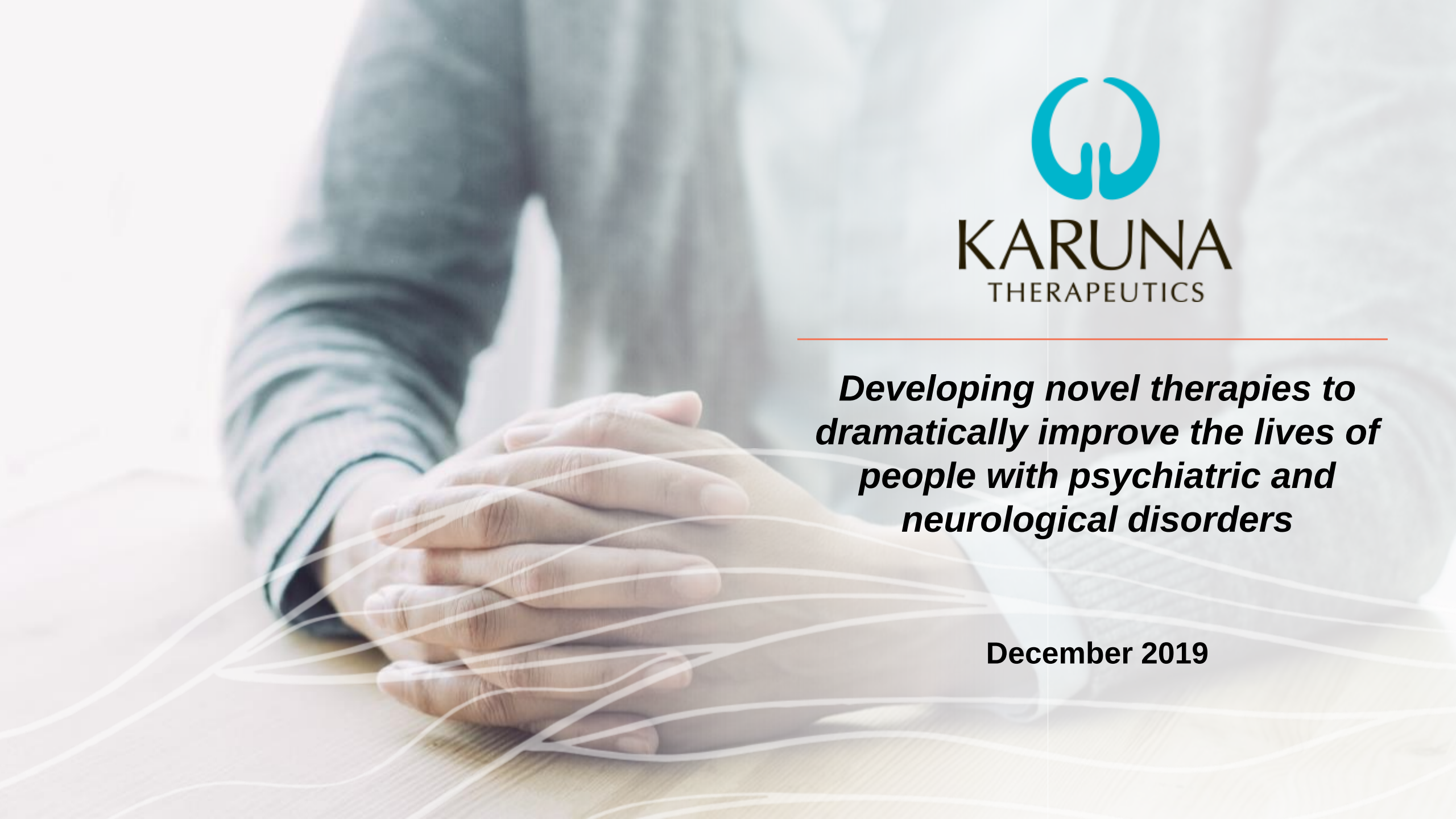

KARUNA
THERAPEUTICS

Developing novel therapies to dramatically improve the lives of people with psychiatric and neurological disorders

December 2019

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Karuna at-a-glance

KarXT

- KarXT is a novel mechanism of action therapeutic targeting CNS indications representing large and underserved patient populations characterized by psychosis and cognitive deficit
- Recently announced Phase 2 clinical trial of KarXT in patients with acute psychosis in schizophrenia met its primary endpoint demonstrating a statistically significant ($p<0.0001$) & clinically meaningful 11.6 point improvement on PANSS total score baseline vs. placebo

