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A preliminary assessment of the effects of ATI-2042 in subjects with paroxysmal atrial fibrillation using implanted pacemaker methodology

Anita Arya[1]*, John Silberbauer[1], Sam L. Teichman[2], Peter Milner[2], Neil Sulke[1], and A. John Camm[3]

[1]Eastbourne District General Hospital, King's Drive, Eastbourne BN21 2UD, UK; [2]ARYx Therapeutics, Inc., Fremont, CA, USA; and [3]St George's Hospital, Tooting, London, UK

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Aims ATI-2042 (budiodarone) is a chemical analogue of amiodarone with a half life of 7 h. It is electrophysiologically similar to amiodarone, but may not have metabolic and interaction side effects. The sophisticated electrocardiograph logs of advanced DDDRP pacemakers were used to monitor the efficacy of ATI-2042. The aim of this study was to determine the preliminary efficacy and safety of ATI-2042 in patients with paroxysmal atrial fibrillation (PAF) and pacemakers.

Methods and results Six women with AF burden (AFB) between 1 and 50% underwent six sequential 2-week study periods. Patients received 200 mg bid of ATI-2042 during Period 2 (p2), 400 mg bid during p3, 600 mg bid during p4, 800 mg bid during p5, and no drug during baseline and washout (p1 and p6). Pacemaker data for the primary outcome measure AFB were downloaded during each period. Mean AFB decreased between baseline and all doses: AFB at baseline (SD) was 20.3 $\pm$ 14.6% and mean AFB at 200 mg bid was 5.2 $\pm$ 4.2%, at 400 mg bid 5.2 $\pm$ 5.2%, at 600 mg bid 2.8 $\pm$ 3.4%, and at 800 mg bid 1.5 $\pm$ 0.5%. The mean reductions in AFB at all doses of ATI-2042 were statistically significant ($P < 0.005$). Atrial fibrillation burden increased in washout. Atrial fibrillation episodes tended to increase with ATI-2042, but this was offset by substantial decreases in episode duration. ATI-2042 was generally well tolerated.

Conclusion ATI-2042 effectively reduced AFB over all doses studied by reducing mean episode duration. A large-scale study will be required to confirm this effect.

Keywords Amiodarone analogue • ATI-2042 • Atrial fibrillation • Efficacy • Safety • Pacemakers • Paroxysmal atrial fibrillation • Pacemaker diagnostics

Introduction

Paroxysmal atrial fibrillation (PAF) is a common and distressing arrhythmia. Current anti-arrhythmic drugs (AADs) are only partially effective at treating this condition, and newer, improved agents would be desirable. Amiodarone is the most effective AAD for PAF with an efficacy of preventing recurrence of as high as 60% at 2 years.[1] However, it has a suboptimal pharmacokinetic and metabolic profile,[2–7] an extremely long half-life ($t_{\frac{1}{2}e} = 35–68$ days), and a large volume of distribution ($V_D = 60–70$ L/kg) that contributes to its slow onset of action and toxicity due to metabolic interactions and long residence times within tissues.

To address these issues, a rationally designed, novel structural analogue of amiodarone, ATI-2042, was created for the chronic

* Corresponding author. Tel: +44 1273 773484, Email: anitaarya@doctors.org.uk

oral treatment of AF. Relative to amiodarone, the ester modification of ATI-2042 markedly shortens the half-life of ATI-2042 in blood and tissues by rendering the drug susceptible to rapid metabolism by plasma and tissue esterases with a half-life of 7 h and elimination within hours (Data on file, ARYx Therapeutics).[8] The similarity of the chemical structure, however, allows ATI-2042 to retain the electrophysiological properties of amiodarone.[9]

This study was a proof of concept design seeking preliminary information on the pharmacodynamic effects, safety, and tolerability of the investigational drug ATI-2042 at a variety of doses, in patients with PAF. Patients with advanced DDDRP pacemakers were selected because of the pacemaker's sophisticated diagnostics and the ability to record continuously and log asymptomatic as well as symptomatic episodes.

Methods

Design

The study protocol was approved by the East Sussex Local Ethics Committee. This was an open-label prospective study of the safety and efficacy of the investigational drug ATI-2042 in patients with PAF.

Study drug

ATI-2042 (budiodarone) tartrate salt is chemically synthesized at Ricerca Biosciences (Concord, OH, USA). The tablets are manufactured in Mississauga, Ontario, Canada. All synthesis and manufacturing is in compliance with the United States (US) Food and Drug Administration (FDA) current Good Manufacturing Practice (cGMP) guidelines.

