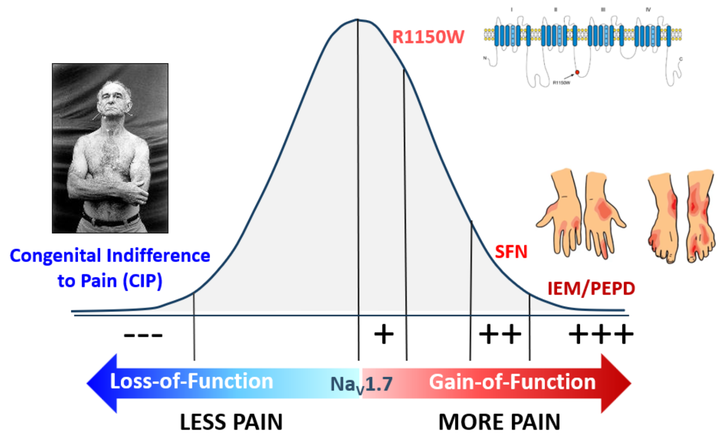
XEN1701, a Phase 2-Ready $Na_V1.7$ Inhibitor: Advancing a Novel Non-Opioid Strategy for Pain

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INTRODUCTION

- $Na_V1.7$ (SCN9A) is a compelling target for the treatment of pain with excellent human genetic validation
- Loss of function mutations identified in the SCN9A gene have been shown to cause congenital indifference to pain (CIP).[1,2] These are otherwise healthy individuals whose normal sensory functions are intact; however, they cannot feel any pain regardless of the noxious stimuli. Gain-of-function mutations in SCN9A cause severe pain disorders, including inherited erythromelalgia (IEM) and paroxysmal extreme pain disorder (PEPD), demonstrating that increased $Na_V1.7$ activity can directly drive pain
- Recent genetic research has better informed the potential level of $Na_V1.7$ inhibition required for efficacy in pain. Individuals have recently been identified in 2 different families, by 2 independent research groups, with an incomplete loss of $Na_V1.7$ and CIP.[3,4] The subjects in these families have SCN9A mutations in both alleles, consisting of one null allele and one hypomorphic allele. Functional characterization demonstrated that these mutations resulted in approximately 75% and 85% reductions in $Na_V1.7$ activity, respectively, yet both families exhibited a complete loss of pain sensation. In-house functional characterization of these variants has confirmed the published electrophysiological findings and reductions in $Na_V1.7$ activity
- Collectively, this human genetic data establishes that approximately >75% $Na_V1.7$ inhibition is associated with a pain free clinical phenotype, indicating that robust therapeutic efficacy may be achieved without requiring near-complete channel blockade



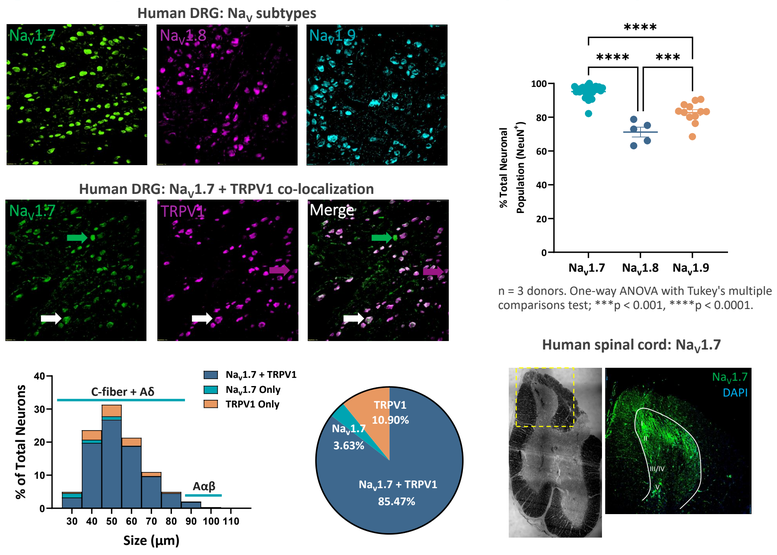
75-85% Reduction in $Na_V1.7$ Function → **Congenital Insensitivity to Pain (CIP)**

