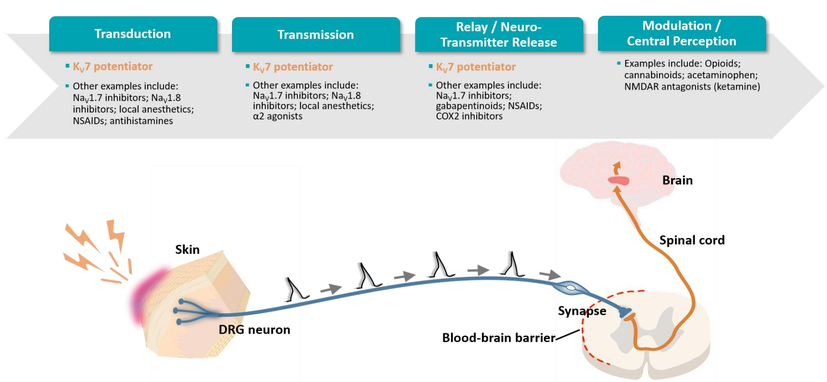
XEN1120, a Phase 2-Ready K_V7 Channel Opener: Advancing a Novel Non-Opioid Strategy for Pain

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INTRODUCTION

- Voltage-gated potassium (K_V7; KCNQ) channels regulate neuronal excitability by stabilizing membrane potential and limiting repetitive action potential firing. Multiple lines of evidence support K_V7 channels as therapeutic targets for pain. K_V7 channels are broadly expressed throughout the peripheral and central pain pathways, including primary sensory neurons, where they act as key regulators of nociceptive signaling[1]
- K_V7 plays a significant role in the initial transduction of pain stimuli into pain signals, the transmission of those pain signals along nociceptive neurons, and the relay from peripheral sensory neurons to spinal cord neurons in the central nervous system
- Dysfunction or downregulation of K_V7 channel activity has been observed in altered pain states[2,3]
- Additionally, flupirtine, a compound previously approved for the treatment of pain has a mechanism of action that involves potassium channel opening[4]
- Lead K_V7 compound, XEN1120, is a novel K_V7 channel opener being developed for pain. In Phase 1 studies, XEN1120 was generally well tolerated and achieved plasma exposures within the predicted therapeutic range established in rodent and non-human primate pain models
- Together, these findings support XEN1120 as a promising non-opioid approach to treat a range of pain conditions, including neuropathic and inflammatory pain