The molecular structure of this new chemical entity is identical to that of amiodarone, except for the presence of a *sec*-butyl acetate side chain at position 2 of the benzofuran moiety (*Figure 1*, Morey *et al.*[9]). The core of the molecule is a benzofuranyl ring system, to which an iodinated diiodophenyl group, a tertiary amine, and the chiral centre of the molecule, an (S)-2-butanyl group, are added over the course of the synthesis. The final drug substance is provided as a tartrate salt.

ATI-2042 is not a prodrug of amiodarone, nor is amiodarone a metabolite of ATI-2042. The electrophysiological activity of ATI-2042 in animals includes (i) inhibition comparable with amiodarone of sodium, potassium, and calcium ion channels, (ii) increased left and right atrial refractoriness comparable with amiodarone, (iii) atrial effects (increased St-A and A-H intervals), (iv) ventricular effects (increased MAPD90 and QT-interval), and (v) a dose-dependent decrease in heart rate (HR)[9] (Data on file, ARYx Therapeutics). The major metabolite (ATI-2000) is electrophysiologically inactive[9] (Data on file, ARYx Therapeutics).

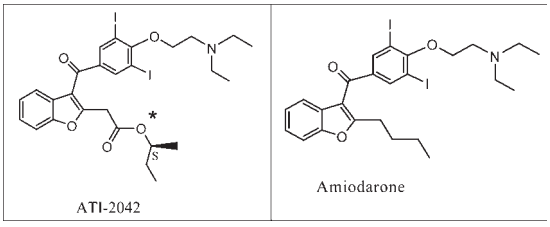

Figure 1 Chemical structures of ATI-2042 (budiodarone) and amiodarone. *Ester bond (see text for details).

Inclusion criteria

Only post-menopausal or surgically sterile females with a significant PAF burden and pacemakers were included. The pacemakers had to have been *in situ* for at least 1 month prior to the study and have appropriate arrhythmia diagnostics. In this study, Vitatron pacemakers, models Selection 9000 or T70 pacemakers, were used. Non-specific but potentially toxic findings were observed in canine testes during pre-clinical safety testing. Although this finding was explored further, it was prudent to commence clinical testing in a population not at risk for this effect. Hence, the present study was limited to post-menopausal or surgically sterile females; the use of the drug in males is being addressed in a subsequent study.

After providing written informed consent, the patients underwent screening assessments to assess suitability for the study and to obtain a baseline medical history and examination. The value of this cohort was that the pacemaker was not inserted for bradycardia but for the treatment of AF using various prevention pacing and rate control techniques. The inclusion criteria were as follows: age 18–85 years; AF burden (AFB) of 1–50%; able to have pacemaker anti-arrhythmic algorithms turned off or remain at a stable setting; stable warfarin regimen; be generally healthy and free from significant comorbid illnesses; and able to understand study requirements.

Exclusion criteria

The exclusion criteria were significant structural heart disease (ejection fraction $<45\%$ and congestive heart failure); abnormal QTc interval (i.e. >470 ms); an abnormal 12-lead electrocardiogram (ECG); known hypersensitivity to amiodarone or iodine; chronic treatment with amiodarone within 3 months; demonstrated lack of efficacy with amiodarone treatment; treatment with any other investigational drug within 30 days; treatment with any anti-arrhythmic medication (exclusive of a stable dose of digoxin or a beta-blocker or calcium blocker) within five half-lives prior to study entry; major surgery within 3 months prior to study entry or any surgery within 2 weeks prior to study entry; or any laboratory assay result that was out of the normal reference range at screening from a standard battery of blood chemistry, haematology, and urinalysis tests.

Protocol

After providing written informed consent, patients were enrolled within 8 weeks of screening. During the study, they were reviewed on days 1, 2, and 8 of each study period. ATI-2042 was increased on day 1 of each 2-week study period, following routine bloods for haematology, biochemistry, and coagulation screens. Plasma samples for pharmacokinetic analysis of ATI-2042 and its metabolites were taken at steady state at the end of each study period just prior to the first escalated dose of the subsequent period and within 15 min prior to the pre-dose ECG for that dose.

Patients were then monitored for at least 3 h continuously post-dose; this included telemetry, vital signs, and oxygen saturations. Electrocardiograms were taken, and the pacemaker data were downloaded prior to drug administration on day 8 and day 14 of each study period.