METHODS

- **Immunohistochemistry of human tissue:** Human tissue cryosections were immunolabeled with primary antibodies against $Na_V1.7$, $Na_V1.8$, $Na_V1.9$ or TRPV1, followed by fluorescent secondary antibodies. Sections were imaged by fluorescence microscopy to assess target localization and expression
- **IEM mouse line and aconitine assay:** Humanized $Na_V1.7$-I848T inherited erythromelalgia (IEM) mice and the aconitine-induced flinching assay were used as previously described by Bankar et al.[8]
- **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
- **Cynomolgus monkey cardiovascular telemetry:** Cardiovascular parameters were assessed in conscious telemetry-implanted cynomolgus monkeys. Arterial blood pressure and heart rate were continuously monitored from at least 2 h pre-dose to 24 h post-dose and compared with pre-dose baseline values
- **Phase 1 first-in-human study:** Healthy participants were enrolled in SAD, MAD, food-effect, and CSF cohorts to assess the safety, tolerability, pharmacokinetics, food effect, and CNS penetration of XEN1701. CSF sampling was performed in open-label cohorts to measure central drug exposure

RESULTS

Figure 1. $Na_V1.7$ is Highly Enriched in Human Nociceptive Pathways



n = 3 donors. One-way ANOVA with Tukey's multiple comparisons test; ***p < 0.001, ****p < 0.0001.

DAPI, 4',6-diamidino-2-phenylindole; DRG, dorsal root ganglion; TPRV1, transient receptor potential vanilloid 1.

- Quantification of sodium channel expression demonstrated that 94.8% of DRG neurons were positive for $Na_V1.7$ protein, compared with 72.9% and 86.3% for $Na_V1.8$ and $Na_V1.9$, respectively
- Approximately 85% of TRPV1-positive neurons co-expressed $Na_V1.7$ and TRPV1 in human DRG neurons
- $Na_V1.7$ expression is enriched in laminae I and II of the human spinal cord, corresponding to the primary termination site of afferent nociceptive fibers

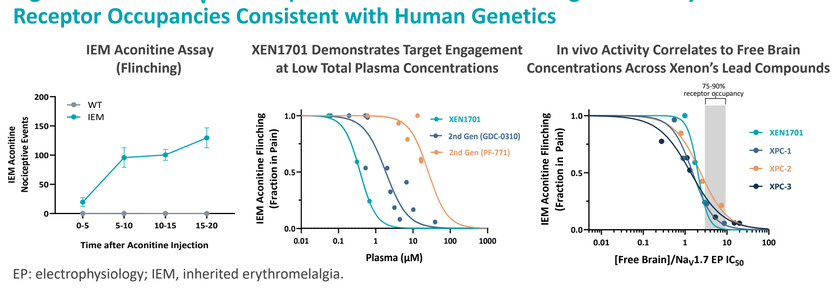
Figure 2. Xenon's Lead $Na_V1.7$ Compounds have a Differentiated Profile

Target Compound Profile

- **CNS exposure**: engagement of $Na_V1.7$ in the spinal cord: best mimics the genetics
- Improved **free drug exposure** and tissue distribution
- Comprehensive **selectivity** over Na_V subtypes

	First-Gen (e.g., Vixotrigine)	Second-Gen (e.g., PF-771, GDC-0276)	Xenon Lead Compounds
CNS Exposure			
Free Drug Exposure			
Selectivity			

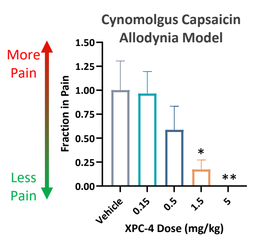
Figure 3. Xenon $Na_V1.7$ Compounds Achieve Robust Analgesic Activity at Receptor Occupancies Consistent with Human Genetics

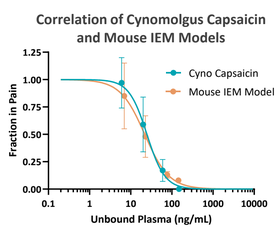


EP: electrophysiology; IEM, inherited erythromelalgia.

