



Clinical trial results:

**Evaluating different rate control therapies in permanent atrial fibrillation:
A prospective, randomised, open-label, blinded endpoint study
comparing digoxin and beta-blockers as initial rate control therapy.
RAte control Therapy Evaluation in permanent Atrial Fibrillation: RATE-
AF**

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-005043-13 |
| Trial protocol | GB |
| Global end of trial date | 26 February 2020 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 14 April 2021 |
| First version publication date | 14 April 2021 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | RG_14-187 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN95259705 |
| ClinicalTrials.gov id (NCT number) | NCT02391337 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University of Birmingham |
| Sponsor organisation address | Aston Webb Building , Birmingham, United Kingdom, B15 2TT |
| Public contact | Dipak Kotecha, University of Birmingham, +44 (0) 7974 115676, d.kotecha@bham.ac.uk |
| Scientific contact | Dipak Kotecha, University of Birmingham, +44 (0) 7974 115676, d.kotecha@bham.ac.uk |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 26 February 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 December 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 February 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Patient-reported quality of life (QoL), with a predefined focus on physical well-being using the SF-36 (a QoL tool) physical component summary at six months.

Protection of trial subjects:

All sites were provided with the Rate-AF protocol that provided specific instruction relating to inclusion/exclusion criteria and trial patient safety. There was clear instruction relating to trial intervention safety and considerations detailed within the protocol. Rate-AF had a Data Monitoring Committee to monitor patient safety throughout the trial.

Background therapy:

Atrial fibrillation is a common heart rhythm disturbance, causing discomfort for patients, a high risk of stroke, frequent hospital admissions and a two-fold increase in death. The number of patients with this condition are expected to double in the next 20 years. Medications to control heart-rate are used in the majority of patients, although the choice of agent is often guided by local preference rather than evidence from controlled trials. Despite the fact that patients with atrial fibrillation have high rates of other cardiac conditions such as heart failure, clinicians have insufficient evidence to personalise the use of different therapies. This feasibility study allowed us to develop a range of methods that could characterise patients according to the pumping and relaxing function of the heart, the burden of symptoms and to identify new blood markers. In this way, the investigators hoped to improve clinical practice guidelines, allowing doctors to prescribe appropriate treatments for the right patients. The research focused around a randomised trial of two medication strategies, providing much-needed data on the comparison of digoxin and beta-blockers (two commonly-used drugs in patients with atrial fibrillation). It also allowed us to identify the best way to record patient-reported quality of life and develop robust techniques to determine heart function using non-invasive imaging, facilitating the conduct of a large-scale clinical trial. The key objectives of the research programme were to define the optimal medications for patients with atrial fibrillation and identify the most valid, reproducible and cost-effective methods to examine patients. The ultimate aim of the project was to improve clinical outcomes in atrial fibrillation, benefiting patients, the National Health Service and the global community.

Evidence for comparator:

A prospective, randomised, open-label, blinded-endpoint (PROBE) study design. Recruited patients will receive either:

Digoxin- The maintenance dose of oral digoxin will be either 62.5µg or 125µg according to the pre-defined treatment schedule and up titrated, as required, to 250µg daily. A single loading dose of four tablets (250 or 500µg according to target maintenance dose) will be prescribed in digoxin-naïve participants, where necessary OR

Beta-blocker- Oral bisoprolol will be commenced at either 1.25mg, 2.5mg or 5mg according to the treatment schedule and uptitrated, as required, to 15mg daily.

Patients will be followed-up for the duration of treatment.

| | |
|---|------------------|
| Actual start date of recruitment | 20 December 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 161 |
| Worldwide total number of subjects | 161 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 15 |
| From 65 to 84 years | 117 |
| 85 years and over | 29 |

Subject disposition

Recruitment

Recruitment details:

First patient was randomised on the 20th December 2016 and the last patient was randomised on the 01st October 2018. A total of 161 patients were randomised into the Rate-AF Trial across one centre. Patients were equally recruited with 80 patients in the Bisoprolol arm and 81 in the Digoxin arm.

Pre-assignment

Screening details:

A total of 390 were screened for the trial, of these screened 161 were randomised.

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | Baseline |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Investigator ^[1] |

Blinding implementation details:

A prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-blockers as initial rate control therapy with investigator blinded endpoint. A prospective, randomised, open-label, blinded-endpoint (PROBE) study design.