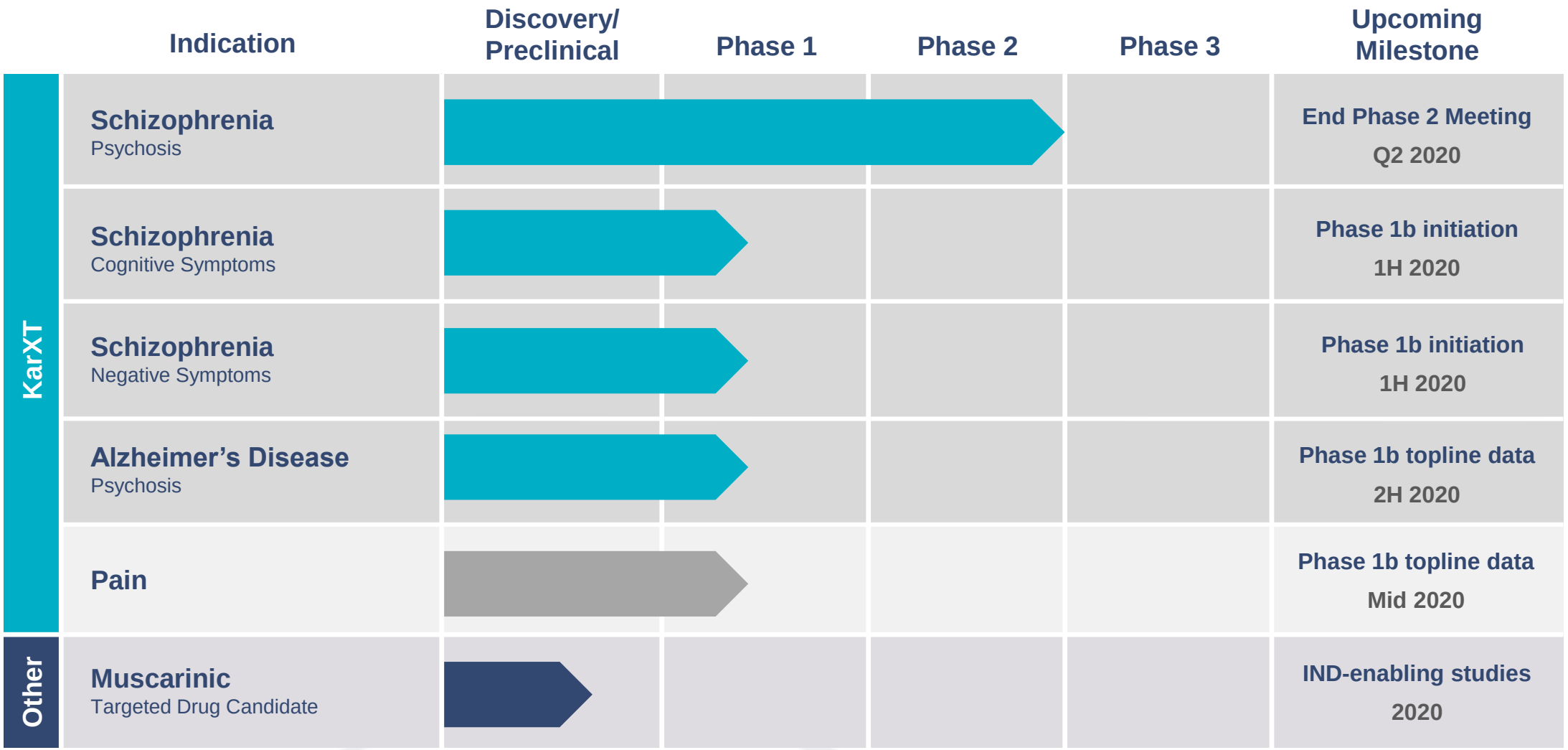
Pipeline-in-a-Product

- End-of-Phase 2 meeting expected in Q2 2020 with Phase 3 initiation expected by the end of 2020 for the treatment of psychosis in schizophrenia
- Near term development opportunities
  - Negative and cognitive symptoms of schizophrenia
  - Psychosis in Alzheimer's disease (and more broadly Dementia Related Psychosis [DRP])
  - Pain
- Advanced formulation development underway to optimize therapeutic window and improve compliance

Experienced Team

- Leadership with proven expertise in CNS drug development and commercialization
- Advised by world experts in schizophrenia, Alzheimer's disease, and neuroscience
- Well-seasoned board of directors and blue-chip biotech investors

Karuna's portfolio of muscarinic receptor-targeted programs



Leadership team with deep expertise in neuroscience and drug development

Steve Paul, M.D. | Chairman and CEO

Former EVP and president at Eli Lilly Research Labs; Co-founder, board member at Sage Therapeutics & Voyager Therapeutics; Former scientific director of NIMH

David Hewitt, M.D. | SVP, Medical

Former CMO, Syneos Health and inVentiv Health; Former Executive Director at Merck; Former Senior Director Ortho-McNeil and Johnson & Johnson

Troy Ignelzi | CFO

Former CFO at scPharmaceuticals and Juventas; Finance, BD, operations and sales executive at Esperion Therapeutics, Insys Therapeutics and Eli Lilly

Christian Felder, Ph.D. | VP, Discovery Research

Adjunct faculty at Monash University and UVA; Former Research Fellow/Director at Eli Lilly; Former Unit Chief at NIMH; Former faculty at Georgetown University

Andrew Miller, Ph.D. | Founder and COO

Founder and inventor of KarXT technology; Former VP at PureTech; 40 under 40 innovators award from MedTech Boston; Director and Former COO at Entrega

