

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, the maintenance of sinus rhythm 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 pro-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 antiarrhythmic agents with a much improved efficacy and safety profile that:

- are selective for atrium-specific channels
- 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

Kv1.5 as a Target for AF

Xention's lead AF programme targets the atrium-specific potassium 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 a preferred target for new AF treatments. No selective Kv1.5 inhibitors are currently marketed.

Our most advanced AF compound is XEN-D0101 is currently in Phase I clinical development and has the potential to deliver a highly beneficial first-in-class therapy for the treatment of AF. We have also identified follow-on compounds that are highly selective Kv1.5 modulators.

XEN-D0101 demonstrates a very high degree of selectivity over non-atrial 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.

XEN-D0101 is able to cause a significant extension of the action potential duration in human atrial tissue, but has no effect on the action potential duration in human ventricular tissue. This is the desired profile of an agent demonstrating atrial selectivity for the treatment of AF.

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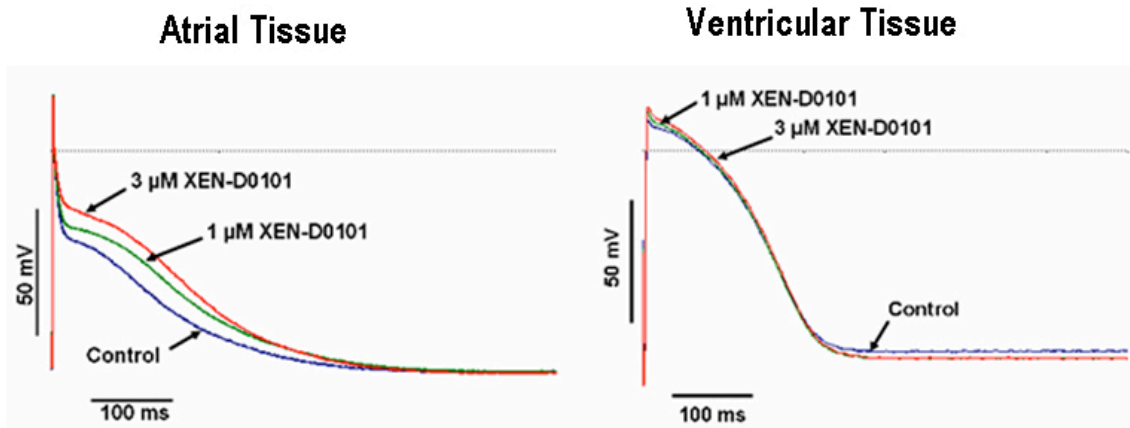
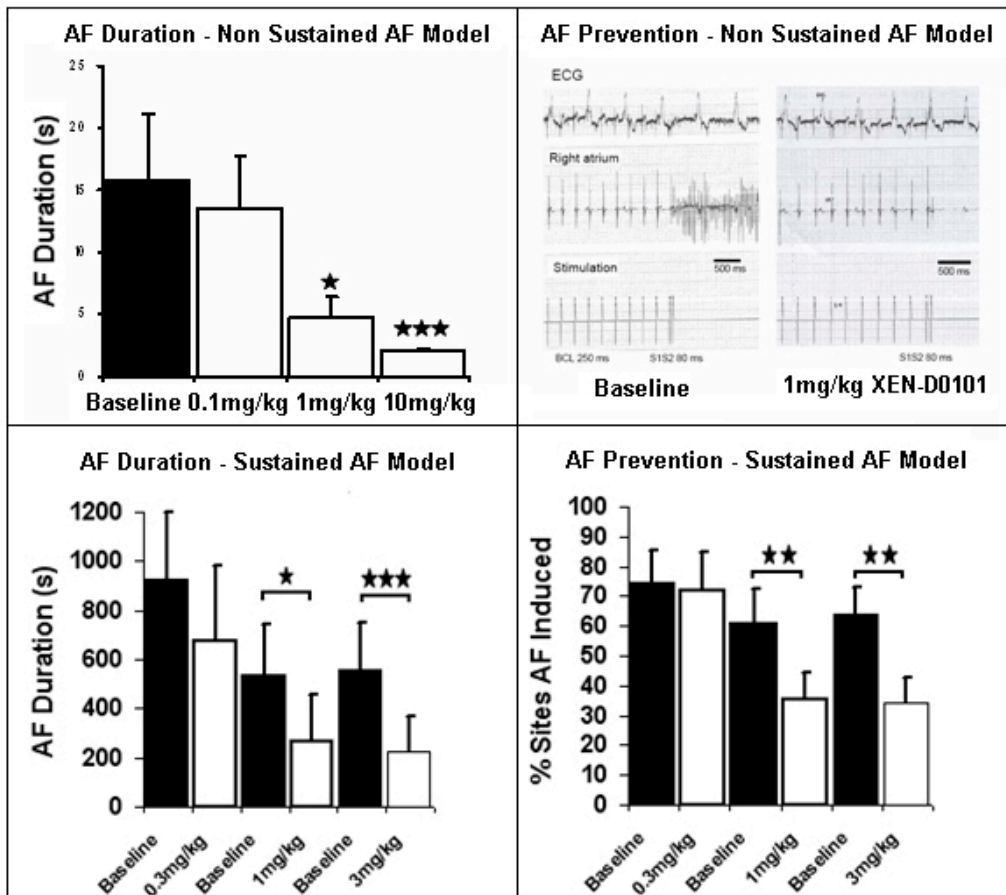


