Summary of Methods

**Trial design**

The DIGIT-HF study was a randomized, double-blind, parallel-group, placebo-controlled, two-arm, multicenter, phase IV trial that was conducted in Germany, Austria and Serbia to evaluate the efficacy and safety of digitoxin in patients with heart failure and reduced ejection fraction (HFrEF). After signed written informed consent and the screening visit, patients eligible for study enrollment who met the defined inclusion and exclusion criteria were randomized in a 1:1 ratio to the digitoxin group or the placebo group. Permuted block randomization was used to randomize patients to the blinded study medication. Randomization was stratified by study site, sex (female, male), New York Heart Association [NYHA] class (II, III, or IV), atrial fibrillation known at randomization (yes, no), and pre-treatment with cardiac glycosides at the time of randomization (yes, no; included in the Study Protocol Amendment 2.0, 26th January 2016). Serum concentrations of digitoxin were determined by a central laboratory of the Institute for Clinical Chemistry, Hannover Medical School (German and Austrian sites), or the laboratory of the Military Academy of the University of Defense, Serbia (Serbian sites).

The starting dose was 0.07 mg digitoxin p.o. daily or placebo p.o. At the first study visit (V1) 6 weeks after starting of treatment with the investigational medical product (IMP), serum concentrations of digitoxin were determined. Data from the analysis of digitoxin serum concentrations were provided to the Institute for Biometry to initiate dose adjustments. Dose adjustment was supported by advice of an independent medical expert, if applicable. For the placebo-patients dose adjustment was randomly assigned and for the digitoxin-group dose adjustment was initiated employing a defined algorithm: If serum levels for digitoxin were lower/higher than the target serum concentration of 8 - 18 ng/ml (10.5 – 23.6 nmol/l), doses were reduced or increased to 0.05 or 0.1 mg digitoxin, respectively. Otherwise, the present dose of digitoxin was maintained. Only in patients in whom the digitoxin dose was up-titrated another measurement of digitoxin serum concentrations was performed 6 weeks after dose adjustment (12 weeks after randomization, visit V1x) in the central laboratory to identify digitoxin serum concentrations higher than the target serum concentration. Again, for the patients assigned to receive placebo, dose adjustment was randomly assigned and for patients assigned to digitoxin group the dose adjustment was initiated employing a defined algorithm: If determined digitoxin serum concentrations were higher than the preferred target range, the digitoxin dose were reduced to the next lower dose (0.07 mg). Otherwise, the present dose of digitoxin was maintained. Data from the analysis of digitoxin serum concentrations were provided to the Institute for Biometry, which made the potential dose adjustment available in the web based random tool, so that the investigator could allocate the next package/s (IMP-Label/s) appropriately at the next meeting.

If digitoxin serum levels determined at study visit V1 exceeded 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 was considered highly unlikely that the target range could 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 was performed as follows: If the measured digitoxin

serum concentration was > 25 ng/ml (33 nmol/l) at study visit V1 (patient's current dose = 0.07 mg/die), medication was paused. After 6 weeks pause, medication was started again with a dose of 0.05 mg taken every second day.

In addition, to keep simplicity of the trial and to avoid unblinding, treatment was switched to placebo in case of safety concerns in the following situations:

1. If digitoxin serum levels were not detectable at V1 or V1x for digitoxin patients and non-compliance must be suspected (i.e. confusion of IMP or blood samples could be excluded and analysis of digitoxin serum concentration was valid), then for safety reasons patients should not continue digitoxin treatment without additional dose adjustment and their treatment was be switched to placebo.
2. If digitoxin serum levels determined at study visit V1x and V3 exceeded a concentration of 25 ng/ml (33 nmol/l) patients should not continue digitoxin treatment for safety reasons and their treatment was switched to placebo. If switching to placebo was not possible e.g. because the next pack of study medication was already handed over to the patients at V3, patients was unblinded.

DIGIT-HF was a double-blind clinical study and placebos matching the three-dose strengths of digitoxin were provided. The sponsor, investigators, the study site personnel, the data management team, the biostatisticians, and the subjects remained blinded to each subject's treatment with digitoxin or placebo throughout the study. An independent Data Monitoring Committee (DMC) was responsible for reviewing unblinded safety data at regular intervals during the study and could recommend stopping the trial because of harmful effects. The logistic team at the Institute for Biostatistics, who ordered study medication and managed dose adjustments, was unblinded to study medication. Emergency unblinding was only supposed to be done when it was essential to know whether the patient was actually treated with digitoxin, especially if digitoxin toxicity was suspected. Despite unblinding, patients were further observed and analyzed as randomized in the primary and key secondary statistical analysis according to the intention-to-treat (ITT) principle. A web-based system for unblinding was provided. The responsibility for backup of unblinding if the web portal, e.g., for technical reasons, was not available, was by the Department of Cardiology & Angiology. The needed information was provided by the Institute for Biostatistics. Emergency unblinding could also take place if required by regulatory reporting guidelines regarding potential Suspected Unexpected Serious Adverse Reactions (SUSARs; see Study Protocol V8.0, Chapter 7.4 available online with the full text of the article at NEJM.org for details). The reason, time, responsible person, and date of unblinding had to be documented in the electronic Case Report Form (eCRF). The trial was designed and overseen by a steering committee and was supported by the German Federal Ministry of Education and Research (BMBF) under grant number 01KG1303/01KG1907, the Braukmann Wittenberg Heart Foundation, and the German Heart Foundation. The funders had no influence on the design or conduct of the trial and were not involved in data collection or analysis, in the writing of the manuscript, or in the decision to submit it for publication. The trial protocol was approved by the respective national competent authorities as well as ethics committees. The trial was conducted and is reported in accordance with the principles of the Declaration of Helsinki and to the current Good Clinical Practice. The authors who had access to the data (U.B., A.G., N.H.T., X.L., A.K., J.B.) vouch for the accuracy and completeness of the data and analyses, and all authors vouch for the fidelity of the trial and this report to the protocol.

**Outcomes**

The primary outcome was a composite of time to all-cause death and hospital admission for worsening heart failure (whichever occurred first). All potential outcome events were adjudicated by an independent clinical event adjudication committee whose members were unaware of the trial-group assignments (see above). Key secondary outcomes were time to all-cause death as well as the number of heart failure hospitalizations and death as an additional event. Other secondary outcomes included cardiovascular and non-cardiovascular death, death from heart failure, sudden cardiac death, cardiovascular and non-cardiovascular hospitalization, and hospitalization due to any cause. Safety was assessed by evaluation of digitoxin serum concentrations, adverse and serious adverse events, suspected unexpected serious adverse reactions, and hospitalizations.

An exception to the Serious Adverse Event (SAE) reporting requirement: SAEs that meet the definitions of primary or secondary outcomes had 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 began upon first administration of the investigational medical product (after the baseline visit) and ended at the end of the study.

The rationale for these exceptions was that DIGIT-HF was designed as a large double-blind trial with mortality and morbidity outcomes in which a high number of patients reach those outcome events. Unblinding for regulatory purposes of SAEs that meet outcome criteria would have been compromise the integrity of this double-blind trial. All these events were documented as outcome event of this trial, were assessed by the CEAC and are reported in the secondary outcome analysis. Moreover, the IMP has a longstanding safety record, and new safety findings are unlikely to arise from this trial. Finally, a DMC reviewed safety data from this trial on a regularly basis at least once a year. This is in accordance with the detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (CT-3) of the European Union[1].

**Sample-size calculation**

The trial was event-driven. The initial sample size estimation was based on the observations in the Ivabradine and Outcomes in Chronic Heart Failure (SHIFT) trial[2]. The following assumptions were made: 26% and 31% of patients in the digitoxin and placebo group, respectively, would have experienced the primary outcome event 24 months after randomization (corresponding to a hazard ratio of 0.811, assuming exponential event times); an accrual period of 36 months and a maximum length of follow-up of 48 months; one interim analysis after 50% information fraction using an O'Brien-Fleming design[3] (spending a two-sided type I error of 1% at the interim analysis); an overall two-sided type I error of 5% and a

power of 80%. A total of 2190 patients were initially required to observe 734 adjudicated primary outcome events to demonstrate superiority of digitoxin to placebo regarding the primary outcome.[4] Furthermore, assuming an all-cause mortality rate of 17% in the placebo group and (in the worst case scenario) digitoxin would have no effect on all-cause mortality (i.e. the hazard ratio is 1), the proposed sample size of 2190 patients should provide a power of 80% to exclude detrimental effects on all-cause mortality with a margin of 1.303 (i.e. non-inferiority of digitoxin to placebo regarding all-cause mortality can be concluded if the upper limit of the two-sided 95% confidence interval for the hazard ratio is below 1.303).

As the actual recruitment rate was lower than expected, 40 months after start of recruitment the study duration was prolonged. Consequently, the required number of patients was reduced from 2190 to 1653. After 84 months the planned number of events for the interim analysis was not yet reached. Furthermore, as the probability of early termination of the trial due to overwhelming efficacy at the interim analysis was expected to be low, the initially planned interim analysis was waived. Thus, the final analysis would then be conducted at a two-sided significance level of 5%. With the initially assumed treatment effect, the required number of primary outcome events was consequently reduced from 734 to 716. During the trial seven protocol amendments were implemented, and the statistical analysis plan was recently published.[5]

**Overall type-I-error control**

A hierarchical testing procedure is applied to control the overall type-1-error. The confirmatory testing hierarchy is as follows:

(1) Superiority of digitoxin vs. placebo in the primary outcome

(2) Non-inferiority of digitoxin vs. placebo regarding time to all-cause death (predefined non-inferiority margin to exclude a detriment: Hazard ratio = 1.303)

(3) Superiority of digitoxin vs. placebo regarding the number of heart failure hospitalizations and death as an additional event.

Since a hierarchical testing strategy is used, no multiplicity adjustment is needed for testing each hypothesis. Statistical significance is determined by the two-sided 95% confidence interval of the respective effect estimate and the comparison of the upper or lower limit with the respective margin. A confirmatory analysis of the key secondary outcomes can only be performed if all preceding null hypotheses have been successfully rejected. Otherwise, the respective analysis of the key secondary outcomes is considered descriptively. All other analyses are exploratory.

**Efficacy analyses**

Analyses of primary and key secondary outcomes are primarily conducted in the modified intention-to-treat (mITT) population, including all patients that have been randomized and have taken at least one dose of the study medication. To identify patients who must be excluded from the ITT population because they did not take at least one dose of the study medication, various variables from the eCRF regarding the study medication are thoroughly reviewed (e.g., starting intake date, dispense and return date, number of returned tablets, information on regular intake, reasons for irregular intake, end of treatment). A patient can

only be excluded from the ITT population if it is clearly verified, that no study medication intake has occurred. Patients are analyzed as randomized independently of their actual treatment (digitoxin or placebo). Of note, one patient that was initially randomized to the digitoxin group received placebo at the first study visit due to incorrect investigational medical product (IMP) dispensation. The blinded study team decided to change the initially randomized treatment to the actually received treatment and the blinded biostatistician decided to analyze this patient as if the patient were initially randomized to the latter treatment group. This decision was made without any knowledge of patient characteristics and the initially randomized treatment.

All attempts were undertaken to collect the information about the primary and key secondary outcomes for patients that did drop out from the study or were withdrawn.

Time-to-event efficacy outcomes, including the primary outcome, were analyzed using a Cox proportional hazards model including the treatment group and the randomization stratification factors as covariates:

- Sex (reference: male)
- NYHA functional class (reference II)
- atrial fibrillation (reference: no)
- and (pooled) study site (reference: site 01)

Specifically, study sites with the number of randomized patients fewer than 10 patients were pooled using the following strategy as defined in the blinded data review meeting:

- The smallest study sites with a number of randomized patients fewer than 10 patients were pooled based on the number of randomized patients, the frequency of primary outcome events and the median observation period, starting with the smallest study site until the new pooled study site consisted of around 20 patients and approximately 50% of them experienced a primary event.
- All study sites with at least 10 randomized patients were not pooled but remained as independent study sites.
- Assuming that the Serbian study sites are more homogeneous among each other compared to the German and Austrian study sites, the Serbian study sites were pooled into one large Serbian study site.