Arms

| | |
|--|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Digoxin |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | Digoxin Tablets |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Trial maintenance doses will initially be 62.5 or 125 µg orally (at the clinician's discretion, taking into account age and renal function), with planned up-titration to 125/250 µg. The maximum trial dose will be 250 µg daily.

A single loading dose of four tablets (250 or 500 µg according to target maintenance dose) will be prescribed in digoxin-naïve participants. The clinician is permitted to omit the loading dose or prescribe a second, where necessary.

Unblinded serum digoxin concentrations will be assessed at visits 2 and 3, with results reported back to the relevant clinician(s). This process will assist in monitoring compliance, adjusting dosage in cases of low serum levels and avoiding toxicity.

| | |
|--|--------------------|
| Arm title | Bisoprolol |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | Bisoprolol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Trial starting doses will be 1.25 or 2.5 or 5 mg (at the clinician's discretion), with planned up-titration to 10 mg in increments of 1.25 or 2.5 mg. The maximum trial dose will be 15 mg daily. No loading dose is required.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Blinding implementation details: A prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-blockers as initial rate control therapy with investigator blinded endpoint. A prospective, randomised, open-label, blinded-endpoint (PROBE) study design.

| Number of subjects in period 1 | Digoxin | Bisoprolol |
|--------------------------------|---------|------------|
| Started | 81 | 80 |
| Completed | 81 | 80 |

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | 6 months follow-up |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Investigator ^[2] |

Blinding implementation details:

A prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-blockers as initial rate control therapy with investigator blinded endpoint. A prospective, randomised, open-label, blinded-endpoint (PROBE) study design.

Arms

| | |
|--|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Digoxin |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | Digoxin Tablets |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Trial maintenance doses will initially be 62.5 or 125 µg orally (at the clinician's discretion, taking into account age and renal function), with planned up-titration to 125/250 µg. The maximum trial dose will be 250 µg daily.

A single loading dose of four tablets (250 or 500 µg according to target maintenance dose) will be prescribed in digoxin-naïve participants. The clinician is permitted to omit the loading dose or prescribe a second, where necessary.

Unblinded serum digoxin concentrations will be assessed at visits 2 and 3, with results reported back to the relevant clinician(s). This process will assist in monitoring compliance, adjusting dosage in cases of

low serum levels and avoiding toxicity.

| | |
|--|--------------------|
| Arm title | Bisoprolol |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | Bisoprolol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Trial starting doses will be 1.25 or 2.5 or 5 mg (at the clinician's discretion), with planned up-titration to 10 mg in increments of 1.25 or 2.5 mg. The maximum trial dose will be 15 mg daily. No loading dose is required.

Notes:

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Blinding implementation details: A prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-blockers as initial rate control therapy with investigator blinded endpoint. A prospective, randomised, open-label, blinded-endpoint (PROBE) study design.

| Number of subjects in period 2 | Digoxin | Bisoprolol |
|---------------------------------------|---------|------------|
| Started | 81 | 80 |
| Completed | 76 | 74 |
| Not completed | 5 | 6 |
| Adverse event, serious fatal | 4 | 5 |
| Consent withdrawn by subject | 1 | 1 |

Period 3

| | |
|------------------------------|-----------------------------|
| Period 3 title | 12 month follow-up |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Investigator ^[3] |

Blinding implementation details:

A prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-blockers as initial rate control therapy with investigator blinded endpoint. A prospective, randomised, open-label, blinded-endpoint (PROBE) study design.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|--|-------------------|
| Arm title | Digoxin |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | Digoxin Tablets |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Trial maintenance doses will initially be 62.5 or 125 µg orally (at the clinician's discretion, taking into account age and renal function), with planned up-titration to 125/250 µg. The maximum trial dose will be 250 µg daily.

A single loading dose of four tablets (250 or 500 µg according to target maintenance dose) will be prescribed in digoxin-naïve participants. The clinician is permitted to omit the loading dose or prescribe a second, where necessary.

Unblinded serum digoxin concentrations will be assessed at visits 2 and 3, with results reported back to the relevant clinician(s). This process will assist in monitoring compliance, adjusting dosage in cases of low serum levels and avoiding toxicity.

| | |
|--|--------------------|
| Arm title | Bisoprolol |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | Bisoprolol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Trial starting doses will be 1.25 or 2.5 or 5 mg (at the clinician's discretion), with planned up-titration to 10 mg in increments of 1.25 or 2.5 mg. The maximum trial dose will be 15 mg daily. No loading dose is required.