Figure X. Selective extension of action potential duration in human atrial tissue by XEN-D0101

In addition to demonstrating in vitro selectivity and the ability to extend the human atrial action potential, XEN-D0101 has also demonstrated efficacy in two canine models representing both paroxysmal and permanent AF in the clinical setting. In both models, administration of XEN-D0101 reduced AF duration, AF inducibility and increased the atrial effective refractory period and AF cycle length in a dose-dependent fashion, without significant effects on ventricular action potential or QTc, data that provide additional support for the potential utility of XEN-D0101 for the treatment of patients with AF.



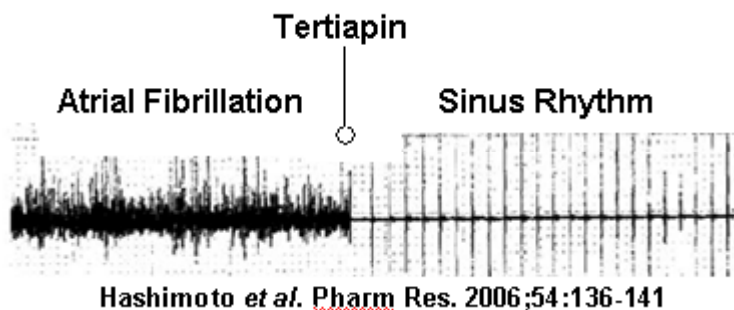
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XEN-D0101 has progressed into clinical development and a single ascending dose safety and tolerability study in healthy volunteers has been completed. A Phase Ib study to determine the electrophysiological effects of XEN-D0101 in subjects following successful catheter ablation treatment is ongoing. In addition to evaluating safety and tolerability, the correlation between atrial effective refractory period (AERP) and pharmacokinetic parameters will provide evidence for clinically-relevant effects of XEN-D0101 and assist with dose selection for future clinical efficacy studies.

The follow-on compounds XEN-D0103 and XEN-D0104, which are chemically distinct from XEN-D0101, are also undergoing evaluation in pre-clinical AF models.

IKACH as a target for AF

The acetylcholine-regulated potassium channel IKACH (Kir3.1/Kir3.4) 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 IKACH is associated with profound shortening of atrial monophasic APD and refractoriness, which increases the vulnerability to transient atrial arrhythmias. Indeed, IKACH is constitutively active in myocytes from patients with chronic AF. Inhibition of IKACH is therefore considered an attractive approach for the conversion of AF and maintenance of sinus rhythm, and the selective IKACH inhibitor tertiapin, a natural peptide isolated from honey bee venom, preferentially prolongs the atrial action potential duration and terminates AF in canine models.



Xention's IKACH programme is aimed at developing small molecule, orally administered, selective inhibitors of IKACH and is funded by the Wellcome Trust. Currently the programme is undergoing lead optimisation and evaluation in pre-clinical AF models is about to commence.