The variable “region (EU vs. Serbia)” is not included in the primary analysis models for the primary and key secondary outcomes, as pooling the Serbian study sites into one large Serbian study site has accounted for this.

Recurrent event outcomes were analyzed with a negative binomial model adjusted in line with the primary analysis of the primary outcome. The logarithm of the observation time per patient was included in the negative binomial model as the offset variable. Hazard or rate ratios with respective 95% confidence intervals were reported.

To assess the robustness of the treatment effect we further conducted the following additional analyses:

(I) Primary analysis model where the primary outcome definition includes left ventricular assist device or heart transplant events.

(II) Worst case analysis where patients that were lost-to-follow-up were either updated with information from the vital status assessment at the end of the study or (if not available) were counted as events at their last contact.
(III) Primary analysis model including ICD therapy as a covariate.
(IV) Competing risk analysis with heart failure hospitalization as event of interest and death as competing risks event.

Treatment effects were assessed in pre-specified subgroups using the primary analysis model as described above. For NYHA functional class, age, eGFR and CRT device some subgroups were pooled. The Subgroup analyses for the mental and physical components of the quality-of-life score SF-12 were not reported as the score was only assessed for patients in Germany or Austria (no translation to Serbian language available at that time) and will therefore be reported separately.

**Safety analyses**

Absolute and relative frequencies of adverse events (AE) and SAEs and suspected unexpected serious adverse reactions (SUSAR) were compared descriptively on patient level between treatment groups. AEs were coded according to MedDRA (English Version: 27.1) and are presented by system organ class and preferred term.

# Supplementary Figures and Tables

**Figure S1. Patient flow (CONSORT).**

IMP – investigational medical product, GCP – good clinical practice, mITT – modified intention-to-treat

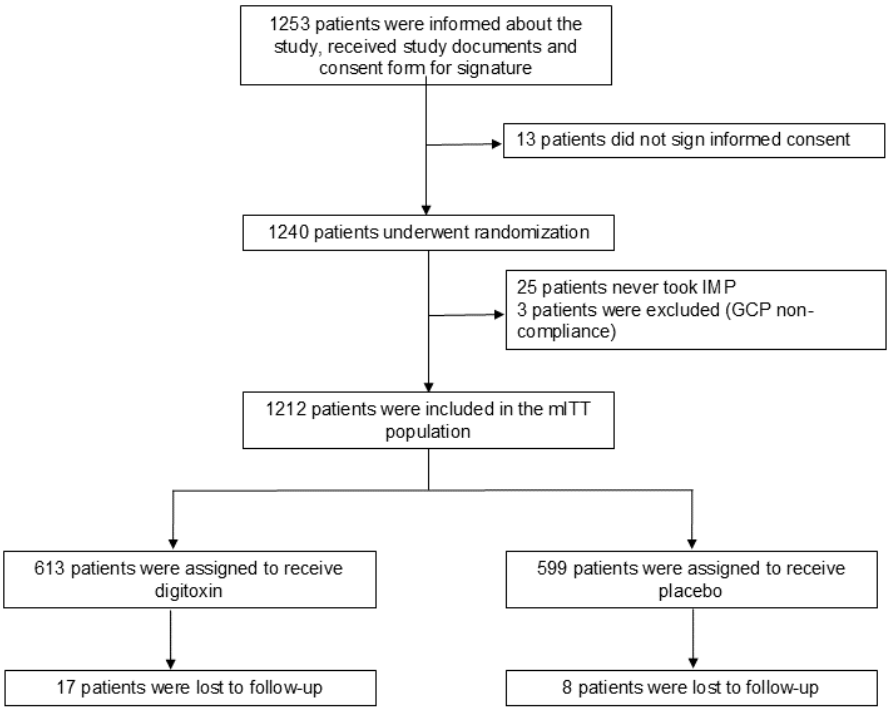

**Table S1. Inclusion and exclusion criteria.**

| **Inclusion criteria** |
|---|
| 1. Signed written informed consent and willingness to comply with treatment and follow-up<br>2. Male or female patients age ≥ 18 years at day of inclusion<br>3. Patients capable of understanding the investigational nature, potential risks and benefits of the clinical trial<br>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 %* AND an evidence-based heart failure therapy at least for six months upon discretion of the treating physician<br>5. Women without childbearing potential defined as one or more of following:<br>• Women at least 6 weeks after surgical sterilization by bilateral tubal ligation or bilateral oophorectomy with or without hysterectomy at the day of inclusion<br>• Women ≥ 50 years of age at the day of inclusion who have been postmenopausal since at least 1 year<br>• 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<br>• 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)<br>• True abstinence (periodic abstinence and withdrawal are not acceptable methods of contraception)<br>• 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))<br>2. Scheduled surgery or catheter intervention for valvular heart disease, scheduled coronary revascularization, scheduled 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)) |

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)

* 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

**Table S2. Number of Patients Enrolled Per Site.**

| | |
|---|---|
| **1 - Medizinische Hochschule Hannover - no. (%)** | 179 (14.8) |
| **2 - Uniklinik RWTH Aachen - no. (%)** | 14 (1.2) |
| **4 - Kerckhoff-Klinik Bad Nauheim - no. (%)** | 76 (6.3) |
| **8 - Charité Campus Virchow Klinikum Berlin - no. (%)** | 15 (1.2) |
| **9 - Sankt Josef-Hospital Bochum - no. (%)** | 3 (0.2) |
| **10 - Universitätsklinikum Bonn - no. (%)** | 26 (2.1) |
| **11 - Klinikum Links der Weser Bremen - no. (%)** | 38 (3.1) |
| **12 - Klinikum Coburg - no. (%)** | 6 (0.5) |
| **13 - Klinikum Lippe Detmold - no. (%)** | 10 (0.8) |
| **14 - Dresden, Universitätsklinik - no. (%)** | 3 (0.2) |
| **15 - Universitätsklinikum Düsseldorf - no. (%)** | 22 (1.8) |
| **16 - Evangelisches Krankenhaus Düsseldorf - no. (%)** | 10 (0.8) |
| **18 - Universitätsklinikum Essen - no. (%)** | 1 (0.1) |
| **19 - Universitätsklinikum Freiburg - no. (%)** | 12 (1.0) |
| **24 - Universitätsklinikum Hamburg-Eppendorf - no. (%)** | 21 (1.7) |
| **25 - Universitätsklinikum Heidelberg - no. (%)** | 12 (1.0) |
| **26 - Universitätsklinikum des Saarlandes Homburg/Saar - no. (%)** | 20 (1.7) |
| **28 - Herzzentrum Uniklinik Köln - no. (%)** | 13 (1.1) |
| **31 - Klinikum Schleswig-Holstein Lübeck - no. (%)** | 4 (0.3) |
| **32 - Universitätsklinikum Magdeburg - no. (%)** | 6 (0.5) |
| **33 - Universitätsmedizin Johannes-Gutenberg-Universität Mainz - no. (%)** | 21 (1.7) |
| **34 - Universitätsklinikum Mannheim - no. (%)** | 5 (0.4) |
| **35 - Universitätsklinikum Gießen Marburg Standort Marburg - no. (%)** | 6 (0.5) |
| **36 - Universitätsklinikum München Campus Innenstadt - no. (%)** | 10 (0.8) |
| **38 - Klinikum Nürnberg Süd - no. (%)** | 190 (15.7) |
| **41 - Elbekliniken Stade-Buxtehude - no. (%)** | 30 (2.5) |
| **45 - Universitätsklinikum Würzburg - no. (%)** | 33 (2.7) |
| **46 - Klinikum Regensburg - no. (%)** | 67 (5.5) |
| **47 - Kardiologisches Zentrum Peine - no. (%)** | 9 (0.7) |

| | |
|---|---|
| **48 - Sankt Elisabeth Hospital Bochum - no. (%)** | 13 (1.1) |
| **52 - Internistische Praxis Dr. Taggeselle Markkleberg - no. (%)** | 10 (0.8) |
| **54 - Carl von Basedow Klinikum Saalekreis Merseburg - no. (%)** | 6 (0.5) |
| **55 - Universitätsklinikum Halle - no. (%)** | 7 (0.6) |
| **59 - Elblandklinikum Riesa - no. (%)** | 17 (1.4) |
| **65 - Kardiologisch-Angiol. Schwerpunktpraxis Mühldorf am Inn - no. (%)** | 18 (1.5) |
| **68 - Herzzentrum Dresden GmbH-Universitätsklinikum - no. (%)** | 60 (5.0) |
| **69 – Klinikum Westmünsterland - no. (%)** | 15 (1.2) |
| **70 - Albertinen-Krankenhaus Hamburg - no. (%)** | 4 (0.3) |
| **71 - Unfallkrankenhaus Berlin - no. (%)** | 22 (1.8) |
| **73 - Universitätsklinikum Jena - no. (%)** | 1 (0.1) |
| **74 - Medizinische Universität Wien - no. (%)** | 20 (1.7) |
| **75 - Krankenhaus Sankt Josef, Braunau - no. (%)** | 13 (1.1) |
| **77 - Universität Leipzig - no. (%)** | 12 (1.0) |
| **78 - Universitätsmedizin Göttingen - no. (%)** | 6 (0.5) |
| **80 - St. Vinzenz-Krankenhaus GmbH Paderborn - no. (%)** | 4 (0.3) |
| **82 - Gemeinschaftspraxis Bamberg - no. (%)** | 9 (0.7) |
| **83 - Leipzig Heart Institute GmbH Leipzig - no. (%)** | 5 (0.4) |
| **84 - MVZ Schwerin West GmbH - no. (%)** | 6 (0.5) |
| **85 - Charité Universitätsmedizin Berlin-CBF - no. (%)** | 1 (0.1) |
| **86 - Klinicko bolnicki centar Bezanijska Kosa Belgrade - no. (%)** | 38 (3.1) |
| **88 - Institut za rehabilitaciju Belgrade - no. (%)** | 1 (0.1) |
| **89 - Institut Za Kardiovaskularne Bloesti "Dedinje" Belgrade - no. (%)** | 28 (2.3) |
| **90 - Klinicko Bolnicki Centar "Zvezdara"- Belgrade - no. (%)** | 12 (1.0) |
| **91 - Univerzitetski Klinicki Centar Nis Nis - no. (%)** | 16 (1.3) |
| **92 - Institut Za Lecenje I Rehabilitciju “Niska Banja” Nis Niska Banja - no. (%)** | 6 (0.5) |
| **All study sites - no. (%)** | 1212 (100.0) |

**Table S3A. Main baseline characteristics for patients that were lost to follow-up*.**

| Characteristic | Digitoxin (N = 17) | Placebo (N = 8) |
|---|---|---|
| **Age — yr** | 63.5 (11.5) | 55.3 (14.3) |
| **Female sex — no. (%)** | 3 (17.6) | 1 (12.5) |
| **Region — no. (%)** | | |
| **Germany — no. (%)** | 15 (88.3) | 8 (100.0) |
| **Austria — no. (%)** | 0 (0.0) | 0 (0.0) |
| **Serbia — no. (%)** | 2 (11.8) | 0 (0.0) |
| **NYHA functional class — no. (%)** | | |
| **II — no. (%)** | 6 (35.3) | 5 (62.5) |
| **III — no. (%)** | 11 (64.7) | 3 (37.5) |
| **IV — no. (%)** | 0 (0.0) | 0 (0.0) |
| **Left ventricular ejection fraction — %** | 29.4 (7.8) | 30.3 (4.8) |
| **Left ventricular ejection fraction <30% — no. (%)** | 6 (35.3) | 2 (25.0) |
| **Main cause of heart failure — no. (%)** | | |
| **Ischemic — no. (%)** | 11 (64.7) | 3 (37.5) |
| **Non-ischemic/Unknown — no. (%)** | 6 (35.3) | 5 (62.5) |
| **Body mass index**** | 27.4 (6.3) | 31.4 (4.9) |
| **Heart rate — beats/min** | 73.4 (12.0) | 81.4 (12.9) |
| **Systolic blood pressure — mmHg** | 121.6 (16.6) | 125.4 (21.3) |
| **Atrial fibrillation — no. (%)** | 3 (17.6) | 1 (12.5) |
| **Estimated glomerular filtration rate — ml/min/1.73 m²** | 71.5 (27.2) | 74.8 (31.8) |
| **Rate of <60 ml/min/1.73 m² — no./total no. (%)** | 5 (29.4) | 4 (50.0) |
| **Device therapy — no. (%)** | | |
| **Implantable cardioverter-defibrillator — no. (%)** | 6 (35.3) | 3 (37.5) |
| **Cardiac resynchronisation therapy-defibrillator — no. (%)** | 6 (35.3) | 0 (0.0) |
| **Cardiac resynchronisation therapy-pacemaker — no. (%)** | 0 (0.0) | 1 (12.5) |
| **Heart failure medication — no. (%)** | | |
| **Beta-blocker — no. (%)** | 16 (94.1) | 7 (87.5) |
| **Angiotensin-converting-enzyme inhibitor — no. (%)** | 7 (41.2) | 3 (37.5) |
| **Angiotensin receptor blocker — no. (%)** | 2 (11.8) | 2 (25.0) |
| **Angiotensin receptor-neprilysin inhibitor — no. (%)** | 7 (41.2) | 2 (25.0) |
| **Mineralocorticoid receptor antagonist — no. (%)** | 16 (94.1) | 6 (75.0) |
| **Sodium-glucose cotransporter 2 inhibitor*** — no. (%)** | 5 (29.4) | 0 (0.0) |
| **Cardiac glycoside — no. (%)** | 0 (0.0) | 0 (0.0) |

* Plus-minus values are means ± SD. Percentages may not total to 100 because of rounding.

