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A First-in-Human Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Pharmacodynamics of a Novel Small Molecule K_V7.2/7.3 Positive Allosteric Modulator (XEN1101) in Healthy Subjects

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BACKGROUND

XEN1101 is a novel chemical entity that enhances activation of neuronal K_V7.2-7.5 (KCNQ2-5) potassium channels and it is currently in clinical development by Xenon Pharmaceuticals as a treatment for epilepsy. The objectives of this first-in-human study were to evaluate the safety, tolerability and pharmacokinetics (PK) of single and multiple ascending doses (SAD and MAD) of oral XEN1101.

METHODS

In the SAD Phase, 32 healthy volunteers were randomized (3:1) to XEN1101 (5, 15, 20, 25 or 30 mg) or placebo. The study featured an adaptive design. A crossover food effect cohort (N=10) was also completed with single doses of 20 mg. A sub-set of 8 male subjects were also assessed with Transcranial Magnetic Stimulation (TMS) for effects on cortical excitability (see poster 3.292).

Repeat doses of XEN1101 (15 mg QD) were evaluated in a fasted and fed state over 7 and 10 days, respectively. Repeat doses of XEN1101 (25 mg QD) were also evaluated in a fed state over 10 days.

XEN1101 was formulated as an immediate release capsule. Serial plasma PK samples were collected for all cohorts. Safety evaluations throughout the study included adverse event (AE) monitoring, clinical laboratory tests, vital signs, ECGs, physical examinations and Columbia-Suicide Severity Rating Scale.

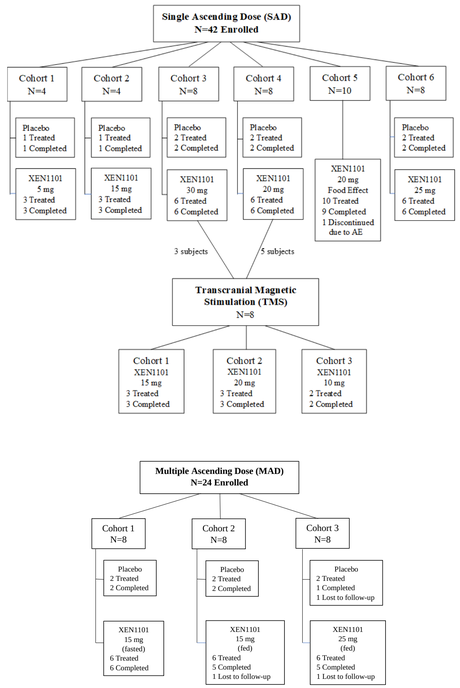
Demographic and Baseline Characteristics for SAD Cohorts (Safety Set)

	Cohort 1 5 mg (N=3)	Cohort 2 15 mg (N=3)	Cohort 3 30 mg (N=6)	Cohort 4 20 mg (N=6)	Cohort 5 20 mg (FE) (N=10)	Cohort 6 25 mg (N=6)	Overall (N=34)	Pooled Placebo (N=8)
Gender, n (%)								
Male	2 (66.7)	2 (66.7)	5 (83.3)	5 (83.3)	5 (50.0)	3 (50.0)	22 (64.7)	6 (75.0)
Female	1 (33.3)	1 (33.3)	1 (16.7)	1 (16.7)	5 (50.0)	3 (50.0)	12 (35.3)	2 (25.0)
Age at informed consent (years)								
Mean	31.3	32.0	24.3	28.0	30.4	23.8	28.0	26.3
SD	4.5	4.0	4.7	6.1	4.4	5.8	5.6	4.3
Range	27-36	28-36	18-31	21-35	23-36	19-35	18-36	21-33
Race, n (%)								
Caucasian	2 (66.7)	3 (100.0)	5 (83.3)	4 (66.7)	7 (70.0)	2 (33.3)	23 (67.6)	6 (75.0)
Black African	0	0	0	0	3 (30.0)	2 (33.3)	5 (14.7)	0
Asian	0	0	1 (16.7)	2 (33.3)	0	2 (33.3)	5 (14.7)	2 (25.0)
Other	1 (33.3)	0	0	0	0	0	1 (2.9)	0
Height (cm)								
Mean	171.3	172.0	172.3	174.8	172.9	169.2	172.3	175.0
SD	4.5	10.0	7.3	6.1	5.1	11.3	7.1	6.9
Weight (kg)								
Mean	74.2	63.6	73.5	71.1	71.5	66.1	70.4	72.0
SD	8.2	12.4	17.1	13.6	12.1	11.3	12.5	4.7
BMI (kg/m²)								
Mean	25.2	21.3	24.5	23.1	23.9	22.9	23.6	23.6
SD	2.3	1.7	3.9	3.0	3.4	1.2	2.9	2.3