Giorgio Attardo, Ph.D. | VP, CMC & Preclinical Development

Former VP of Discovery and Preclinical Development at Avid Radiopharmaceuticals (Eli Lilly); Held senior CMC and research positions at Gemin X, Shire, BioChem Pharma and Chlorion

Stephen Brannan, M.D. | CMO

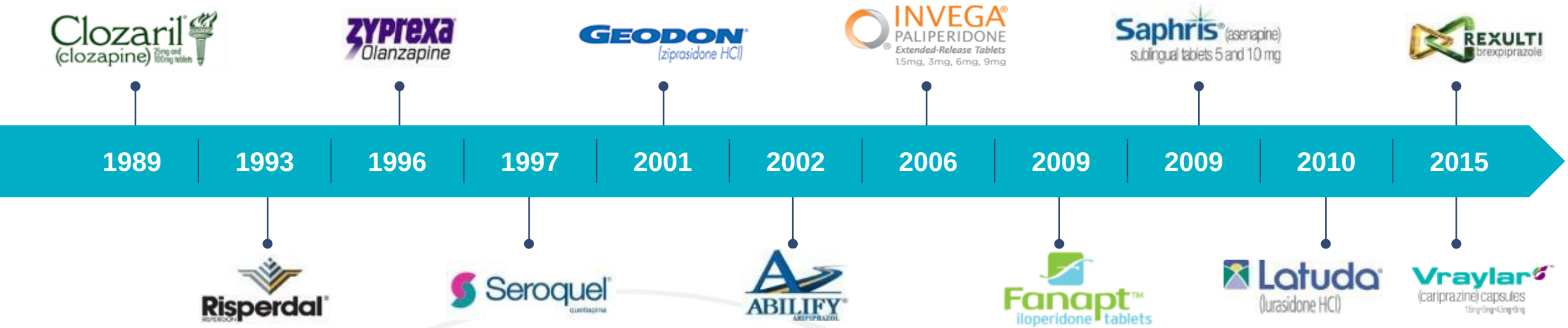
Former Therapeutic Head of Neuroscience at Takeda; senior positions at Novartis (Exelon patch), Eli Lilly (Cymbalta), Cyberonics, & Forum Pharmaceuticals

Gregory Brophy, Ph.D. | Senior Regulatory Consultant

Former Senior Head of Neuroscience Regulatory at Eli Lilly; Former executive leader of regulatory (consulting) at Acadia

Antipsychotics: Blockbuster sales, but little innovation

- Today's drugs rely on **same mechanism as drugs of the 1950s** (first antipsychotic drug, chlorpromazine, discovered in 1952)
- Sales of antipsychotic drugs were **>$11B in 2015** and are expected to be **>$14B by 2025 worldwide**
- Despite limited efficacy, severe side effects, and the availability of generic medicines, antipsychotic drugs such as Zyprexa, Seroquel and Abilify each achieved **>$5B peak sales worldwide**
- Antipsychotics are a **protected Medicare Part D class**



Unmet need. Significant opportunity.

Schizophrenia

- Positive (psychosis), negative and cognitive symptom domains
- Antipsychotics currently approved only to treat psychosis and offer modest efficacy in many patients; nothing to treat negative and cognitive symptoms
- Significant side effects including movement disorders, weight gain, sedation, etc.
- >21 million patients with schizophrenia worldwide with ~2.7m in the US

Alzheimer's disease psychosis

- No medicines approved for treatment
- Current antipsychotics used despite black box warning for increased morbidity and mortality
- Afflicts up to 50% of AD patients; 5.8m AD patients in the US
- Psychosis also associated broadly with dementia (Dementia Related Psychosis)

