A thorough QT study with dalbavancin: A novel lipoglycopeptide antibiotic for the treatment of acute bacterial skin and skin-structure infections

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A B S T R A C T

Two hundred healthy subjects were enrolled in a randomised, partially double-blinded, single-centre, parallel design thorough QT study to demonstrate that dalbavancin had no clinical effect on the 12-lead ECG QTc. Fifty patients in each group received either dalbavancin 1000 mg intravenous (i.v.), dalbavancin 1500 mg i.v. or placebo i.v., each infused over 30 min, or 400 mg oral moxifloxacin. Ten replicate 12-lead ECGs were extracted at pre-defined time points before and up to 24 h post dosing and at corresponding time points during baseline. Dalbavancin did not have an effect on the QTcF interval, and an effect exceeding 10 ms could be excluded at all time points after a single i.v. dose of 1000 mg and 1500 mg. The largest placebo-corrected change-from-baseline QTcF (ΔQTcF) was 1.5 ms in the 1000 mg dalbavancin group at 6 h and 0.2 ms in the 1500 mg group at 24 h. A small concentration-dependent effect of dalbavancin on ΔQTcF was identified with an estimated negative population slope of −0.0051 ms per µg/mL. Assay sensitivity was demonstrated by the effect of 400 mg moxifloxacin, which peaked at 2 h at ΔQTcF of 12.9 ms, with the lower bound of the 90% CI of the effect exceeding 5 ms at all three pre-defined time points. Dalbavancin did not exert a relevant effect on heart rate or PR or QRS intervals. Dalbavancin in i.v. doses up to 1500 mg did not prolong the QTc interval and had no effect on heart rate or PR and QRS intervals.

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1. Introduction

Dalbavancin is a lipoglycopeptide antibiotic that is obtained by chemical modification of a natural glycopeptide. Glycopeptide antibiotics inhibit the biosynthesis of bacterial cell wall peptidoglycan. By binding to the N-alanyl-D-alanine terminus of the stem pentapeptide in nascent peptidoglycan, the formation of cross-links that stabilise the cell wall structure is blocked. In vitro and in vivo non-clinical microbiology and pharmacology data provide evidence for the potential therapeutic usefulness of dalbavancin in the treatment of clinical infections caused by Gram-positive bacteria. The safety and efficacy of intravenous (i.v.) dalbavancin for the treatment of acute bacterial skin and skin-structure infections (ABSSSIs), in particular those caused by staphylococci and streptococci, have been studied in two phase 3 clinical trials [1].

In safety pharmacology studies, dalbavancin did not affect the cardiac hERG current or the action potential duration in in vitro assays and did not prolong the QTc interval in conscious or anaesthetised dogs at plasma concentrations exceeding clinical, therapeutic peak plasma levels (Cmax). Several studies in conscious and anaesthetised dogs identified a slight but consistent tendency for blood pressure to decrease during or soon after dalbavancin infusion, with a slight increase in heart rate, which was interpreted as compensatory to the reduction in blood pressure. These haemodynamic effects were accompanied by clinical signs of facial or paw erythema and swelling and are therefore considered possibly related to histamine release in this species.

The pharmacokinetic (PK) profile of dalbavancin in humans is characterised by very low interpatient variability and a terminal half-life of ca. 14 days. These characteristics support the two-dose regimen approved by the US Food and Drug Administration (FDA)
for treatment of ABSSSI of 1000 mg i.v. over 30 min followed 1 week later by 500 mg.

As part of the overall safety assessment of dalbavancin, this study was conducted to evaluate whether dalbavancin at therapeutic and supratherapeutic plasma levels has any clinically relevant effects on electrocardiogram (ECG) parameters, as recommended by regulatory guidance [23]. A supratherapeutic dose of 1500 mg was chosen as it was expected to result in plasma levels significantly above those seen in patients on the first day of dosing.

