

Administration of xanomeline and trospium chloride

ICD-10 Coordination and Maintenance Committee Update

March 2025

Contents

- Background on Schizophrenia
- Clinical Overview of COBENFY

Schizophrenia

Chronic psychiatric syndrome impacting **24M** people **worldwide** and **~2.8M** people in the U.S.

Comprised of three symptom domains (positive, negative, cognitive) affecting how one **thinks, feels, and behaves**

One of the **leading causes of disability** worldwide, with onset in late-teens/early-adulthood

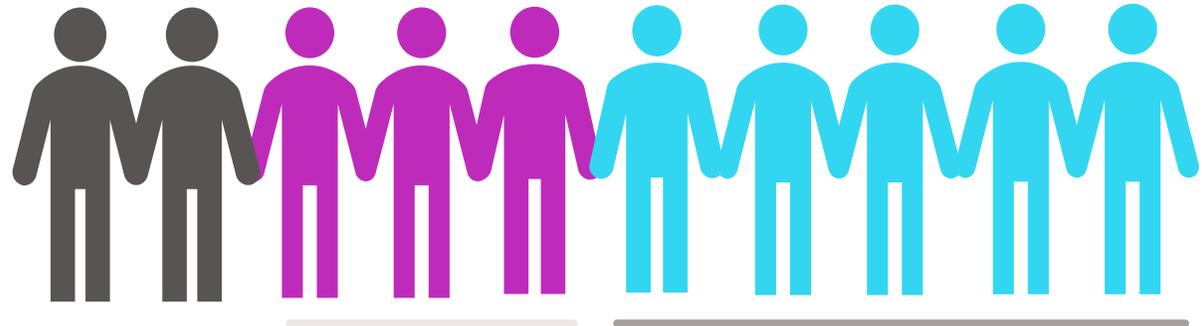
Estimated **potential life lost is ~30 years** compared to general population; this is partially attributed to cardiovascular and metabolic comorbidities and an increased suicide rate

~40% of people with schizophrenia are eligible for Medicare, of which over 80% qualify for Medicaid, highlighting the significant overlap between schizophrenia, disability, and dual eligibility



Need for new pharmacological approach for the treatment of schizophrenia

Historically, antipsychotic medicines all rely on the dopaminergic and/or serotonergic pathway



Up to **30%** of patients **do not respond** to therapy

~50% experience only a **partial improvement in positive symptoms** or **unacceptable side effects**

~75% of patients discontinue treatment in the first **18 months**

Sources: Kane et al. 2019, Patel et al. 2014, Lieberman et al. 2005

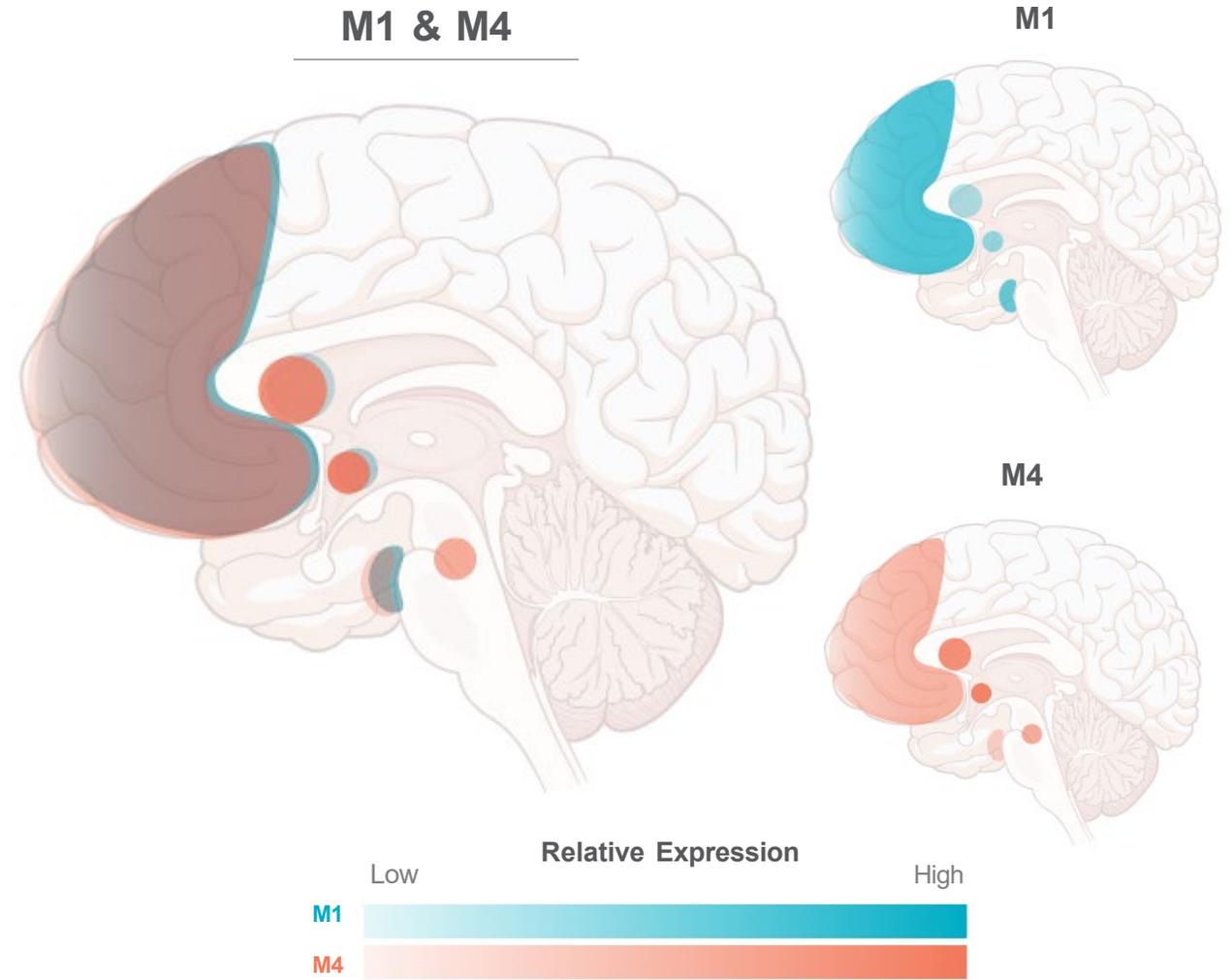
COBENFY: A new pharmacological approach for treating schizophrenia