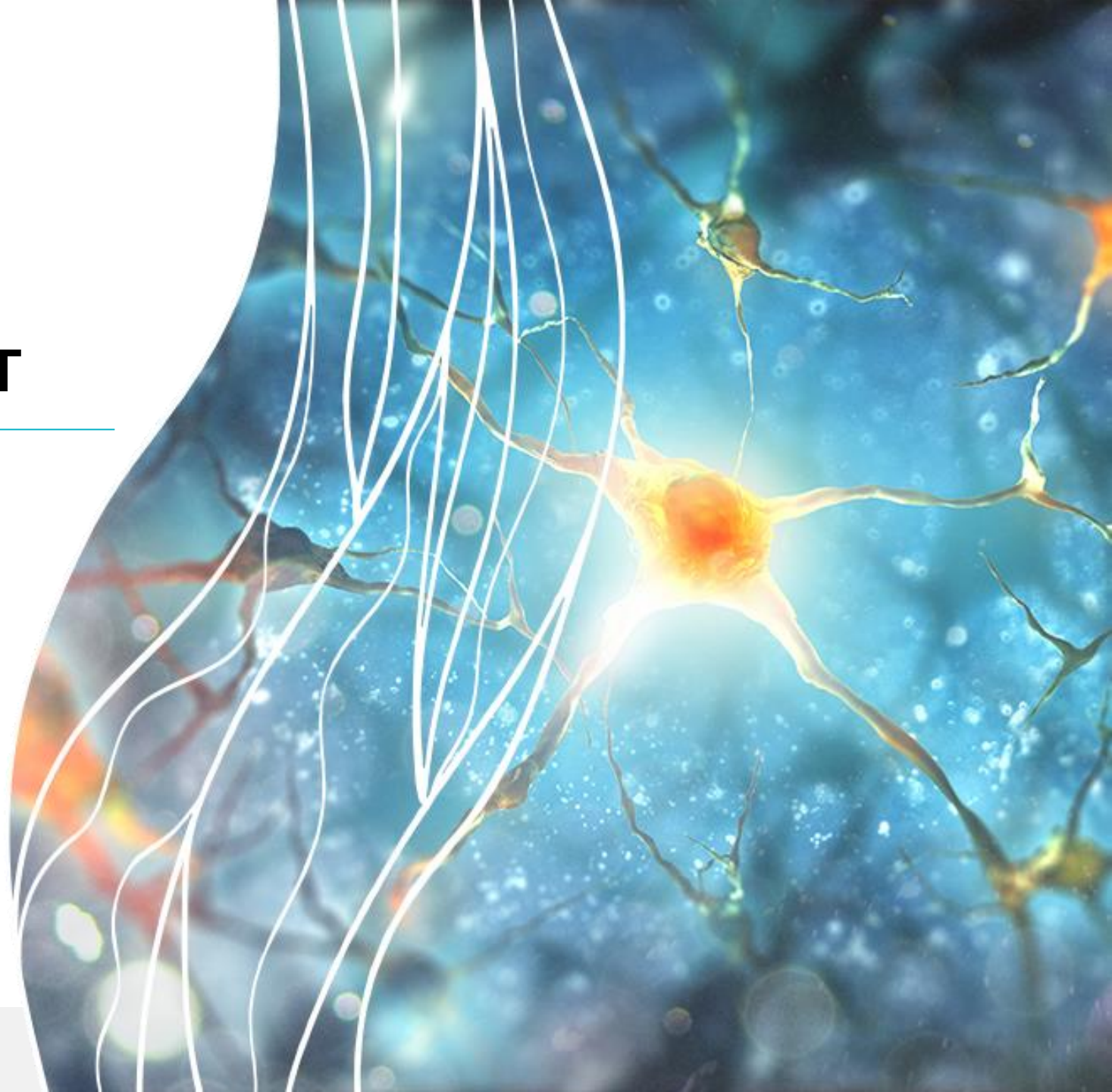
Pain

- Multiple opportunities across different pain modalities: acute (post-op), inflammatory, and neuropathic
- Reducing or eliminating opioid use is major public health need






The Rationale for KarXT



Unrealized potential of muscarinic receptors

Muscarinic receptors in the brain are promising targets for schizophrenia, Alzheimer's and pain

Many companies pursued development, but were stymied by side effects caused by peripheral muscarinic receptors

A novel approach is needed to realize potential of muscarinic agonists

Our proprietary lead product candidate: KarXT

xanomeline
(muscarinic *agonist*)

- Human PoC in double-blind, placebo-controlled trials in schizophrenia and Alzheimer's
- Trials enrolled over 1,000 patients including 68 patients for ≥ 1year
- Exclusively licensed from Eli Lilly

KarXT

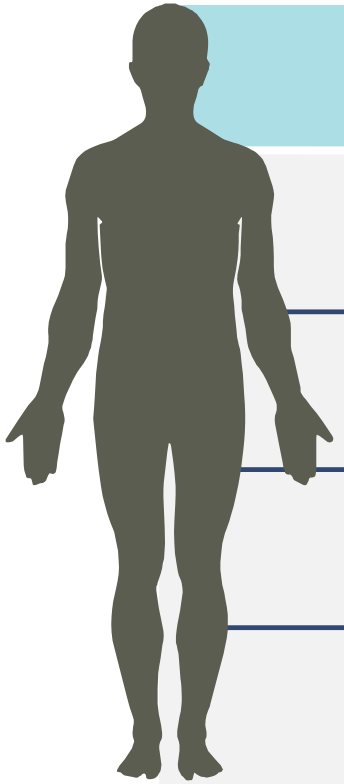
xanomeline + trospium chloride

KarXT is designed to maintain efficacy of xanomeline while ameliorating its cholinergic AEs

trospium chloride
(muscarinic *antagonist*)

- Does not meaningfully cross the blood brain barrier, limiting effects to peripheral tissues
- No known metabolic overlap with xanomeline
- Generic drug for overactive bladder used since the 1960s