** Body mass index is the weight in kilograms divided by the square of the height in meters.

*** Information on Sodium-glucose cotransporter 2 inhibitor available in electronic case report form after 1 December 2019.

Missing values are not reported separately but considered in the calculation of the relative frequencies.

**Table S3B. Descriptives on availability of vital status assessment at end of study and preceding primary end point events in patients lost to follow-up.**

| | Digitoxin (N=17) | Placebo (N=8) |
|---|---|---|
| Alive at vital status assessment in 2024 — no. (%) | 3 (17.6) | 2 (25.0) |
| Death at vital status assessment — no. (%) | 3 (17.6) | 2 (25.0) |
| Primary end point before lost to follow-up — no. (%) | 0 (0.0) | 1 (12.5) |
| No information at vital status assessment in 2024 — no. (%) | 9 (52.9) | 3 (37.5) |
| No vital status assessment due to legal reason (Serbia) — no. (%) | 2 (11.8) | 0 (0.0) |

**Table S3C. Results of worst-case analysis for lost to follow-up in the primary outcome definition.**

| Analysis model | Digitoxin (N=613) | | Placebo (N=599) | | Hazard Ratio (95% CI) |
|---|---|---|---|---|---|
| | no. (%) | events/ 100 pt-yr | no. (%) | events/ 100 pt-yr | |
| Primary end point including patients with no information on follow-up as primary end points — primary analysis model* | 256 (41.8) | 13.4 | 269 (44.9) | 15.9 | 0.85 (0.71 to 1.01) |

* Patients that were alive or dead at the vital status assessment were updated in the analysis with the respective information. Patients with no information at the vital status assessment were counted as event at date of last contact.

**Table S4. Unblinding.**

| | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Unblinding — no. (%) | 54 (8.8) | 28 (4.7) |
| Cause of unblinding | | |
| Emergency unblinding — no. (%) | 7 (13.2)* | 9 (33.3) |
| Blood level determination outside central laboratory (e.g. at general practitioner) — no. (%) | 13 (24.5) | 9 (33.3) |
| Blood level determination at central laboratory — no. (%) | 33 (62.3)* | 9 (33.3) |
| Unblinding due to suspect of potential suspected unexpected serious adverse reactions by pharmacovigilance — no. (%) | 1 (0.2) | 1 (0.2) |

* Including n=18 patients which were unblinded by the medical expert due to Digitoxin level > 33 nmol/l in the first study phase. Thereafter, the trial protocol was amended enclosing different measures to be taken at digitoxin levels > 33 nmol/l to avoid unnecessary unblinding but verifying patient safety (for details see trial protocol and trial design described above).

**Table S5. Overview of end of treatment.**

| End of Treatment | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Treatment until end of study — no. (%) | 172 (28.1) | 183 (30.6) |
| Treatment ended due to death — no. (%) | 80 (13.1) | 86 (14.4) |
| Treatment ended due to premature site closure — no. (%) | 10 (1.6) | 9 (1.5) |
| Treatment ended due to premature termination — no. (%) | 351 (57.3) | 321 (53.6) |

**Table S6. Baseline characteristics.**

| | | Digitoxin (n=613) | Placebo (n=599) |
|---|---|---|---|
| **Randomization strata and demographics** | Age – years | 66.0 ± 11.1 | 65.8 ± 11.4 |
| | Female sex — no. (%) | 122 (19.9) | 125 (20.9) |
| | Atrial fibrillation — no. (%) | 169 (27.6) | 161 (26.9) |
| | NYHA functional class — no. (%) | | |
| | II | 181 (29.5) | 178 (29.7) |
| | III | 408 (66.6) | 399 (66.6) |
| | IV | 24 (3.9) | 22 (3.7) |
| | Pre-treatment with cardiac glycosides — no. (%) | 3 (0.5) | 6 (1.0) |
| | Region — no. (%) | | |
| | Germany | 545 (88.9) | 533 (89.0) |
| | Austria | 19 (3.1) | 14 (2.3) |
| | Serbia | 49 (8.0) | 52 (8.7) |
| **Vitals** | Body mass index — kg/m$^2$ | 29.3 ± 5.7 | 28.9 ± 5.6 |
| | Systolic blood pressure — mmHg | 120.5 ± 18.6 | 121.4 ± 18.8 |
| | Diastolic blood pressure — mmHg | 73.5 ± 11.7 | 73.3 ± 10.9 |
| | Heart rate — bpm | 73.7 ± 11.9 | 74.1 ± 12.3 |
| **Heart failure characteristics and cardiac diagnosis** | LVEF — % | 28.4 ± 6.9 | 28.9 ± 6.7 |
| | Left ventricular ejection fraction ≤ 30% — no. (%) | 403 (65.7) | 383 (63.9) |
| | Cardiomyopathy — no. (%) | 296 (48.8) | 308 (51.9) |
| | Time since diagnosis of heart failure, years — median (IQR) | 5 (2-10) | 5 (1-10) |
| | Main cause of heart failure — no. (%) | | |
| | Coronary artery disease (CAD) | 323 (53.1) | 310 (52.4) |
| | Myocardial infarction | 248 (76.8) | 235 (75.8) |
| | Cardiomyopathy | 177 (29.1) | 174 (29.4) |
| | Other reason | 30 (4.9) | 34 (5.7) |
| | Not clearly determinable | 30 (4.9) | 34 (5.7) |
| | Hypertension | 32 (5.3) | 26 (4.4) |
| | Primary valvular heart disease | 15 (2.5) | 12 (2.0) |
| | Congenital heart disease | 1 (0.2) | 2 (0.3) |
| **Cardiac risk factors** | Treated diabetes mellitus — no. (%) | 222 (36.3) | 231 (38.6) |
| | Obesity[a] — no. (%) | 238 (38.9) | 229 (38.3) |
| | Treated arterial hypertension — no. (%) | 492 (80.3) | 468 (78.4) |
| | Treated hyperlipidemia — no. (%) | 377 (61.7) | 343 (57.6) |
| | Smoker — no. (%) | | |
| | No (Never smoked) | 205 (35.8) | 234 (41.8) |

| | | | |
|---|---|---|---|
| | Yes | 123 (21.5) | 105 (18.8) |
| | Ex-smoker (> 6 months clean) | 245 (42.8) | 221 (39.5) |
| | Chronic alcohol consumption — no. (%) | 31 (5.3) | 27 (4.7) |
| | Known peripheral artery disease — no. (%) | 67 (10.9) | 66 (11.1) |
| | Stroke — no. (%) | 53 (8.7) | 64 (10.7) |
| | Known depression — no. (%) | 42 (6.9) | 40 (6.7) |
| | Known COPD — no. (%) | 79 (12.9) | 93 (15.6) |
| | Known liver cirrhosis — no. (%) | 4 (0.7) | 2 (0.3) |
| | Known malignancy — no. (%) | 41 (6.7) | 48 (8.1) |
| | Known hypothyroidism — no. (%) | 70 (11.5) | 51 (8.6) |
| | Known hyperthyroidism — no. (%) | 24 (3.9) | 17 (2.9) |
| | Diagnosed periodontal disease/periodontitis with loss of bone — no. (%) | | |
| | No | 420 (68.5) | 410 (68.4) |
| | Yes | 14 (2.3) | 14 (2.3) |
| | Unknown | 179 (29.2) | 175 (29.2) |
| **Previous cardiovascular intervention** | PCI/Stent — no. (%) | 292 (47.9) | 275 (45.9) |
| | Coronary bypass surgery — no. (%) | 146 (23.9) | 109 (18.3) |
| | Valvular surgery — no. (%) | 66 (10.8) | 68 (11.4) |
| | RV pacemaker (VVI, DDD) — no. (%) | 31 (5.1) | 31 (5.2) |
| | ICD — no. (%) | 261 (42.6) | 225 (37.6) |
| | CRT-D — no. (%) | 154 (25.1) | 139 (23.2) |
| | CRT-P — no. (%) | 8 (1.3) | 5 (0.8) |
| | Cardiac contractility modulation — no. (%) | 7 (1.1) | 11 (1.9) |
| | Vagus stimulation — no. (%) | 4 (0.7) | 2 (0.3) |
| | Assist device — no. (%) | 1 (0.2) | 3 (0.5) |
| | Heart transplantation — no. (%) | 1 (0.2) | 0 |
| | Reanimation/defibrillation — no. (%) | 47 (7.7) | 40 (6.7) |
| **Concomitant medication** | Beta-blocker — no. (%) | 593 (96.7) | 567 (94.7) |
| | ACE-inhibitor — no. (%) | 222 (36.2) | 213 (35.6) |
| | AT1-receptor blocker — no. (%) | 113 (18.4) | 115 (19.2) |
| | ARNI — no. (%) | 248 (40.5) | 231 (38.6) |
| | MRA — no. (%) | 466 (76.0) | 458 (76.5) |
| | SGLT-2 inhibitor — no. (%) | | |
| | No | 98 (16.0) | 96 (16.0) |
| | Yes | 121 (19.7) | 113 (18.9) |
| | Not available[b] | 394 (64.3) | 390 (65.1) |
| | Ivabradine — no. (%) | 59 (9.6) | 47 (7.8) |
| | Diuretic — no. (%) | 536 (87.4) | 517 (86.3) |
| | Loop diuretic — no. (%) | 501 (81.7) | 491 (82.0) |
| | Thiazide diuretic — no. (%) | 81 (13.2) | 77 (12.9) |
| | Other diuretic — no. (%) | 54 (8.8) | 45 (7.5) |
| | Hemoglobin — g/l | 137.4 ± 18.4 | 137.1±18.1 |

| | | | |
|---|---|---|---|
| **Laboratory parameters** | Anemia — no. (%) | | |
| | Men | 131 (26.6) | 126 (26.5) |
| | Women | 24 (20.0) | 25 (20.5) |
| | Leucocytes — Tsd/µL | 7.9 ± 2.3 | 7.8 ± 2.1 |
| | Creatinine — µmol/l | 116.3 ± 54.5 | 116.2 ± 49.9 |
| | eGFR, ml/min/1.73 $m^2$ | 65.0 ± 23.0 | 65.2 ± 23.7 |
| | <30 ml/min/1.73$m^2$ — no. (%) | 34 (5.6) | 39 (6.5) |
| | 30-60 ml/min/1.73$m^2$ — no. (%) | 229 (37.4) | 218 (36.4) |
| | >60 ml/min/1.73$m^2$ — no. (%) | 349 (57.0) | 342 (57.1) |
| | Urea — mmol/l | 9.0 ± 5.1 | 8.8 ± 5.1 |
| | Sodium — mmol/l | 139.7 ± 3.1 | 139.7 ± 3.1 |
| | Potassium — mmol/l | 4.5 ± 0.5 | 4.5 ± 0.5 |
| | ASAT — U/l | 28.1 ± 15.4 | 29.8 ± 34.7 |
| | ALAT —U/l | 27.5 ± 26.0 | 29.8 ± 42.3 |
| | gamma-glutamatyl-transferaseT, U/l | 67.8 ± 77.0 | 77.1 ± 135.0 |

Plus-minus values are means ± SD. Percentages may not total to 100 because of rounding. The number of missing values is not reported separately but considered in the calculation of the relative frequencies.