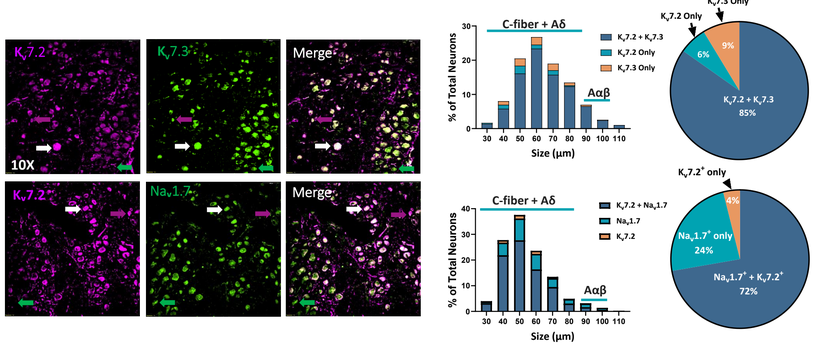


METHODS

- **Immunohistochemistry of human tissue:** Human tissue cryosections were immunolabeled with primary antibodies against $K_V7.2$, $K_V7.3$ or $Na_V1.7$, followed by fluorescent secondary antibodies and imaged by fluorescence microscopy
- **Electrophysiology recordings in human DRGs:** Whole-cell current clamp recordings were conducted on dissociated human DRGs. Rheobase, resting membrane potential and number of action potentials were measured at baseline and after compound application
- **Mouse Formalin Assay:** Licking behavior during the acute nociceptive (0-5 min) and inflammatory (30-45 min) phases following formalin administration in male CD-1 mice was quantified from video recordings using automated analysis software developed at Xenon
- **Voltage clamp automated electrophysiology** was used to assess potency of K_V7 openers in HEK cell lines stably expressing $K_V7.2/7.3$
- **Cynomolgus monkey capsaicin allodynia model:** Six animals were tested in a two-period crossover design. Following baseline assessments, animals received a single oral dose of vehicle or test article and crossed over to the alternate treatment. Heat pain responses at 42°C were measured 0.5 h after topical application of a 4 mM capsaicin solution
- **Phase 1 first-in-human study:** Healthy participants were enrolled in SAD, MAD, food-effect cohorts to assess the safety, tolerability, pharmacokinetics and food effect of XEN1120

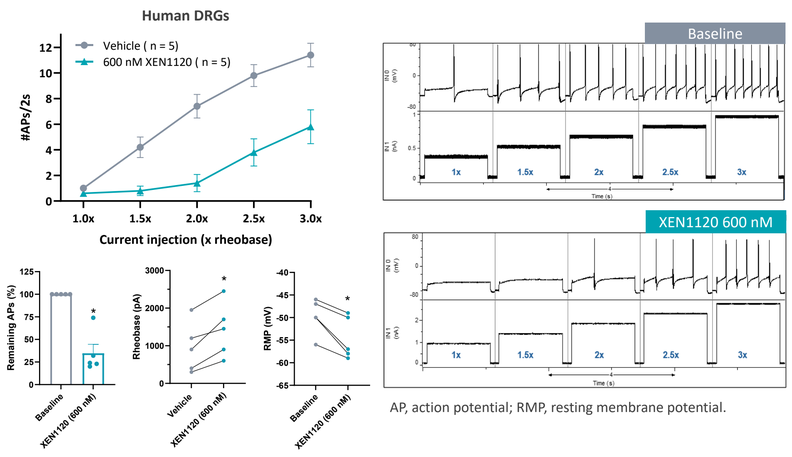
RESULTS

Figure 1. $K_V7.2$ and $K_V7.3$ are Highly Expressed in Human Dorsal Root Ganglion (DRG) Neurons and Overlap with $Na_V1.7$



- Immunohistochemistry of $K_V7.2$ and $K_V7.3$ in human DRG neurons demonstrated extensive co-localization within individual sensory neurons
- Quantification of $K_V7.2$ and $K_V7.3$ expression across DRG neuron size distributions demonstrates a high level of K_V7 expression within the small- to medium-diameter neurons, corresponding to C and Aδ fibers
- 85% of DRG neurons co-expressed $K_V7.2$ and $K_V7.3$, while only a small proportion expressed $K_V7.2$ alone (6%) or $K_V7.3$ alone (9%)
- Quantification of $K_V7.2$ and $Na_V1.7$ expression across neuronal size distributions showed the greatest overlap within small- to medium-diameter neurons, corresponding to C and Aδ fibers
- Among $K_V7.2$- and/or $Na_V1.7$-positive neurons, 72% co-expressed both $K_V7.2$ and $Na_V1.7$, while 24% expressed $Na_V1.7$ alone and 4% expressed $K_V7.2$ alone, demonstrating substantial overlap between $K_V7.2$ and $Na_V1.7$ expression in nociceptive sensory neurons