2. Methods

This study was randomised and partially double-blinded with the primary objective of demonstrating that therapeutic and supratherapeutic plasma exposures to dalbavancin after a single i.v. infusion of 1000 mg and 1500 mg does not have an effect on the QTc interval exceeding 10 ms. In total, 200 healthy adult subjects (with >30% females) were to be enrolled in the study. Subjects who met all eligibility criteria and who agreed to participate in the study were randomly assigned to one of the following treatment groups:

- **A (therapeutic dalbavancin dose):** 325 mL of 1000 mg dalbavancin solution administered intravenously over 30 min;  
- **B (supratherapeutic dalbavancin dose):** 325 mL of 1500 mg dalbavancin solution administered intravenously over 30 min;  
- **C (placebo):** 325 mL of dalbavancin placebo solution (5% Dextrose for Injection, USP, 250 mL with Sterile Water for Injection, USP, 75 mL) administered intravenously over 30 min; and  
- **D (oral moxifloxacin):** 325 mL of dalbavancin placebo solution (5% Dextrose for Injection, USP, 250 mL with Sterile Water for Injection, USP, 75 mL) administered intravenously over 30 min and one tablet of 400 mg moxifloxacin hydrochloride (AVELOX®; Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ) administered orally at the start of the infusion with ca. 240 mL (8 fluid ounces) of room temperature water.

Subjects were screened within 28 days (between Day-30 and Day-2) prior to the study and were admitted to the clinical unit on Day-2 and were confined until Day 2. During and across all study treatment groups, meals, fluid intake and environmental factors remained as constant as possible.

2.1. Electrocardiogram assessment

Continuous 12-lead ECGs were recorded on Day-1 and Day 1 and until 24 h post dose on Day 2 using an M12R Holter recorder (Global Instrumentation, Manlius, NY). The continuous 12-lead digital ECG data were stored onto SD memory cards and were not available for review until the cards were received by the central ECG laboratory (iCardiac Technologies, Rochester, NY) and analysed. ECGs were extracted at time points that were selected to cover the anticipated peak plasma level of dalbavancin and a sufficient number of time points thereafter to characterise any potential effect on the QT/QTc interval post dosing: 10 min prior to dosing (0 h) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h after the start of infusion and at corresponding time points at baseline (Day-1). ECGs were extracted from the continuous recording using proprietary software (TQT Plus; iCardiac Technologies) in up to 10 replicates at each time point. Non-overlapping 10-s ECG recordings were extracted from the 5-min time window preceding each time point. QT and RR interval were measured in all recorded beats with the High Precision QT technique, whereby measurements on beats deemed ‘high confidence’ were performed using the COMPAS (University of Rochester, Rochester, NY) software [4]. All low confidence beats were reviewed manually and were either rejected using pass–fail criteria or accepted without manual adjustment of fiducial points. The final QC assessment was performed by a cardiologist. Categorical T-wave morphology analysis and measurement of PR and QRS intervals were performed manually in three of the ten ECG replicates with the highest quality at each time point, based on prospective defined criteria [5].

2.2. Pharmacokinetic determination

Blood samples were collected before dosing and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h after the start of infusion. Only plasma samples from the dalbavancin treatment groups were analysed using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method.

2.3. Statistical analysis

The primary analysis for each dose of dalbavancin was based on the QT/QTc analysis set. An analysis of covariance model with the change from time-matched baseline as dependent variable, treatment (supratherapeutic dose, therapeutic dose, placebo) and sex as factor, and time-matched baseline as covariate was fitted. A two-sided 90% confidence interval (CI) was calculated for the contrasts ‘therapeutic dose of dalbavancin–placebo’ and ‘supratherapeutic dose of dalbavancin–placebo’. Such a model was fitted for each time point on Day 1. Hypotheses were based upon the intersection–union test as specified below. To evaluate the drug effect, the statistical hypotheses can be stated as follows:

\[ H_0: \bigcup_{i=1}^{10} [\mu_{\text{drug}(i)} - \mu_{\text{placebo}(i)}] \geq x, \ i = 1, 2, \ldots, 10 \]

\[ H_A: \bigcap_{i=1}^{10} [\mu_{\text{drug}(i)} - \mu_{\text{placebo}(i)}] < x, \ i = 1, 2, \ldots, 10. \]