COBENFY (xanomeline and trospium chloride) stimulates **M1/M4 muscarinic receptors** in the brain

Muscarinic receptors are **expressed in brain regions** implicated in psychosis and cognition, suggesting that their modulation could treat symptoms of schizophrenia

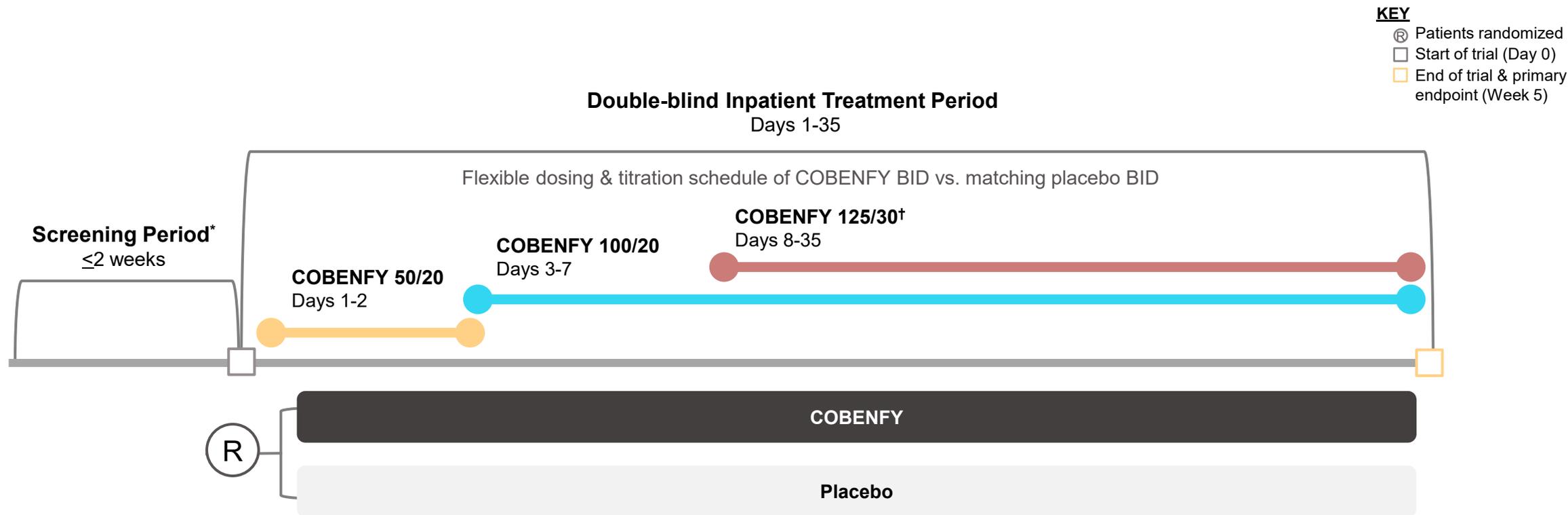
COBENFY **does not directly modulate dopamine or serotonin receptors**, providing a clear rationale for the lack of dopamine- and serotonin-related side effects