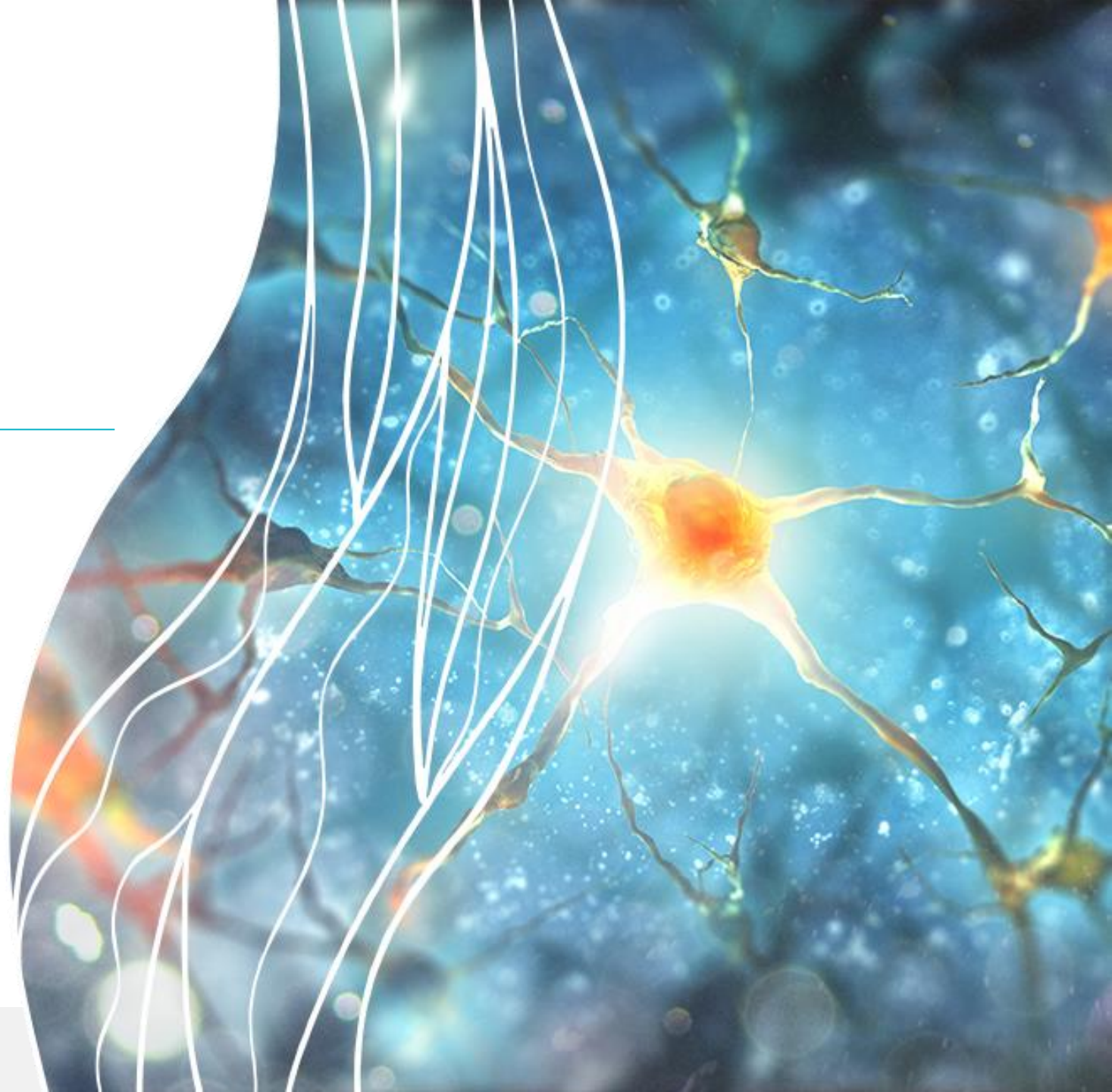
KarXT selectively activates muscarinic receptors in the brain



System	Potential Impact on Symptoms: xanomeline	+ trospium	= KarXT	Commentary
Central Nervous System	↑	N/A	↑	Improvement in psychosis and cognition
Salivation Glands	↑	↓	—	Tolerability from neutralization of peripheral activation
Sweat Glands	↑	↓	—	
GI Tract	↑	↓	—	
Bladder	↑	↓	—	