where \( \mu_{\text{drug}(i)} \) and \( \mu_{\text{placebo}(i)} \) are the mean change from baseline of QTcF for the drug and placebo at each time point, respectively. Since the intersection–union test can be applied here, no multiple endpoint adjustment was needed [6]. If the upper limit of the two-sided 90% CI for the supratherapeutic dose of dalbavancin versus placebo falls below 10 ms for all time points, it was to be concluded that the supratherapeutic dose does not prolong the QTc interval to a clinically significant degree. The procedure was repeated for the therapeutic dose of dalbavancin. The analysis to show assay sensitivity was based on \( \Delta QTcF \) in the moxifloxacin treatment group. For each time point, an analysis of covariance model was fitted with treatment (moxifloxacin, placebo) and sex as factor and time-matched baseline as covariate. For the time points 2, 3 and 4 h after dosing, a two-sided 90% CI was calculated for the contrast ‘moxifloxacin–placebo’. Since the alternative hypothesis is that at least one of the time points is ≥5 ms, a multiplicity adjustment was necessary [7]. Therefore, the CIs were calculated using an adjusted \( \alpha \) level based on the Hochberg procedure [8]. Assay sensitivity was established if there was at least one time point at which the lower confidence bound of the mean difference of moxifloxacin and placebo was >5 ms.

For heart rate and for PR and QRS intervals as well as change from baseline for QTcF, similar figures were generated based on descriptive statistics. Categorical outliers and T-wave morphology were summarised by treatment and visit in frequency tables with counts and percentages for both number of subjects and number of time points. For categorical outliers, the number (%) of subjects as well as time points that had increases in QTc from baseline of >30 ms and >60 ms and absolute QTc values >450, >480 and >500 ms were presented by treatment group, respectively. For T-wave morphology, the analysis was focused on change from baseline (treatment-emergent changes).
The relationship between placebo-corrected ΔQTcF (ΔΔQTcF) and dalbavancin concentrations was investigated by a linear mixed-effects modelling approach [9,10]:

\[ \Delta \Delta QTcF_{ij} = \text{Intercept}_i \times \text{slope}_i \times C_{ij} + \varepsilon_{ij} \]

where ΔΔQTcF was the time-matched, placebo-corrected change-from-baseline QTcF for subject i at time j with dalbavancin concentration C_{ij}. The residual ε_{ij} was assumed to be identical, independent, normally distributed (iidN) with mean 0 and variance \( \sigma^2 \).

Three linear models were considered: (a) with an intercept; (b) with mean intercept fixed to 0 (with variability); and (c) with no intercept, i.e. a linear model with only slope. Time-matched concentration was included in the model as a variable and subjects as a random effect for both intercept and slope, whenever applicable. A plot of standardised residuals versus fitted values was used to examine departure from model assumptions. The normal Q–Q plots of the random effects and the within-subject errors were used to investigate the normality of the random effects and the within-subject errors, respectively. A final assessment of the adequacy of the linear mixed-effects model was provided by a goodness-of-fit plot (i.e. the observed concentration quantile–ΔΔQTcF plot) as proposed by the FDA’s Interdisciplinary Review Team [11]. Such a plot was used to check the assumption of linearity between dalbavancin concentrations and ΔΔQTcF and how well the predicted ΔΔQTcF matched the observed data in the regions of interest. The mean ΔΔQTcF at the observed geometric mean C_{max} was calculated. Since C_{max} is usually log-normally distributed, the geometric mean is more appropriate to use than the arithmetic mean [11].

3. Results

In total, 200 healthy subjects (119 female and 81 male) were enrolled and 50 were assigned to each of the four treatments. The analysed population consisted of 50 subjects each in the dalbavancin 1000 mg and moxifloxacin treatment groups, 49 subjects in the placebo group and 48 subjects in the dalbavancin 1500 mg group; 3 patients did not have ECG data available post baseline. The mean ± standard deviation (S.D.) age of the subjects was 28.8 ± 10.0 years (range, 18–55 years) and the mean ± S.D. weight was 73.1 ± 11.6 kg.

3.1. Pharmacokinetics

Plasma concentrations after infusion of 1000 mg and 1500 mg dalbavancin are shown in Fig. 1. After receiving a 1000 mg dalbavancin i.v. infusion, the mean exposure after 24 h [24-h area under the concentration–time curve (AUC0–24h)] was 3184.82 µg h/mL with a mean C_{max} of 287.3 µg/mL occurring at a median of 0.62 h. After receiving a 1500 mg dalbavancin i.v. infusion, the mean AUC0–24h was 4836.64 µg h/mL with a mean C_{max} of 422.6 µg/mL occurring at a median of 0.62 h.