Criteria for drug discontinuation included a fall in systolic blood pressure (BP) to <90 mmHg systolic, an increase in BP >200 mmHg, intolerable side-effects, a change in rhythm that in the opinion of the investigator constituted a risk to safety, or a QRS increase $>50\%$. Where possible, ECGs of intrinsic rhythm rather than ventricular-paced rhythm were obtained, as paced complexes can be difficult to interpret for QT prolongation. An increase in QT interval >470 ms for intrinsic and >550 ms for paced beats or an increase of 30% was considered significant.

Drug titration

The study consisted of six 2-week periods: a baseline period (p1), four treatment periods (p2–p5), and a washout period where return to baseline was observed (p6).

The initial ATI-2042 dosage for all subjects was 200 mg orally bid, and it was then increased by 200 mg bid for each subsequent study period. Patients received 200 mg bid of ATI-2042 during period 2, 400 mg bid during period 3, 600 mg bid during period 4 and 800 mg bid during period 5, and no drug was administered during baseline and washout periods.

Device characteristics

Selection 9000 and T70 pacemakers (Vitatron, Arnhem, The Netherlands) are dual-chamber pacemakers with sophisticated and similar algorithms for AF detection and prevention. Atrial fibrillation detection is based on atrial rate; atrial tachyarrhythmias are detected when the median atrial cycle length is less than that programmed for AT or AF detection. In all patients, atrial fibrillation was detected if the atrial rate was >200 bpm for six consecutive beats, and its end logged if the atrial rate dropped below 200 bpm for 10 beats. An arrhythmia diary of up to 400 episodes and 15 detailed onset reports (DORs) were recorded with rate profile, interval plots, and electrograms to confirm diagnosis. Pacemaker anti-arrhythmic algorithms were turned off prior to entry into the baseline period and remained turned off until after washout.

Data collection

Pacemaker data, for the primary outcome measure AFB, were downloaded on days 8 and 14 of each 2-week period to allow up to 800 episodes of AF to be recorded.

Outcome measures

The primary outcome measure, AFB, was defined as the duration of time the subject's cardiac rhythm was AF divided by the total time recorded for that study period, expressed as per cent. The total duration of time that the rhythm was AF is a function of the number of PAF episodes and the duration of each episode. Therefore, a reduction in AFB can occur through reduction in either or both of these variables. Atrial fibrillation burden was compared with baseline during the treatment periods. Secondary outcome measures were the number of AF episodes, the safety of ATI-2042, and the incidence and severity of adverse events (AEs).

Data analysis

The minimum study interval was 2 weeks; data were acquired from the pacemaker and averaged to give a final value. Atrial fibrillation burden is given as the percentage of total storage duration.

Statistical analysis

The sample size for this study was selected empirically. All patients who received any amount of study medication were included in the efficacy and safety analysis. Efficacy variables for the study group are described as mean and standard deviation for each study period; individual responses to ATI-2042 are also presented. Due to the small number of subjects, comparisons of periods 2–6 with baseline were made using estimates from a mixed-effects regression model. This model had a fixed, categorical effect of period and a random patient effect to account for correlations over time. A *P*-value of <0.05 was considered significant.

Electrocardiogram parameters (ventricular HR, PR, QRS, QT, QTc interval) were summarized by baseline, dosing period, and washout using descriptive statistics. Changes from baseline in ECG values at day 8 of dosing and day 14 of washout were also summarized. Baseline values of ECG parameters are defined as the mean of three values recorded prior to the first dose of ATI-2042.

An AE was defined as any untoward medical occurrence in a study subject administered a medicinal product (either study drug or marketed product), whether or not the event had a causal relationship with this product.

Trough concentrations of ATI-2042 and its metabolites (ATI-2000, ATI-2100, and ATI-2142), measured at pre-dose on day 1 of each of the four treatment periods and on days 1 and 8 of the washout period, were summarized by time point. Spearman's rank correlation was used to examine the relationship between trough concentrations of ATI-2042 and AFB.

Levels of pacemaker malsensing of AF or over- and under-sensing were evaluated by the manual examination of each DOR; this was performed for all patients and or every pacemaker download throughout the study and confirmed by an independent observer. It is presented as a percentage of the DORs.