↑ Increase Activity ↓ Decrease Activity — Offsetting Effect

KarXT Phase 2 Trial Results Analysis



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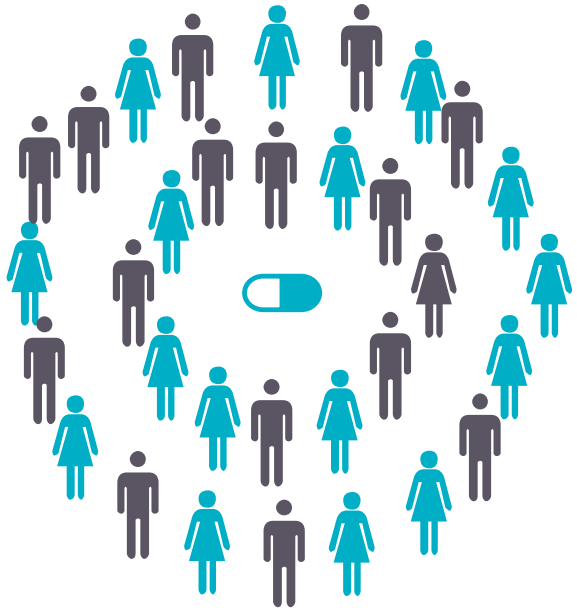
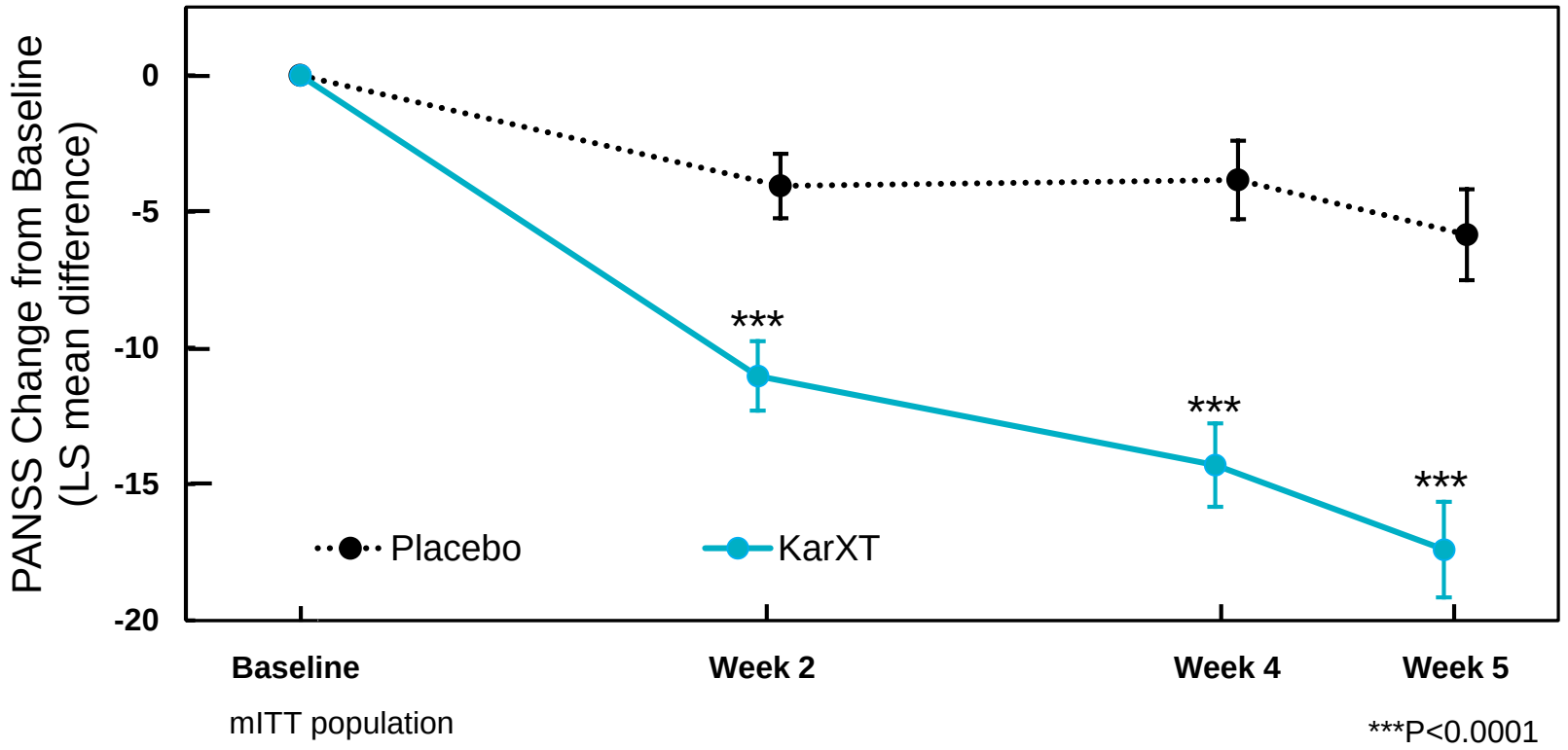
Phase 2 trial design overview

- Same fundamental trial design and primary endpoint used in pivotal studies to support registration of other antipsychotic drugs
- Randomized, double-blind, placebo-controlled, five week, inpatient trial
- Enrolled 182 schizophrenia patients with acute psychosis (N=90 on KarXT, N=92 on Placebo)
- Patients were washed out of any antipsychotic drugs prior to randomization
- Flexible dose, two-arm trial with 1:1 randomization to KarXT or placebo with a five-week treatment period
  - Days 1-2: 50/20 KarXT BID (50 mg xanomeline/20 mg trospium)
  - Days 3-7: 100/20 KarXT BID
  - Days 8-35: 100/20 KarXT BID with optional increase to 125/30 KarXT BID; *titration based only on tolerability*
- Primary endpoint of change in total PANSS from baseline vs. placebo at week 5 in the modified intent to treat population (mITT)
- Other endpoints: PANSS-positive and –negative subscales, CGI, PANSS Marder factor, cognitive battery, and others



