XEN901

XEN901: A Novel, Highly Selective NaV1.6 Inhibitor for the Treatment of Epilepsy

XEN901 inhibits NaV1.6 with high potency and selectivity

Novel binding site and mechanism of inhibition. Isoform selectivity enables high therapeutic index . Best in class safety margin. Demonstrated seizure freedom in rodent models. Excellent PK, safety, tolerability to date in Phase 1 at predicted therapeutic plasma concentration. Promising for treatment of both focal seizures in adults and as a precision medicine for treating infants with EIEE13 or other childhood epilepsies

We are developing XEN901, a potent, highly selective NaV1.6 sodium channel inhibitor, for the treatment of epilepsy, including treatment resistant adult and pediatric focal seizures, as well as rare, pediatric forms of epilepsy, such as EIEE13, an early infantile epileptic encephalopathy associated with gain-of-function mutations in the SCN8A gene, which encodes the NaV1.6 sodium channel. By selectively targeting NaV1.6, it is anticipated that XEN901 may achieve efficacy conferred by this well-validated epilepsy target, but with a potentially improved therapeutic index compared with currently available non-selective sodium channel inhibitors.

There is strong human genetic validation supporting the rationale for treating epilepsy by blocking the NaV1.6 sodium channel. Nav1.6 is the most highly expressed sodium channel in the excitatory pathways in the CNS. When mutations in the SCN8A gene result in a gain of function in the NaV1.6 sodium channel, children can present with a very severe form of epilepsy. This early infantile epileptic encephalopathy is known as EIEE13. We have examined XEN901 in a pre-clinical model of genetically defined epilepsy as well as models representative of focal seizures. These studies showed that XEN901 is efficacious against seizures in both an SCN8A (NaV1.6) gain-of-function model, which is designed to be predictive of the pediatric genetic epilepsy EIEE13, and in the maximal electroshock seizure, or MES, model, which is designed to be predictive of adult focal seizures. When compared to phenytoin in both the SCN8A and MES models, XEN901 achieved the same degree of efficacy as phenytoin at one thousand fold lower brain exposures. XEN901 also was observed to have an improved therapeutic index relative to phenytoin as assessed by tests of rodent behavior and motor impairment.

In February 2018, following acceptance of our CTA for XEN901 by the MHRA in the United Kingdom, we initiated a randomized, double-blind, placebo-controlled Phase 1 clinical trial to evaluate XEN901's safety, tolerability and pharmacokinetics in both SAD and MAD cohorts of approximately 64 healthy subjects in total. We expect to present an update on XEN901, including pre-clinical data, at the 14th EILAT Conference on New Antiepileptic Drugs and Devices to be held in Madrid, Spain on May 15, 2018. Upon completion of the Phase 1 clinical trial, a read-out of results is anticipated in the second half of 2018, followed by a Phase 2 trial evaluating XEN901's efficacy as a treatment for adult focal seizures. We also intend to pursue a parallel plan to advance XEN901 into rare, pediatric forms of epilepsy as soon as feasible thereafter.