Safety Trial Methodology Considerations for Novel Mechanisms of Action in Psychiatry Trials

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Disclosures

- Former Employee of Karuna Therapeutics and Bristol Myers Squibb
- Viewpoints in this presentation are reflective of my personal views and interpretations and not of Bristol Myers Squibb or my current employer

Novel MOA Paradigm Shift in Psychiatry

- Numerous psychiatric agents with novel MOAs are currently in development
- Since the Standard of Care (SoC) for disorders like **schizophrenia**, **bipolar disorder**, and **major depressive disorder** has remained static for decades, **novel MOAs** present **heightened uncertainty** regarding their safety and tolerability profiles and breadth of patient exposure
- These uncertainty's include unknown long-term effects, rare adverse events (AEs), complex physiological interactions, as well as drug-drug interactions

Limitations of Double-Blind Placebo-Controlled RCTs

- Sample bias that results in patient population not representative of a broader "general" population
- Duration of RCTs prohibit ability to detect rare AEs or longer- term signals
- From a safety perspective this could result in limited safety and tolerability information of novel agent:
  - Co administration with commonly prescribed medicines
  - Durability of unique TEAEs specific to new MOA
  - Frequency and Recurrence data on unique adverse events
  - Duration and intensity of AESIs

RCT: Randomized Controlled Trials; TEAEs: Treatment Emergent Adverse Events; AESIs: Adverse Events of Special Interest

Case Study: Long Term Safety Studies Evaluating KarXT for Schizophrenia

- Development opportunity with KarXT: Leveraging a novel MOA to achieve robust efficacy while establishing a non-traditional safety benchmark
- The Phase 3 development program for KarXT included 2 long term open label safety studies:
  - EMERGENT-4: 52-week open label extension trial for participants who completed the two double blind placebo-controlled phase 3 studies (EMERGENT 2 and 3)
  - **EMERGENT-5:** 52-week, open label trial in **de novo** participants
- **EMERGENT-5** serves as a good case for safety study considerations and lessons learned when evaluating novel MOAs in psychiatry

Conceiving the Long-Term Safety Methodology

Regulatory Expectations

- NCEs, particularly those with a novel MOA, generally expected to have a predefined number of unique exposures in participants prior to NDA filing
  - Long term safety for a chronically administered drug is another expectation

- This expectation influenced design of EMERGENT-5 trial (Sample size + trial duration)

NCE: New Chemical Entity

Safety Considerations Impacting Design

- The safety profile of KarXT prior to **June 2021** was based on limited historical data from legacy xanomeline monotherapy trials and Phase 1 and Phase 2 studies
  - Pivotal trials (EMERGENTs 2 and 3) were ongoing at the time

Safety Evidence Available Prior to EMERGENT-5 Trial:

- Legacy studies evaluating xanomeline in Alzheimer's Disease (AD)
- Phase 1 Heathy Volunteer Trial using KarXT
- Phase 2 EMERGENT-1 Trial

Established KarXT Safety Data Prior to EMERGENT Program

Xanomeline Monotherapy[1]

- **Procholinergic** GI specific dose dependent TEAEs observed in people with mild to moderate AD at doses of 75,150, and 220 mg TID
- **Syncope** occurred in 12.6% of people in the high dose group
- These safety findings were **inherent** to the **novel MOA** of xanomeline

Kar-XT Phase 1 Data[2]

- HV study demonstrated **reduced incidence** of **cholinergic AEs** by **46%** and individual cholinergic AEs by≥29% in people receiving KarXT versus xanomeline alone
- **No cases** of **syncope** reported with KarXT
  - 11.4 % of participants receiving KarXT reported postural dizziness vs 27.2% with xanomeline[2]
- **Trospium** was **effective** in **mitigating cholinergic AEs** driven by xanomeline

1. Bodick et al. Effects of Xanomeline, a Selective Muscarinic Receptor Agonist, on Cognitive Function and Behavioral Symptoms in Alzheimer Disease. Jama Neurology. 1997;54;(4):465-473.
2. Breier et al. Evidence of trospium's ability to mitigate cholinergic adverse events related to xanomeline: phase 1 study results. Psychopharmacology (2023) 240:1191–1198

KarXT Safety Data From EMERGENT-1 Program[1]

- Most common adverse events reported in the KarXT group were **constipation** (17%), **nausea** (17%), **dry mouth** (9%), **dyspepsia** (9%), and **vomiting** (9%)
  - **None** of these adverse events resulted in the **discontinuation** of Kar-XT and were rated as either **mild** or **moderate** in severity
  - Majority of nausea, vomiting, and diarrhea occurred earlier in the study while constipation was consistently reported across 5 weeks
- **No** events of **syncope** reported
- **Small** mean **BP/HR elevations** were observed early (Weeks 1–2) followed by stabilization/attenuation with continued dosing
- Incidences of **weight gain**, **somnolence**, **restlessness**, and **extrapyramidal** symptoms were **similar** between KarXT and placebo

1. Brannan et al. Muscarinic Cholinergic Receptor Agonist and Peripheral Antagonist for Schizophrenia. N Engl J Med 2021;384:717-26

Risk Assessment of KarXT Prior to EMERGENT-5 Trial

Procholinergic and anticholinergic AEs specific to MOA

- **Onset**: Majority of these AEs begin soon after treatment initiation
- **Duration**: nausea, vomiting, and dry mouth are likely transient, but 5-week trial duration limits this interpretation
- **Severity**: Cholinergic AEs are mild and moderate in severity and do not lead to discontinuation

Transitioning Treatment

- Can outpatients safely transition from a dopamine blocker to KarXT and avoid worsening symptoms of schizophrenia?
- What happens to patients who experienced AEs attributed to the prior treatment after switching?