Results

Recruitment

Six females, mean age (SD) 70.8 ± 7.1 years with PAF of mean duration 4.7 ± 2.3 years, were recruited from Eastbourne District General Hospital between March and July 2005. One patient withdrew in period 3 due to gastric AEs (nausea, flatulence, and loose stools) and for logistical reasons.

Baseline characteristics

Patients were treated with a mean of 1.8 ± 1.0 AADs, range 1–3, for PAF prior to study entry. Three patients had Vitatron T70 pacemakers and three had Selection 9000s. All patients had echocardiographic assessments prior to the study; mean (SD) left atrial diameter 3.66 ± 0.54 cm and mean fractional shortening 41.4 ± 10.7% (*Table 1*).

Pharmacokinetics

All patients were compliant with study medication. Mean trough levels of ATI-2042 were 0.0 ± 0.0 ng/mL at baseline, 2.4 ± 0.9 ng/mL at 200 mg bid, 5.2 ± 1.7 ng/mL at 400 mg bid, 13.1 ± 5.6 ng/mL at 600 mg bid, and 19.8 ± 17.9 ng/mL at 800 mg bid, indicating some dose proportionality. In washout, trough levels of ATI-2042 were 0.3 ± 0.4 ng/mL, and its metabolites were low or undetectable. There was a trend towards correlation between AFB, AF episodes

Table 1 Patients' characteristics

Patient	Age	LAD (cm)	FS (%)	No. of AADs	Arrhythmia duration (years)
1	71	3.12	39.25	2	8
2	81	4.36	33.88	1	4
3	75	3.05	59.9	1	4
4	72	4.09	34.8	1	7
5	65	3.4	48.18	3	3
6	61	3.95	32.43	3	2

Table 2 **Mean (SD) absolute atrial fibrillation burden, relative reductions (RR), and changes in episode number and episode duration per study period**

	p1	p2	p3	p4	p5	p6
N	**6**	**6**	**6**	**5**	**5**	**6**
Dose (bid) of ATI-2042	Baseline	200 mg	400 mg	600 mg	800 mg	Washout
AFB (%)	20.4 ± 14.6	5.2 ± 4.2*	5.2 ± 5.2*	2.8 ± 3.4*	1.5 ± 0.5*	11.7 ± 14.0
P-value vs. p1	—	0.0045	0.0047	0.0023	0.0013	0.1880
RR-AFB (%)	—	71.2 ± 31.3	71.7 ± 20.6	79.9 ± 26.4	86.8 ± 9.8	27.4 ± 78.3
Episodes (no.)	19.3 ± 22.1	31.4 ± 38.0	31.9 ± 42.3	41.6 ± 66.2	22.1 ± 27.8	30.9 ± 46.3
Episode duration (hrs)	4.8 ± 5.2	1.7 ± 2.5*	0.6 ± 0.7*	0.1 ± 0.2*	0.5 ± 0.7*	2.4 ± 3.0
Trough PK level (ng/mL)	0.0 ± 0.0	2.4 ± 0.9	5.2 ± 1.7	13.1 ± 5.6	19.8 ± 17.9	0.3 ± 0.4

p1 is baseline, p2 200 mg bid, p3 400 mg bid, p4 600 mg bid, p5 800 mg bid, and p6 is the washout period. *$P < 0.05$ when compared with p1.

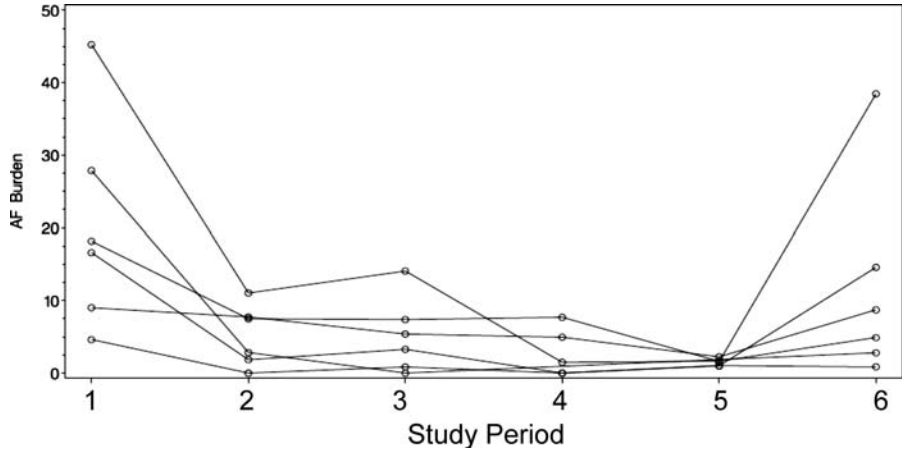

Figure 2 Individual plots of atrial fibrillation burden by study period.

or averaged sinus rhythm duration, and trough levels of ATI-2042, but this did not reach statistical significance.