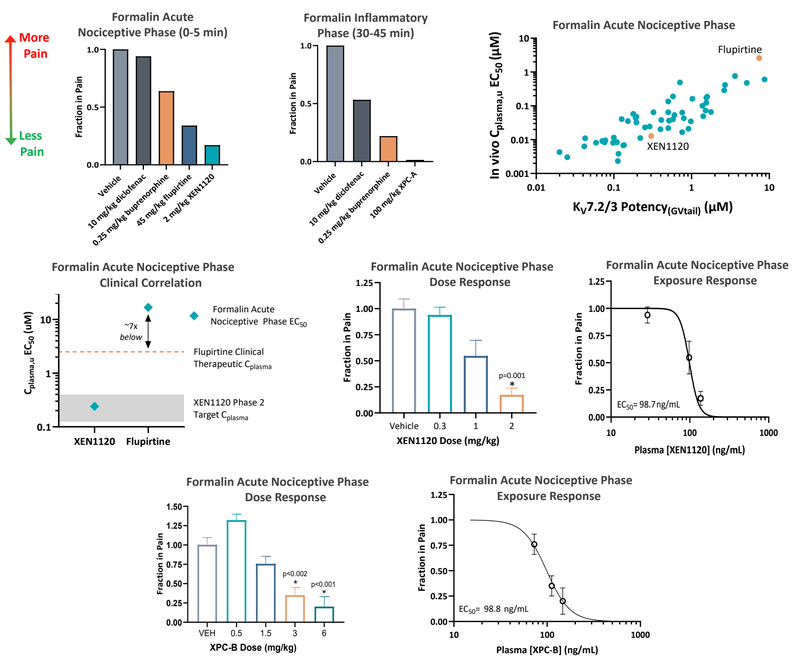
Figure 2. XEN1120 Reduces Excitability of Human Dorsal Root Ganglion Neurons



AP, action potential; RMP, resting membrane potential.

- Human DRG neurons were evaluated using whole-cell current-clamp electrophysiology to assess the effects of XEN1120 on neuronal excitability
- Treatment with XEN1120 (600 nM) reduced action potential firing across a range of depolarizing current injections relative to rheobase compared with vehicle-treated neurons, indicating a reduction in neuronal excitability and an increase in the current required to elicit repetitive firing
- Representative current-clamp recordings acquired at baseline and following application of XEN1120 (600 nM) demonstrate a marked reduction in evoked action potential firing
- XEN1120 had a significant effect on rheobase, resting membrane potential and action potential firing compared to baseline
- These findings demonstrate that XEN1120 suppresses excitability in human dorsal root ganglion neurons, consistent with enhanced K_V7 channel activity and reduced nociceptor firing

Figure 3. K_V7 Channel Modulation Produces Robust Analgesic Efficacy in the Mouse Formalin Model

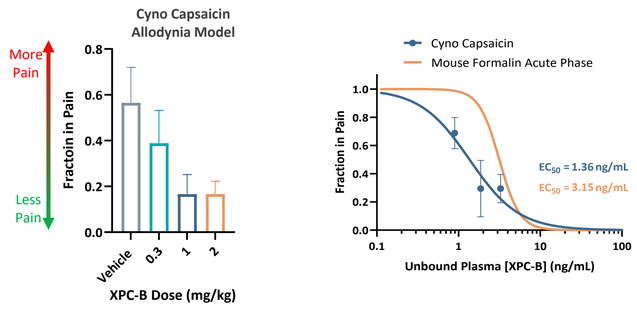


GV_{tail}, conductance-voltage relationship derived from tail-current measurements.

K_V7 Channel Modulation Produces Robust Analgesic Efficacy in the Mouse Formalin Model (Figure 3)