Demographic and Baseline Characteristics for MAD Cohorts (Safety Set)

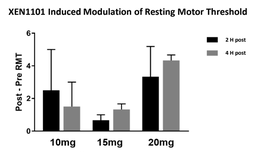
	Cohort 1 15 mg (N=6)	Cohort 2 15 mg (N=6)	Cohort 3 25 mg (N=6)	Overall (N=18)	Placebo (N=6)
Gender, n (%)					
Male	4 (66.7)	4 (66.7)	4 (66.7)	12 (66.7)	3 (50.0)
Female	2 (33.3)	2 (33.3)	2 (33.3)	6 (33.3)	3 (50.0)
Age at informed consent (years)					
Mean	32.5	24.2	24.7	27.1	25.0
SD	5.8	5.2	4.4	6.2	5.1
Range	26-39	18-31	20-31	18-39	20-34
Race, n (%)					
Caucasian	4 (66.7)	3 (50.0)	4 (66.7)	11 (61.1)	5 (83.3)
Black African	1 (16.7)	1 (16.7)	1 (16.7)	3 (16.7)	1 (16.7)
Asian	1 (16.7)	1 (16.7)	0 (0.0)	2 (11.1)	0 (0.0)
Other	0 (0.0)	1 (16.7)	1 (16.7)	2 (11.1)	0 (0.0)
Height (cm)					
Mean	176.0	175.8	176.0	175.9	171.8
SD	11.9	6.6	11.7	9.7	9.5
Weight (kg)					
Mean	68.9	76.1	68.6	71.2	71.5
SD	7.8	10.3	11.8	10.2	7.9
BMI (kg/m2)					
Mean	22.3	24.5	22.1	22.3	24.2
SD	1.7	2.3	2.8	2.4	2.4

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.

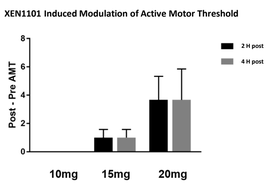


PILOT TMS RESULTS

XEN1101 increased motor thresholds (but not SICI) assessed with TMS/EMG. For full discussion of TMS results see accompanying poster (Abst.# 3.292).



Black bars show effect at 2 hours post-drug intake, grey bars represent 4 hours post-drug (change from baseline as % max stimulator output, mean ± SEM). N=2 for 10 mg, N=3 for 15 mg and 20 mg.

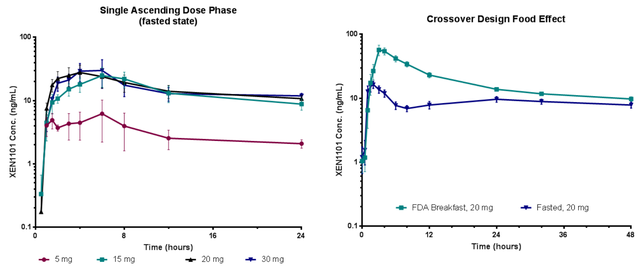


Black bars show effect at 2 hours post-drug intake, grey bars represent 4 hours post-drug (change from baseline as % max stimulator output, mean ± SEM). XEN1101 10 mg did not change AMT. N=2 for 10 mg, N=3 for 15 mg and 20 mg.

PHARMACOKINETICS

XEN1101 displayed a PK profile suitable for once a day dosing with low peak to trough ratio. XEN1101 had less than dose-proportional exposure in the fasted state, with absorption enhanced by food (~1.8 fold for AUC_{inf}). With multiple doses in the fed state, exposure increased in proportion to dose. Apparent steady state was achieved by Day 6-9, based on the 90% CI for the successive day's exposure ratio within the range 0.8 - 1.25.