Notes:

[3] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Blinding implementation details:

A prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-blockers as initial rate control therapy with investigator blinded endpoint. A prospective, randomised, open-label, blinded-endpoint (PROBE) study design.

| Number of subjects in period 3 | Digoxin | Bisoprolol |
|---------------------------------------|---------|------------|
| Started | 76 | 74 |
| Completed | 73 | 72 |
| Not completed | 3 | 2 |
| Adverse event, serious fatal | - | 2 |
| Consent withdrawn by subject | 1 | - |
| Lost to follow-up | 2 | - |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|------------|
| Reporting group title | Digoxin |
| Reporting group description: - | |
| Reporting group title | Bisoprolol |
| Reporting group description: - | |

| Reporting group values | Digoxin | Bisoprolol | Total |
|---|---------|------------|-------|
| Number of subjects | 81 | 80 | 161 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 11 | 4 | 15 |
| From 65-84 years | 59 | 58 | 117 |
| 85 years and over | 11 | 18 | 29 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 74.4 | 76.8 | |
| standard deviation | ± 8.4 | ± 8.1 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 36 | 38 | 74 |
| Male | 45 | 42 | 87 |
| On anticoagulant before randomisation | | | |
| Units: Subjects | | | |
| No | 9 | 17 | 26 |
| Yes | 72 | 63 | 135 |
| EHRA class | | | |
| *Minimisation variables | | | |
| Note: EHRA Class was categorised into (Class 1, 2a) and (Class 2b, 3, 4) for the minimisation algorithm | | | |
| Units: Subjects | | | |
| Cat 1 | 0 | 0 | 0 |
| Cat 2a | 3 | 3 | 6 |
| Cat 2b | 35 | 40 | 75 |
| Cat 3 | 38 | 27 | 65 |
| Cat 4 | 5 | 10 | 15 |
| NYHA class | | | |
| Units: Subjects | | | |
| Class I | 0 | 0 | 0 |
| Class II | 47 | 53 | 100 |
| Class III | 32 | 24 | 56 |

| Class IV | 2 | 3 | 5 |
|---|--------|--------|-----|
| Previous diagnosis of heart failure? Units: Subjects | | | |
| No | 46 | 56 | 102 |
| Yes | 35 | 24 | 59 |
| Any signs of heart failure at baseline Units: Subjects | | | |
| No | 32 | 45 | 77 |
| Yes | 49 | 35 | 84 |
| Type I diabetes Units: Subjects | | | |
| No | 81 | 80 | 161 |
| Yes | 0 | 0 | 0 |
| Type II diabetes Units: Subjects | | | |
| No | 65 | 58 | 123 |
| Yes | 16 | 22 | 38 |
| Unplanned admission for AF or HF in last 12 months Units: Subjects | | | |
| No | 65 | 65 | 130 |
| Yes | 16 | 15 | 31 |
| Any previous cardioversions Units: Subjects | | | |
| No | 74 | 71 | 145 |
| Yes | 7 | 9 | 16 |
| Previously undergone AF ablation Units: Subjects | | | |
| No | 79 | 79 | 158 |
| Yes | 2 | 1 | 3 |
| Previous history of anti-arrhythmic drugs Units: Subjects | | | |
| No | 75 | 72 | 147 |
| Yes | 6 | 8 | 14 |
| Self-declared ethnicity Units: Subjects | | | |
| White - English / Welsh / Scottish / Northern Irish | 72 | 66 | 138 |
| White - Irish | 4 | 8 | 12 |
| Asian / Asian British – Indian | 3 | 2 | 5 |
| Asian / Asian British – Pakistani | 0 | 3 | 3 |
| Black / African / Caribbean / Black British – Afri | 0 | 1 | 1 |
| Black / African / Caribbean / Black British – Cari | 2 | 0 | 2 |
| Creatinine Units: (micromol/L) | | | |
| arithmetic mean | 87.9 | 91.4 | |
| standard deviation | ± 25.1 | ± 23.1 | - |
| Baseline NTproBNP Units: (pg/mL) | | | |
| arithmetic mean | 1473.3 | 1339.2 | |