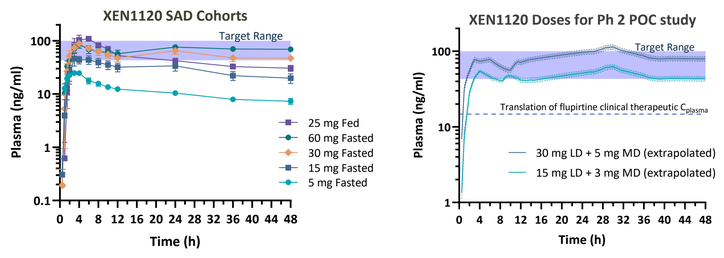
- Formalin injection produces a biphasic pain response consisting of an acute nociceptive phase (0-5 min), followed by a longer lasting inflammatory phase (30-45 min). Most analgesics only work in the inflammatory phase, whereas only opioids typically show efficacy in the acute nociceptive phase
- Diclofenac, a non-steroidal anti-inflammatory drug, is not effective in the acute nociceptive phase, but does reduce the inflammatory response. The opioid buprenorphine reduces both the nociceptive and inflammatory pain responses
- Flupirtine, a compound previously approved for the treatment of pain with a mechanism of action that involves potassium channel opening, reduces both the acute nociceptive and inflammatory responses, as do Xenon K_V7 potentiators
- Across a broad range of exemplary Xenon K_V7 modulators, in vivo free plasma EC_{50} values in the formalin acute phase strongly correlate with $K_V7.2/7.3$ in vitro potency, supporting K_V7 channel modulation as the primary driver of analgesic efficacy. Although flupirtine also demonstrates $GABA_A$ activity, its in vivo efficacy correlates with $K_V7.2/7.3$ potency, suggesting K_V7 as the main driver of its analgesic efficacy
- Flupirtine demonstrated efficacy in the formalin acute nociceptive phase but required free plasma exposures ~7x higher than those used for post-operative pain clinically. In contrast, XEN1120 demonstrated efficacy at substantially lower exposures, with predicted clinical therapeutic plasma concentrations overlapping the efficacious exposure range defined in the acute phase of the mouse formalin model[5]
- Dose-dependent reductions in the acute phase of the formalin model were observed for both XEN1120 and XPC-B
- Exposure-response modeling identified plasma EC_{50} values for XEN1120 and XPC-B, supporting a quantitative relationship between exposure and analgesic efficacy

Figure 4. XPC-B Demonstrates Analgesic Efficacy in a Cynomolgus Monkey Capsaicin Allodynia Model



- In cynomolgus monkeys, XPC-B produced dose-dependent reductions in capsaicin-evoked thermal allodynia
- Exposure-response analysis identified an unbound plasma EC_{50} of 1.36 ng/mL in the cynomolgus capsaicin model, compared with 3.15 ng/mL in the mouse formalin acute phase, indicating that analgesic efficacy was achieved at approximately 2.3-fold lower exposures in the cynomolgus model
- These data suggest the mouse formalin acute nociceptive model is a stringent efficacy model that may provide a conservative foundation for clinical dose selection

Figure 5. XEN1120 Clinical PK Achieves Target Therapeutic Exposures Based on Preclinical Efficacy Models



SAD, single ascending dose; Ph 2 POC, Phase 2 proof-of-concept; LD, loading dose; MD, maintenance dose. Dashed line indicates the predicted XEN1120 efficacious exposure, derived from preclinical-to-clinical translation of flupirtine efficacy exposures (Figure 3).

- PK data from healthy volunteers demonstrated that XEN1120 achieved plasma levels consistent with the predicted efficacious exposure range derived from preclinical rodent and non-rodent efficacy models (target exposure range shaded in blue). Food increased C_{max} (93%) and $AUC_{0\text{-}48}$ (30%)
- A loading dose rapidly achieves target exposures, while maintenance dosing sustains plasma concentrations within the predicted efficacious range for the duration required for an acute pain study

Table 1. SAD: TEAEs Considered Related in >1 XEN1120-Treated Participant

Preferred Term	5 mg Fasted (N=6) n	15 mg Fasted (N=6) n	30 mg Fasted (N=6) n	60 mg Fasted (N=6) n	25 mg Fed (N=6) n	XEN1120 Overall (N=30) n (%)	Pooled Placebo (N=10) n (%)
Nervous System Disorders							
Headache	1	0	2	2	1	6 (20.0%)	1 (10.0%)
Dizziness	0	0	0	3	2	5 (16.7%)	1 (10.0%)
Dizziness postural	0	1	0	0	1	2 (6.7%)	0
Somnolence	0	0	0	0	2	2 (6.7%)	0
Vascular Disorders							
Orthostatic hypotension	0	1	0	1	2	4 (13.3%)	0
Investigations							
HR increased	0	1	1	0	0	2 (6.7%)	1 (10.0%)
Gastrointestinal Disorders							
Nausea	0	0	0	1*	1*	2 (6.7%)	0
Vomiting	0	0	0	1	1*	2 (6.7%)	0
Cardiac Disorders							
Palpitations	0	1	0	1	0	2 (6.7%)	0

Participant counts shown; more than one event per participant is possible.
*Includes at least 1 moderate event.
HR, heart rate; N, number of participants; n, number of participants with >1 related TEAE; SAD, single ascending dose; TEAE, treatment-emergent adverse event.