NYHA denotes New York Heart Association, COPD chronic obstructive lung disease, PCI percutaneous coronary intervention, RV right ventricle, ICD implantable cardioverter defibrillator, CRT-D cardiac resynchronisation therapy - implantable cardioverter defibrillator, CRT-P cardiac resynchronisation therapy-pacemaker, ARNI angiotensin receptor – neprilysin inhibitor, SGLT2 sodium-glucose cotransporter 2, eGFR estimated glomerular filtration rate, ASAT aspartate-aminotransferase and ALAT alanine-aminotransferase.

[a] Defined as body mass index ≥ 30 kg/m².

[b] DIGIT-HF: Information on SGLT-2 inhibitor available in eCRF after 1st Dec. 2019

**Table S7A. Components of the primary outcome*.**

| | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| No primary event — no. (%) | 371 (60.5) | 335 (55.9) |
| First heart failure hospitalization — no. (%) | 172 (28.1) | 182 (30.4) |
| Death — no. (%) | 70 (11.4) | 82 (13.7) |

* Depicted are the numbers of the components of the outcome events that occur first, therefore counting for the primary end point event, only.

**Table S7B. Cause of death.**

| | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Cardiovascular death — no. (%) | 125 (20.4) | 132 (22.0) |
| Death from heart failure — no. (%) | 46 (36.8) | 47 (35.6) |
| Fatal myocardial infarction — no. (%) | 6 (4.8) | 2 (1.5) |
| Sudden cardiac death — no. (%) | 12 (9.6) | 12 (9.1) |
| Fatal stroke — no. (%) | 5 (4.0) | 6 (4.6) |
| Other cardiovascular death — no. (%)* | 56 (44.8) | 65 (49.2) |
| Non-cardiovascular death — no. (%) | 42 (6.9) | 45 (7.5) |

The percentages for the specific cause of cardiovascular death refer to the total number of cardiovascular deaths per treatment group.

* As pre-specified, unless an unequivocal non-cardiovascular cause is established, a death was considered as cardiovascular (see above section ***DIGIT-HF End Point Definitions***).

**Table S8. Left ventricular assist device or heart transplantation.**

| | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Left ventricular assist device — no. (%) | 10 (1.6) | 10 (1.7) |
| Heart transplant — no. (%) | 5 (0.8) | 7 (1.2) |
| Left ventricular assist device and heart transplant — no. (%) | 1 (0.2) | 3 (0.5) |

**Table S9. Results of additional analyses including ICD therapy as a covariable.**

| Analysis model | Digitoxin (N=613) | | Placebo (N=599) | | Hazard Ratio (95% CI) |
|---|---|---|---|---|---|
| | no. (%) | events/ 100 pt-yr | no. (%) | events/ 100 pt-yr | |
| Primary end point — primary analysis model and ICD | 242 (39.5) | 12.8 | 264 (44.0)* | 15.6* | 0.82 (0.69 to 0.98) |

* For one patient ICD status is missing.

**Table S10. Results of competing risks analysis.**

| Analysis model | Hazard Ratio (95% CI) |
|---|---|
| Cox proportional hazards model of time to first heart failure hospitalization with patients who died without experiencing a heart failure hospitalization being censored at the time of death | 0.85 (0.69 to 1.05) |
| Competing risks analysis model with heart failure hospitalization as event of interest and death as competing risks event | 0.88 (0.71 to 1.08) |

Both analysis models are adjusted in line with the primary analysis of the primary end point.

**Table S11. Further pre-specified subgroup analyses.**

| Variable | Digitoxin (N=613) no. of patient with events / total no. (%) | Placebo (N=599) No. of patient with events / total no. (%) | Hazard Ratio (95% CI) |
|---|---|---|---|
| NYHA class — NYHA class II | 57 / 181 (31.5) | 63 / 178 (35.4) | 0.76 (0.52 to 1.11) |
| NYHA class — NYHA class III | 174 / 408 (42.6) | 190 / 399 (47.6) | 0.81 (0.66 to 1.01) |
| NYHA class — NYHA class IV | 11 / 24 (45.8) | 11 / 22 (50.0) | 2.47 (0.53 to 11.42) |
| Age group (years) — <70 | 116 / 362 (32.0) | 142 / 350 (40.6) | 0.76 (0.59 to 0.98) |
| Age group (years) — 70-80 | 101 / 203 (49.8) | 90 / 204 (44.1) | 0.97 (0.71 to 1.33) |
| Age group (years) — >80 | 25 / 48 (52.1) | 32 / 45 (71.1) | 0.77 (0.39 to 1.51) |
| eGFR (ml/min/1.73m²) — <30 | 24 / 34 (70.6) | 21 / 39 (53.8) | 2.33 (0.88 to 6.15) |
| eGFR (ml/min/1.73m²) — 30-60 | 108 / 229 (47.2) | 121 / 218 (55.5) | 0.64 (0.48 to 0.85) |
| eGFR (ml/min/1.73m²) — >60 | 110 / 349 (31.5) | 122 / 342 (35.7) | 0.81 (0.62 to 1.06) |
| ICD group — No | 141 / 352 (40.1) | 165 / 373 (44.2) | 0.78 (0.62 to 0.98) |
| ICD group — Yes | 101 / 261 (38.7) | 98 / 225 (43.6) | 0.88 (0.65 to 1.18) |
| CRT-D group — No | 164 / 459 (35.7) | 199 / 459 (43.4) | 0.74 (0.60 to 0.92) |
| CRT-D group — Yes | 78 / 154 (50.6) | 64 / 139 (46.0) | 1.02 (0.71 to 1.45) |

| | | | |
|---|---|---|---|
| CRT-P group — No | 236 / 604 (39.1) | 262 / 592 (44.3) | 0.81 (0.68 to 0.97) |
| CRT-P group — Yes | 6 / 8 (75.0) | 1 / 5 (20.0) | NE* |
| Duration of heart failure (years) - <1 | 15 / 57 (26.3) | 22 / 56 (39.3) | 0.63 (0.28 to 1.45) |
| Duration of heart failure (years) - 1 to 5 | 96 / 260 (36.9) | 122 / 275 (44.4) | 0.76 (0.57 to 1.02) |
| Duration of heart failure (years) - >5 | 130 / 292 (44.5) | 120 / 262 (45.8) | 0.84 (0.65 to 1.10) |
| Depression — No | 222 / 569 (39.0) | 241 / 557 (43.3) | 0.83 (0.69 to 1.00) |
| Depression — Yes | 18 / 42 (42.9) | 21 / 40 (52.5) | 0.78 (0.32 to 1.91) |
| SGLT2i — No | 32 / 98 (32.7) | 36 / 96 (37.5) | 0.59 (0.34 to 1.04) |
| SGLT2i — Yes | 24 / 121 (19.8) | 32 / 113 (28.3) | 0.70 (0.40 to 1.23) |
| SGLT2i — Not available | 186 / 394 (47.2) | 196 / 390 (50.3) | 0.88 (0.72 to 1.09) |
| Quadruple therapy — No | 36 / 118 (30.50) | 40 / 110 (36.40) | 0.64 (0.39 to 1.07) |
| Quadruple therapy — Yes | 20 / 101 (19.80) | 28 / 99 (28.30) | 0.77 (0.41 to 1.42) |
| Quadruple therapy – (due to SGLT2i) not available | 186 / 394 (47.2) | 196 / 390 (50.3) | 0.88 (0.72 to 1.09) |

* Not estimable

**Table S12. Digitoxin concentration and dose titration.**

| | | Visit 1 (week 6) | | Visit 3 (month 12)* | |
|---|---|---|---|---|---|
| | | **Digitoxin** | **Placebo** | **Digitoxin** | **Placebo** |
| Digitoxin serum concentration, ng/ml** | No. | 550 | 534 | 394 | 391 |
| | Mean ± SD | 17.0 ± 5.9 | 4.5 ± 0.8 | 13.5 ± 5.1 | 2.1 ± 0.6 |
| | Median (Min - Max) | 16.5 (1.9-52.6) | 1.9 (1.9-20.3) | 13.8 (1.5-28.5) | 1.9 (1.5-25.7) |
| Dose titration | Reduction — no. (%) | 187 (34.0) | 175 (32.8) | | |
| | No change in dose — no. (%) | 321 (58.4) | 328 (61.4) | | |
| | Increase of dose — no. (%) | 21 (3.8) | 30 (5.6) | | |
| | No titration — no. (%) | 21 (3.8) | 1 (0.2) | | |

* Determination at month 12 was done for safety and scientific purposes only (i.e. no dose adjustments based on these values were planned/performed)

** Detection limit of digitoxin immunoassay 1.9 ng/ml.

**Table S13: Serious adverse events.**

| System order class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) | Risk Difference (95% CI) |
|---|---|---|---|
| **Serious adverse event*** | 29 (4.7)** | 17 (2.8) | 1.89 (-0.25 to 4.04) |
| Cardiac disorders — no. (%) | 21 (3.4) | 11 (1.8) | 1.59 (-0.21 to 3.39) |
| Acute myocardial infarction — no. (%) | 1 (0.2) | 0 (0.0) | |
| Arrhythmic — no. (%) storm | 1 (0.2) | 0 (0.0) | |
| Atrial fibrillation — no. (%) | 2 (0.3) | 0 (0.0) | |
| Cardiac arrest — no. (%) | 0 (0.0) | 1 (0.) | |
| Cardiac failure — no. (%) | 0 (0.0) | 1 (0.2) | |
| Cardiac failure chronic — no. (%) | 1 (0.2) | 0 (0.0) | |
| Cardiac tamponade — no. (%) | 1 (0.2) | 0 (0.0) | |
| Cardiogenic shock — no. (%) | 0 (0.0) | 1 (0.2) | |
| Cardiorenal syndrome — no. (%) | 1 (0.2) | 0 (0.0) | |
| Myocardial infarction — no. (%) | 1 (0.2) | 0 (0.0) | |
| Pulseless electrical activity — no. (%) | 0 (0.0) | 1 (0.2) | |
| Ventricular fibrillation — no. (%) | 10 (1.6) | 3 (0.5) | 1.13 (-0.02 to 2.28) |
| Ventricular tachycardia — no. (%) | 7 (1.1) | 5 (0.8) | 0.31 (-0.81 to 1.42) |
| Hepatobiliary disorders — no. (%) | 0 (0.0) | 1 (0.2) | -0.17 (-0.16 to 0.49) |
| Cholelithiasis — no. (%) | 0 (0.0) | 1 (0.2) | |
| Infections and infestations — no. (%) | 2 (0.3) | 1 (0.2) | 0.16 (-0.40 to 0.72) |
| Gastroenteritis clostridial — no. (%) | 1 (0.2) | 0 (0.0) | |
| Pneumonia — no. (%) | 1 (0.2) | 0 (0.0) | |
| Pneumonia klebsiella — no. (%) | 1 (0.2) | 0 (0.0) | |
| Respiratory tract infection — no. (%) | 0 (0.0) | 1 (0.2) | |
| Staphylococcal sepsis — no. (%) | 1 (0.2) | 0 (0.0) | |
| Injury, poisoning and procedural complications — no. (%) | 1 (0.2) | 0 (0.0) | 0.16 (-0.16 to 0.48) |
| Toxicity to various agents — no. (%) | 1 (0.2) | 0 (0.0) | |
| Metabolism and nutrition disorders — no. (%) | 2 (0.3) | 0 (0.0) | 0.33 (-0.13 to 0.78) |
| Hyperglycaemia — no. (%) | 1 (0.2) | (0.0) | |
| Respiratory acidosis — no. (%) | 1 (0.2) | (0.0) | |
| Musculoskeletal and connective tissue disorders — no. (%) | 1 (0.2) | 0 (0.0) | 0.16 (-0.16 to 0.48) |

