3.211

A First in Human Phase 1 Study to Assess the Safety, Tolerability and Pharmacokinetics of a Novel $Na_V1.6$ Selective Small Molecule Sodium Channel Inhibitor (XEN901) in Healthy Subjects

Rostam Namdari; Lisa Buchy; Jay Cadieux; Heather Kato; Lena Legkaia; Y. Paul Goldberg; Greg Beatch; JP Johnson Jr.; Simon N. Pimstone; Robin Sherrington; Charles J. Cohen; James Empfield; Ernesto Aycardi

Xenon Pharmaceuticals, 200-3650 Gilmore Way, Burnaby, BC V5G 4W8 Canada

BACKGROUND

XEN901 is a potent and highly selective $Na_V1.6$ inhibitor currently in clinical development for the treatment of epilepsy. The objective of this study is to evaluate the safety, tolerability and pharmacokinetics (PK) of single and multiple ascending oral doses of XEN901 in healthy subjects. XEN901 is expected to have an enhanced safety profile over non-selective inhibitors through potent block of $Na_V1.6$, with >100 fold selectivity over $Na_V1.1$ (CNS inhibitory) and $Na_V1.5$ (cardiac) sodium channels.

METHODS

In this randomized, double blind study, 40 healthy subjects (3:1 active:placebo) received single ascending doses (SAD) of XEN901 once daily (QD) and 30 subjects (3:1 active:placebo) received multiple ascending doses (MAD) once (QD) or two times (BID) daily for 7 days. A food effect (FE) cohort received single doses of XEN901 in fed and fasted states in a crossover design. XEN901 was formulated as an immediate release capsule. Safety evaluations throughout the study included adverse event (AE) monitoring, laboratory tests, vital signs, electrocardiograms (ECGs), physical examinations, Columbia Suicide Severity Rating Scale (C SSRS) and a brief cognitive assessment. Pilot TMS assessments were done in 50 and 75 mg QD cohorts. The study features an adaptive design and is ongoing.

Demographic and Baseline Characteristics for SAD Cohorts (Safety Set)

	5 mg (N=3)	10 mg (N=3)	15 mg (N=6)	30 mg (N=6)	45 mg (N=6)	80 mg (N=6)	Overall (N=30)	Pooled Placebo (N=10)
Gender, n (%)								
Male	1 (33.3)	3 (100)	4 (66.7)	3 (50.0)	2 (33.3)	4 (66.7)	17 (56.7)	3 (30.0)
Female	2 (66.7)	0	2 (33.3)	3 (50.0)	4 (66.7)	2 (33.3)	13 (43.3)	7 (70.0)
Age at informed consent (years)								
Mean	33.7	36.3	30.5	34.2	41.7	34.7	35.2	35.5
SD	11.7	9.1	10	10.9	13.6	13.9	11.5	8.9
Range	25-47	26-43	21-48	20-44	23-54	18-51	18-54	22-49
Race, n (%)								
Caucasian	3 (100)	3 (100)	6 (100)	6 (100)	5 (83.3)	6 (100)	29 (96.7)	9 (90.0)
Black African	0	0	0	0	1 (16.7)	0	1 (3.3)	1 (10.0)
Asian	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0
BMI (kg/m²)								
Mean	28.10	27.53	25.65	26.45	23.10	27.82	26.17	24.09
SD	2.66	3.42	2.61	2.36	1.85	1.93	2.80	3.67

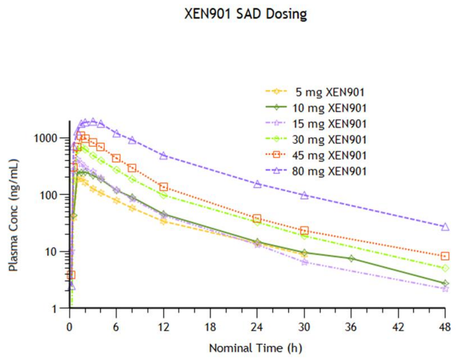
Demographic and Baseline Characteristics for MAD Cohorts (Safety Set)