| | | | |
|---|-----------------|-----------------|---|
| standard deviation | ± 2134 | ± 1107.5 | - |
| Radial artery heart rate Units: bpm arithmetic mean standard deviation | 87.8 ± 12 | 86.9 ± 10.3 | - |
| Apex beat heart rate Units: bpm arithmetic mean standard deviation | 98.3 ± 15.1 | 99 ± 16.8 | - |
| 12-Lead ECG Heart Rate Units: bpm arithmetic mean standard deviation | 100.3 ± 16.8 | 99.2 ± 19.2 | - |
| Systolic BP Units: mmHg arithmetic mean standard deviation | 134.5 ± 14.9 | 137.1 ± 17.5 | - |
| Estimated ejection fraction Units: Percentage arithmetic mean standard deviation | 56.2 ± 8.8 | 57.6 ± 10.5 | - |

End points

End points reporting groups

| | |
|--------------------------------|------------|
| Reporting group title | Digoxin |
| Reporting group description: - | |
| Reporting group title | Bisoprolol |
| Reporting group description: - | |
| Reporting group title | Digoxin |
| Reporting group description: - | |
| Reporting group title | Bisoprolol |
| Reporting group description: - | |
| Reporting group title | Digoxin |
| Reporting group description: - | |
| Reporting group title | Bisoprolol |
| Reporting group description: - | |

Primary: Primary outcome- SF36v2 PCS

| | |
|--|--|
| End point title | Primary outcome- SF36v2 PCS ^[1] |
| End point description: The primary outcome is the SF-36v2 physical component summary (PCS) score at 6 months. | |
| End point type | Primary |
| End point timeframe: 6 months | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The CI instructed that we do not provide the analyses and just to enter the minimum fields only. Full analysis result has already been published in the paper, Jama.

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 80 | 76 | 74 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 28.9 (± 11.6) | 27.2 (± 10.2) | 31.9 (± 11.7) | 29.7 (± 11.4) |

Statistical analyses

No statistical analyses for this end point

Secondary: SF36v2 Physical Component Summary (PCS)

| | |
|---|---|
| End point title | SF36v2 Physical Component Summary (PCS) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: 6 and 12 months | |

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|--------------------|--------------------|------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 80 | 72 | 72 |
| Units: score | | | | |
| arithmetic mean (standard deviation) | 28.9 (\pm 11.6) | 27.2 (\pm 10.2) | 32.5 (\pm 13) | 29.4 (\pm 12.4) |

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36v2 Mental Component Summary (MCS)

| | |
|---------------------------|--|
| End point title | SF-36v2 Mental Component Summary (MCS) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 6 and 12 months | |

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|--------------------|------------------|--------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 80 | 76 | 74 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 50.4 (\pm 10.2) | 49.5 (\pm 10) | 51.1 (\pm 10.6) | 50 (\pm 10.4) |

| End point values | Digoxin | Bisoprolol | | |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 72 | 72 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 53.6 (\pm 8.9) | 51.3 (\pm 10.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36v2 Physical Function Domain Score (PF)

| | |
|-----------------|---|
| End point title | SF-36v2 Physical Function Domain Score (PF) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 6 and 12 months.

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 80 | 76 | 74 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 26.8 (± 12.6) | 25.9 (± 12.2) | 29.2 (± 13.7) | 27.7 (± 13.6) |

| End point values | Digoxin | Bisoprolol | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 72 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 31.5 (± 14.1) | 27.5 (± 13) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36 Role Limitation Due to Physical Domain score (RP)

| | |
|-----------------|---|
| End point title | SF-36 Role Limitation Due to Physical Domain score (RP) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 6 and 12 months

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 80 | 76 | 74 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 31.8 (± 12.6) | 29.6 (± 12.1) | 34.2 (± 12) | 31.3 (± 12.8) |

| End point values | Digoxin | Bisoprolol | | |
|------------------|---------|------------|--|--|
|------------------|---------|------------|--|--|

| | | | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 72 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 37 (\pm 12.6) | 32 (\pm 12.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36 Role Limitation Due to Emotional Problems Domain score (RE)

| | |
|-----------------|---|
| End point title | SF-36 Role Limitation Due to Emotional Problems Domain score (RE) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 6 and 12 .