PK Profiles for XEN1101 SAD Cohorts



Selected Pharmacokinetic Parameters in Plasma (Mean ±SD) for SAD Cohorts

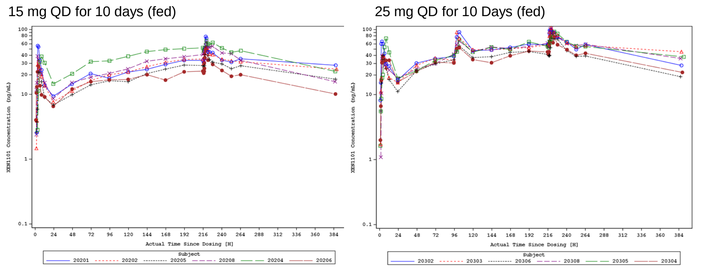
Parameter	XEN1101 5 mg[a] (N=3)	XEN1101 15 mg[a] (N=3)	XEN1101 20 mg[a] (N=6)	XEN1101 25 mg[b] (N=6)	XEN1101 30 mg[a] (N=6)
tmax (h)	3.17 ± 2.47	4.50 ± 2.60	3.69 ± 2.05	4.51 ± 1.22	3.17 ± 1.48
Cmax (ng/mL)	7.13 ± 6.12	27.3 ± 11.1	31.5 ± 21.1	45.8 ± 14.3	35.5 ± 33.5
$t_{1/2}$ (h)	49.2 ± 31.1	41.9 ± 31.1	48.9 ± 14.7	97.2 ± 18.0	63.4 ± 28.2
AUC0-24 (ng*h/mL)	74.6 ± 50.5	328 ± 141	376 ± 220	482 ± 130	369 ± 219
AUC0-t (ng*h/mL)[c]	91.3 ± 54.2	397 ± 166	709 ± 337	1470 ± 270	837 ± 280

[a] Fasted for 8 hours prior to dosing and 1 hour after dosing

[b] Fed a standard breakfast 30 minutes prior to dosing followed by no food for 4 hours

[c] t_{Last} was 32 h for 5 and 15 mg Cohorts, 72 h for 20 and 30 mg Cohorts, 146 h for 25 mg Cohort and

PK Profiles for XEN1101 MAD Cohorts



Individual PK profiles for subjects dosed with 15 mg QD XEN1101 (administered 0.5h after a meal).

Individual PK profiles for subjects dosed at 25 mg QD XEN1101 (administered 0.5h after a meal).

Selected Pharmacokinetic Parameters in Plasma for MAD Cohorts

	XEN1101 15 mg QD Fasted[a] (N=6)		XEN1101 15 mg QD Fed[b] (N=6)		XEN1101 25 mg QD Fed[b] (N=6)	
Parameter	Day 1	Day 7	Day 1	Day 10	Day 1	Day 10
tmax (h)	2.68 ± 1.15	2.69 ± 1.19	4.37 ± 1.85	3.69 ± 0.506	4.38 ± 1.86	4.99 ± 1.69
Cmax (ng/mL)	10.5 ± 2.01	45.1 ± 11.4	35.9 ± 11.9	60.8 ± 11.2	49.6 ± 15.7	96.7 ± 8.6
$t_{1/2}$ (h)	--	167 ± 36.8	--	239 ± 179	--	218 ± 136
AUC0-24 (ng*h/mL)	125 ± 32.9	757 ± 200	353 ± 105	1020 ± 246	592 ± 133	1720 ± 198
AUC0-t (ng*h/mL)	--	4260 ± 992	--	4950 ± 1250	--	8010 ± 1520

[a] On Days 1 and 7, fasted for 8 hours prior to dosing and 4 hours after dosing. On Days 2-6, fasted for 8 hours prior to dosing and 1 hour after dosing

[b] Fed a standard breakfast 30 minutes prior to dosing on each dosing day followed by no food for 4 hours

SAFETY

Single and multiple doses of XEN1101 were well tolerated at individual C_{max} levels up to 104 ng/mL and 107 ng/mL, respectively. The majority of AEs were mild or moderate, resolved spontaneously and were consistent with antiepileptic drugs of this class (e.g., dizziness, sedation). There have been no SAEs, deaths, or clinically significant ECG or laboratory findings.

Adverse Events occurring in ≥2 subjects overall for SAD Cohorts

System Organ Class / Preferred Term	XEN1101 Cohort 1 5 mg (N=3)	XEN1101 Cohort 2 15 mg (N=3)	XEN1101 Cohort 3 30 mg (N=6)	XEN1101 Cohort 4 20 mg (N=6)	XEN1101 Cohort 5[a] 20 mg (N=9)	XEN1101 Cohort 6 25 mg (N=6)	XEN1101 Overall (N=27)	Pooled Placebo (N=8)
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Subjects with at least one TEAE	0 (0.0) 0	2 (66.7) 4	3 (50.0) 7	4 (66.7) 8	5 (55.6) 11	4 (66.7) 7	18 (54.5) 37	2 (25.0) 2
Eye Disorders	0	1 (33.3) 1	1 (16.7) 1	0	0	1 (16.7) 1	3 (9.1) 3	0
Vision blurred	0	0	1 (16.7) 1	0	0	1 (16.7) 1	2 (6.1) 2	0
Musculoskeletal and Connective Tissue Disorders	0	0	1 (16.7) 1	2 (33.3) 2	1 (11.1) 1	0	4 (12.1) 4	0
Myalgia	0	0	1 (16.7) 1	*1 (16.7) 1	1 (11.1) 1	0	3 (9.1) 3	0
Nervous System Disorders	0	1 (33.3) 1	2 (33.3) 3	2 (33.3) 3	2 (22.2) 4	3 (50.0) 5	10 (30.3) 17	0
Dizziness	0	0	0	2 (33.3) 2	1 (11.1) 1	3 (50.0) 3	6 (18.2) 6	0
Headache	0	1 (33.3) 1	1 (16.7) 1	1 (16.7) 1	1 (11.1) 2	0	4 (12.1) 5	0
Presyncope	0	0	*2 (33.3) 2	0	0	0	2 (6.1) 2	0
Somnolence	0	1 (33.3) 1	0	0	0	2 (33.3) 2	3 (9.1) 3	0