3.2. Electrocardiographic effects

At baseline (Day-1), ECG parameters were well balanced across treatment groups, with mean heart rate between 63 bpm and 67 bpm, mean QTcF between 405.3 ms and 407.9 ms, mean PR between 135.6 ms and 141.2 ms, and mean QRS between 103.7 ms and 105.9 ms.

There was an initial small increase of heart rate immediately before and after the infusion compared with the baseline day in all treatment groups (Fig. 2). This effect peaked at 1 h (30 min after the end of the infusion), with a change-from-baseline HR (ΔHR) of 3–5 bpm in all treatment groups. Heart rate changes at all other time points were small and within 4 bpm for all groups. The mean placebo-corrected change-from-baseline heart rate (ΔΔHR) was small for all active treatments. The largest mean ΔΔHR was 2.0 bpm (90% CI 0.2 to 3.9) at 3 h in the dalbavancin 1000 mg group, 2.4 bpm (90% CI −0.2 to 4.9) at 8 h in the dalbavancin 1500 mg group and 3.4 bpm (90% CI 1.1 to 5.7) at 3 h in the moxifloxacin group.
Table 1
Placebo-corrected change from time-matched baseline QTcF (ΔQTcF, in ms)*.

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<th>90% CI Upper</th>
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SE, standard error; CI, confidence interval.
* Results from the statistical modelling.

In all treatment groups, mean QTcF was somewhat shorter at the pre-dose, 0.5-h and 1-h time points compared with the time-matched baseline, with no clear differences across treatments (Fig. 3). In the dalbavancin group, a clear increase of the change-from-baseline QTcF (ΔQTcF) was observed from 2 to 12 h post dosing, and this effect peaked at 4 h with a mean ΔQTcF of 10.0 ms (90% CI 8.0 to 11.9). Dalbavancin did not have an effect on the QTcF interval, with the ΔQTcF pattern across time points being similar between both doses of dalbavancin and placebo. The largest mean placebo-corrected ΔQTcF (ΔΔQTcF) was 1.5 ms (90% CI −0.6 to 3.6) at 6 h after dosing of dalbavancin 1000 mg and 0.2 ms (90% CI −1.7 to 2.0) at 24 h after dosing of dalbavancin 1500 mg; ΔΔQTcF was negative at all other time points after the 1500 mg dose, with the largest shortening observed at 3 h (−4.1 ms; 90% CI −7.1 to −1.2) (Table 1). The study’s ‘assay sensitivity’ was confirmed by the placebo-corrected ΔQTcF (ΔΔQTcF) response after a single-dose of 400 mg moxifloxacin. The mean peak ΔΔQTcF effect reached 12.9 ms at 2 h, with the lower bound of the 90% CI exceeding 5 ms at all three pre-specified time points (lower bound of 90% CI 10.5 ms at 2 h, 7.1 ms at 3 h and 8.6 ms at 4 h) (Table 1).

There were no subjects with a QTcF value exceeding 480 ms at any time point post dosing. Two subjects in the dalbavancin 1000 mg had QTcF values exceeding 450 ms at a total of six time points, and no subjects in the dalbavancin 1500 mg had QTcF values above this threshold. Two subjects in the placebo group (at 8 time points) and four subjects in the moxifloxacin group (at 13 time points) had QTcF values exceeding 450 ms. No subjects had a ΔQTcF exceeding 60 ms at any of the time points. One subject in the dalbavancin 1500 mg had a slightly negative T-wave at one time point, but no other T-wave morphology changes were observed in the dalbavancin treatment groups. Notched, flattened, diphasic or slightly negative T-waves were occasionally observed in the placebo and moxifloxacin treatment groups.

The precision of the QTc measurements was calculated as the standard deviation of the ΔQTcF. The mean standard deviation for ΔQTcF across time points and subjects was 6.2 ms on placebo, 7.6 ms on moxifloxacin, 6.6 ms on dalbavancin 1000 mg and 8.8 ms on dalbavancin 1500 mg.