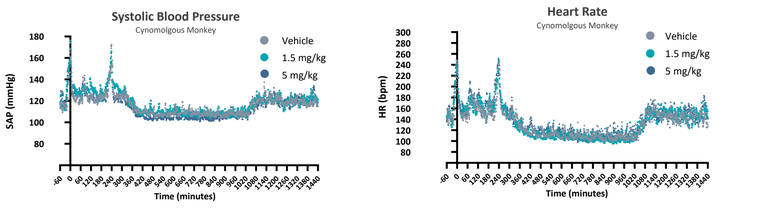
- The IEM model utilizes transgenic mice expressing a human gain-of-function $Na_V1.7$ mutation identified in patients with IEM. Following intraplantar administration of the sodium channel activator aconitine, IEM mice exhibit robust pain-related flinching behaviors that are absent in wild-type animals, enabling assessment of human $Na_V1.7$ target engagement and analgesic efficacy in vivo
- XEN1701 reduced pain-related behaviors in the mouse IEM model at substantially lower plasma exposures than second-generation $Na_V1.7$ inhibitors. Relative to GDC-0310 and PF-771, XEN1701 demonstrated in vivo efficacy at approximately 10-fold and 100-fold lower total plasma concentrations, respectively
- Across Xenon's lead $Na_V1.7$ compounds, in vivo efficacy was observed to strongly correlate with free brain exposure normalized to $Na_V1.7$ electrophysiological potency
- Robust analgesic activity was observed when compounds achieved approximately 75-90% CNS receptor occupancy, with similar or greater levels of peripheral target engagement
- This receptor occupancy range aligns with human genetic data suggesting that >75% $Na_V1.7$ inhibition is required for analgesia[3,4]

Figure 4. XPC-4 Reduces Capsaicin-Evoked Pain in Monkeys without Observed Cardiovascular Effects at the Doses Tested





Dose (mg/kg)	XPC-4 Predicted Receptor Occupancies (at C_{max}) Peripheral	Central
0.15	70%	57%
0.5	88%	80%
1.5	96%	93%
5	99%	98%

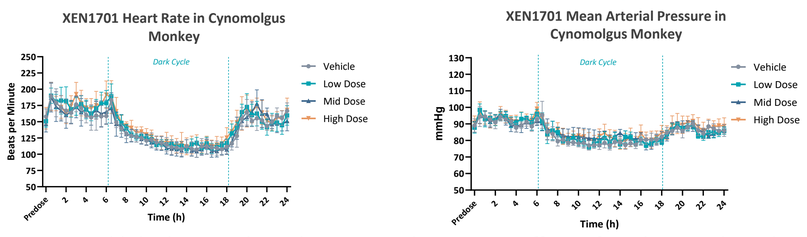


IEM, inherited erythromelalgia; SAP, systolic arterial pressure.

XPC-4 Reduces Capsaicin-Evoked Pain in Monkeys without Observed Cardiovascular Effects at the Doses Tested (Figure 4)

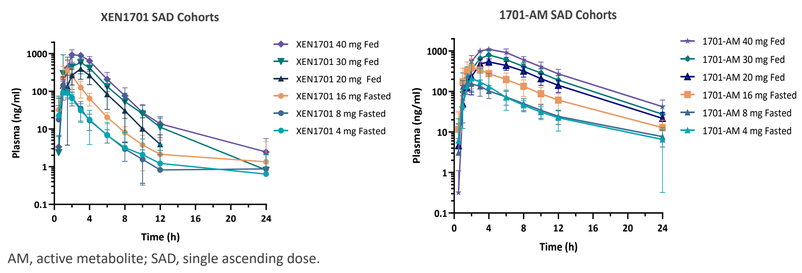
- Representative Xenon $Na_V1.7$ inhibitor, XPC-4, produced dose-dependent reductions in capsaicin-evoked heat allodynia in the cynomolgus monkey, with target engagement observed at doses ≥0.5 mg/kg
- Efficacious exposures in the cynomolgus capsaicin model closely correlated with the mouse IEM model
- Doses achieving >75% $Na_V1.7$ predicted central and peripheral receptor occupancy were associated with reductions in capsaicin-evoked allodynia in the monkey capsaicin model
- No clinically meaningful change in systolic arterial blood pressure, heart rate or the cardiovascular response to technician room entry and handling (t = 240 min) was observed with XPC-4 at the two highest efficacious doses evaluated in the cynomolgus capsaicin model

Figure 5. XEN1701 Achieves Predicted Therapeutic Exposures without Observed Effects on Heart Rate or Blood Pressure in Cynomolgus Monkey