E = number of events; n = number of subjects having an adverse event; N = Number of subjects at risk.

[a] Note that cohort 5 was dosed under fed and fasted conditions according to a crossover design. For reasons of comparability frequencies presented in this table are based on the fasted condition.

* Denotes moderate AEs. All other AEs were mild, except for 1 severe AE of syncope (a vasovagal reaction following a PK blood draw during a standing BP assessment) in a single subject, 2 hours following a 30 mg dose in Cohort 3. A fed subject in the food effect cohort also had an unrelated moderate AE of varicella (chicken pox) which led to withdrawal.

Adverse Events occurring in ≥2 subjects overall for MAD Cohorts

System Organ Class / Preferred Term	XEN1101 Cohort 1 15 mg (fasted) (N=6)	XEN1101 Cohort 2 15 mg (fed) (N=6)	XEN1101 Cohort 3 25 mg (fed) (N=6)	XEN1101 Overall (N=18)	Placebo Pooled (N=6)
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Subjects with at least one TEAE	4 (66.7) 11	4 (66.7) 18	6 (100.0) 39	14 (77.8) 68	2 (33.3) 5
Cardiac Disorders	0	2 (33.3) 2	0	2 (11.1) 2	0
Palpitations	0	2 (33.3) 2	0	2 (11.1) 2	0
Eye Disorders	1 (16.7) 1	0	5 (83.3) 5	6 (33.3) 6	0
Vision blurred	0	0	5 (83.3) 5	5 (27.8) 5	0
Musculoskeletal and Connective Tissue Disorders	0	0	2 (33.3) 3	2 (11.1) 3	1 (16.7) 1
Muscle twitching	0	0	2 (33.3) 2	2 (11.1) 2	1 (16.7) 1
Nervous System Disorders	3 (50.0) 6	3 (50.0) 13	6 (100.0) 23	12 (66.7) 42	2 (33.3) 4
Balance disorder	1 (16.7) 1	1 (16.7) 1	1 (16.7) 1	3 (16.7) 3	0
Dizziness	0	1 (16.7) 1	2 (33.3) 2	3 (16.7) 3	0
Headache	1 (16.7) 1	3 (50.0) 3	3 (50.0) 4	7 (38.9) 8	0
Memory impairment	2 (33.3) 2	1 (16.7) 1	2 (33.3) 2	5 (27.8) 5	0
Sensory disturbance	0	0	2 (33.3) 2	2 (11.1) 2	0
Somnolence	0	3 (50.0) 3	4 (66.7) 4	7 (38.9) 7	*1 (16.7) 1
Speech disorder	0	2 (33.3) 2	4 (66.7) 4	6 (33.3) 6	0
Vascular Disorders	0	1 (16.7) 1	4 (66.7) 4	5 (27.8) 5	0
Hot flush	0	1 (16.7) 1	2 (33.3) 2	3 (16.7) 3	0
Orthostatic hypotension	0	0	*2 (33.3) 2	2 (11.1) 2	0

E = number of events; n = number of subjects having an adverse event; N = Number of subjects at risk.

* Denotes moderate AEs. All other AEs were mild. There were no severe AEs, withdrawals due to AEs, or SAEs. Two active and 1 placebo were not reachable to complete the 30 day follow-up telephone call (lost to follow-up).

CONCLUSIONS

The current results suggest that XEN1101 is safe and well-tolerated up to doses examined (single doses of up to 30 mg and multiple doses of 25 mg QD).

The PK profile (including an effective half-life >24 hours), supports a once per day dosing schedule using an immediate release formulation, with attainment of steady state in 1 week without the need for titration.