Primary Endpoint: PANSS total score at week 5



mITT population

***P<0.0001

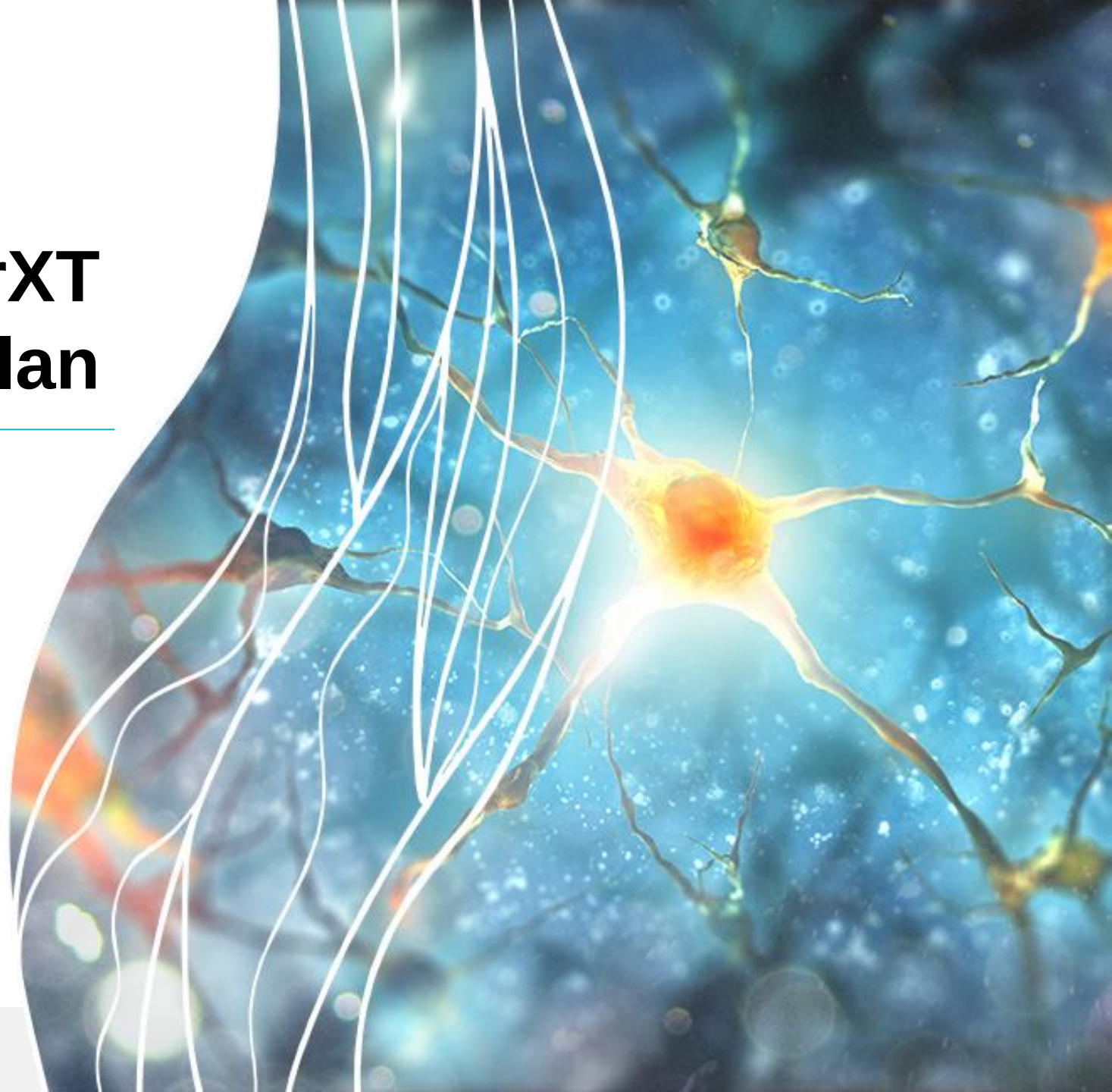
- Clinically meaningful and statistically significant improvement in total PANSS vs. placebo
- 11.6 point improvement at week 5 with p<0.0001 (-17.4 KarXT vs. -5.9 placebo)
- Statistical separation at every assessed time point
- PANSS-positive and PANSS-negative subscores also statistically significant improvements at each time point

Summary of safety and tolerability

- KarXT was well tolerated
  - Overall discontinuation rate on KarXT (20%) similar to placebo (21%)
  - The number of discontinuations due to treatment emergent adverse events was equal in the KarXT and placebo arms (N=2 in each group)
  - Dose escalation rate on KarXT was high and similar to placebo
    - 91% of KarXT subjects escalated to 125/30 KarXT (vs. 97% on placebo);
    - 4% percent de-escalated back to 100/20 KarXT dose (vs. 1% on placebo)
  - Overall treatment emergent adverse event rate on KarXT was 54% vs. 43% on placebo
  - Most common adverse events were constipation, nausea, dry mouth, dyspepsia, and vomiting, which were all mild or moderate in severity and did not lead to discontinuations
  - Somnolence, weight gain, and extrapyramidal symptoms/akathisia similar to placebo
  - No syncope, no mean change in BP, 5.5 bpm peak mean placebo adjusted resting HR increase with downward trend after week 2, and one discontinuation due to elevated GGT
  - One serious adverse event on KarXT: patient discontinued treatment and subsequently sought hospital care for worsening psychosis, meeting the regulatory definition of an SAE. All other TEAEs were mild or moderate