Risk Assessment of Kar-XT Prior to EMERGENT-5 Trial (Cont)

Cardiac Signal?

- Are small increases in BP and HR clinically significant? Or are they transient?

Symptomatic Orthostasis

- Low incidence (~2-5%) and generally mild; notably distinct from the $\alpha_1$mediated orthostatic hypotension common in traditional D2-antagonists

Hepatic Safety (AESI)

- ~3% of people experienced elevations in transaminases (ALT/AST)
- Generally transient and asymptomatic; thought to be related to biliary system dynamics rather than direct hepatoxicity.

EMERGENT-5 Design and Implementation Considerations

EMERGENT-5 Trial Design[1]

- 52-Week, open label, **outpatient** trial in participants 18 to 65 years old with **no prior** Kar-XT exposure
- Conducted at 54 sites in the USA between June 2021 and May 2024
- Participants were psychiatrically stable (PANSS ≤80 and CGI-S ≤4)
- Participants discontinued prior antipsychotics before the baseline visit at their discretion
- 14-day screening phase followed by a baseline phase of 5 days

1.Kaul et al. Long-term efficacy, safety, and tolerability of xanomeline and trospium chloride in schizophrenia: A 52-week, open-label trial (EMERGENT-5). *Schizophrenia Research.* 288:86-94. 2026

EMERGENT-5 Trial Design (Cont)

- Primary endpoint: Incidence of TEAEs assessed via the following methods:
  - Spontaneous reporting
  - Physical examinations: body weight, **BMI**, **vital signs**
  - Clinical laboratory assessments
    - Unique labs include **prolactin and hBA1C**
  - 12-Lead ECGs

Choosing Grading Scale:

- AEs were graded via a **mild, moderate,** and **severe** intensity scale
- AE grading was left to **investigator discretion**

AESI Management

Hepatic Safety

- AESI: LFTs>3x the ULN inclusive of drug-induced liver injury
- Outpatient nature of the trial makes management more difficult given the reliance on patient-reported symptoms (like right upper quadrant pain) rather than weekly lab draws
  - Patient and investigator education become even more essential

Impacts to Design

- **Pre-treatment:** Baseline LFTs and bilirubin are mandatory
- **Exclusion**: Do not use in Child-Pugh Class B or C impairment
- **Discontinuation**: Stop treatment if ALT/AST > 5x ULN or if jaundice/biliary symptoms appear

AESI Management (Cont)

Symptomatic orthostasis

- Risk: Low frequency of symptomatic orthostasis

Impacts to Design

- Protocol: Baseline and periodic orthostatic vitals; patient education on "slow transitions" from sitting to standing during the initial titration phase.

Enrollment

- Most sponsors wish to speed recruitment on these trials
- Consider investing the same level of enrollment support utilized in a RCT
- Many sites are simultaneously participating in placebo-controlled studies with the same sponsor
  - Sponsors need to determine which studies sites should prioritize

Data Collection Methods: Consider What Is Important to Know When Starting Treatment

- Ensure methods used **prevent misclassification bias** and **errors**
- Consider **standardizing collection methods** in **EDC** to the same rigor of a randomized controlled trial
- In EMERGENT-5, prior antipsychotics were collected in eligibility intake forms and initially left off EDC
  - Resulted in extra effort to verify data

Most Common Antipsychotics Received in 6 Months Prior to Enrollment
Quetiapine (34.3%)
Risperidone (28.4%)
Aripiprazole (18.2%)
Olanzapine (17.0%)

Outcomes

- Confirming the initial risk assessment of KarXT:
  - KarXT was generally well tolerated in a larger population of 52 weeks
  - Cholinergic AEs occurred within the first few weeks of treatment in participants who reported them
  - Duration of cholinergic AEs ranged between a 2-7 days confirming the transitory nature of these AEs
  - Observed increases in BP and HR occurred early on with treatment and partially attenuated with repeat dosing
- Risk assessment related to SOC:
  - No clinically meaningful extrapyramidal motor symptoms, hyperprolactinemia, somnolence/sedation, weight gain, or adverse changes in metabolic or lipid parameters

Advantages of Initiating Safety Trials Pre Approval

- Switch study design aids prescribers in knowing how to stop SOC treatment and start novel medicine
- Satisfying regulatory requirements and potentially accelerating time to approval
- Present opportunity to fully distinguish safety profile from established standard of care preapproval as part of integrated evidence generation plan
- Opportunity to test “novel endpoints” such as ecological momentary assessments
- Opportunity to investigate other drug interactions including pharmacogenetics (opportunity for academia in the post marketing setting)