| | | | |
|---|---|---|---|
| Bursitis — no. (%) | 1 (0.2) | (0.0) | |
| Nervous system disorders — no. (%) | 3 (0.5) | 1 (0.2) | 0.32 (-0.32 to 0.96) |
| Cerebral haemorrhage — no. (%) | 0 (0.0) | 1 (0.2) | |
| Cerebrovascular accident — no. (%) | 1 (0.2) | 0 (0.0) | |
| Dizziness — no. (%) | 1 (0.2) | 0 (0.0) | |
| Epilepsy — no. (%) | 1 (0.2) | 0 (0.0) | |
| Renal and urinary disorders | 1 (0.2) | 0 (0.0) | 0.16 (-0.16 to 0.48) |
| Acute kidney injury | 1 (0.2) | 0 (0.0) | |
| Surgical and medical procedures — no. (%) | 0 (0.0) | 1 (0.2) | -0.17 (-0.16 to 0.49) |
| Ventricular assist device insertion — no. (%) | 0 (0.0) | 1 (0.2) | |
| Vascular disorders — no. (%) | 1 (0.2) | 2 (0.3) | -0.17 (-0.73 to 0.39) |
| Gangrene — no. (%) | 1 (0.2) | 0 (0.0) | |
| Myocardial infarction — no. (%) | 0 (0.0) | 1 (0.2) | |
| Syncope — no. (%) | 0 (0.0) | 1 (0.2) | |

* All death and hospitalization events were excluded from the reporting of serious adverse events per protocol and were provided within the analysis of the primary and secondary end points (for details see supplement methods).

