XEN1101 in Primary Generalized Tonic-Clonic Seizures (PGTCS)

JUNE 2022

Forward Looking Statement/Safe Harbor

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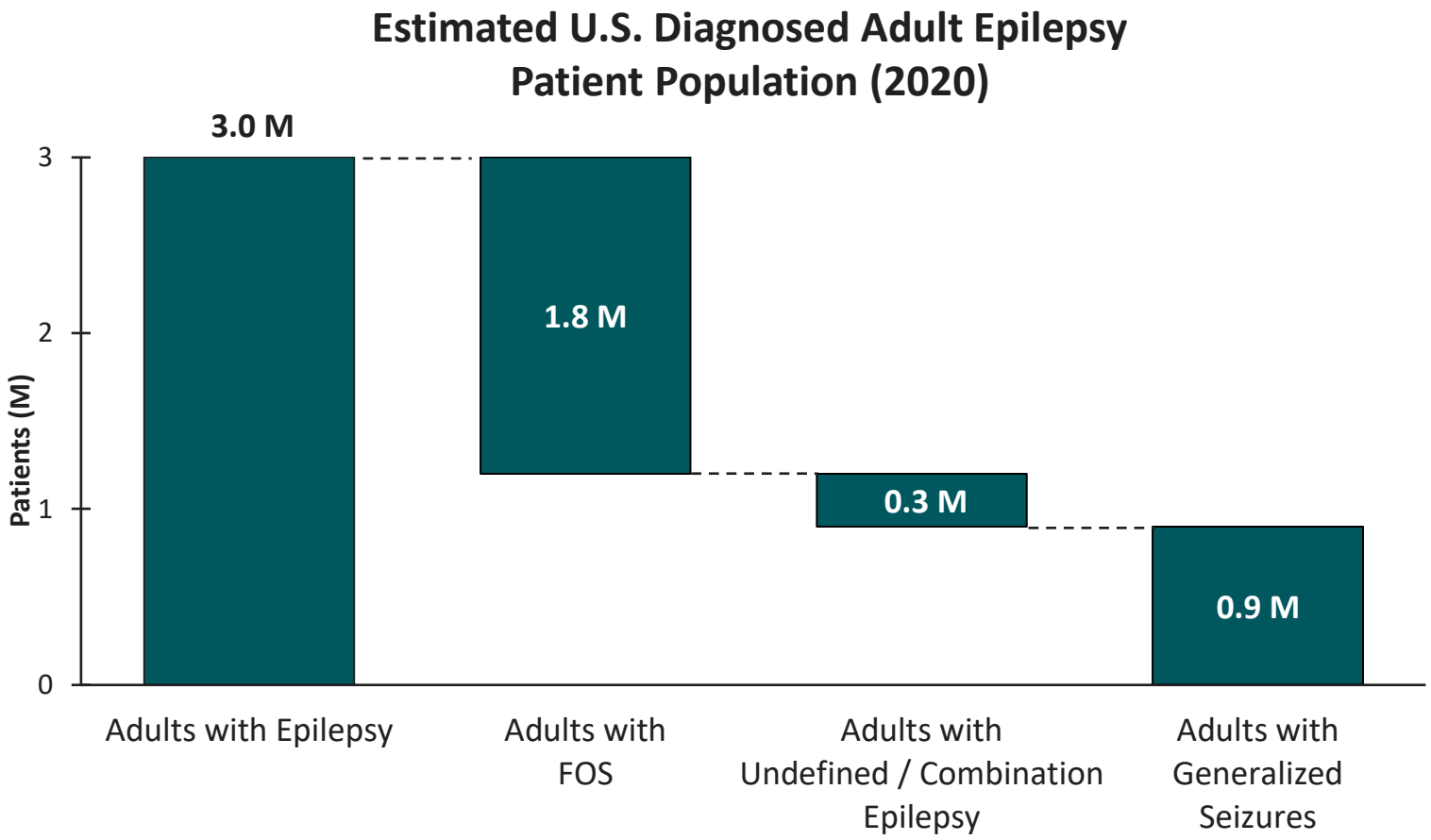
These statements are based on estimates and information available to us at the time of this presentation and are not guarantees of future performance. Actual results could differ materially from our current expectations as a result of many factors, including but not limited to: the impact of the COVID-19 pandemic on our business, research and clinical development plans and timelines and results of operations, including impact on our clinical trial sites, collaborators, and contractors who act for or on our behalf, may be more severe and more prolonged than currently anticipated; clinical trials may not demonstrate safety and efficacy of any of our or our collaborators' product candidates; promising results from pre-clinical development activities or early clinical trial results may not be replicated in later clinical trials; our assumptions regarding our planned expenditures and sufficiency of our cash to fund operations may be incorrect; our ongoing discovery and pre-clinical efforts may not yield additional product candidates; any of our or our collaborators' product candidates, including XEN1101, may fail in development, may not receive required regulatory approvals, or may be delayed to a point where they are not commercially viable; we may not achieve additional milestones in our proprietary or partnered programs; regulatory agencies may impose additional requirements or delay the initiation of clinical trials; regulatory agencies may be delayed in reviewing, commenting on or approving any of our or our collaborators' clinical development plans as a result of the COVID-19 pandemic, which could further delay development timelines; the impact of competition; the impact of expanded product development and clinical activities on operating expenses; impact of new or changing laws and regulations; adverse conditions in the general domestic and global economic markets; as well as the other risks identified in our filings with the Securities and Exchange Commission and the securities commissions in British Columbia, Alberta and Ontario. Except as required by law, we assume no obligation and do not intend to update these forward-looking statements or to conform these statements to actual results or to changes in our expectations.