- Prior published reports have demonstrated autonomic effects after pharmacological inhibition of $Na_V1.7$, however these compounds differ from Xenon's target compound profile[5,6,7]
- In the preclinical studies conducted to date, XEN1701 did not show a consistent pattern of autonomic cardiovascular effects at exposures greater than predicted therapeutic levels
- No change in heart rate or mean arterial pressure was observed in cynomolgus monkeys across the range of doses tested (high dose predicted at 97% peripheral receptor occupancy)

Figure 6. Pharmacokinetic Profile of XEN1701 and Active Metabolite 1701-AM

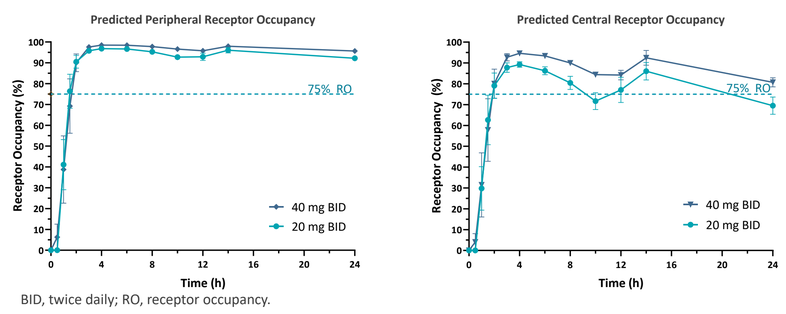


AM, active metabolite; SAD, single ascending dose.

- XEN1701 exhibited dose-dependent increases in plasma exposure across the evaluated dose range
- The active metabolite, 1701-AM, was detected in all cohorts and demonstrated a consistent metabolite-to-parent exposure ratio across all doses
- The combined exposure profile of XEN1701 and the active metabolite 1701-AM, support the potential for achieving clinically relevant $Na_V1.7$ inhibition

Figure 7. Proposed Phase 2 Doses Achieve High Levels of $Na_V1.7$ Receptor Occupancy in the Peripheral and Central Nervous System

Time (h)	Mean Predicted Receptor Occupancy 20 mg BID Peripheral	20 mg BID Central	40 mg BID Peripheral	40 mg BID Central
0	0	0	0	0
0.5	0	0	9	5
1	54	41	94	88
1.5	94	88	96	89
2	96	89	97	93
3	97	90	98	95
4	97	90	99	95
6	97	88	99	94
8	96	83	98	90
10	94	74	97	85
12	95	86	96	86
14	97	90	99	96
24	94	73	96	82



BID, twice daily; RO, receptor occupancy.

- Predicted receptor occupancy modeling indicates that the proposed Phase 2 doses achieve and sustain ≥75% $Na_V1.7$ receptor occupancy in the peripheral and central nervous systems, with peripheral receptor occupancy approaching 99% and >90% central occupancy maintained for the majority of the dosing interval
- CSF sampling confirmed central exposures of XEN1701 and its active metabolite, supporting the predicted central receptor occupancy estimates. At the high dose, target occupancy is achieved within approximately 1 hour in both compartments
- Collectively, this data supports rapid and sustained $Na_V1.7$ target engagement in both the peripheral and central nervous systems at the dose levels proposed for Phase 2 evaluation

Table 1. SAD: TEAEs Considered Related in >1 XEN1701-Treated Participant

Preferred Term	4 mg Fasted (N=6) n	8 mg Fasted (N=6) n	16 mg Fasted (N=6) n	20 mg Fed (N=6) n	30 mg Fed (N=6) n	40 mg Fed (N=6) n	XEN1701 Overall (N=36) n (%)	Pooled Placebo (N=12) n (%)
Nervous System Disorders								
Dizziness	0	1	1	0	0	0	2 (5.6%)	0
Headache	0	1	0	0	1	0	2 (5.6%)	1 (8.3%)

Participant counts shown; more than one event per participant is possible.
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 TEAEs
- No TEAEs leading to study-drug or study discontinuation

SAD:

- No serious or severe TEAEs; all TEAEs were mild
- TEAEs considered related to study treatment in >1 XEN1701 participant shown in Table 1

MAD:

- No serious TEAEs, most events were mild
- TEAEs considered related to study treatment in >1 XEN1701 participant shown in Table 2