Summary of FIH Phase 1 SAD and MAD TEAEs

- No dose-limiting treatment-emergent adverse events (TEAEs)
- No serious or severe TEAEs
- No TEAEs leading to discontinuations in XEN1120-treated participants

Single ascending dose (SAD):

- Majority of events were mild
- Moderate TEAEs included nausea in 2 participants (1 in each of 25 mg fed and 60 mg fasted groups), and vomiting in 1 participant (25 mg fed group)
- TEAEs considered related to study treatment in >1 XEN1120 participant shown in Table 1

Multiple ascending dose (MAD):

- All events in XEN1120-treate participants were mild
- One placebo participant experienced moderate TEAEs of headache, nausea, and vomiting; all related, and led to that participant's discontinuation from the study
- TEAEs considered related to study treatment in >1 XEN1120 participant shown in Table 2

Table 2. MAD: TEAEs Considered Related in >1 XEN1120-Treated Participant

Preferred Term	15 mg QD (N=6) n	10 mg QD (N=6) n	30 mg Loading + 5 mg BID (N=6) n	30 mg Loading + 5 mg TID (N=6) n	XEN1120 Overall (N=24) n (%)	Pooled Placebo (N=8) n (%)
Cardiac Disorders						
Tachycardia	0	2	2	4	8 (33.3%)	1 (12.5%)
Nervous System Disorders						
Dizziness	4	1	0	2	7 (29.2%)	0
Somnolence	2	0	3	1	6 (25.0%)	0
Headache	0	0	1	3	4 (16.7%)	1 (12.5%)*
Disturbance in attention	3	0	0	0	3 (12.5%)	1 (12.5%)
Gastrointestinal Disorders						
Abdominal pain	1	0	0	1	2 (8.3%)	0
Gastrooesophageal reflux disease	0	0	2	0	2 (8.3%)	0
Nausea	1	0	0	1	2 (8.3%)	1 (12.5%)*
General Disorders and Administration Site Conditions						
Fatigue	2	0	2	1	5 (20.8%)	1 (12.5%)
Vascular Disorders						
Orthostatic hypotension	3	1	0	1	5 (20.8%)	0
Psychiatric Disorders						
Bradyphrenia (cognitive slowing)	2	0	0	0	2 (8.3%)	0

Participant counts shown; more than one event per participant is possible.
*Includes at least 1 moderate event.
BID, twice daily; MAD, multiple ascending dose; N, number of participants; n, number of participants with >1 related TEAE; QD, once daily; TEAE, treatment-emergent adverse event; TID, three times daily.

CONCLUSIONS

- $K_V7.2$ and $K_V7.3$ are highly expressed in human DRG neurons, including nociceptive populations that co-express $Na_V1.7$, supporting K_V7 as a compelling non-opioid target to modulate pain signaling
- Xenon's lead K_V7 pain compound, XEN1120, decreased excitability in human DRG neurons and demonstrated robust efficacy in the acute nociceptive phase of the mouse formalin model
- In vivo efficacy across structurally distinct K_V7 potentiators correlated with $K_V7.2/7.3$ potency, supporting K_V7 channel modulation as a primary driver of analgesic effects
- Predicted clinical therapeutic exposures of XEN1120 align with efficacious exposures in the mouse formalin acute model, whereas flupirtine required substantially higher (~7-fold) exposures than those associated with clinical efficacy in post-operative pain
- Representative Xenon K_V7 potentiator, XPC-B, demonstrated dose-dependent efficacy in the cynomolgus monkey capsaicin allodynia model at lower plasma exposures than those required for efficacy in the mouse formalin model
- XEN1120 was generally well tolerated in the Phase 1 first-in-human study, with no dose limiting or serious TEAEs, and achieved plasma exposures in line with the predicted efficacious range established from rodent and non-rodent models
- Collectively, these findings position XEN1120 as an exciting potential non-opioid therapy ready to advance into Phase 2 proof-of-concept studies in pain

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