Executive Summary: XEN1101 in PGTCS

Unmet Medical Need in PGTCS	• Generalized epilepsy accounts for at least 30% of epilepsy in the US, of which approximately 80% have primary generalized tonic-clonic seizures (PGTCS) • PGTCS are severe, life-threatening seizures, also known as grand mal seizures or convulsions • Compared to FOS, there are fewer ASMs available, and an unmet need exists for improved efficacy, particularly given the mortality risk of PGTCS
Kv7 Mechanistic Background	• XEN1101 is a differentiated "next generation" K_V7 potassium channel modulator being developed for the treatment of epilepsy and other neurological disorders • Preclinical models and clinical studies suggest K_V7 channel potentiators may be efficacious in patients with generalized epilepsy, including PGTCS
XEN1101 Clinical Experience	• Announced in June 2022, the Phase 3 X-ACKT clinical trial is a randomized, placebo-controlled, double-blind study of XEN1101 in patients with PGTCS • Alignment with FDA regarding single trial to support NDA submission

XEN1101 Commercial Opportunity	• In market research, physicians reacted positively to the potential XEN1101 profile:
	  • Broad spectrum efficacy with rapid onset
	  • Novel MOA that can be used in polypharmacy
	  • QD dosing

Adult Epilepsy Epidemiology



- Focal onset seizures (FOS) represent the largest segment of the epilepsy population in the U.S.
- Generalized epilepsy is the next most common form; the majority of adult patients with generalized epilepsy experience PGTCS (~80%)
- Despite the availability of multiple antiseizure medications (ASMs), a substantial unmet medical need exists for novel therapeutic options that can reduce seizure burden in patients who experience consistent seizures

Source: Xenon sponsored market research

Primary Generalized Tonic-Clonic Seizures (PGTCS) Overview

Description

- Primary generalized tonic-clonic seizures (PGTCS) are a type of seizure lasting a few seconds to minutes
- PGTCS start in both hemispheres of the brain simultaneously (generalized onset) and comprised of tonic and clonic phases
  - Tonic phase: muscle stiffening, loss of consciousness
  - Clonic phase: muscle jerking, risk of inflicting self-harm
- PGTCS (formerly known as *Grand Mal* seizures) are one of the most severe forms of seizures