	15 mg BID (N=7)	23 mg BID (N=6)	50 mg QD (N=6)	75 mg QD (N=4)	XEN901 Overall (N=23)	Pooled Placebo (N=7)
Gender, n (%)						
Male	5 (71.4)	2 (33.3)	6 (100)	4 (100)	17 (73.9)	5 (71.4)
Female	2 (28.6)	4 (66.7)	0	0	6 (26.1)	2 (28.6)
Age at informed consent (years)						
Mean	30.6	33.5	40.0	36.3	34.8	32.1
SD	6.8	13.6	11.2	15.8	11.4	12.0
Range	20-40	20-52	23-53	19-52	19-53	20-52
Race, n (%)						
Caucasian	4 (57.1)	5 (83.3)	6 (100)	1 (25.0)	16 (69.6)	6 (85.7)
Black African	2 (28.6)	0	0	1 (25.0)	3 (13.0)	1 (14.3)
Asian	1 (14.3)	1 (16.7)	0	1 (25.0)	3 (13.0)	0
Other	0	0	0	1 (25.0)	1 (4.3)	0
BMI (kg/m²)						
Mean	26.00	22.92	24.00	26.83	26.20	24.82
SD	4.01	2.64	2.81	0.66	3.12	3.19

Notes: Age, height, weight and body mass index are taken at screening. BMI = body mass index; SD = standard deviation. Demographic data for FE cohort (not shown here) were similar to SAD & MAD cohorts.

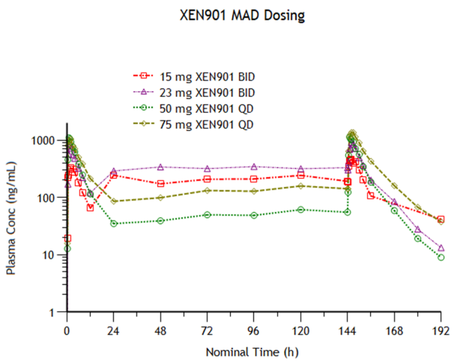
PHARMACOKINETICS

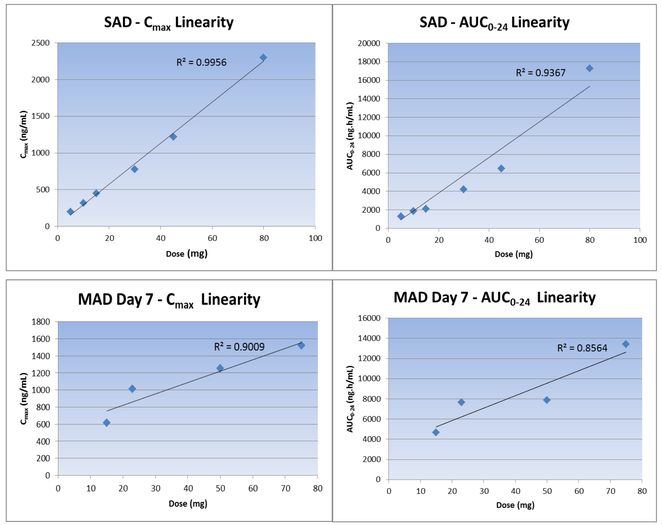
XEN901's PK profile displayed a reasonable dose proportional exposure with a mild food effect (1.3-fold increase in C_{max} and 1.6-fold in AUC). Typically modest (≤40%) inter-individual variability was observed for the PK parameters. The median T_{max} was similar among cohorts and typically ranged from 1-2 h. The mean $t_{1/2}$ was 8-11 h across cohorts and did not change with increasing dose or upon repeated administration. No significant drug accumulation was observed upon 7 days of QD (75 mg) or BID (23 mg x 2; i.e., 46 mg/day) dosing and steady state was achieved by Day 2-3. Significantly higher trough levels were maintained via BID dosing.



Accumulation Ratios (Day 7/Day1) for MAD Cohorts

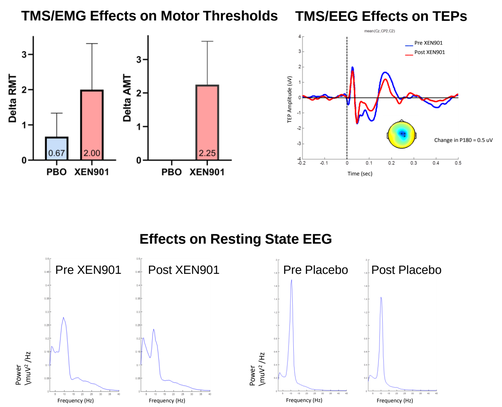
Parameter	15 mg BID (N=7)	23 mg BID (N=6)	50 mg QD (N=6)	75 mg QD (N=4)
RC_{max}	1.3	1.2	1.0	1.2
RAUC	1.6	1.5	1.3	1.3





PILOT TMS RESULTS

XEN901's effects on Transcranial Magnetic Stimulation (TMS) measurements and EEG were assessed in 8 subjects with plasma levels >1000 ng/mL from the 50 and 75 mg QD cohorts and compared to 3 placebo subjects. TMS measures were recorded at baseline and on Day 5/6. In this pilot study XEN901 showed trends for increases in resting and active motor thresholds (RMT/AMT), decrease in amplitude of TMS evoked potential (TEP) at 180 ms (P180) and an increase in delta power in the resting state EEG.



