

Fact Sheet – Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia facing physicians with recent epidemiological studies estimating that there are over 11 million AF sufferers in the seven major economies. The prevalence of AF is predicted to increase two- to three-fold in the next 50 years.

AF is clinically significant because it contributes to the incidence of stroke and overall cardiovascular morbidity and mortality. Patients with AF have a five-fold increased risk for stroke; indeed, in the US approximately 15-25% of all strokes can be attributed to AF.

The treatment of AF is controversial and often problematic. Whereas electrical cardioversion restores sinus rhythm in many patients with AF, up to 40% of patients revert to AF within a year and the maintenance of sinus rhythm thus often requires chronic treatment with anti-arrhythmic drugs. Although there is a consensus amongst cardiologists that sinus rhythm control with anti-arrhythmic drugs is the preferred and most effective treatment of AF, none of the existing drugs are able to maintain rhythm without significant negative side effects and new anti-arrhythmic drugs are desperately needed. For example, existing anti-arrhythmic drugs may increase mortality by inducing ventricular arrhythmia, this being the result of drugs interacting with targets that are expressed in the ventricle as well as the atrium. The safety of existing anti-arrhythmic drugs in AF patients is further complicated by the presence of other cardiovascular co-morbidities such as heart failure. To address this unmet medical need, Xention is developing novel anti-arrhythmic agents with a much improved efficacy and safety profile that:

- are selective for an atrium-specific ion channel
- extend action potential duration in human atrial myocytes but not ventricular myocytes
- demonstrate efficacy in the best available preclinical models
- have a once or twice daily dosing regimen
- have no QTc liability
- demonstrate clinical efficacy in AF patients
- are safe and well-tolerated when administered chronically

I_{kur} as a Target for AF

Xention's most advanced AF programme targets the atrium-specific potassium current I_{kur} , which is mediated by the ion channel channel Kv1.5. Kv1.5 plays a significant role in the early stages of repolarisation of the atrial action potential and is widely viewed as an excellent target for new AF treatments. No selective Kv1.5 inhibitors are currently marketed.

Xention has identified two potent, selective antagonists of Kv1.5. The first of these, XEN-D0101, has been assessed in a Phase 1 study that utilised extensive cardiovascular safety monitoring to establish the safety of modulating the Kv1.5 target. This compound is currently being assessed in a clinical proof-of-mechanism electrophysiology Phase 1 study at multiple European sites.

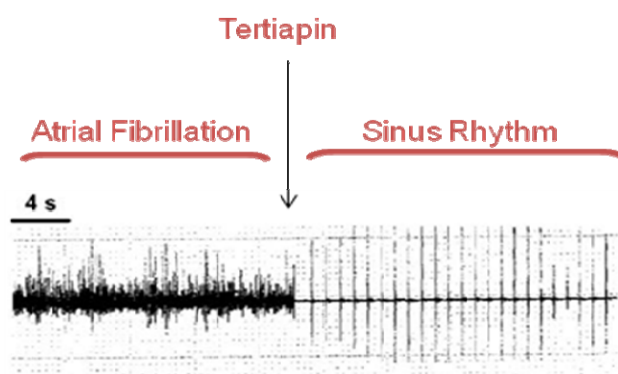
XEN-D0103 is more potent and more selective than XEN-D0101 and has recently completed pre-clinical development. XEN-D0103 demonstrates a very high degree of selectivity over

other cardiac ion channels such as hERG, Nav1.5 and the L-type cardiac calcium channel. Such selectivity is important for the avoidance of QTc liability and ventricular effects.

In addition to demonstrating in vitro selectivity, XEN-D0103 has also demonstrated efficacy in a canine model representing persistent AF in the clinical setting. Administration of XEN-D0103 reduced AF duration, AF inducibility and increased the atrial effective refractory period, without effect on QTc, heart rate or blood pressure. XEN-D0103 will be evaluated in a first time in man study in 2011.

$I_{K_{ACh}}$ as a target for AF

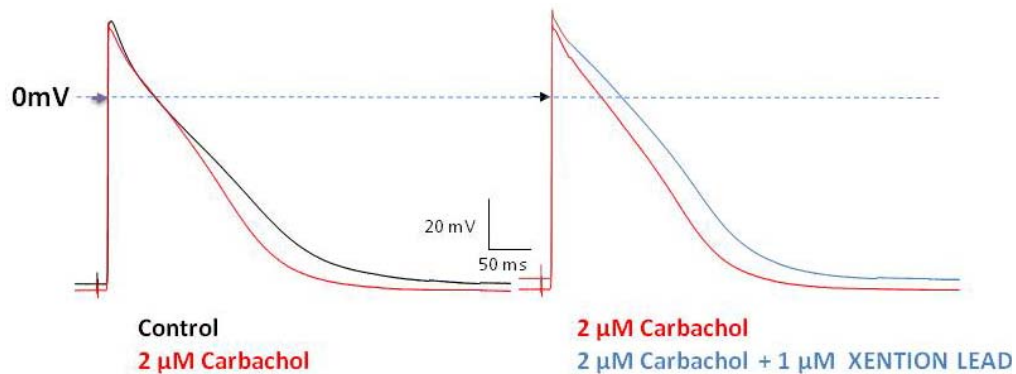
The acetylcholine-activated potassium current $I_{K_{ACh}}$ (carried by the Kir3.1/3.4 channel) is also present predominantly in the atria where it plays a role in stabilizing the resting membrane potential and influencing the action potential duration of atrial cardiac muscle. Activation of $I_{K_{ACh}}$ is associated with profound shortening of atrial action potential duration and refractoriness, which increases the vulnerability to atrial arrhythmias. Indeed, $I_{K_{ACh}}$ is constitutively active in myocytes from patients with chronic AF. Inhibition of $I_{K_{ACh}}$ is therefore considered an attractive approach for the termination of AF and maintenance of sinus rhythm, and the selective $I_{K_{ACh}}$ inhibitor tertiapin, a natural peptide isolated from honey bee venom, preferentially prolongs the atrial action potential duration and terminates AF in canine models.



Hashimoto *et al.* Pharm Res. 2006;54:136-141

Our research programme in this area has identified a number of preferred chemical series and these are currently being optimised. The most advanced series has already provided low nanomolar inhibitors of the target channel with excellent selectivity over other cardiac ion channels. Furthermore these molecules have demonstrated inhibition of the $I_{K_{ACh}}$ current in human atrial tissue as well as showing good efficacy in a canine model of AF.

The diagram below demonstrates the ability of a Xention lead compound to prolong the human atrial action potential duration in vitro. The left panel shows a control cardiac action potential (black line) and the shortened action potential caused by activation of the $I_{K_{ACh}}$ current with carbachol. The right hand side panel shows the ability of a Xention lead compound to reverse the action potential shortening caused by carbachol. The resulting longer action potential duration would be expected to terminate and prevent the recurrence of AF.



In canine efficacy studies of atrial fibrillation the same compound showed a dose-related increase in atrial effective refractory period (AERP) as well as a substantial decrease in AF burden, providing further evidence of the suitability of this approach to prevent the occurrence of AF and maintain sinus rhythm.