** Including one patient with a suspected unexpected serious adverse reaction.

**Table S14: Adverse events.**

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| **Adverse event** | **369 (60.2%)** | **341 (56.9%)** |
| **Blood and lymphatic system disorders** | **14 (2.3%)** | **13 (2.2%)** |
| Anemia | 8 (1.3%) | 3 (0.5%) |
| Coagulopathy | - | 1 (0.2%) |
| Hemorrhagic diathesis | 1 (0.2%) | - |
| Iron deficiency anaemia | 3 (0.5%) | 3 (0.5%) |
| Leukocytosis | - | 1 (0.2%) |
| Lymphadenopathy | 1 (0.2%) | 1 (0.2%) |
| Macrocytosis | - | 1 (0.2%) |
| Microcytic anaemia | - | 1 (0.2%) |
| Pancytopenia | 1 (0.2%) | - |
| Polycythaemia | - | 1 (0.2%) |
| Thrombocytopenia | 2 (0.3%) | 2 (0.3%) |
| **Cardiac disorders** | **147 (24.0%)** | **126 (21.0%)** |
| Acute coronary syndrome | - | 2 (0.3%) |
| Acute myocardial infarction | 2 (0.3%) | 1 (0.2%) |
| Angina pectoris | 12 (2.0%) | 9 (1.5%) |
| Angina unstable | 2 (0.3%) | - |
| Aortic valve stenosis | 1 (0.2%) | - |
| Arrhythmia | 6 (1.0%) | 2 (0.3%) |
| Arrhythmia supraventricular | - | 1 (0.2%) |
| Arteriosclerosis coronary artery | 1 (0.2%) | - |
| Atrial fibrillation | 33 (5.4%) | 31 (5.2%) |
| Atrial flutter | 2 (0.3%) | 4 (0.7%) |
| Atrial tachycardia | 3 (0.5%) | 5 (0.8%) |
| Atrial thrombosis | 1 (0.2%) | - |
| Atrioventricular block | 3 (0.5%) | 5 (0.8%) |
| Atrioventricular block first degree | 3 (0.5%) | 5 (0.8%) |
| Atrioventricular block second degree | 1 (0.2%) | - |
| Bradyarrhythmia | 5 (0.8%) | - |
| Bradycardia | 10 (1.6%) | 3 (0.5%) |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Bundle branch block left | 4 (0.7%) | 2 (0.3%) |
| Bundle branch block right | - | 4 (0.7%) |
| Cardiac aneurysm | - | 1 (0.2%) |
| Cardiac arrest | - | 1 (0.2%) |
| Cardiac discomfort | - | 1 (0.2%) |
| Cardiac failure | 29 (4.7%) | 26 (4.3%) |
| Cardiac failure chronic | 2 (0.3%) | 1 (0.2%) |
| Cardiac failure congestive | - | 1 (0.2%) |
| Cardiac fibrillation | 1 (0.2%) | 1 (0.2%) |
| Cardiac tamponade | 1 (0.2%) | - |
| Cardiac ventricular thrombosis | - | 2 (0.3%) |
| Cardiogenic shock | - | 1 (0.2%) |
| Cardiorenal syndrome | 1 (0.2%) | 1 (0.2%) |
| Cardiovascular disorder | 1 (0.2%) | 1 (0.2%) |
| Coronary artery disease | 5 (0.8%) | 1 (0.2%) |
| Coronary artery stenosis | 3 (0.5%) | 1 (0.2%) |
| Extrasystoles | - | 2 (0.3%) |
| Left ventricular dysfunction | 1 (0.2%) | - |
| Left ventricular failure | - | 1 (0.2%) |
| Mitral valve incompetence | 1 (0.2%) | 2 (0.3%) |
| Myocardial infarction | 1 (0.2%) | 1 (0.2%) |
| Myocardial ischaemia | 2 (0.3%) | - |
| Palpitations | 9 (1.5%) | 2 (0.3%) |
| Pericarditis | 1 (0.2%) | - |
| Pulseless electrical activity | - | 1 (0.2%) |
| Sinus bradycardia | 1 (0.2%) | 3 (0.5%) |
| Sinus node dysfunction | 1 (0.2%) | - |
| Sinus tachycardia | 4 (0.7%) | 5 (0.8%) |
| Supraventricular tachycardia | 5 (0.8%) | 2 (0.3%) |
| Tachyarrhythmia | - | 3 (0.5%) |
| Tachycardia | 4 (0.7%) | 7 (1.2%) |
| Tricuspid valve incompetence | - | 1 (0.2%) |
| Ventricular extrasystoles | 6 (1.0%) | 9 (1.5%) |
| Ventricular fibrillation | 13 (2.1%) | 5 (0.8%) |
| Ventricular tachycardia | 36 (5.9%) | 38 (6.3%) |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| **Congenital, familial and genetic disorders** | **-** | **1 (0.2%)** |
| Anophthalmos | - | 1 (0.2%) |
| **Ear and labyrinth disorders** | **21 (3.4%)** | **11 (1.8%)** |
| Ear discomfort | 1 (0.2%) | - |
| Ear pain | 2 (0.3%) | - |
| Hypoacusis | - | 1 (0.2%) |
| Middle ear effusion | - | 1 (0.2%) |
| Middle ear inflammation | 1 (0.2%) | - |
| Sudden hearing loss | 1 (0.2%) | - |
| Tinnitus | 3 (0.5%) | 1 (0.2%) |
| Vertigo | 12 (2.0%) | 8 (1.3%) |
| Vertigo positional | 1 (0.2%) | - |
| **Endocrine disorders** | **5 (0.8%)** | **3 (0.5%)** |
| Goiter | 1 (0.2%) | - |
| Hyperthyroidism | 1 (0.2%) | 1 (0.2%) |
| Hypothyroidism | 4 (0.7%) | 1 (0.2%) |
| Toxic nodular goiter | - | 1 (0.2%) |
| **Eye disorders** | **19 (3.1%)** | **21 (3.5%)** |
| Amaurosis fugax | - | 1 (0.2%) |
| Blepharitis | 1 (0.2%) | - |
| Cataract | 5 (0.8%) | 4 (0.7%) |
| Chromatopsia | 1 (0.2%) | 1 (0.2%) |
| Corneal deposits | 1 (0.2%) | - |
| Endocrine ophthalmopathy | - | 1 (0.2%) |
| Eye haematoma | - | 1 (0.2%) |
| Eye haemorrhage | 1 (0.2%) | - |
| Glaucoma | 1 (0.2%) | - |
| Lacrimation increased | 1 (0.2%) | - |
| Myopia | 1 (0.2%) | - |
| Optic atrophy | 1 (0.2%) | - |
| Photophobia | 1 (0.2%) | 1 (0.2%) |
| Pseudophakia | 1 (0.2%) | - |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Retinopathy | 1 (0.2%) | - |
| Vision blurred | 1 (0.2%) | 1 (0.2%) |
| Visual acuity reduced | 1 (0.2%) | - |
| Visual field defect | 1 (0.2%) | - |
| Visual impairment | 3 (0.5%) | 10 (1.7%) |
| Vitreous detachment | - | 1 (0.2%) |
| Vitreous hemorrhage | 1 (0.2%) | - |
| **Gastrointestinal disorders** | **89 (14.5%)** | **72 (12.0%)** |
| Abdominal discomfort | 2 (0.3%) | 7 (1.2%) |
| Abdominal distension | 2 (0.3%) | 3 (0.5%) |
| Abdominal hernia | 1 (0.2%) | - |
| Abdominal pain | 1 (0.2%) | 5 (0.8%) |
| Abdominal pain lower | 2 (0.3%) | 1 (0.2%) |
| Abdominal pain upper | 5 (0.8%) | 5 (0.8%) |
| Anal fissure | - | 2 (0.3%) |
| Anal incontinence | 1 (0.2%) | - |
| Ascites | 1 (0.2%) | 3 (0.5%) |
| Chronic gastritis | 2 (0.3%) | 1 (0.2%) |
| Chronic gastrointestinal bleeding | 1 (0.2%) | - |
| Colitis | 1 (0.2%) | - |
| Constipation | 6 (1.0%) | 2 (0.3%) |
| Diarrhea | 37 (6.0%) | 18 (3.0%) |
| Diverticulum intestinal | - | 1 (0.2%) |
| Duodenitis | 2 (0.3%) | - |
| Dyspepsia | 3 (0.5%) | 6 (1.0%) |
| Dysphagia | 2 (0.3%) | 1 (0.2%) |
| Enterocolitis hemorrhagic | - | 1 (0.2%) |
| Flatulence | 1 (0.2%) | - |
| Gastritis | 3 (0.5%) | 5 (0.8%) |
| Gastritis hemorrhagic | 1 (0.2%) | - |
| Gastrointestinal hemorrhage | 3 (0.5%) | 1 (0.2%) |
| Gastrointestinal inflammation | - | 1 (0.2%) |
| Gastrooesophageal reflux disease | 3 (0.5%) | 2 (0.3%) |
| Hematochezia | 1 (0.2%) | 3 (0.5%) |
| Hemorrhagic erosive gastritis | - | 1 (0.2%) |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Hemorrhoids | - | 1 (0.2%) |
| Hiatus hernia | 2 (0.3%) | - |
| Inguinal hernia | 2 (0.3%) | - |
| Intestinal polyp | 1 (0.2%) | - |
| Large intestine polyp | 1 (0.2%) | - |
| Melaena | 1 (0.2%) | - |
| Mouth hemorrhage | 1 (0.2%) | - |
| Nausea | 29 (4.7%) | 22 (3.7%) |
| Oesophagitis | - | 1 (0.2%) |
| Pancreatitis acute | 1 (0.2%) | - |
| Proctalgia | 1 (0.2%) | - |
| Retching | 2 (0.3%) | - |
| Salivary gland calculus | 1 (0.2%) | - |
| Salivary hypersecretion | - | 1 (0.2%) |
| Swollen tongue | 1 (0.2%) | - |
| Toothache | - | 1 (0.2%) |
| Umbilical hernia | 1 (0.2%) | - |
| Vomiting | 8 (1.3%) | 5 (0.8%) |
| **General disorders and administration site conditions** | **87 (14.2%)** | **65 (10.9%)** |
| Adverse drug reaction | 1 (0.2%) | - |
| Asthenia | 4 (0.7%) | 1 (0.2%) |
| Chest discomfort | 6 (1.0%) | 3 (0.5%) |
| Chest pain | 7 (1.1%) | 13 (2.2%) |
| Chills | 1 (0.2%) | 1 (0.2%) |
| Condition aggravated | 1 (0.2%) | - |
| Cyst | - | 1 (0.2%) |
| Drug intolerance | 3 (0.5%) | 2 (0.3%) |
| Exercise tolerance decreased | 2 (0.3%) | - |
| Fatigue | 21 (3.4%) | 12 (2.0%) |
| Foreign body reaction | - | 1 (0.2%) |
| Gait disturbance | 1 (0.2%) | - |
| General physical health deterioration | 2 (0.3%) | - |
| Generalised edema | - | 1 (0.2%) |
| Illness | 1 (0.2%) | - |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Impaired healing | 1 (0.2%) | - |
| Implant site pain | - | 1 (0.2%) |
| Inflammation | 1 (0.2%) | 1 (0.2%) |
| Influenza like illness | 16 (2.6%) | 18 (3.0%) |
| Localized edema | 1 (0.2%) | 1 (0.2%) |
| Malaise | 5 (0.8%) | 1 (0.2%) |
| Medical device site discomfort | 1 (0.2%) | - |
| Medical device site fistula | 1 (0.2%) | - |
| Medical device site hemorrhage | - | 1 (0.2%) |
| Non-cardiac chest pain | - | 1 (0.2%) |
| Edema | 3 (0.5%) | 2 (0.3%) |
| Edema peripheral | 16 (2.6%) | 8 (1.3%) |
| Pain | 5 (0.8%) | 2 (0.3%) |
| Peripheral swelling | 4 (0.7%) | 6 (1.0%) |
| Pyrexia | 1 (0.2%) | 3 (0.5%) |
| Swelling | 1 (0.2%) | - |
| Thirst | 1 (0.2%) | - |
| **Hepatobiliary disorders** | **4 (0.7%)** | **5 (0.8%)** |
| Bile duct stone | - | 1 (0.2%) |
| Cholecystitis | - | 1 (0.2%) |
| Cholecystitis chronic | - | 1 (0.2%) |
| Congestive hepatopathy | 1 (0.2%) | - |
| Hepatic failure | - | 1 (0.2%) |
| Hepatic lesion | 1 (0.2%) | - |
| Hepatic steatosis | - | 1 (0.2%) |
| Hepatomegaly | 1 (0.2%) | - |
| Jaundice | 1 (0.2%) | - |
| **Immune system disorders** | **3 (0.5%)** | **2 (0.3%)** |
| Allergy to arthropod sting | - | 1 (0.2%) |
| Amyloidosis | 1 (0.2%) | - |
| Drug hypersensitivity | 1 (0.2%) | 1 (0.2%) |
| Rubber sensitivity | 1 (0.2%) | - |
| **Infections and infestations** | **123 (20.1%)** | **123 (20.5%)** |
| Abscess of external ear | - | 1 (0.2%) |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Abscess oral | - | 1 (0.2%) |
| Acarodermatitis | - | 1 (0.2%) |
| Arthritis infective | 1 (0.2%) | 1 (0.2%) |
| Atypical pneumonia | 1 (0.2%) | - |
| Bacteraemia | 1 (0.2%) | - |
| Bacterial disease carrier | 1 (0.2%) | 2 (0.3%) |
| Bacterial infection | - | 1 (0.2%) |
| Bronchitis | 11 (1.8%) | 15 (2.5%) |
| COVID-19 | 31 (5.1%) | 28 (4.7%) |
| COVID-19 pneumonia | - | 1 (0.2%) |
| Coronavirus infection | 7 (1.1%) | 13 (2.2%) |
| Cystitis | 1 (0.2%) | 1 (0.2%) |
| Diabetic foot infection | 1 (0.2%) | - |
| Enterococcal infection | 1 (0.2%) | - |
| Enterocolitis bacterial | - | 1 (0.2%) |
| Erysipelas | 4 (0.7%) | 2 (0.3%) |
| Febrile infection | 2 (0.3%) | 1 (0.2%) |
| Furuncle | - | 1 (0.2%) |
| Gangrene | 1 (0.2%) | - |
| Gastroenteritis | 7 (1.1%) | 9 (1.5%) |
| Gastroenteritis clostridial | 1 (0.2%) | - |
| Gastrointestinal infection | - | 1 (0.2%) |
| Gingivitis | 2 (0.3%) | - |
| Groin abscess | 1 (0.2%) | - |
| Herpes zoster | 6 (1.0%) | 2 (0.3%) |
| Hordeolum | - | 1 (0.2%) |
| Impetigo | - | 1 (0.2%) |
| Implant site infection | 1 (0.2%) | - |
| Infection | 3 (0.5%) | 2 (0.3%) |
| Influenza | 3 (0.5%) | 5 (0.8%) |
| Klebsiella infection | 1 (0.2%) | - |
| Laryngitis | - | 1 (0.2%) |
| Localized infection | 1 (0.2%) | 1 (0.2%) |
| Lower respiratory tract infection | 1 (0.2%) | 1 (0.2%) |
| Mastitis | - | 1 (0.2%) |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Nasopharyngitis | 25 (4.1%) | 21 (3.5%) |
| Onychomycosis | 1 (0.2%) | - |
| Oral candidiasis | 1 (0.2%) | - |
| Oral fungal infection | 1 (0.2%) | - |
| Oral herpes | 1 (0.2%) | - |
| Orchitis | 1 (0.2%) | - |
| Otitis media | - | 1 (0.2%) |
| Penile infection | 1 (0.2%) | - |
| Periodontitis | 2 (0.3%) | - |
| Pharyngitis | 1 (0.2%) | - |
| Pneumonia | 6 (1.0%) | 17 (2.8%) |
| Pneumonia aspiration | 1 (0.2%) | - |
| Pneumonia klebsiella | 1 (0.2%) | - |
| Post-acute COVID-19 syndrome | - | 1 (0.2%) |
| Pulpitis dental | - | 1 (0.2%) |
| Respiratory tract infection | 12 (2.0%) | 9 (1.5%) |
| Respiratory tract infection viral | - | 1 (0.2%) |
| Severe acute respiratory syndrome | 1 (0.2%) | - |
| Sialoadenitis | 1 (0.2%) | - |
| Sinusitis | 1 (0.2%) | 1 (0.2%) |
| Staphylococcal infection | 1 (0.2%) | 2 (0.3%) |
| Staphylococcal sepsis | 1 (0.2%) | - |
| Superinfection | 1 (0.2%) | - |
| Tinea pedis | - | 1 (0.2%) |
| Upper respiratory tract infection | 5 (0.8%) | 3 (0.5%) |
| Urinary tract infection | 9 (1.5%) | 9 (1.5%) |
| Urinary tract infection bacterial | 2 (0.3%) | - |
| Viral infection | 1 (0.2%) | 1 (0.2%) |
| Vulvovaginal mycotic infection | 1 (0.2%) | - |
| Wound infection | 1 (0.2%) | - |
| **Injury, poisoning and procedural complications** | **32 (5.2%)** | **33 (5.5%)** |
| Anemia postoperative | 1 (0.2%) | - |
| Animal bite | - | 1 (0.2%) |
| Arthropod bite | - | 2 (0.3%) |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Arthropod sting | - | 1 (0.2%) |
| Cervical vertebral fracture | 1 (0.2%) | - |
| Clavicle fracture | 1 (0.2%) | 1 (0.2%) |
| Contusion | 4 (0.7%) | 4 (0.7%) |
| Coronary artery restenosis | - | 1 (0.2%) |
| Craniofacial fracture | 2 (0.3%) | - |
| Electric injury | - | 3 (0.5%) |
| Epicondylitis | - | 1 (0.2%) |
| Fall | 4 (0.7%) | 6 (1.0%) |
| Femur fracture | - | 1 (0.2%) |
| Fibula fracture | 1 (0.2%) | 1 (0.2%) |
| Foot fracture | 1 (0.2%) | 1 (0.2%) |
| Fracture | 1 (0.2%) | - |
| Head injury | - | 1 (0.2%) |
| Immunization reaction | 1 (0.2%) | 1 (0.2%) |
| Joint injury | - | 1 (0.2%) |
| Ligament sprain | - | 1 (0.2%) |
| Limb crushing injury | - | 1 (0.2%) |
| Limb injury | 2 (0.3%) | 1 (0.2%) |
| Lip injury | 1 (0.2%) | 1 (0.2%) |
| Lumbar vertebral fracture | 1 (0.2%) | - |
| Medication error | 1 (0.2%) | 1 (0.2%) |
| Meniscus injury | - | 1 (0.2%) |
| Muscle strain | 1 (0.2%) | - |
| Nasal injury | 1 (0.2%) | - |
| Overdose | 3 (0.5%) | 1 (0.2%) |
| Poisoning | 1 (0.2%) | - |
| Post-procedural complication | 1 (0.2%) | - |
| Post-procedural hemorrhage | 1 (0.2%) | - |
| Psychosis postoperative | 1 (0.2%) | - |
| Radial nerve injury | - | 1 (0.2%) |
| Rib fracture | 2 (0.3%) | 1 (0.2%) |
| Skin laceration | 1 (0.2%) | - |
| Spinal fracture | - | 1 (0.2%) |
| Tendon injury | 1 (0.2%) | - |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Tendon rupture | 1 (0.2%) | - |
| Tooth fracture | - | 1 (0.2%) |
| Traumatic hematoma | - | 1 (0.2%) |
| Traumatic intracranial hemorrhage | 1 (0.2%) | - |
| Upper limb fracture | 1 (0.2%) | - |
| Vascular graft stenosis | - | 1 (0.2%) |
| Wound | 3 (0.5%) | 3 (0.5%) |
| Wrist fracture | 1 (0.2%) | 1 (0.2%) |
| **Investigations** | **60 (9.8%)** | **37 (6.2%)** |
| Arthroscopy | 1 (0.2%) | - |
| Biopsy heart | - | 1 (0.2%) |
| Blood bilirubin increased | 1 (0.2%) | - |
| Blood creatine phosphokinase increased | 2 (0.3%) | - |
| Blood creatinine increased | 3 (0.5%) | - |
| Blood glucose fluctuation | - | 1 (0.2%) |
| Blood glucose increased | 2 (0.3%) | - |
| Blood potassium decreased | 1 (0.2%) | - |
| Blood potassium increased | 4 (0.7%) | 1 (0.2%) |
| Blood pressure abnormal | - | 2 (0.3%) |
| Blood pressure increased | 1 (0.2%) | - |
| Blood thyroid stimulating hormone decreased | - | 1 (0.2%) |
| Blood triglycerides increased | 5 (0.8%) | - |
| Blood uric acid increased | 1 (0.2%) | 2 (0.3%) |
| Blood urine | 1 (0.2%) | - |
| Blood urine present | - | 2 (0.3%) |
| C-reactive protein increased | 1 (0.2%) | 1 (0.2%) |
| Cardiac murmur | - | 2 (0.3%) |
| Cardioactive drug level above therapeutic | 2 (0.3%) | 1 (0.2%) |
| Cardioactive drug level increased | 2 (0.3%) | - |
| Catheterization cardiac | 1 (0.2%) | - |
| Coronavirus test positive | 1 (0.2%) | - |
| Device function test | 2 (0.3%) | 2 (0.3%) |