data from safety population

KarXT Development Plan



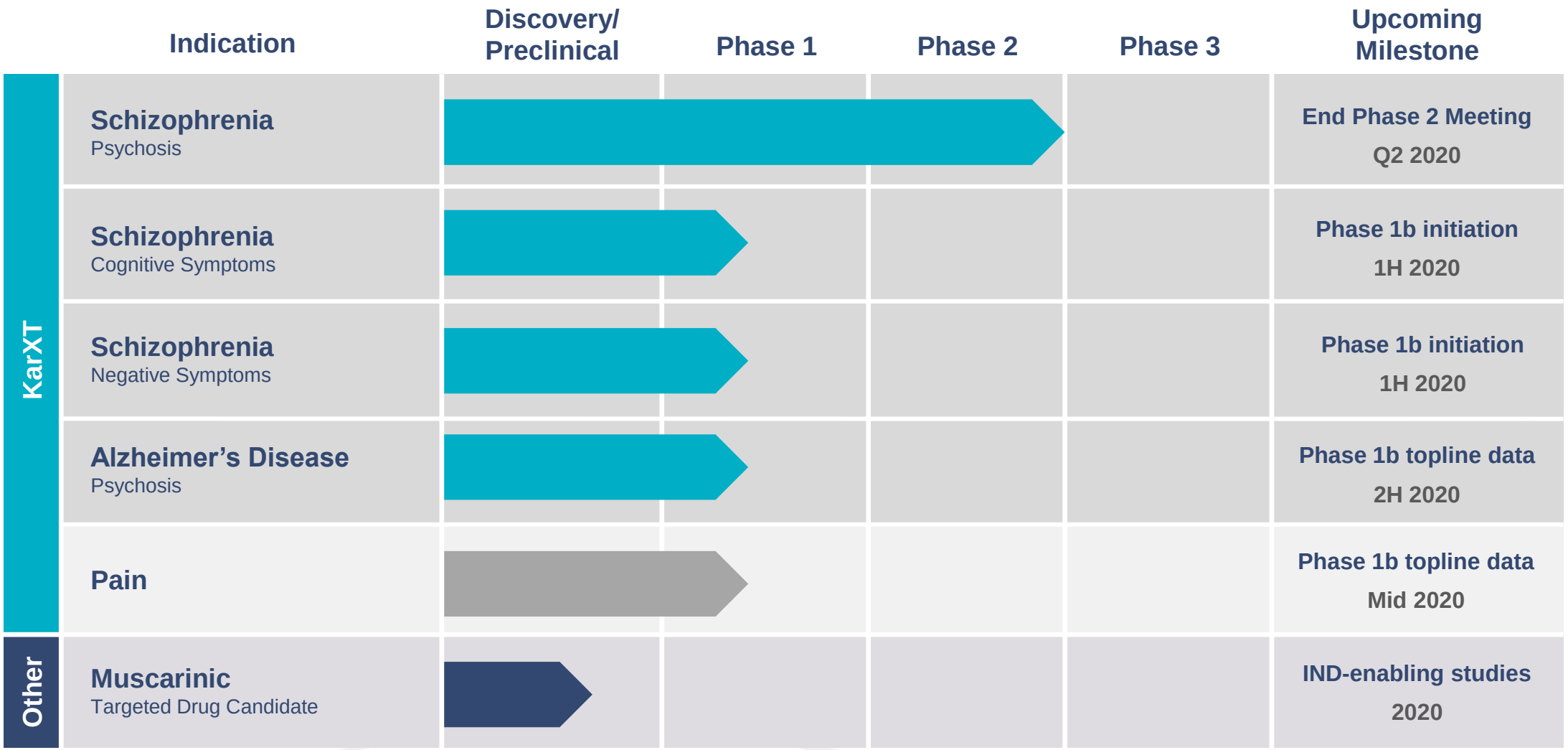
Multiple efficacy and safety studies support Phase 3 development of KarXT

- Three double-blind, placebo-controlled studies supporting therapeutic benefit of xanomeline/KarXT
  - KarXT Phase 2 study in patients with schizophrenia
  - Small Phase 2 study in patients with schizophrenia with xanomeline-alone
  - Phase 2 study in patients with Alzheimer's disease with xanomeline-alone
- Large existing safety database with xanomeline and KarXT:
  - >1000 patients enrolled in studies with KarXT or xanomeline
  - 68 Alzheimer's disease patients treated with xanomeline for at least one year
- Robust data including 3 efficacy studies and long-term safety going into Phase 3

KarXT development moving forward

- Complete final analysis of all data and endpoints from Phase II study to further inform path forward
- Planning an end of Phase 2 meeting for Q2 2020 with FDA to discuss data and development path including Phase 3 trial design
- Pending FDA meeting, we anticipate advancing to Phase 3 using a similar trial design as our Phase 2 trial with trial initiation anticipated by the end of 2020
- Initiate Phase 1b in negative/cognitive symptoms of schizophrenia in 1H 2020
- Topline Phase 1b data in pain expected in mid 2020
- Topline Phase 1b data in healthy elderly volunteers expected in 2H 2020

Karuna's portfolio of muscarinic receptor-targeted programs



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