Pacemaker data

A summary of ATI-2042 efficacy measures is shown in *Table 2*. Mean AFB at baseline ranged from 4.6 to 45.3%, mean (SD) 20.3 ± 14.6%. Absolute values of AFB decreased between baseline and all doses; mean AFB (SD) at 200 mg bid was 5.2 ± 4.2%, at 400 mg bid 5.2 ± 5.2%, at 600 mg bid 2.8 ± 3.4%, and at 800 mg bid 1.5 ± 0.5%. There was a 71.2 ± 31.3% relative reduction (RR) in p2 from baseline ($P = 0.0045$), 71.7 ± 20.6% in p3 ($P = 0.0047$), 79.9 ± 26.4% in p4 ($P = 0.0023$), and 86.8 ± 9.8% in p5 ($P = 0.0013$). Atrial fibrillation burden increased towards baseline in washout; mean (SD) 11.7 ± 14.0%, range 0.8–38.4 ($P = 0.1880$ compared with baseline). Individual dose–response curves are shown in *Figure 2*.

The number of AF episodes increased initially with ATI-2042 and remained elevated in washout (*Table 2* and *Figure 3*). Mean episode duration (SD) decreased from baseline at 4.8 ± 5.2 to

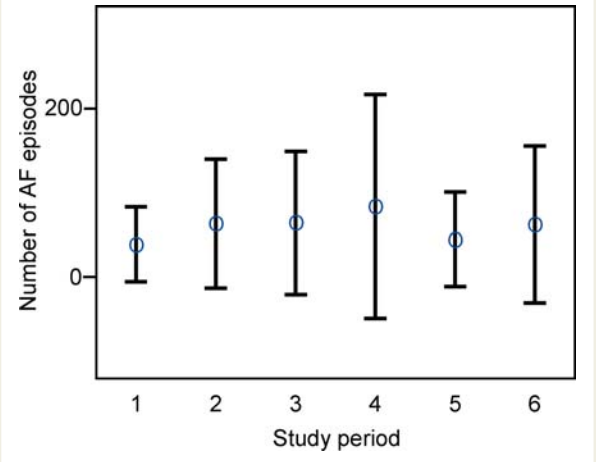

Figure 3 Mean (95% CI) (SD) plot of number of atrial fibrillation episodes by study period.

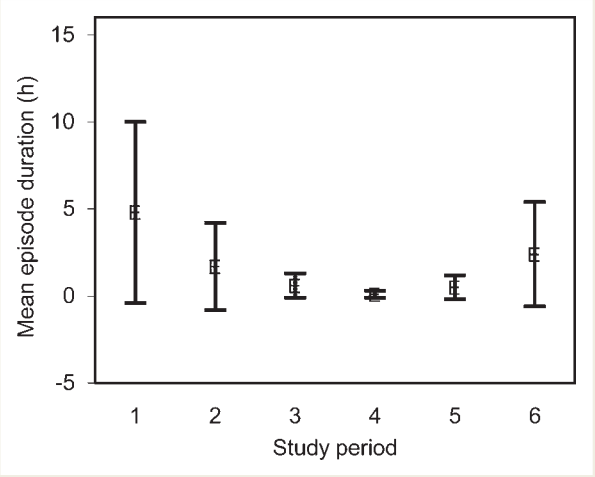

Figure 4 Mean (95% CI) (SD) plot of atrial fibrillation episode duration by study period.

1.7 ± 2.5 h in p2, to 0.6 ± 0.7 h in p3, to 0.1 ± 0.2 h in p4, to 0.5 ± 0.7 h in p5 (*Figure 4*). Mean episode duration increased in washout to 2.4 ± 3.0 h, but did not reach baseline values.