Disease Burden

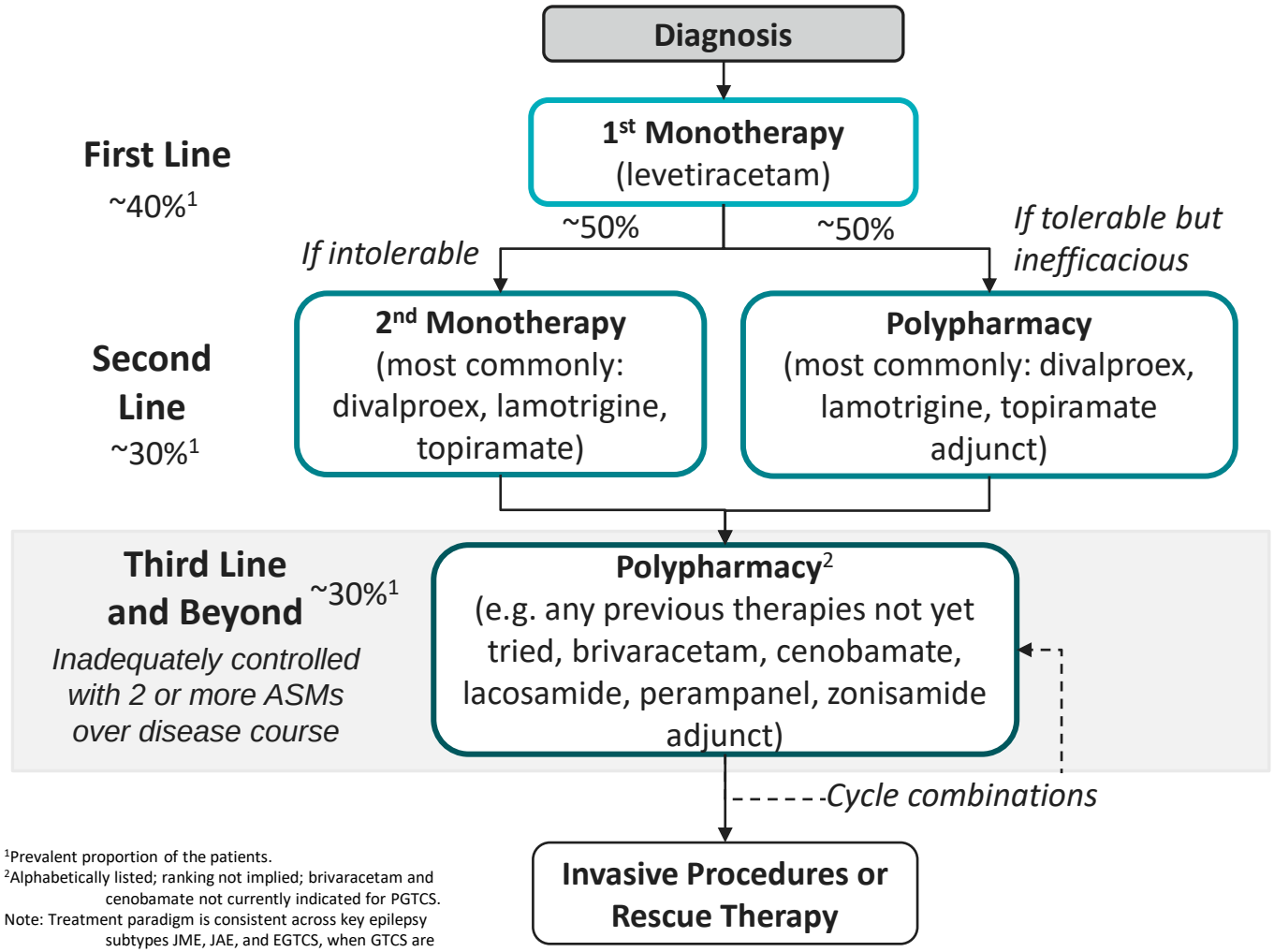
- Seizure frequency varies, usually with recurrences ranging from weeks to months, with a tendency to cluster, and can be fatal
  - 30-50% of people who have one unprovoked tonic-clonic seizure have a subsequent event
- PGTCS also has a substantial negative impact on quality of life
  - High unemployment rates (25-69%) in epilepsy patients
  - Unable to drive unless 6-12 months seizure free in most states
- Social stigma and concern of having a seizure in a public setting

Outcomes

- Given the danger and risk of death, PGTCS are generally considered more serious and dangerous than FOS
- Death can be caused by seizure injury or SUDEP (sudden unexpected death in epilepsy)
  - Tonic phase can result in falls and clonic phase can result in additional injury
  - Generalized tonic-clonic seizures increase the risk of SUDEP
  - Not well understood but involved impaired brain, heart, and lung function
- Mortality rate is 1.6-9.3x higher in epilepsy patients than the general population