The **unique pharmacology of COBENFY** enables its differentiated efficacy and safety profile, as seen across multiple positive clinical trials



Sources: Paul et al. 2022, Yohn et al. 2022, Bodick et al. 1997, Shekhar et al. 2008, Brannan et al. 2021

Consistent Trial Design Across EMERGENT-1, 2, & 3



Select Eligibility Criteria:

- 18-65[^] years of age
- Confirmed diagnosis of schizophrenia and experiencing symptoms of psychosis
- PANSS total score between 80 and 120
- CGI-S ≥4 at baseline

Primary Endpoint:

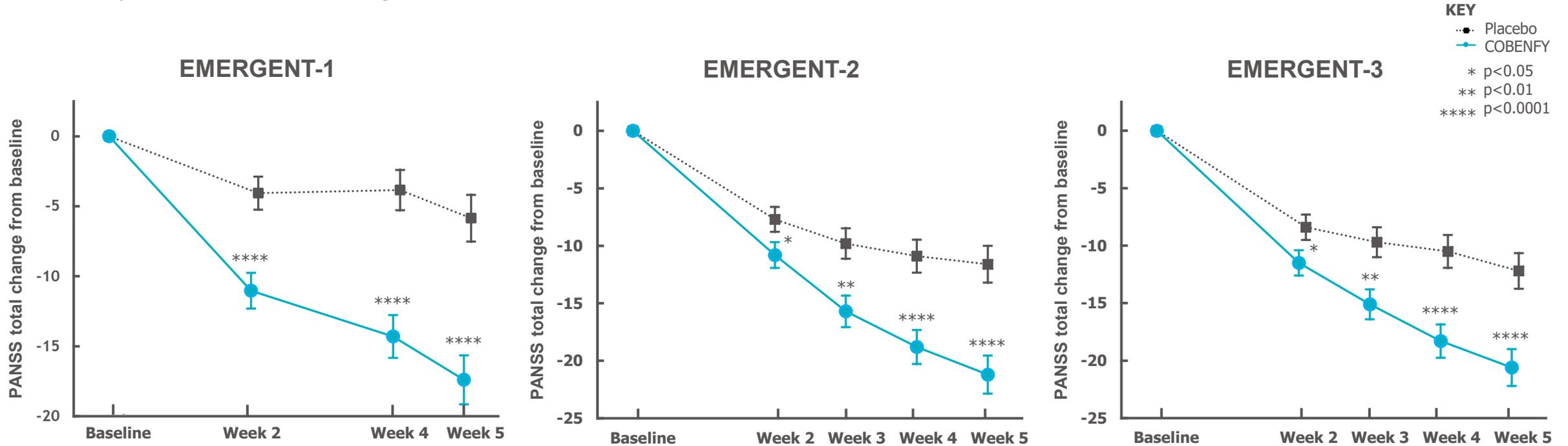
- CFB in PANSS total score compared to placebo at Week 5

Prespecified Secondary Outcome Measures:

- CFB in PANSS positive, PANSS negative, PANSS negative Marder factor subscales, CGI-S[‡] compared to placebo at Week 5
- PANSS responder (% of patients with 30% reduction)

Clinically Meaningful Improvements In Symptoms Of Schizophrenia

Primary endpoint: Change in baseline PANSS total score vs. placebo at Week 5



11.6-point reduction at Week 5
 (-17.4 COBENFY vs. -5.9 placebo)
 p<0.0001
 Cohen's d=0.75