| Ejection fraction decreased | - | 1 (0.2%) |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Electrocardiogram PR prolongation | 1 (0.2%) | 1 (0.2%) |
| Electrocardiogram QRS complex abnormal | - | 1 (0.2%) |
| Electrocardiogram QT prolonged | - | 3 (0.5%) |
| Electrocardiogram ST segment depression | 2 (0.3%) | - |
| Electrocardiogram T wave inversion | 1 (0.2%) | - |
| Electrocardiogram change | 1 (0.2%) | - |
| Gamma-glutamyltransferase increased | 6 (1.0%) | - |
| General physical condition abnormal | 1 (0.2%) | - |
| Glomerular filtration rate abnormal | 4 (0.7%) | 1 (0.2%) |
| Glomerular filtration rate decreased | - | 1 (0.2%) |
| Glycosylated hemoglobin increased | 3 (0.5%) | - |
| Heart rate decreased | 2 (0.3%) | - |
| Heart rate increased | - | 2 (0.3%) |
| Hepatic enzyme increased | - | 1 (0.2%) |
| Inflammatory marker increased | 1 (0.2%) | - |
| International normalized ratio abnormal | 1 (0.2%) | - |
| International normalized ratio increased | 2 (0.3%) | - |
| Intraocular pressure increased | - | 1 (0.2%) |
| Liver function test abnormal | 1 (0.2%) | 1 (0.2%) |
| Liver function test increased | 4 (0.7%) | 1 (0.2%) |
| N-terminal prohormone brain natriuretic peptide increased | 1 (0.2%) | 2 (0.3%) |
| Renal function test abnormal | 3 (0.5%) | - |
| Sensory level abnormal | 1 (0.2%) | 1 (0.2%) |
| Serum ferritin increased | 1 (0.2%) | - |
| Transaminases increased | 1 (0.2%) | - |
| Transferrin saturation decreased | - | 1 (0.2%) |
| Transplant evaluation | 1 (0.2%) | - |
| Troponin T increased | 1 (0.2%) | 1 (0.2%) |
| Troponin increased | 2 (0.3%) | 1 (0.2%) |
| Vascular resistance pulmonary increased | 1 (0.2%) | - |
| Venous pressure jugular | - | 1 (0.2%) |
| Weight decreased | 6 (1.0%) | 3 (0.5%) |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Weight increased | 3 (0.5%) | 2 (0.3%) |
| White blood cell count increased | - | 1 (0.2%) |
| **Metabolism and nutrition disorders** | **84 (13.7%)** | **71 (11.9%)** |
| Abnormal loss of weight | - | 1 (0.2%) |
| Cachexia | 1 (0.2%) | - |
| Decreased appetite | 8 (1.3%) | 3 (0.5%) |
| Dehydration | 2 (0.3%) | 2 (0.3%) |
| Diabetes mellitus | 9 (1.5%) | 8 (1.3%) |
| Diabetes mellitus inadequate control | 7 (1.1%) | 5 (0.8%) |
| Folate deficiency | 1 (0.2%) | - |
| Food aversion | - | 1 (0.2%) |
| Food craving | - | 1 (0.2%) |
| Glucose tolerance impaired | - | 2 (0.3%) |
| Gout | 19 (3.1%) | 10 (1.7%) |
| Hypercholesterolaemia | 1 (0.2%) | 1 (0.2%) |
| Hyperglycemia | 3 (0.5%) | 2 (0.3%) |
| Hyperkalemia | 22 (3.6%) | 25 (4.2%) |
| Hyperlipidemia | - | 1 (0.2%) |
| Hypernatremia | 1 (0.2%) | - |
| Hyperphosphatemia | 1 (0.2%) | - |
| Hypertriglyceridemia | 1 (0.2%) | - |
| Hyperuricemia | 2 (0.3%) | 1 (0.2%) |
| Hypocalcemia | 1 (0.2%) | - |
| Hypoglycemia | 4 (0.7%) | 1 (0.2%) |
| Hypokalemia | 9 (1.5%) | 12 (2.0%) |
| Hyponatremia | 2 (0.3%) | 1 (0.2%) |
| Iron deficiency | 5 (0.8%) | - |
| Metabolic acidosis | 1 (0.2%) | 1 (0.2%) |
| Type 1 diabetes mellitus | 1 (0.2%) | - |
| Type 2 diabetes mellitus | 6 (1.0%) | 4 (0.7%) |
| Vitamin B12 deficiency | 2 (0.3%) | - |
| Vitamin D deficiency | 1 (0.2%) | 2 (0.3%) |
| **Musculoskeletal and connective tissue disorders** | **59 (9.6%)** | **50 (8.3%)** |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Arthralgia | 5 (0.8%) | 9 (1.5%) |
| Arthritis | 1 (0.2%) | 1 (0.2%) |
| Arthropathy | 1 (0.2%) | - |
| Back pain | 11 (1.8%) | 6 (1.0%) |
| Bursa disorder | 1 (0.2%) | 1 (0.2%) |
| Bursitis | 2 (0.3%) | 1 (0.2%) |
| Coccydynia | - | 1 (0.2%) |
| Exostosis | 1 (0.2%) | - |
| Gouty arthritis | 2 (0.3%) | 3 (0.5%) |
| Haemarthrosis | - | 1 (0.2%) |
| Intervertebral disc protrusion | - | 2 (0.3%) |
| Joint effusion | 1 (0.2%) | - |
| Joint impingement | 1 (0.2%) | - |
| Joint range of motion decreased | - | 1 (0.2%) |
| Joint swelling | 1 (0.2%) | 1 (0.2%) |
| Meniscal degeneration | 1 (0.2%) | - |
| Muscle discomfort | 1 (0.2%) | - |
| Muscle spasms | 9 (1.5%) | 4 (0.7%) |
| Muscular weakness | 1 (0.2%) | - |
| Musculoskeletal chest pain | - | 2 (0.3%) |
| Musculoskeletal discomfort | 4 (0.7%) | 3 (0.5%) |
| Musculoskeletal stiffness | 1 (0.2%) | - |
| Myalgia | 2 (0.3%) | 4 (0.7%) |
| Myopathy | 1 (0.2%) | - |
| Neck mass | 1 (0.2%) | - |
| Osteoarthritis | 3 (0.5%) | 7 (1.2%) |
| Osteochondrosis | 1 (0.2%) | 1 (0.2%) |
| Osteolysis | 1 (0.2%) | 1 (0.2%) |
| Osteopenia | 1 (0.2%) | - |
| Pain in extremity | 10 (1.6%) | 4 (0.7%) |
| Pain in jaw | 1 (0.2%) | - |
| Plantar fasciitis | 1 (0.2%) | - |
| Polyarthritis | - | 1 (0.2%) |
| Polymyalgia rheumatica | 1 (0.2%) | - |
| Rhabdomyolysis | - | 1 (0.2%) |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Rheumatoid arthritis | - | 1 (0.2%) |
| Rotator cuff syndrome | - | 1 (0.2%) |
| Spinal osteoarthritis | - | 2 (0.3%) |
| Spinal pain | 2 (0.3%) | 3 (0.5%) |
| Spondylitis | - | 1 (0.2%) |
| Synovial cyst | 1 (0.2%) | - |
| Tendon pain | 1 (0.2%) | - |
| Weight bearing difficulty | - | 1 (0.2%) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **9 (1.5%)** | **9 (1.5%)** |
| Adenocarcinoma of colon | 2 (0.3%) | - |
| Basal cell carcinoma | 2 (0.3%) | - |
| Bladder cancer | - | 1 (0.2%) |
| Bowen's disease | - | 1 (0.2%) |
| Colorectal adenoma | 1 (0.2%) | - |
| Diffuse large B-cell lymphoma recurrent | 1 (0.2%) | - |
| Lung neoplasm malignant | 1 (0.2%) | 1 (0.2%) |
| Metastases to bone | - | 1 (0.2%) |
| Myeloproliferative neoplasm | 1 (0.2%) | - |
| Esophageal carcinoma | 1 (0.2%) | - |
| Prostate cancer | 1 (0.2%) | 3 (0.5%) |
| Skin papilloma | - | 1 (0.2%) |
| Squamous cell carcinoma | - | 1 (0.2%) |
| Squamous cell carcinoma of skin | - | 1 (0.2%) |
| Thymoma malignant recurrent | - | 1 (0.2%) |
| Tongue neoplasm | - | 1 (0.2%) |
| **Nervous system disorders** | **96 (15.7%)** | **73 (12.2%)** |
| Ageusia | - | 1 (0.2%) |
| Aphasia | 2 (0.3%) | - |
| Carotid artery stenosis | 2 (0.3%) | - |
| Carpal tunnel syndrome | - | 1 (0.2%) |
| Cerebral haemorrhage | - | 1 (0.2%) |
| Cerebral infarction | 1 (0.2%) | 1 (0.2%) |
| Cerebrovascular accident | 1 (0.2%) | - |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Chronic inflammatory demyelinating polyradiculoneuropathy | 1 (0.2%) | - |
| Cognitive disorder | 1 (0.2%) | - |
| Cold dysesthesia | 1 (0.2%) | - |
| Diabetic neuropathy | 1 (0.2%) | 1 (0.2%) |
| Dizziness | 47 (7.7%) | 39 (6.5%) |
| Dizziness exertional | - | 1 (0.2%) |
| Dizziness postural | 1 (0.2%) | 3 (0.5%) |
| Epilepsy | 1 (0.2%) | 1 (0.2%) |
| Headache | 5 (0.8%) | 12 (2.0%) |
| Hypersomnia | - | 1 (0.2%) |
| Hypoesthesia | 2 (0.3%) | 1 (0.2%) |
| Hypoglycemic unconsciousness | - | 1 (0.2%) |
| Loss of consciousness | 1 (0.2%) | - |
| Lumbosacral radiculopathy | 1 (0.2%) | - |
| Memory impairment | 1 (0.2%) | - |
| Migraine | 1 (0.2%) | - |
| Migraine with aura | - | 1 (0.2%) |
| Neuralgia | 1 (0.2%) | - |
| Neuromyopathy | 1 (0.2%) | - |
| Nystagmus | 1 (0.2%) | - |
| Paraesthesia | 6 (1.0%) | 5 (0.8%) |
| Parkinson's disease | 1 (0.2%) | 3 (0.5%) |
| Parkinsonism | 1 (0.2%) | - |
| Polyneuropathy | 3 (0.5%) | 2 (0.3%) |
| Poor quality sleep | 1 (0.2%) | - |
| Presyncope | 2 (0.3%) | 3 (0.5%) |
| Sciatica | 2 (0.3%) | 1 (0.2%) |
| Seizure | - | 1 (0.2%) |
| Sensory disturbance | - | 1 (0.2%) |
| Somnolence | - | 1 (0.2%) |
| Syncope | 22 (3.6%) | 13 (2.2%) |
| Taste disorder | 1 (0.2%) | - |
| Tongue biting | - | 1 (0.2%) |
| Tremor | 3 (0.5%) | 2 (0.3%) |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Vertebral artery occlusion | - | 1 (0.2%) |
| Visual field defect | 1 (0.2%) | - |
| **Product issues** | **5 (0.8%)** | **3 (0.5%)** |
| Device dislocation | - | 1 (0.2%) |
| Device malfunction | 3 (0.5%) | 2 (0.3%) |
| Device pacing issue | 1 (0.2%) | - |
| Undersensing | 1 (0.2%) | - |
| **Psychiatric disorders** | **19 (3.1%)** | **19 (3.2%)** |
| Aggression | - | 1 (0.2%) |
| Anxiety | 2 (0.3%) | 1 (0.2%) |
| Apathy | - | 1 (0.2%) |
| Confusional state | 1 (0.2%) | 1 (0.2%) |
| Delirium | 1 (0.2%) | - |
| Depressed mood | - | 1 (0.2%) |
| Depression | 2 (0.3%) | 3 (0.5%) |
| Disorientation | - | 1 (0.2%) |
| Hallucination | 1 (0.2%) | - |
| Initial insomnia | 1 (0.2%) | - |
| Insomnia | - | 3 (0.5%) |
| Intensive care unit delirium | 1 (0.2%) | - |
| Middle insomnia | 1 (0.2%) | 3 (0.5%) |
| Mood swings | 1 (0.2%) | - |
| Nervousness | 1 (0.2%) | - |
| Nightmare | - | 2 (0.3%) |
| Panic attack | 1 (0.2%) | - |
| Restlessness | 4 (0.7%) | 3 (0.5%) |
| Sleep disorder | 6 (1.0%) | 3 (0.5%) |
| **Renal and urinary disorders** | **38 (6.2%)** | **21 (3.5%)** |
| Acute kidney injury | 10 (1.6%) | 12 (2.0%) |
| Azotaemia | 1 (0.2%) | - |
| Chronic kidney disease | 2 (0.3%) | 1 (0.2%) |
| Cystitis hemorrhagic | 1 (0.2%) | - |
| Cystitis noninfective | 4 (0.7%) | 1 (0.2%) |
| Dysuria | - | 1 (0.2%) |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Hematuria | 2 (0.3%) | 3 (0.5%) |
| Incontinence | 1 (0.2%) | - |
| Leukocyturia | 1 (0.2%) | - |
| Nephrolithiasis | 1 (0.2%) | - |
| Nocturia | 2 (0.3%) | - |
| Oliguria | - | 1 (0.2%) |
| Pollakiuria | 1 (0.2%) | 1 (0.2%) |
| Prerenal failure | - | 1 (0.2%) |
| Renal cyst | 1 (0.2%) | 1 (0.2%) |
| Renal failure | 6 (1.0%) | 2 (0.3%) |
| Renal impairment | 5 (0.8%) | 2 (0.3%) |
| Renal mass | 1 (0.2%) | - |
| Ureteric stenosis | 1 (0.2%) | - |
| Urethral hemorrhage | 1 (0.2%) | - |
| Urethral obstruction | - | 1 (0.2%) |
| Urethral stenosis | 1 (0.2%) | - |
| Urinary hesitation | 3 (0.5%) | 2 (0.3%) |
| Urinary incontinence | 1 (0.2%) | - |
| Urinary tract inflammation | - | 1 (0.2%) |
| **Reproductive system and breast disorders** | **21 (3.4%)** | **7 (1.2%)** |
| Benign prostatic hyperplasia | 5 (0.8%) | 2 (0.3%) |
| Breast engorgement | 1 (0.2%) | - |
| Erectile dysfunction | 1 (0.2%) | 2 (0.3%) |
| Gynecomastia | 8 (1.3%) | 3 (0.5%) |
| Hematospermia | 1 (0.2%) | - |
| Nipple pain | 2 (0.3%) | 1 (0.2%) |
| Penile swelling | 1 (0.2%) | - |
| Peyronie's disease | 1 (0.2%) | - |
| Postmenopausal hemorrhage | 1 (0.2%) | - |
| Prostatic disorder | 1 (0.2%) | - |
| Prostatitis | 1 (0.2%) | - |
| Uterine polyp | 1 (0.2%) | - |
| **Respiratory, thoracic and mediastinal disorders** | **57 (9.3%)** | **55 (9.2%)** |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Asthma | 1 (0.2%) | - |
| Chronic obstructive pulmonary disease | 3 (0.5%) | - |
| Cough | 6 (1.0%) | 8 (1.3%) |
| Diaphragmatic spasm | 1 (0.2%) | 1 (0.2%) |
| Dysphonia | 2 (0.3%) | 1 (0.2%) |
| Dyspnea | 18 (2.9%) | 23 (3.8%) |
| Dyspnea at rest | 1 (0.2%) | 1 (0.2%) |
| Dyspnea exertional | 7 (1.1%) | 4 (0.7%) |
| Dyspnea paroxysmal nocturnal | 1 (0.2%) | 1 (0.2%) |
| Epistaxis | 6 (1.0%) | 7 (1.2%) |
| Hemoptysis | 2 (0.3%) | 1 (0.2%) |
| Hypersensitivity pneumonitis | 1 (0.2%) | - |
| Lung infiltration | 1 (0.2%) | - |
| Nasal septum deviation | 1 (0.2%) | - |
| Nasal turbinate hypertrophy | 1 (0.2%) | - |
| Nocturnal dyspnoea | 2 (0.3%) | 1 (0.2%) |
| Obstructive airways disorder | 1 (0.2%) | - |
| Obstructive sleep apnoea syndrome | 1 (0.2%) | 1 (0.2%) |
| Oropharyngeal pain | - | 1 (0.2%) |
| Orthopnoea | - | 2 (0.3%) |
| Pharyngeal inflammation | 2 (0.3%) | - |
| Pleural effusion | 2 (0.3%) | 5 (0.8%) |
| Pleurisy | 1 (0.2%) | - |
| Pneumonitis | - | 2 (0.3%) |
| Pneumothorax | - | 1 (0.2%) |
| Productive cough | 3 (0.5%) | 1 (0.2%) |
| Pulmonary congestion | 1 (0.2%) | - |
| Pulmonary embolism | - | 1 (0.2%) |
| Pulmonary fibrosis | 1 (0.2%) | - |
| Pulmonary hypertension | - | 1 (0.2%) |
| Pulmonary edema | 1 (0.2%) | - |
| Respiratory acidosis | 1 (0.2%) | - |
| Respiratory disorder | - | 1 (0.2%) |
| Respiratory failure | 3 (0.5%) | - |
| Rhinorrhea | 1 (0.2%) | - |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Rhonchi | - | 2 (0.3%) |
| Sleep apnoea syndrome | 4 (0.7%) | 2 (0.3%) |
| Tracheal pain | 1 (0.2%) | - |
| Vocal cord erythema | - | 1 (0.2%) |
| Vocal cord inflammation | 1 (0.2%) | - |
| **Skin and subcutaneous tissue disorders** | **40 (6.5%)** | **32 (5.3%)** |
| Acne | 1 (0.2%) | - |
| Actinic keratosis | 2 (0.3%) | 4 (0.7%) |
| Blister | 1 (0.2%) | - |
| Decubitus ulcer | 1 (0.2%) | - |
| Dermal cyst | 1 (0.2%) | - |
| Dermatitis allergic | 1 (0.2%) | - |
| Diabetic foot | 1 (0.2%) | 1 (0.2%) |
| Ecchymosis | - | 1 (0.2%) |
| Eczema | 1 (0.2%) | 1 (0.2%) |
| Erythema | 3 (0.5%) | 1 (0.2%) |
| Hirsutism | - | 1 (0.2%) |
| Hyperhidrosis | 5 (0.8%) | 7 (1.2%) |
| Ingrowing nail | - | 1 (0.2%) |
| Nail psoriasis | 1 (0.2%) | - |
| Night sweats | 2 (0.3%) | 1 (0.2%) |
| Onychoclasis | 1 (0.2%) | - |
| Pigmentation disorder | - | 1 (0.2%) |
| Pruritus | 7 (1.1%) | 10 (1.7%) |
| Psoriasis | 1 (0.2%) | - |
| Pyoderma gangrenosum | 1 (0.2%) | - |
| Rash | 5 (0.8%) | 5 (0.8%) |
| Skin disorder | 2 (0.3%) | - |
| Skin erosion | 1 (0.2%) | - |
| Skin hemorrhage | 1 (0.2%) | - |
| Skin induration | 1 (0.2%) | - |
| Skin irritation | 1 (0.2%) | - |
| Skin ulcer | 3 (0.5%) | - |
| Stasis dermatitis | 1 (0.2%) | - |
| Swelling face | - | 1 (0.2%) |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Urticaria | 2 (0.3%) | - |
| **Surgical and medical procedures** | **16 (2.6%)** | **17 (2.8%)** |
| Cardiac resynchronisation therapy | 3 (0.5%) | 1 (0.2%) |
| Cardioversion | 4 (0.7%) | 6 (1.0%) |
| Carotid endarterectomy | - | 1 (0.2%) |
| Cataract operation | 5 (0.8%) | - |
| Cerebrospinal fluid drainage | - | 1 (0.2%) |
| Fistula repair | - | 1 (0.2%) |
| Implantable defibrillator insertion | 1 (0.2%) | - |
| Implantable defibrillator replacement | 1 (0.2%) | - |
| Large intestinal polypectomy | 1 (0.2%) | - |
| Mitral valve repair | - | 1 (0.2%) |
| Salpingo-oophorectomy bilateral | - | 1 (0.2%) |
| Skin cyst excision | - | 1 (0.2%) |
| Skin lesion removal | - | 1 (0.2%) |
| Tooth extraction | - | 2 (0.3%) |
| Ventricular assist device insertion | - | 1 (0.2%) |
| Wrist surgery | 1 (0.2%) | - |
| **Vascular disorders** | **32 (5.2%)** | **29 (4.8%)** |
| Achenbach syndrome | - | 1 (0.2%) |
| Aneurysm | - | 1 (0.2%) |
| Aortic stenosis | - | 1 (0.2%) |
| Arteriovenous fistula | 1 (0.2%) | - |
| Bleeding varicose vein | 1 (0.2%) | - |
| Blood pressure fluctuation | - | 2 (0.3%) |
| Circulatory collapse | 3 (0.5%) | 2 (0.3%) |
| Deep vein thrombosis | - | 1 (0.2%) |
| Extremity necrosis | - | 1 (0.2%) |
| Hemorrhage | 1 (0.2%) | - |
| Hot flush | 1 (0.2%) | - |
| Hypertension | 4 (0.7%) | 3 (0.5%) |
| Hypertensive crisis | - | 2 (0.3%) |
| Hypotension | 18 (2.9%) | 10 (1.7%) |
| Iliac artery stenosis | 1 (0.2%) | - |