Electrocardiographic effects of ATI-2042

There were no significant changes in HR, QRS, QT, or QTc between baseline and dosing or washout. There were no clinically significant changes in overall ECG interpretation. The PR interval showed a trend towards decreasing: reductions from baseline were 16.6 ± 23.9% at 200 mg bid, 11.4 ± 22.6% at 400 mg bid, 27.0 ± 32.1% at 600 mg bid, 35.1 ± 30.9% at 800 mg bid, and 30.7 ± 24.3% at washout. There were no group or individual trends to QT or QTc prolongation with dosing. One patient exhibited a 30–60 ms change in QTc from baseline at 400 mg bid; this patient had had a previous atrioventricular (AV) node ablation and had permanently paced rhythm. A change in the paced QTc amounted to 15% from baseline. No patient exhibited >30% change from baseline QT or QTc with dosing, despite the presence or absence of pacing.

Safety

The drug was generally well tolerated. There were no serious AEs related to study drug. The number of subjects with AEs was similar in all groups, and most were of mild severity. The highest number of AEs was in period 5 (800 mg bid) and the fewest in period 4 (600 mg bid); gastric AEs, including transient nausea, flatulence, and loose stools, were more prevalent at 800 mg bid, clinically insignificant biochemical abnormalities at 400 mg bid, and cardiac AEs (transient palpitations) while taking 200 mg bid of ATI-2042.

There were no cases of proarrhythmia, clinical hypothyroidism, or hyperthyroidism. Three patients demonstrated dose–responsive increases in thyroid-stimulating hormone, which were outside the normal range. The level in one patient increased from 2.53 to 4.82 mU/L (normal range 0.27–4.2), another increased from 3.51 to 9.49 mU/L, and a third increased from 0.68 to 16.12 mU/L. None was associated with clinical abnormalities, and all returned towards normal after drug discontinuation in washout. There were minor fluctuations in free T4 and free T3, which were felt not to be clinically significant.

Accuracy

A total of 524 DORs were manually overread for accuracy, mean 87 ± 69 per patient. A total of 10.9% of the DORs exhibited under- or over-sensing, and 6.3% of the DORs were undersensed almost exclusively due to blanking of P waves during AV delay as opposed to P wave fallout. Over-sensing was entirely due to farfield R sensing (4.6%) and was present in one patient; this patient had an excessive inter-electrode distance of 17 mm on the atrial pacing lead. The mean number of malsensed DORs/patient was 10 ± 12.

Discussion

During anti-arrhythmic drug (AAD) development, establishing human drug efficacy in phase I to III studies is often hindered by problems of proarrhythmia and tolerability. In addition, arrhythmic conditions are challenging to treat and evaluate because of heterogeneous temporal patterns of arrhythmia behaviour.

This study was novel in using the sophisticated data logs of pacemakers to monitor drug efficacy continuously throughout the study and to record all episodes of AF including those which were asymptomatic. Patients with refractory PAF who had failed at least one AAD therapy were included in this study. ATI-2042 was significantly effective in reducing AFB at all doses in this group of patients. The endpoint of AFB can be affected by a reduction in the number of episodes of AF, indicating an effect on AF initiation, or by a reduction in the duration of episodes, indicating an effect on the sustainability of the episodes. In this study, therapy with ATI-2042 was associated with a mild trend for the number of episodes to increase with doses up to 600 mg bid, but this was offset by a substantial shortening of mean AF episode duration at all doses that reached statistical significance. The overall effect was a clinically and statistically significant reduction in AFB.

It was also apparent that the effects of ATI-2042, despite its short half-life, have a prolonged cardiac effect after discontinuation of the drug. Even in washout, AF parameters did not completely return to baseline. Trough levels of ATI-2042 and its metabolite were low or negligible within days of drug discontinuation, making drug persistence unlikely. It is difficult to generalize the effects of ATI-2042 at this stage or to rule out random effects, but it is possible that even relatively short courses of this drug may promote atrial reverse-remodelling, which have a carry-over effect longer than its metabolism.

Overall, the drug was well tolerated. The absence of the electrocardiographic changes that were seen in animal testing may be due to the small sample size and/or the inclusion of patients with prior AV nodal ablation procedures with paced rhythms. One patient withdrew due to moderate gastric side effects and logistical reasons. There were no serious AEs related to study drug and no cases of proarrhythmia. Minor changes in thyroid function studies were likely reflective of the iodine content of ATI-2042. These resolved during continued study drug administration or

after discontinuing the study medication. This pattern of thyroid function study changes is consistent with those reported for amiodarone.[2] These findings require additional evaluation in future studies.