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|--------------------|------------------|------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 80 | 76 | 74 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 40.2 (\pm 14.3) | 39.8 (\pm 15) | 42 (\pm 13.3) | 38.7 (\pm 14.9) |

| End point values | Digoxin | Bisoprolol | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 72 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 45.2 (\pm 12.9) | 40.7 (\pm 15.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36v2 Social Functioning Domain Score (SF)

| | |
|-----------------|--|
| End point title | SF-36v2 Social Functioning Domain Score (SF) |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 6 and 12 months.

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|--------------------|------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 80 | 76 | 74 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 42.8 (\pm 12.3) | 41.3 (\pm 12) | 46.1 (\pm 11.5) | 43.5 (\pm 12.5) |

| End point values | Digoxin | Bisoprolol | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 72 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 45.6 (\pm 12.3) | 43.3 (\pm 11.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36v2 Mental Health Domain (MH)

| | |
|----------------------------|-----------------------------------|
| End point title | SF-36v2 Mental Health Domain (MH) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 6 and 12 months. | |

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|------------------|-------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 80 | 76 | 74 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 48 (\pm 11.6) | 48.2 (\pm 9.5) | 48.2 (\pm 10.7) | 49.4 (\pm 11.2) |

| End point values | Digoxin | Bisoprolol | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 72 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 51.3 (\pm 9.3) | 51.8 (\pm 9.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36v2 Energy/Vitality Domain Score (EV)

| | |
|-----------------|---|
| End point title | SF-36v2 Energy/Vitality Domain Score (EV) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 6 and 12 months.

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 80 | 76 | 74 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 43.4 (± 9.6) | 40.3 (± 10) | 44.9 (± 10.4) | 43 (± 10) |

| End point values | Digoxin | Bisoprolol | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 72 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 47.1 (± 9.9) | 42 (± 10) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36v2- Pain Score (Pain)

| | |
|-----------------|----------------------------|
| End point title | SF-36v2- Pain Score (Pain) |
|-----------------|----------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 6 and 12 months

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|--------------------|--------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 80 | 76 | 74 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 39.1 (\pm 12.2) | 37.5 (\pm 10.9) | 42 (\pm 12.1) | 41 (\pm 11.6) |

| End point values | Digoxin | Bisoprolol | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 72 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 40.5 (\pm 12.7) | 41.9 (\pm 12.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36v2- General Health Perception Domain Score (GHP)

| | |
|---------------------------|---|
| End point title | SF-36v2- General Health Perception Domain Score (GHP) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 6 and 12 months | |

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|-------------------|-----------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 80 | 76 | 74 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 40.5 (\pm 9.4) | 39 (\pm 9.4) | 41.6 (\pm 9.6) | 40 (\pm 9.8) |

| End point values | Digoxin | Bisoprolol | | |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 72 | 72 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 42.8 (\pm 9.9) | 39.6 (\pm 10) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D-5L summary index score

| | |
|-----------------|------------------------------|
| End point title | EQ-5D-5L summary index score |
|-----------------|------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 6 and 12 months.

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 80 | 76 | 74 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 0.67 (± 0.19) | 0.63 (± 0.22) | 0.66 (± 0.27) | 0.65 (± 0.23) |

| End point values | Digoxin | Bisoprolol | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 72 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 0.66 (± 0.27) | 0.62 (± 0.29) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D-5L visual analogue scale (VAS) score

| | |
|-----------------|--|
| End point title | EQ-5D-5L visual analogue scale (VAS) score |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 6 and 12 months.

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 80 | 76 | 74 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 64 (\pm 16.6) | 61.6 (\pm 20.3) | 71.8 (\pm 16.3) | 68.5 (\pm 17.1) |

| End point values | Digoxin | Bisoprolol | | |
|--------------------------------------|------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 72 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 72.2 (\pm 17) | 66.2 (\pm 17.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: AFEQT overall score

| | |
|---------------------------|---------------------|
| End point title | AFEQT overall score |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 6 and 12 months | |

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 80 | 76 | 74 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 62.2 (\pm 16.7) | 57.2 (\pm 17.6) | 72.1 (\pm 17.9) | 65.6 (\pm 16.8) |

| End point values | Digoxin | Bisoprolol | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 72 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 75.6 (\pm 17.1) | 68.1 (\pm 16.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Echocardiographic LVEF

| | |
|-----------------|------------------------|
| End point title | Echocardiographic LVEF |
|-----------------|------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and 12 months.