Source: Xenon sponsored market research

PGTCS Treatment Paradigm



[1]Prevalent proportion of the patients.
[2]Alphabetically listed; ranking not implied; brivaracetam and cenobamate not currently indicated for PGTCS.
Note: Treatment paradigm is consistent across key epilepsy subtypes JME, JAE, and EGTCS, when GTCS are present.
Source: Xenon sponsored market research

Treatment Considerations

- Fewer ASMs are approved to treat PTGCS despite the more severe seizure phenotype
- Cycling through treatment options is common after initial monotherapy as patients seek seizure freedom
- Select ASMs, particularly sodium channel blockers and GABAergic agents, may exacerbate idiopathic generalized epilepsies (IGEs) and can provoke absence or myoclonic seizures

Factors Influencing Clinical Decision-Making

Types of Seizures and Efficacy

- Broad spectrum coverage is a key consideration
  - *"It's very helpful if one drug can cover multiple seizure types." – PGTCS KOL*
- Avoiding ASMs that can exacerbate certain seizures is equally important

Patient Characteristics and Comorbidities

- Patient characteristics (e.g. women of childbearing age)
- Patient history including comorbidities (e.g. mood disorders) considered in context of side effects and drug-drug interactions

Safety and Tolerability

- Many ASMs impact mood or weight; if a patient is sensitive to either, physicians adjust medication choice
  - *"If patients can't tolerate a drug, it does us no good." – PGTCS KOL*

Titration, Onset of Action and Dosing

- Titration requirements can be complicated for patients to follow
- Quick onset of action is valuable for patients with uncontrolled seizures
- Once-daily oral treatment is ideal for ongoing maintenance

Source: Xenon sponsored market research

Key Unmet Needs for PGTCS Patients

Key Unmet Needs	Key Insights
Effective Treatments for Third Line and Beyond Patients	• PGTCS is heterogenous and 30% of patients are third line and beyond with high unmet need, particularly as tonic-clonic seizures are dangerous and can lead to falls or death – *"There are patients who don't respond initially to several drugs. There is still much unmet need for therapies for them." – PGTCS KOL*
More Options with Once-Daily Dosing	• Disease severity limits use of select agents (e.g. lamotrigine) as patients look for more potent alternatives • Compliance is critical; a drug with daily dosing and a longer half-life to provide coverage for missed doses would gain favor among prescribers
Improved Safety/Tolerability	• ASMs impact mood, dizziness, weight and more; patients on multiple ASMs experience compounding adverse events and therefore tolerability is a top consideration for physicians to improve patient QOL – *"This is a lifelong disease so I would not want to put a patient on something that will make them miserable every day." – PGTCS KOL*
Novel MOAs for Rational Polypharmacy	• As existing options do not achieve desired efficacy on all patients, physicians are looking for novel MOAs to bolster the treatment paradigm – *"If I have tried a few sodium channel blockers and GABA agents and they are not working, I would rather try a drug with a novel MOA than another one of those." – PGTCS KOL*

Source: Xenon sponsored market research

Potential for XEN1101 to address unmet needs in PGTCS, particularly for patients with persistent seizures despite prior ASM treatment