Table 2. MAD: TEAEs Considered Related in >1 XEN1701-Treated Participant

Preferred Term	10 mg QD Fasted (N=6) n	20 mg QD Fed (N=6) n	20 mg BID Fed (N=6) n	30 mg BID Fed (N=6) n	40 mg BID Fed (N=6) n	XEN1701 Overall (N=30) n (%)	Pooled Placebo (N=10) n (%)
Nervous System Disorders							
Headache	0	0	3	0	0	3 (10.0%)	1 (10.0%)
Dizziness	0	0	1	0	1	2 (6.7%)	1 (10.0%)
Dizziness postural	1	0	1	0	0	2 (6.7%)	0

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

XEN1701 Did Not Show a Pattern of Autonomic Cardiovascular Effects

- Selected TEAEs potentially related to autonomic function (Table 3) were infrequent, 5/76 (6.6%) XEN1701-treated subjects and 1/24 (4.2%) placebo-treated subjects, with no consistent dose- or exposure-related pattern, and none occurred at the highest SAD or MAD dose levels
- All but one of these TEAEs were mild
- One event, a brief (~2 min) severe syncope, was reported in a subject with pre-existing low blood pressure and a heart rate variability (postural increase) at baseline. The event occurred prior to morning dose on day 3 (~10.5 hours after previous dose). The subject remained on study and completed the remaining dosing (7 days) without recurrence

Table 3. Selected TEAEs Potentially Related to Autonomic Function

Adverse Event	XEN1701 Single Doses (N=6/group) 4 mg Fasted n	8 mg Fasted n	8 mg FE (N=10) n	16 mg Fasted n	20 mg Fed n	30 mg Fed n	40 mg Fed n	XEN1701 Multiple Dosing (7 days) (N=6/group) 10 mg QD Fasted n	20 mg QD Fed n	20 mg BID Fed n	30 mg BID Fed n	40 mg BID Fed n	Total XEN1701 N=76 n (%)	Total Placebo N=24 n (%)
Hypotension	0	0	0	**1**	0	0	0	0	0	0	0	0	**1**	0
Dizziness postural	0	0	0	0	**1**	0	0	**1**	0	**1**	0	0	**3**	0
Orthostatic hypotension	0	0	0	0	**1**	0	0	0	**1**	**1**	0	0	**3**	**1**
Postural orthostatic tachycardia	0	0	0	0	0	0	0	0	0	**1**	0	0	**1**	0
Syncope	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**1**	**0**
Total Subjects	**0**	**0**	**0**	**1**	**1***	**0**	**0**	**1**	**1**	**1***	**0**	**0**	**5 (6.6%)**	**1 (4.2%)**

*1 subject experienced all TEAEs shown within the respective dose group.
BID, twice daily; FE, food effect; N, number of participants; n, number of participants with >1 related TEAE; QD, once daily; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Human genetic and protein expression data strongly support $Na_V1.7$ as a non-opioid therapeutic target for pain
- Selective $Na_V1.7$ inhibition produced robust analgesic activity across mouse and non-human primate pain models at central and peripheral receptor occupancies consistent with human genetic data, without observed effects on blood pressure or heart rate in these preclinical models
- In the preclinical studies conducted to date, XEN1701 did not show a consistent dose- or exposure-related pattern of autonomic cardiovascular effects at exposures greater than predicted therapeutic levels, and the human safety data to date (Table 3) likewise showed no consistent dose- or exposure-related pattern of TEAEs potentially related to autonomic function
- Phase 1 PK and CSF data demonstrated that XEN1701 and its active metabolite 1701-AM rapidly achieved and maintained ≥75% $Na_V1.7$ receptor occupancy at proposed therapeutic dose levels
- XEN1701 was generally well tolerated in the Phase 1 first-in-human study, with no dose limiting or serious TEAEs and no consistent dose- or exposure-related pattern of TEAEs-potentially related to autonomic function
- Collectively, these findings position XEN1701 as an exciting potential non-opioid therapy ready to advance into Phase 2 proof-of-concept studies in pain

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DISCLOSURES:
All authors are current or former employees who may own securities of Xenon Pharmaceuticals Inc. (Vancouver, BC, Canada).

FUNDING:
This work was funded by Xenon Pharmaceuticals Inc.