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 80 | 73 | 72 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 56.2 (± 8.8) | 57.6 (± 10.5) | 59.7 (± 8.7) | 59.8 (± 7.3) |

Statistical analyses

No statistical analyses for this end point

Secondary: Diastolic Function E/e

| | |
|-----------------|------------------------|
| End point title | Diastolic Function E/e |
|-----------------|------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and 12 months.

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 80 | 73 | 72 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 10.7 (± 4.5) | 10.2 (± 4.7) | 10.8 (± 5.1) | 10.8 (± 5.5) |

Statistical analyses

No statistical analyses for this end point

Secondary: Composite of diastolic indices

| | |
|-----------------|--------------------------------|
| End point title | Composite of diastolic indices |
|-----------------|--------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and 12 months.

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 80 | 73 | 72 |
| Units: Percentages | | | | |
| No | 68 | 72 | 65 | 65 |
| Yes | 13 | 8 | 8 | 7 |

Statistical analyses

No statistical analyses for this end point

Secondary: Radial Heart Rate (bpm)

| | |
|-----------------|-------------------------|
| End point title | Radial Heart Rate (bpm) |
|-----------------|-------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 6 and 12 months.

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 80 | 76 | 74 |
| Units: bpm | | | | |
| arithmetic mean (standard deviation) | 87.8 (± 12) | 86.9 (± 10.3) | 76.2 (± 9.7) | 73.9 (± 10.8) |

| End point values | Digoxin | Bisoprolol | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 72 | | |
| Units: bpm | | | | |
| arithmetic mean (standard deviation) | 76 (± 9) | 73.8 (± 10) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Apical Heart rate

| | |
|-----------------|-------------------|
| End point title | Apical Heart rate |
|-----------------|-------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 6 and 12 months.

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 80 | 76 | 74 |
| Units: bpm | | | | |
| arithmetic mean (standard deviation) | 98.3 (± 15.1) | 99 (± 16.8) | 78.4 (± 10.5) | 76.2 (± 11.1) |

| End point values | Digoxin | Bisoprolol | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 72 | | |
| Units: bpm | | | | |
| arithmetic mean (standard deviation) | 78.3 (± 9.2) | 76.2 (± 10.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 12-lead ECG Heart rate (bpm)

| | |
|-----------------|------------------------------|
| End point title | 12-lead ECG Heart rate (bpm) |
|-----------------|------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 6 and 12 months.

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 80 | 76 | 74 |
| Units: bpm | | | | |
| arithmetic mean (standard deviation) | 100.3 (± 16.8) | 99.2 (± 19.2) | 76.9 (± 12.1) | 74.8 (± 11.6) |

| End point values | Digoxin | Bisoprolol | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 72 | | |
| Units: bpm | | | | |
| arithmetic mean (standard deviation) | 75.4 (± 9.9) | 74.3 (± 11.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 24-hour ambulatory average Heart rate (bpm)

| | |
|-----------------|---|
| End point title | 24-hour ambulatory average Heart rate (bpm) |
|-----------------|---|

End point description:

This measurement was just done once. Change in heart rate using 24-hour ambulatory ECG.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24-hour time period

| End point values | Digoxin | Bisoprolol | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 76 | 78 | | |
| Units: bpm | | | | |
| arithmetic mean (standard deviation) | 78.9 (± 11.3) | 73.7 (± 10.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Distance covered (in metres) from the six-minute walk test

| | |
|----------------------------|--|
| End point title | Distance covered (in metres) from the six-minute walk test |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 6 and 12 months. | |

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|---------------------------------------|------------------|-----------------|--------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 79 | 74 | 73 |
| Units: Metres | | | | |
| median (inter-quartile range (Q1-Q3)) | 321 (120 to 419) | 330 (90 to 450) | 335.5 (180 to 422) | 348 (180 to 431) |

| End point values | Digoxin | Bisoprolol | | |
|---------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 71 | 69 | | |
| Units: Metres | | | | |
| median (inter-quartile range (Q1-Q3)) | 366 (233 to 435) | 329 (120 to 429) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: NTproBNP

| | |
|------------------------|-----------|
| End point title | NTproBNP |
| End point description: | |
| End point type | Secondary |

End point timeframe:

Baseline, 6 and 12 months.