A concentration–effect model with a mean intercept fixed to zero with variability was found to fit the data best. The relationship between dalbavancin plasma levels and ΔΔQTcF was very shallow (Fig. 4A); a small, concentration-dependent effect of dalbavancin on the placebo-corrected, change-from-baseline QTcF (ΔΔQTcF) was identified with an estimated slight negative population slope of −0.0051 ms per μg/mL (90% CI −0.0078 to −0.0024) (Fig. 4B). The predicted ΔΔQTcF at the geometric mean peak dalbavancin plasma concentration observed after 1000 mg (285 μg/mL; 90% CI 275 to 294) was −1.5 ms and after 1500 mg (421 μg/mL; 90% CI 408 to 434) was −2.1 ms.

The effect of dalbavancin on cardiac conduction (PR and QRS intervals) was small and there were no notable differences across treatments groups. The placebo-corrected effect (ΔΔPR) was slightly reduced in the dalbavancin groups with a biggest change...
of −2.8 ms (90% CI−5.5 to −0.1) at 3 h in the 1000 mg group and of −3.6 ms (90% CI−6.3 to −0.8) at 4 h in the 1500 mg group. The reduction in the moxifloxacin group was of the same magnitude [−3.8 ms (90% CI−5.9 to −1.7) at 3 h]. Treatment with dalbavancin had no meaningful effect on the QRS interval. The mean placebo-corrected change from baseline QRS (ΔΔQRS) were between −1.0 ms and 0.7 ms at all time points post dosing of dalbavancin.

3.3. Safety

One serious adverse event of ectopic pregnancy, unrelated to the study drug, occurred in the dalbavancin 1000 mg treatment group. Two subjects discontinued study treatment: one subject administered dalbavancin 1500 mg exhibited red man syndrome and one subject in the placebo group experienced infusion-related reactions. One subject administered dalbavancin 1000 mg developed asymptomatic thrombocytopenia on Day 2; recovery started on Day 3 and was complete by Day 26 without treatment.

4. Discussion

Dalbavancin is indicated for the treatment of ABSSSI known or suspected to be caused by Gram-positive pathogens. Based on favourable pharmacokinetics with a long half-life, dalbavancin can be given in a weekly dosing regimen, which has the potential to decrease the burden of care associated with this disease by eliminating the need for an indwelling catheter. This simplified treatment regimen will enable selected patients to be treated in an outpatient setting. Patients with serious skin infections are typically >50 years of age and tend to have multiple co-morbidities, including diabetes, congestive heart failure and atherosclerotic heart disease. For these patients, it is important for clinicians to understand the impact of an antibiotic on ECG parameters. Another lipoglycopeptid antibiotic, telavancin, has been found to prolong the QTc interval and consequently it is important to evaluate whether this is a class effect or an effect specific to telavancin.

Data from PK studies of dalbavancin demonstrate that the pharmacokinetics are dose-proportional [12]. Based on data from healthy volunteers, the projected mean Cmax after a single i.v. dose of 1500 mg over 30 min is ca. 428 µg/mL. Such plasma levels would well exceed the maximum Cmax observed in the vast majority of patients receiving the therapeutic dose of 1000 mg, including a significant majority of those with impaired renal or hepatic function. A population PK study using Monte Carlo simulation demonstrated that patients with both renal impairment and low body surface area, the most extreme outlying population, would have a Cmax of ca. 430 µg/mL, which is 130% of the Cmax of 287 µg/mL seen in the normal population. Plasma levels in ‘worst-case scenario’ patients are therefore substantially below the achieved mean Cmax level after the 1500 mg dose in this study, thereby demonstrating that the ECG assessment in this study was done at plasma levels well exceeding those in patients, as required by the ICH E14 guidance [2,3]. Furthermore, given the lack of QT signal in prior phase 1 studies or in ECG data from over 500 patients in phase 3 studies, it was deemed that if a QTc effect of 10 ms could be excluded at plasma levels achieved by a dose of 1500 mg, it can be concluded that dalbavancin would not cause clinically relevant QTc prolongation in patients.

QT prolongation is quite commonly associated with anti-infective drugs from various classes, e.g. fluoroquinolones (moxifloxacin and levofloxacin[13,14]), macrolides[15], azole antifungals[16], antimalariais[16,17] and some drugs used for the treatment of tuberculosis, e.g. bedaquiline[18]. Within the group of anti-infectives indicated for ABSSSI[19], telavancin has been shown to prolong the QTc interval [20,21] and is classified as a drug with ‘possible’ torsades de pointes risk (https://www.credibledmds.org). The thorough QT study with telavancin was conducted before the implementation of the ICH E14 guidance and the analysis was therefore not performed in the same way as in the current study: endpoints included the mean and maximum QTc effect within each subject over 17 post-dosing time points [20]. Telavancin, placebo and moxifloxacin were administered to healthy volunteers in a parallel designed study with 160 subjects (n = 40 in each

![Fig. 4](https://example.com/fig4.png)

(4A) Scatter plot of observed ΔΔQTcF-plasma concentration pairs from all subjects receiving dalbavancin. Data from the 1000 mg dalbavancin group are shown as open circles and data from the 1500 mg group as grey squares. The mean population predicted QTc effect is shown as a solid red line. (B) Goodness-of-fit plot for observed and predicted relation between dalbavancin plasma levels and ΔΔQTcF. The solid black line and grey shaded area show the predicted mean effect using a linear model with an intercept with 90% confidence interval (CI). The horizontal red lines with notches shows the range of dalbavancin plasma concentrations divided into deciles. Red squares with vertical bars denote the observed mean ΔΔQTcF with 90% CI displayed at the median plasma concentration within each decile.
treatment group). The placebo-corrected maximum effect on QTcF on Day 3 was 11.6 ms (upper bound of 90% CI 16 ms) after telavancin 7.5 mg/kg and 15.1 ms (upper bound of 90% CI 20 ms) after 15 mg/kg. By extrapolation of data from these two doses, a QTc effect of 12–15 ms can be estimated at the end of a 10 mg/kg infusion [21]. In phase 3 trials, the incidence of QTc prolongation of >60 ms from baseline or QTcF >500 ms was 8% (52 patients) in the telavancin group compared with 7% (48 patients) among vancomycin-treated patients [21].

In contrast, no evidence of a clinically relevant effect of dalbavancin on cardiac repolarisation was identified in this trial. The largest mean placebo-corrected ΔQTcF (ΔΔQTcF) was 1.5 ms at 6 h after dosing of dalbavancin 1000 mg (90% CI –0.6 to 3.6) and only 0.2 ms (90% CI –1.7 to 2.0) at 24 h after 1500 mg, with negative values at all other post-dosing time points (Table 1). The study’s ‘assay sensitivity’ was clearly confirmed by the moxifloxacin response with a largest ΔΔQTcF of 12.9 ms at 2 h, with the lower bound of the 90% CI exceeding 5 ms at all three pre-specified time points (Table 1). There were no subjects with a QTcF value exceeding 480 ms and no subjects with a ΔQTcF exceeding 60 ms at any of the post-dosing time points.

Response exposure analysis of QTc/plasma level data demonstrated a very shallow relationship (Fig. 4A) with a small, negative concentration-dependent effect of dalbavancin on ΔΔQTcF with a population slope of −0.0051 ms per μg/mL (90% CI –0.0078 to –0.0024) (Fig. 4B). The ΔΔQTcF effects using the linear concentration–effect model can be estimated to −1.5 ms and −2.1 ms after dosing with 1000 mg and 1500 mg, respectively, which is clearly without any clinical significance. Similarly, the effects of dalbavancin on cardiac conduction (PR and QRS intervals) were small and without clinical relevance.

Based on these data, it can be concluded that dalbavancin does not affect cardiac repolarisation or conduction and will not cause clinically relevant QTc prolongation in patients.

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Competing interests

At the time of this study, MWV was the Chief Medical Officer of Durata Therapeutics, Inc. (Branford, CT) and owned stock and stock options in Durata Therapeutics, Inc.; BD is the Global Medical Director for iCardiac Technologies (Rochester, NY) and owns stock and stock options in the company; MZ is an employee of iCardiac Technologies.

Ethical approval

The protocol and informed consent form were approved by the PRACS Institute, Ltd. IRB. All patients provided informed consent at the time of screening.

References