Rationale Supporting XEN1101 Development in PGTCS

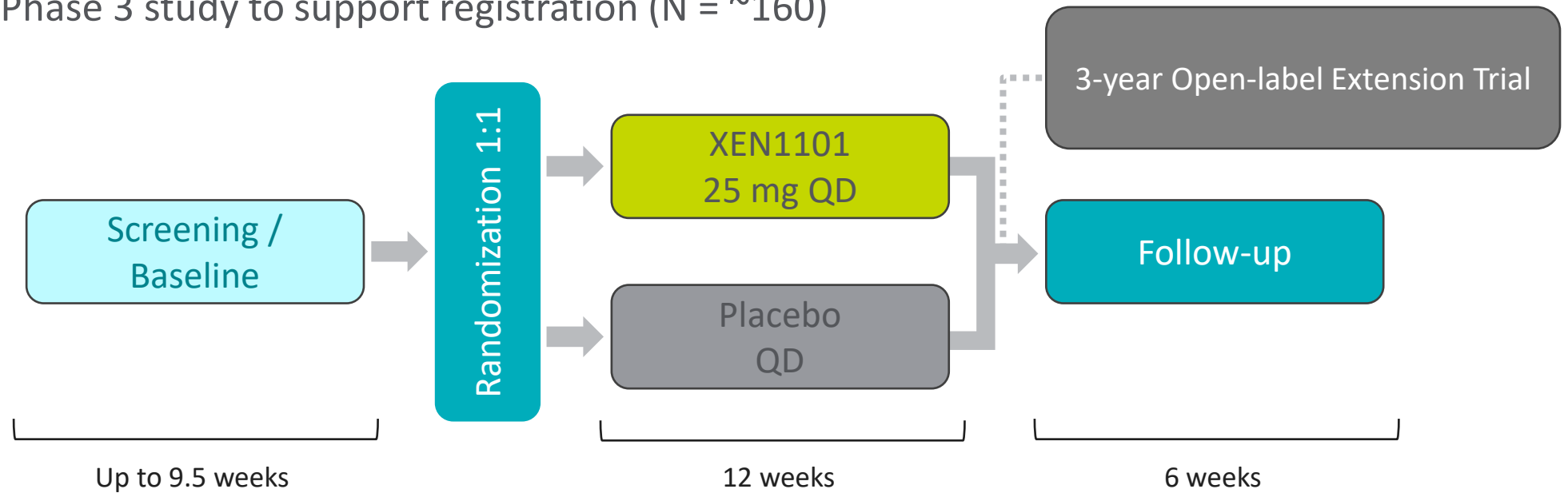
- XEN1101 anti-seizure activity in maximum electroshock seizure and pentylenetetrazole preclinical models, both known to predict efficacy for primary generalized seizures
- ICA-105665 (Kv7 potassium channel opener) suppressed photosensitivity (EEG model) in generalized epilepsy patients[1]
- Levetiracetam, valproic acid, lamotrigine, and brivaracetam (not approved for PGTCS) suppressed photosensitivity in generalized epilepsy patients and demonstrate PGTCS efficacy[2]
- In X-TOLE, XEN1101 demonstrated broad impact across all focal seizure subtypes, including those that progressed to generalized seizures

[1]Kasteleijn-Nolst Trenité et al, Epilepsia. 2013;54(8)
[2]Verotti et al, Epileptic Disord. 2012;14(4)

Significant unmet need remains in PGTCS despite available treatment options and an opportunity remains for a broad-spectrum agent with activity across seizure types

XEN1101 “X-ACKT” PGTCS Phase 3 Trial Design

- Aligned with FDA regarding clinical development plan in PGTCS to conduct a single, multi-center, placebo-controlled Phase 3 study to support registration (N = ~160)



- **Primary Objective:**
  - MPC of 25 mg dose of XEN1101 vs placebo on seizure frequency in adults with primary generalized tonic-clonic seizures (PGTCS) taking 1 to 3 ASMs in the DBP
- **Secondary Objectives** include assessing the effect on XEN1101 vs placebo on RR50, seizure freedom and PGI-C

XEN1101 Value Proposition

Efficacy

- Compelling data in difficult-to-treat adult FOS patient population in Phase 2b
- Rapid onset of action, with seizure reduction observed at Week 1
- Durable seizure reductions demonstrated in OLE
- Broad spectrum activity expected to be applicable across FOS and PGTCS

Ease of Use

- One pill, once-daily
- No titration required
- Unique and novel MOA can be leveraged in rational polypharmacy

Safety Profile / Tolerability[1]

- Well-tolerated with AE profile in line with other ASMs
- Evening dose results in C_{max} during sleep
- No drug allergic reactions observed
- No TEAEs of pigmentary abnormalities

[1]Company Poster. 2018 American Epilepsy Society (AES) Annual Meeting: "A First-in-Human Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Pharmacodynamics of a Novel Small Molecule KV7.2/7.3 Positive Allosteric Modulator (XEN1101) in Healthy Subjects." December 3, 2018

We are in alignment with the FDA and have a clear path forward for clinical development for XEN1101 in FOS and PGTCS