Paroxsymal atrial fibrillation is a common, distressing arrhythmia, which is often difficult to treat due to its heterogeneity and the tendency for AADs with class III action to exhibit reverse-use dependency. Drugs with multiple classes of action rather than specific class action, such as amiodarone, are the most efficacious in treating AF, but many drugs are limited to low-risk patients because of concerns regarding proarrhythmia. Amiodarone has been shown to be superior to other AADs in the maintenance of sinus rhythm post-cardioversion,[1,10,11] but it is less effective in preventing recurrence in PAF than chronic AF.[11] It has a pharmacokinetic and metabolic profile that contributes to its slow onset and offset of action and its toxicity. Prescribing class I agents, such as flecanide and quinidine, tends to be limited to patients without ischaemic heart disease, who have preserved left ventricular function. This is due to the observation of increased mortality of post-myocardial infarction patients in the Cardiac Arrhythmia Suppression Trial[12] and concerns regarding Torsades de Pointes extending to 'pure' class III agents such as dofetilide and ibutilide.[13–18] New atrio-selective drugs that prolong atrial refractoriness without significant effects on ventricular refractoriness or the QT interval appear promising, but are early in development.[19,20] In the present study, ATI-2042 was well tolerated and effective in reducing AFB, with decreases of at least 70% in AFB at all doses. Its short half-life, rapid onset and offset, small volume of distribution, and cytochrome P450-independent elimination represent attractive drug features of an AAD.

This study used the sophisticated monitoring capacity of pacemakers to record all episodes of AF and differed from the conventional means of assessing drug efficacy by the 'time to first recurrence' of AF. 'Time to first recurrence' is the time taken for an atrial tachyarrhythmia to recur post-chemical or electrical cardioversion.[1] This measure makes the assumption that AF episodes are uniformly random, i.e. the risk of having an episode at any given time is uniform.[21–25] However, recent data from pacemaker and defibrillator studies suggest a tendency to clustering of fibrillation episodes with the highest instantaneous risk of AF being immediately after termination.[24] Human arrhythmia patterns vary between patients and the majority of episodes are asymptomatic,[25–27] making assessment of drug efficacy in PAF patients challenging even with frequent study follow-up or trans-telephonic monitoring. Despite the complexities and heterogeneous nature of PAF, we propose that pacemaker data logs provide a comprehensive documentation of arrhythmia events. The degree of accuracy of the pacemaker diagnostics as determined by manual overreading supports the use of this method to measure AFB. Pacemaker logs may also monitor for proarrhythmia and can be used with handheld activators to correlate symptoms with events.

Study limitations

The small number of subjects enrolled and the limited duration of exposure to ATI-2042 limit generalization of the study results. The study was also limited to post-menopausal females, which have in some studies been identified as a higher responder group to amiodarone;[1] the inclusion of men is to be addressed in a subsequent study.

The use of a novel methodology to document the antiarrhythmic effects of ATI-2042 is also a limitation of the study. The inclusion of a positive comparator arm with a well-characterized drug such as amiodarone or sotalol would have strengthened the study design by aiding in the interpretation of results, but would have made the study more complex to conduct.

Nevertheless, the information from this study is useful in establishing preliminary electrophysiological effects of ATI-2042 in patients and in guiding future studies. In order to generalize any effects of ATI-2042 on AF mechanism and confirm dose effects, a parallel-design study including a placebo control with a larger cohort of patients with longer follow-up is required.

Accurate sensing of arrhythmias is a consideration for all methods of monitoring, particularly in relation to drug efficacy. In this study, levels of malsensing were low because rigorous attempts were made to eliminate malsensing at screening. Sensing can often be optimized with appropriate expertise, and oversensing can be reduced by the use of short tip-to-ring electrodes.[28–31]

Conclusion

Despite limitations, this study preliminarily suggests that ATI-2042 is safe, well tolerated and may reduce AFB in patients with PAF. It has a promising electrophysiological and pharmacokinetic profile that makes it an attractive alternative to amiodarone. This study provides support for further clinical trials that evaluate the use of this investigational drug in an expanded cohort of patients with PAF and supports the concept of using implanted pacemaker devices to monitor AAD efficacy. Such a randomized, double-blind, placebo-controlled clinical trial of ATI-2042 is currently being completed.

Conflict of interest: P.M. is an employee and shareholder of ARYx Therapeutics, Inc. S.L.T. was an employee of ARYx Therapeutics, Inc.

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