| System organ class<br>Preferred term | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Ischemia | - | 1 (0.2%) |
| Jugular vein occlusion | - | 1 (0.2%) |
| Lymphatic fistula | - | 1 (0.2%) |
| Orthostatic hypotension | 1 (0.2%) | - |
| Peripheral arterial occlusive disease | 2 (0.3%) | 1 (0.2%) |
| Peripheral artery stenosis | 1 (0.2%) | - |
| Peripheral venous disease | - | 1 (0.2%) |
| Phlebitis | - | 1 (0.2%) |
| Scalp hematoma | 1 (0.2%) | - |
| Thrombophlebitis | - | 1 (0.2%) |
| Thrombosis | 1 (0.2%) | - |
| Venous occlusion | - | 1 (0.2%) |

**Table S15: Table of representativeness of study participants**

| | |
|---|---|
| Disease, problem or condition under investigation | Heart failure with reduced ejection fraction (HFrEF) |
| Age | The prevalence of HFrEF increases with age with most patients having an age of >60 years; the average age is 70 years in clinical trials and registries and women with HFrEF are older than men with HFrEF. |
| Sex and gender | HFrEF affects men more than women (20 to 30 % of patients are women). |
| Race or ethnic group | HFrEF affects 25 to 30% of Black individuals and 10 to 15% Hispanic individuals disproportionately in the United States. Differentiation in European registries is less frequent. |
| Geography | The proportion of patients with HFrEF represents approximately 50% of all patients with heart failure in most countries. Age and cause vary among countries (e.g. 50% ischemic cause in industrial countries and primarily non-ischemic cause in non-industrial countries). In addition, availability and access to medications and devices recommended for patients with heart failure varies around the world. |
| Other considerations | HFrEF develops at a younger age and more often has a noncoronary cause in Black patients than in White patients. Throughout the world, mortality and hospitalization rates vary widely within and between countries. |
| Overall representativeness of this trial | The participants in the present trial demonstrated the expected ratio of men to women with HFrEF. The average age in the study population is slightly lower than that encountered in the enrolling countries. Cause of heart failure and other features, such as coexisting comorbidities, including kidney dysfunction, were consistent with epidemiological and registry data available from participating countries. No patients were enrolled in Africa, America, Asia, and Australia. |

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# Potential conflicts of interest

U.B. and J.B. represent the study heads of the DIGIT-HF-study and applied for funding of DIGIT-HF described above. U.B., J.B., A.K., H. v. d. L., C. V., S.S., and M.B. are members of the DIGIT-HF trial steering committee.
U.B. received travel support and honoraria for lectures/consulting from Alnylam Pharmaceutical, Amgen, Astra Zeneca, Bayer Vital, Bristol Myers Squibb, Boehringer Ingelheim, German Cardiac Society, Lilly, Novartis, Novo Nordisk, and Pfizer and institutional research support from Alnylam Pharmaceuticals, all not related to this article.
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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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