SAFETY

Single and multiple doses of XEN901 were well tolerated at plasma levels up to and including 2660 ng/mL and 2280 ng/mL, respectively. The majority of AEs for the SAD, MAD and FE cohorts were deemed unrelated to XEN901, were mild or moderate, transient and resolved spontaneously. There have been no SAEs, deaths, or clinically significant ECG, vital signs or laboratory findings. The possibly related AEs in the SAD cohorts included dizziness, headache, nausea and restlessness. The AEs for the MAD cohorts are presented here.

System Organ Class Preferred Term	15 mg BID (N=7)	23 mg BID (N=6)	50 mg QD (N=6)	75 mg QD (N=4)	Overall (N=23)	Pooled Placebo (N=7)
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Subjects with at least one TEAE	5 (71.4) 5	3 (50.0) 6	3 (50.0) 8	1 (25.0) 1	12 (52.2) 20	4 (57.1) 4
Eye Disorders	0	0	0	1 (25.0) 1	1 (4.3) 1	0
Eye pain*	0	0	0	1 (25.0) 1	1 (4.3) 1	0
Gastrointestinal Disorders	1 (14.3) 1	0	1 (16.7) 2	0	2 (8.7) 3	0
Flatulence	0	0	1 (16.7) 1	0	1 (4.3) 1	0
Nausea*	1 (14.3) 1	0	1 (16.7) 1	0	2 (8.7) 2	0
General Disorders and Administration Site Conditions	2 (28.6) 2	2 (33.3) 3	1 (16.7) 1	0	5 (21.7) 6	1 (14.3) 1
Fatigue*	0	1 (16.7) 1	0	0	1 (4.3) 1	0
Feeling cold*	1 (14.3) 1	0	0	0	1 (4.3) 1	0
Medical device site reaction	1 (14.3) 1	2 (33.3) 2	0	0	3 (13.0) 3	1 (14.3) 1
Vessel puncture site thrombosis	0	0	1 (16.7) 1	0	1 (4.3) 1	0
Infections and Infestations	1 (14.3) 1	0	0	0	1 (4.3) 1	1 (14.3) 1
Ear infection	0	0	0	0	0	1 (14.3) 1
Nasopharyngitis	1 (14.3) 1	0	0	0	1 (4.3) 1	0
Injury, Poisoning and Procedural Complications	0	1 (16.7) 1	0	0	1 (4.3) 1	0
Thermal burn	0	1 (16.7) 1	0	0	1 (4.3) 1	0
Musculoskeletal and Connective Tissue Disorders	0	1 (16.7) 1	0	0	1 (4.3) 1	0
Arthralgia	0	1 (16.7) 1	0	0	1 (4.3) 1	0
Nervous System Disorders	0	0	3 (50.0) 4	0	3 (13.0) 4	1 (14.3) 1
Dizziness*	0	0	1 (16.7) 1	0	1 (4.3) 1	0
Headache*	0	0	2 (33.3) 2	0	2 (8.7) 2	1 (14.3) 1
Nerve compression*	0	0	1 (16.7) 1	0	1 (4.3) 1	0
Respiratory, Thoracic and Mediastinal Disorders	0	1 (16.7) 1	1 (16.7) 1	0	2 (8.7) 2	0
Epistaxis	0	1 (16.7) 1	0	0	1 (4.3) 1	0
Nasal congestion	0	0	1 (16.7) 1	0	1 (4.3) 1	0
Skin and Subcutaneous Tissue Disorders	1 (14.3) 1	0	0	0	1 (4.3) 1	1 (14.3) 1
Rash	0	0	0	0	0	1 (14.3) 1
Rash papular	1 (14.3) 1	0	0	0	1 (4.3) 1	0

* Represents possibly related AEs; E = number of events; n = number of subjects having an AE; N = Number of subjects at risk

CONCLUSIONS

The results to date suggest that XEN901, a novel, first-in-class $Na_V1.6$ inhibitor, is safe and well-tolerated at the doses examined (single doses of up to 80 mg/day and multiple doses of up to 75 mg/day for 7 days).

In addition, XEN901 exhibited linear PK over the dose range examined. The $t_{1/2}$ of 8 to 11 h suggests that XEN901 could be compatible with a QD or a BID dosing regimen. No significant accumulation was observed upon repeated dosing and steady state was achieved in 2-3 days.

Changes in TMS/EMG and TMS/EEG parameters suggest XEN901 has effects on corticospinal and cortical excitability.

The favorable PK, tolerability, safety and pilot TMS data support the further clinical development of XEN901 in the treatment of epilepsy.