| End point values | Digoxin | Bisoprolol | Digoxin | Bisoprolol |
|---------------------------------------|--------------------|------------------------|------------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 80 | 76 | 74 |
| Units: ng/L | | | | |
| median (inter-quartile range (Q1-Q3)) | 1091 (710 to 1522) | 1040.5 (752.5 to 1480) | 1057.5 (625.5 to 1531) | 1209 (837 to 1531) |

| End point values | Digoxin | Bisoprolol | | |
|---------------------------------------|-------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 72 | | |
| Units: ng/L | | | | |
| median (inter-quartile range (Q1-Q3)) | 960 (626 to 1531) | 1249.5 (847 to 1890) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Targeted AEs reported on the CRF were reportable to the RATE-AF Trial Office up to 30 days post last IMP administration. Any SUSAR related to the IMP was expected to be reported irrespective of how long after IMP administration the reaction has occurred.

Adverse event reporting additional description:

Adverse events (AEs) were recorded in the medical records and CRFs. Most AE/ARs that occurred in the trial, whether they are serious or not, were 'expected' treatment-related toxicities due to the drugs used in this trial.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|--------------------|-------|
| Dictionary name | CTCAE |
| Dictionary version | 4 |

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Digoxin |
|-----------------------|---------|

Reporting group description: -

| | |
|-----------------------|------------|
| Reporting group title | Bisoprolol |
|-----------------------|------------|

Reporting group description: -

| Serious adverse events | Digoxin | Bisoprolol | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 13 / 81 (16.05%) | 21 / 80 (26.25%) | |
| number of deaths (all causes) | 4 | 7 | |
| number of deaths resulting from adverse events | 4 | 7 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Secondary Malignancy | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 2 / 80 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Vascular disorders | | | |
| Haemorrhage/Bleeding | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|----------------|----------------|--|
| Vascular | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 80 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Constitutional Symptoms | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary/Upper Respiratory | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 4 / 80 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac Arrhythmia | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 3 / 80 (3.75%) | |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac general | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 4 / 80 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 2 / 80 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 2 | |
| Nervous system disorders | | | |
| Pain | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurology | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Lymphatics | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastrointestinal | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 3 / 80 (3.75%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatobiliary disorders | | | |
| Hepatobiliary/Pancreas | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatology/Skin | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal/Genitourinary | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal/Soft Tissue | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infection | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 4 / 80 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Digoxin | Bisoprolol | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 20 / 81 (24.69%) | 51 / 80 (63.75%) | |
| Cardiac disorders | | | |
| Symptomatic bradycardia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 5 / 80 (6.25%) | |
| occurrences (all) | 0 | 5 | |
| Symptomatic hypotension | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 6 / 80 (7.50%) | |
| occurrences (all) | 0 | 7 | |

| | | | |
|--|----------------|------------------|--|
| General disorders and administration site conditions | | | |
| Peripheral oedema | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 11 / 80 (13.75%) | |
| occurrences (all) | 1 | 12 | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 81 (4.94%) | 24 / 80 (30.00%) | |
| occurrences (all) | 4 | 28 | |
| Headache | | | |
| subjects affected / exposed | 5 / 81 (6.17%) | 9 / 80 (11.25%) | |
| occurrences (all) | 5 | 11 | |
| Lethargy | | | |
| subjects affected / exposed | 7 / 81 (8.64%) | 30 / 80 (37.50%) | |
| occurrences (all) | 7 | 37 | |
| Eye disorders | | | |
| Blurred Vision | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 1 / 80 (1.25%) | |
| occurrences (all) | 2 | 1 | |
| Gastrointestinal disorders | | | |
| Gastrointestinal upset | | | |
| subjects affected / exposed | 5 / 81 (6.17%) | 8 / 80 (10.00%) | |
| occurrences (all) | 5 | 8 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Upper respiratory tract symptoms | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 13 / 80 (16.25%) | |
| occurrences (all) | 1 | 15 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 80 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 24 July 2017 | Addition of new site. |
| 29 May 2018 | * Changes made to protocol. * Changes made to Participant Optional Consent Form. New documents submitted: - Optional Sub Study 'Nerve Activity and Heart Rate' Patient information leaflet. - Optional Sub Study 'Physical Activity and Heart Rate Monitoring' Patient information leaflet. |
| 21 November 2019 | Change of Principle Investigator. |
| 13 December 2019 | Changes made to protocol. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported.

Notes: