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A randomized trial of budiodarone in paroxysmal atrial fibrillation

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Abstract
Objective The aim of this study was to investigate the preliminary safety and efficacy of three doses of budiodarone in patients with paroxysmal atrial fibrillation.
Background Budiodarone is a chemical analogue of amiodarone and shares its mixed ion channel electrophysiological properties. It has a shorter half-life than amiodarone.
Methods Patients with paroxysmal atrial fibrillation and a previously implanted dual-chamber pacemaker capable of storing electrograms for at least 4 weeks were enrolled. Pacemaker memories were used to quantify atrial tachycardia/atrial fibrillation burden (AT/AFB). All antiarrhythmic drugs were stopped for greater than five half-lives and amiodarone greater than 3 months prior to enrollment. Following a 4-week baseline period to assess AT/AFB off antiarrhythmic drugs, patients with AT/AFB between 3% and 70% were blindly randomized to placebo, 200, 400, or 600 mg BID of budiodarone for 12 weeks followed by a 4-week washout period. Pacemakers were interrogated and safety assessed every 4 weeks. Pacemaker-derived electrograms were adjudicated blinded to treatment assignment. The primary study endpoint was percent change from baseline AT/AFB over 12 weeks of treatment compared to placebo.
Results Of 72 randomized patients, 61 completed the study. The median reduction of AT/AFB for the 400 and 600 mg BID groups vs. placebo was 54% and 74% ($p=0.01$ and 0.001), respectively. The budiodarone dose–response was statistically significant ($p<0.001$). Number and duration of AT/AF episodes were reduced.
Conclusions In this preliminary study, budiodarone at both higher doses significantly reduced AT/AFB. The study is novel because dual-chamber pacemakers, previously placed for standard clinical indications, were successfully used to monitor AT/AFB.

Keywords Antiarrhythmic drugs · Arrhythmia · Atrial fibrillation · Atrial tachycardia · Pacemakers

Abbreviations

AT/AFB	Atrial tachycardia/atrial fibrillation burden
AFSS	Atrial Fibrillation Severity Scale

Clinical trials comparing rhythm and rate-control strategies in patients with atrial fibrillation have not found significant differences in morbidity and mortality [1–6]. However, for patients who are symptomatic, rhythm control continues to be preferred [7]. Currently, amiodarone is the most effective antiarrhythmic drug for maintenance of sinus rhythm [8, 9].

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It is widely used in patients with atrial fibrillation. Unfortunately, amiodarone has significant toxicities that hamper its use. Discontinuation rates due to unwanted effects are as high as 18% within the first year of use [10]. Drug toxicity and discontinuation rates may have masked benefits of the sinus rhythm strategy [11]. Thus, there is an urgent need for a new effective and safe antiarrhythmic drug for the treatment of patients with atrial fibrillation.

Budiodarone was developed to capitalize on the proven efficacy of amiodarone and to avoid its side effects. It has a short plasma half-life (7 h) and a lower volume of distribution (13 L/kg). It is cleared from the body in 48 h. Like amiodarone, budiodarone has balanced, multiple cardiac ion channel inhibiting activity, giving it properties of all four Vaughan Williams antiarrhythmic drug classes [12]. Budiodarone, unlike amiodarone, undergoes rapid metabolism by plasma and tissue esterases [13]. It is thus expected to be less susceptible to drug–drug interactions with drugs that inhibit CYP450 mediated metabolism. After oral administration, it has a rapid onset of action and steady state is reached within 2 to 3 days.

The present study was designed to provide a preliminary indication of the efficacy and safety of budiodarone at three doses in patients with symptomatic paroxysmal atrial fibrillation. The study design is unique. This is the first controlled trial to use implanted permanent pacemakers capable of continuous storage of rhythm and rate for assessment of an antiarrhythmic medication. The diagnostic capabilities of these pacemakers allow precise evaluation of atrial tachycardia/atrial fibrillation (AT/AF) burden [14–17], permitting the collection of large quantities of data from individual patients not possible using non-continuous monitoring.

1 Methods

PASCAL was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 44 centers in the USA, Canada, Poland, and Germany during November 2006 to May 2008. The study was conducted in accordance with the Declaration of Helsinki. Institutional Review Boards or Research Ethics Boards approved the study at each center. Written informed consent was obtained from each patient. The trial was sponsored by ARYx Therapeutics. It was designed with the assistance and advice of a steering committee. A Pacemaker Committee provided advice on the programming of dual-chamber pacemakers to optimize the detection and logging of AT/AF episodes. The data was analyzed by an independent statistician.

1.1 Study population

Patients with paroxysmal atrial fibrillation documented by electrocardiogram, Holter monitor, or pacemaker electrogram and who had a previously implanted dual-chamber pacemaker for standard clinical indications that was capable of detecting and logging AT/AF episodes and storing atrial electrograms were eligible if they also met the following criteria: an AT/AF burden between 3% and 70% during the baseline period, no evidence of persistent atrial fibrillation, and able to have pacemaker antitachyarrhythmia algorithms turned off for the duration of the trial. Exclusion criteria included: amiodarone treatment within 3 months of screening or a history of amiodarone toxicity, catheter ablation within 3 months or cardioversion within 1 month

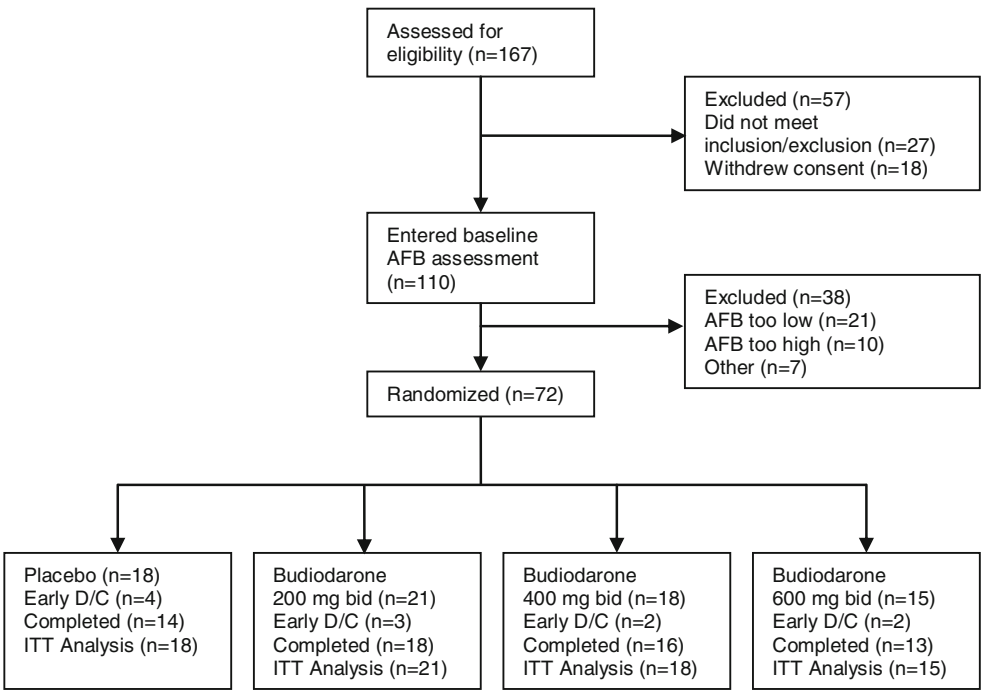

Fig. 1 Patient flow. *AFB* Atrial fibrillation burden, *D/C* discontinuation, *ITT* intention-to-treat

of screening, a left ventricular ejection fraction <25% or New York Heart Association class III or IV heart failure, unstable angina, myocardial infarction, percutaneous transluminal coronary angioplasty or coronary artery bypass surgery within 3 months of screening, or any history of sustained ventricular tachycardia. Concomitant treatment with other antiarrhythmic drugs was prohibited, but use of rate-control therapy was permitted.

1.2 Study procedures

After informed consent, pacemaker programming parameters, related to the detection and logging of AT/AF episodes were optimized. The pacemaker core laboratory, which was blinded to treatment assignment, provided technical training to all participating centers to standardize the programming of the pacemakers. The lower rate of sensing/tracking was set at 70 beats per minute and the upper rate at 80% of the maximum age-predicted heart rate. Investigators were permitted to set rates that were optimal for patient care. Atrial sensitivity was set to minimize under- and over-sensing of true atrial events, with optimization of the signal-to-noise ratio. Once set, atrial sensitivity was not changed for the duration of the study period (baseline, treatment, and washout phases). Inappropriate sensing or inadvertent modifications of these settings were communicated by the

Table 1 Baseline characteristics of the study subjects

Characteristic	Placebo (*N*=18)	Budiodarone			All (*N*=72)
		200 mg BID (*N*=21)	400 mg BID (*N*=18)	600 mg BID (*N*=15)	
Age – mean years (range)	66.7 (57–79)	67.1 (51–88)	70.0 (57–81)	74.2 (65–85)	69.2 (51–88)
Male	14 (77.8%)	12 (57.1%)	8 (44.4%)	7 (46.7%)	41 (56.9%)
Coronary artery disease	8 (44.4%)	9 (42.9%)	5 (27.8%)	2 (13.3%)	24 (33.3%)
Hypertension	12 (66.7%)	15 (71.4%)	15 (83.3%)	14 (93.3%)	56 (77.8%)
Congestive heart failure, NYHA class I or II	11 (61.1%)	12 (57.1%)	9 (50.0%)	11 (73.3%)	43 (59.7%)
Left ventricular ejection fraction – mean% (SD)	58.1 (9.1)	55.6 (10.7)	55.2 (8.9)	55.1 (8.6)	56.0 (9.3)
Left atrial diameter – mean mm (SD)	40.7 (3.6)	43.7 (7.6)	40.3 (4.2)	41.5 (4.2)	41.6 (5.3)
Indication for pacemaker implantation					
Sick sinus syndrome	9 (50.0%)	13 (61.9%)	10 (55.6%)	9 (60.0%)	41 (56.9%)
Tachy–Brady syndrome	7 (38.9%)	8 (38.1%)	12 (66.7%)	9 (60.0%)	36 (50.0%)
A–V Block	3 (16.7%)	5 (23.8%)	2 (11.1%)	0 (0.0%)	10 (13.9%)
Duration of PAF – mean months (SD)	44.2 (36.4)	51.7 (35.3)	77.4 (83.5)	47.5 (53.8)	55.4 (55.5)
Symptomatic PAF	12 (66.7%)	16 (76.2%)	18 (100.0%)	10 (66.7%)	56 (77.8%)
Baseline AT/AF burden – mean% (SD)	20.9 (21.4)	29.8 (28.9)	23.2 (21.5)	28.7 (22.2)	25.6 (23.7)
Prior cardioversion	1 (5.6%)	7 (33.3%)	2 (11.1%)	2 (13.3%)	12 (16.7%)
Prior ablation	4 (22.2%)	5 (23.8%)	5 (27.8%)	2 (13.3%)	16 (22.2%)
Amiodarone use in the past 2 years	1 (5.6%)	4 (19.0%)	3 (16.7%)	3 (20.0%)	11 (15.3%)
Prior rate-control therapy	8 (44.4%)	14 (66.7%)	11 (61.1%)	9 (60.0%)	42 (58.3%)
Medications in use at baseline					
Any antithrombotic therapy	17 (94.4%)	21 (100.0%)	17 (94.4%)	15 (100.0%)	70 (97.2%)
Antiplatelet	11 (61.1%)	8 (38.1%)	5 (27.7%)	8 (53.3%)	32 (44.4%)
Anticoagulation	12 (66.7%)	19 (90.5%)	13 (72.2%)	12 (80.0%)	56 (77.8%)
Beta blockers	14 (77.8%)	17 (81.0%)	16 (88.9%)	13 (86.7%)	60 (83.3%)
Cholesterol-lowering medication	12 (66.7%)	15 (71.4%)	9 (50.0%)	10 (66.7%)	46 (63.9%)
ACEI or ARB	9 (50.0%)	7 (33.3%)	7 (38.9%)	7 (46.7%)	30 (41.7%)
Calcium channel blockers	5 (27.8%)	3 (14.3%)	4 (22.2%)	4 (26.7%)	16 (22.2%)
Cardiac glycosides	3 (16.7%)	2 (9.5%)	4 (22.2%)	2 (13.3%)	11 (15.3%)
Diuretics	3 (16.7%)	6 (28.6%)	2 (11.1%)	4 (26.7%)	15 (20.8%)

All data presented as "number (percentage)" unless otherwise noted

ACEI Angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *AT/AF* atrial tachycardia/atrial fibrillation, *NYHA* New York Heart Association, *PAF* paroxysmal atrial fibrillation

pacemaker core lab to the participating centers, where the devices were reprogrammed. Atrial rates above 200 beats per minute were defined as episodes of AT/AF. The AT/AF burden was calculated as the percentage time in AT/AF during the total observation period.

AT/AF burden was recorded during a 4-week baseline period. Eligible patients were then centrally randomized to placebo, 200, 400, or 600 mg BID on a 1:1:1:1 basis. The total treatment duration was 3 months, followed by a 4-week washout period. Pacemakers were interrogated at monthly visits. Reports of AT/AF episodes were downloaded and adjudicated at the pacemaker core laboratory blinded to treatment assignment. Safety evaluations at the monthly visits included adverse events, vital signs, a standard 12-lead electrocardiogram, and clinical laboratory tests (chemistry, hematology, urinalysis, and thyroid function tests). Male patients were also tested monthly for inhibin B, follicle-stimulating hormone, luteinizing hormone, and testosterone levels as earlier dog toxicology studies showed reversible inhibition of spermatogenesis. Pulmonary function tests, including carbon monoxide diffusion capacity, were performed at screening and repeated if symptoms suggestive of pulmonary toxicity developed during treatment. Chest X-ray examinations were performed at screening and at the end of treatment. Patients were contacted by telephone midway between each clinic visit to inquire about adverse events. A slit lamp examination was performed at screening for patients who had been on amiodarone within 2 years of study enrollment and at the end of therapy for all patients to assess for corneal microcrystalline deposits. In anticoagulated patients, the international normalized ratio was monitored at weekly intervals for the first 4 weeks of budiodarone therapy and then at least monthly thereafter. Digoxin plasma concentrations were measured monthly if the patient was on digoxin.

1.3 Endpoints

The primary endpoint was the percent change in AT/AF burden over the 12-week treatment period compared to the baseline AT/AF burden. Secondary endpoints were mean duration of AT/AF episodes, mean number of AT/AF episodes, and mean duration of normal sinus rhythm. Part C of the University of Toronto AFSS was assessed at each visit [18]. The AFSS includes seven common symptoms of atrial fibrillation rated on a scale of 0 to 5 where 0 was "no symptoms in the past 4 weeks" and 5 was "the patient has been bothered a great deal by symptoms." The questionnaire was administered at screening, baseline and the end of the baseline period, monthly during treatment, and at the end of the washout period. The pretreatment score is the mean of the screening and baseline scores. The on-treatment score is the mean of the three monthly on-treatment scores. The washout score is the score at 1 month after discontinuing treatment. A patient global clinical impression questionnaire, similar to the patient global assessment used as a primary endpoint in the Ferinject assessment in patients with iron deficiency and chronic heart failure trial, was given at trial termination [19]. At the end of each follow-up visit (every

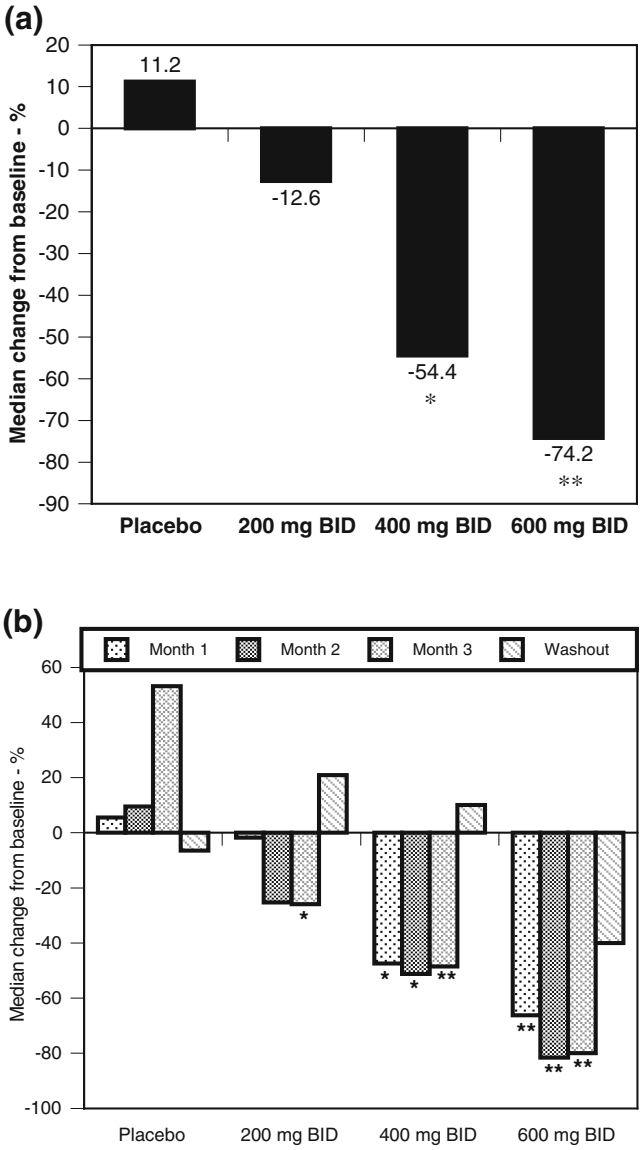

Fig. 2 (**a**) Percent change (median) in atrial tachycardia/atrial fibrillation burden from baseline to 3 months. $p<0.001$ for dose response. *$p<0.05$ for treatment group vs. placebo. **$p<0.01$ for treatment group vs. placebo. (**b**) Percent change (median) in atrial tachycardia/atrial fibrillation burden from baseline by month of treatment. *$p<0.05$ for treatment group vs. placebo within the given month. **$p<0.01$ for treatment group vs. placebo within the given month

4 weeks), patients were asked two questions: "How well did the test medication control your atrial fibrillation symptoms?" and "How satisfied are you with the test medication?" A Likert scale was used to record the patients' responses.

1.4 Statistical analysis

The statistical analysis was based on the intent-to-treat population, which included all randomized patients who had at least one assessment of AT/AF burden during the treatment period. For analysis of the primary endpoint, the Wilcoxon rank-sum test was used for pairwise comparison between each budiodarone treatment group and the placebo group. Dose response was assessed with the Jonckheere–Terpstra test. The secondary endpoints were analyzed using the same statistical tests as for the primary endpoint. Median values are presented to minimize the effect of extreme values in the pacemaker data. The patient global clinical impression questionnaire was analyzed using the Cochran–Mantel–Haenszel mean score test comparing each budiodarone dose group to placebo. A two-sided p value<0.05 was considered statistically significant.

1.5 Role of the funding source

The sponsor (ARYx Therapeutics) participated in the study design together with the academic authors. The sponsor collected the trial data, which were statistically analyzed by a contract research organization (Synteract). The data was interpreted by the steering committee.

2 Results

2.1 Patient population

Of 167 consented patients, 57 were screen failures mostly due to insufficient AT/AF burden or because of withdrawal of consent (Fig. 1). Of the 110 patients enrolled, 38 were excluded after the baseline period because of insufficient AT/AF burden or persistent atrial fibrillation. After randomization, 11 patients discontinued prematurely and 61 completed the study. Of the 11 patients discontinuing early, 3 were for adverse events, 3 were by patient request, 3 were discontinued by the investigator or sponsor, and 2 were discontinued because they did not meet enrollment criteria. The baseline characteristics are described in Table 1. The

Table 2 Change in AF burden

		Budiodarone			*P* value
AFB	Placebo (*N*=18)	200 mg BID (*N*=21)	400 mg BID (*N*=18)	600 mg BID (*N*=15)	
Baseline (pretreatment)					
Mean	20.9 (21.4)	29.8 (28.9)	23.2 (21.5)	28.7 (22.2)	0.5195
Mean (in minutes)	9,029	12,874	10,022	12,398	
Median	10.5	18.6	19.4	17.8	
P value		0.225	0.646	0.180	
Week 8 (on treatment)					
Mean	24.2 (30.8)	27.6 (28.5)	18.8 (25.7)	15.3 (22.4)	0.1258
Mean (in minutes)	10,454	11,923	8,122	6,610	
Median	11.1	16.0	7.7	4.0	
P value		0.4857	0.6295	0.2924	
Week 12 (on treatment)					
Mean	28.2 (34.9)	20.4 (19.3)	16.6 (19.9)	10.4 (19.9)	0.0317
Mean (in minutes)	12,182	8,813	7,171	4,493	
Median	13.7	16.2	9.4	2.5	
P value		0.8424	0.5531	0.0675	
Week 16 (on treatment)					
Mean	28.9 (32.4)	17.2(30.3)	14.8 (21.3)	11.4 (20.5)	0.0244
Mean (in minutes)	12,485	7,430	6,394	4,925	
Median	14.1	8.8	9.0	3.3	
P value		0.3121	0.1393	0.0455	

majority of patients had failed strategies to maintain sinus rhythm with either cardioversion, prior ablation, or attempts at rhythm control with other antiarrhythmic drugs.

2.2 Effects of study drug

There was a dose-dependent decrease in AT/AF burden with increasing dosages of budiodarone ($p<0.001$) (Fig. 2(a) and Table 2). Administration of 400 and 600 mg BID budiodarone resulted in a decrease in AT/AF burden of 54% ($p=0.01$ vs. placebo) and 74% ($p=0.001$ vs. placebo), respectively. This decrease was evident within the first month of treatment for both groups and persisted for the 3-month treatment phase (Fig. 2(b)). AT/AF burden is a summation of the total number of episodes and their duration. Pacemaker interrogation allows for the independent assessment of each of these components. Analysis of the median percent changes from baseline showed that reductions in duration of AT/AF episodes (Fig. 3(c)) and in the number of episodes (Fig. 3 (a)) both contributed to the net reduction in AT/AF burden. These reductions in duration and number of AT/AF episodes led to a reciprocal increase from baseline in the duration of periods in sinus rhythm (Fig. 3(b)). The sample size was too small to perform a gender-based subgroup analysis. However, no consistent gender-based differences in the efficacy parameters were noted (Table 2).

2.3 Safety evaluations

There were no respiratory symptoms suggestive of pulmonary toxicity. There were no deaths on treatment. Serum creatinine showed a reversible and non-progressive elevation of 12% to 21% compared to baseline. Serum-free T3 concentrations decreased between 27% and 35% compared to baseline. Thyroid-stimulating hormone concentrations increased by 65% to 109%, and the only change in free T4 values was an increase of 11.8% in the 600 mg BID group. There was no evidence of clinically overt hyperthyroidism. In all male patients, there were no significant changes in testosterone, luteinizing hormone, follicle-stimulating hormone, or inhibin B hormone levels. No corneal microdeposits in budiodarone-treated patients were detected by slit lamp examination at the end of treatment. There were no end-of-study chest X-ray findings suggestive of drug-induced pneumonitis. No prolongation of the QTc interval was seen in budiodarone-treated patients during periods of sinus rhythm.

2.4 Quality of life assessment

The on-treatment individual AFSS scores were generally low, reflecting low symptom burden (Table 3). There was a positive effect on the overall AFSS score.

3 Discussion

Modern pacemakers are capable of accurately recording and storing cardiac rate and rhythm information over long periods of time, allowing for a more objective assessment

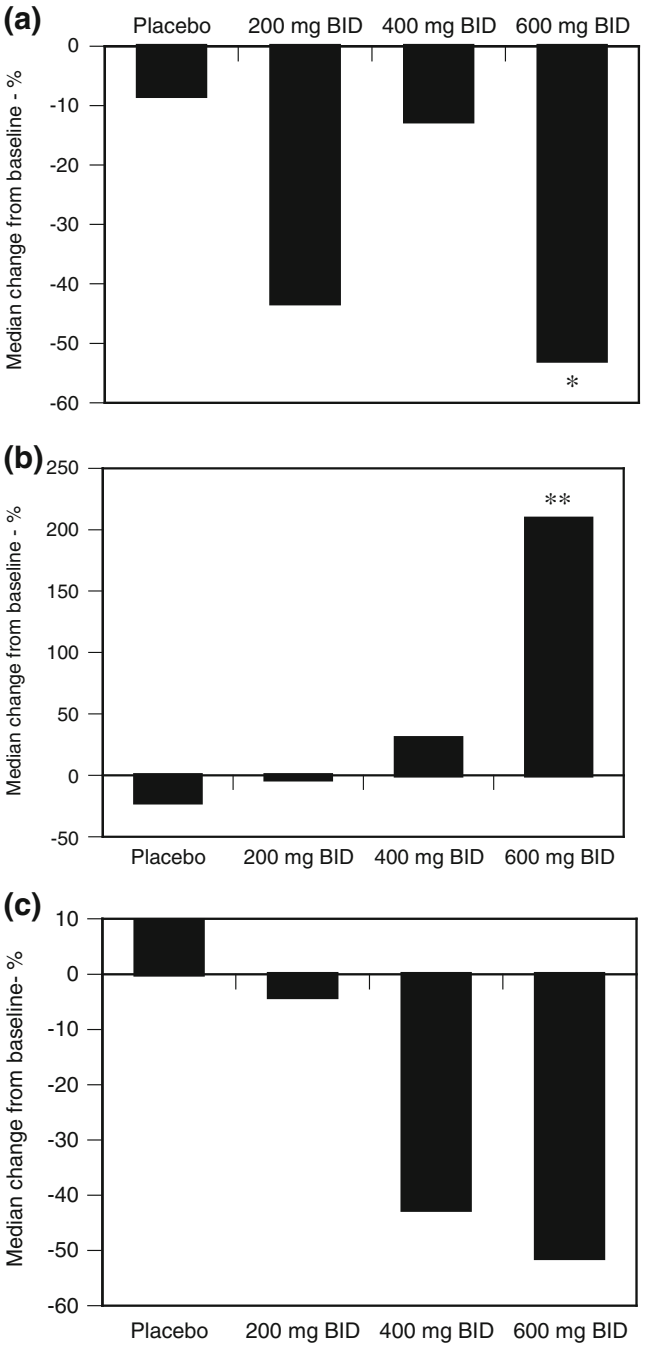

Fig. 3 (**a**) Percent change (median) in number of atrial tachycardia/atrial fibrillation episodes from baseline. $p=0.04$ for dose response. *$p<0.05$ for treatment group vs. placebo. (**b**) Percent change (median) in duration of sinus rhythm episodes from baseline. $p=0.002$ for dose response. **$p<0.01$ for treatment group vs. placebo. (**c**) Percent change (median) in duration of atrial tachycardia/atrial fibrillation episodes from baseline. $p=0.01$ for dose response

Table 3 Mean University of Toronto Atrial Fibrillation Severity Scale (AFSS) symptom scores

Dose group and study period	Mean severity score (0–5)							
	Palpitations	SOB at rest	SOB w activity	Exercise intolerance	Fatigue at rest	Lightheadedness/ dizziness	Chest pain or pressure	Overall AFSS score
Placebo								
Pretreatment	1.3	0.8	1.7	1.5	0.8	1.3	0.6	8.1
On treatment	1.4	0.9	2.1	2.0	1.0	1.1	0.6	9.1
Washout	1.4	0.8	2.0	1.8	0.6	1.0	1.0	8.7
200 mg BID								
Pretreatment	1.6	0.6	1.3	1.2	0.4	0.7	0.3	6.2
On treatment	1.4	0.5	1.3	1.3	0.4	0.9	0.2	6.1
Washout	1.5	0.7	1.2	1.2	0.6	0.9	0.5	6.4
P value[a]	NS	NS	0.06	0.05	NS	NS	NS	0.08
400 mg BID								
Pretreatment	2.5	0.9	1.8	1.6	0.8	0.7	0.5	8.8
On treatment	1.5	0.6	1.8	1.6	0.9	0.4	0.5	7.3
Washout	2.3	0.9	2.7	2.3	0.9	0.8	0.7	10.5
P value[a]	NS	NS	NS	NS	NS	NS	NS	NS
600 mg BID								
Pretreatment	1.4	0.5	1.3	1.1	1.0	0.6	0.5	6.3
On treatment	0.9	0.4	0.8	0.9	1.0	0.6	0.5	5.0
Washout	1.1	0.3	1.3	1.4	1.1	0.5	0.3	6.0
P value[a]	NS	NS	0.004	0.007	NS	NS	NS	0.04

[a] On treatment score compared to placebo using Wilcoxon rank-sum test

of arrhythmia burden. Only patients with dual-chamber pacemakers were included in this study, as an atrial lead is necessary to detect atrial activity.

The first major conclusion of this study is that it is possible to use pacemakers to assess the effects of an antiarrhythmic compound in patients with paroxysmal atrial fibrillation. This methodology is better than less continuous monitoring [20].

The second finding was the demonstration of a significant, dose-dependent decrease in atrial fibrillation burden in patients assigned to budiodarone, with the maximum effect in the 400 and 600 mg BID dose groups, respectively. All doses evaluated were well-tolerated in this short-term study.

In the management of atrial fibrillation, drugs simultaneously targeting multiple electrophysiological mechanisms hold promise [21]. Multimechanistic drugs such as amiodarone [8, 9] and dronedarone [22] are effective in patients with atrial fibrillation. However, amiodarone is not FDA-approved for the management of atrial fibrillation in the USA and its use is hampered by its extracardiac toxicity and complex pharmacokinetic/dynamic profile. Dronedarone, while well-tolerated except in patients with advanced heart failure [23], lacks a dose–response relationship and is generally thought not to be as effective as amiodarone.

Budiodarone targets multiple ion channels [12]. It is eliminated from the body within 48 h following oral administration. In this short-term study, there was no evidence of the toxic effects attributable to amiodarone. Unlike amiodarone [24], slit lamp examinations revealed no evidence of corneal microdeposits after 3 months of therapy with budiodarone. Budiodarone does affect thyroid function with a biochemical profile of hypothyroidism. Hyperthyroidism may be possible. Close monitoring of thyroid function is needed in a phase III trial.

Physiologic pacing (DDDR) has been associated with a reduced risk of atrial fibrillation [25–27]. Since only patients with dual-chamber pacemakers were included in this study, it is important to recognize that the baseline atrial fibrillation burden and symptoms might be lower in these patients than in those without pacemakers, increasing the validity of the outcome. The small sample size and short follow-up duration are limitations. However, the comprehensive nature of the endpoint allowed a statistically significant result with fewer patients.

This study and the recently published, six-patient study of budiodarone [28] are the only studies using continuous monitoring to evaluate an antiarrhythmic drug. Past trials have relied on time to first atrial fibrillation recurrence after

cardioversion [1, 2, 8, 9], providing a less comprehensive evaluation of drug efficacy.

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