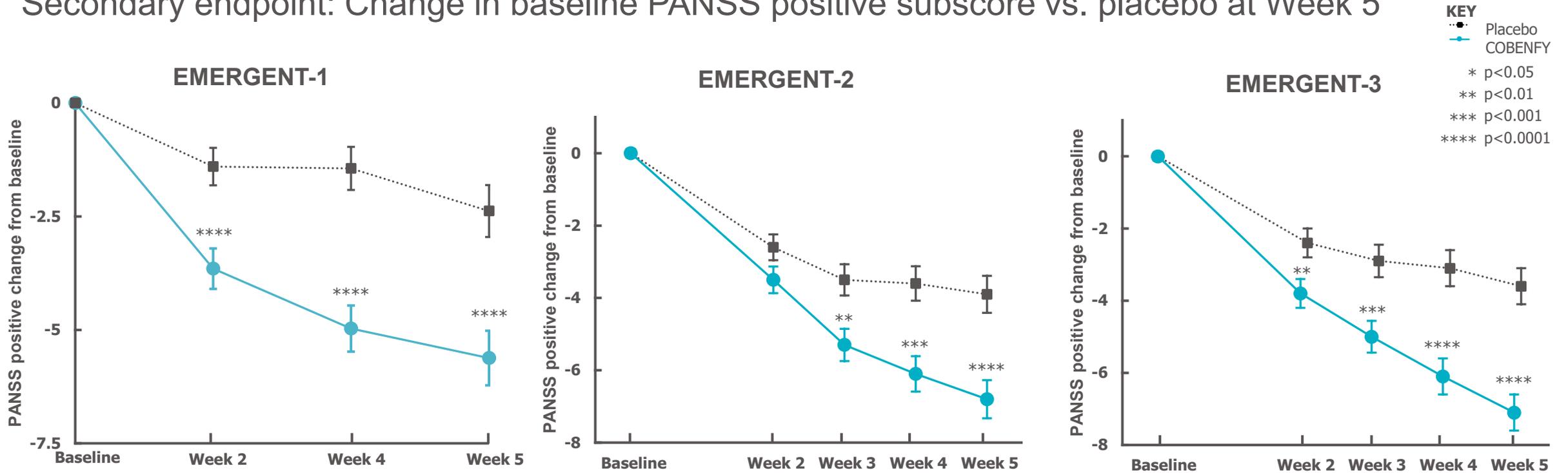
9.6-point reduction at Week 5
 (-21.2 COBENFY vs. -11.6 placebo)
 p<0.0001
 Cohen's d=0.61

8.4-point reduction at Week 5
 (-20.6 COBENFY vs. -12.2 placebo)
 p<0.0001
 Cohen's d=0.60

All efficacy analyses performed using the modified intent-to-treat (mITT) analysis set, defined as all randomized participants who received at least one dose of study medication at baseline and at least one post-baseline PANSS assessment (EMERGENT-1: COBENFY n=83, placebo n=87; EMERGENT-2: COBENFY n=117, placebo n=119; EMERGENT-3: COBENFY n=114, placebo n=120)

Improvements in positive symptoms of schizophrenia

Secondary endpoint: Change in baseline PANSS positive subscore vs. placebo at Week 5



3.2-point reduction at Week 5
 (-5.6 COBENFY vs. -2.4 placebo)
 p<0.0001

2.9-point reduction at Week 5
 (-6.8 COBENFY vs. -3.9 placebo)
 p<0.0001

3.5-point reduction at Week 5
 (-7.1 COBENFY vs. -3.6 placebo)
 p<0.0001

All efficacy analyses performed using the modified intent-to-treat (mITT) analysis set, defined as all randomized participants who received at least one dose of study medication at baseline and at least one post-baseline PANSS assessment (EMERGENT-1: COBENFY n=83; placebo n=87; EMERGENT-2: COBENFY n=117, placebo n=119; EMERGENT-3: COBENFY n=114, placebo n=120)
 Source for EMERGENT-1 graph: Brannan et al. 2021

COBENFY Is Generally Well Tolerated Across EMERGENT-1, 2 and 3

Substantially consistent safety and tolerability profile across trials



Similar TEAE-related discontinuation rates between COBENFY and placebo groups



Most common TEAEs ($\geq 5\%$) were mild to moderate in severity, with most being cholinergic in nature and resolving over time with repeated dosing



Vital signs were consistent across all registrational trials of COBENFY in schizophrenia



COBENFY does not have atypical antipsychotic class warnings and precautions, nor does it have a boxed warning

Treatment emergent adverse events (TEAE); All safety & tolerability analyses performed using safety population (EMERGENT-1: COBENFY n=89, placebo n=90; EMERGENT-2: COBENFY n=126, placebo n=125; EMERGENT-3: COBENFY n=125, placebo n=128)

COBENFY Administration and Dosage

Administration

- COBENFY is a fixed-dose combination of xanomeline and trospium chloride used for the treatment of schizophrenia in adults.
- COBENFY is administered orally in capsule form at least one hour before a meal or at least two hours after a meal.
- In the inpatient setting, the use of COBENFY would be documented in the progress notes and medication administration record.

Dosage

- The recommended starting dose is one 50mg/20mg capsule orally twice daily for at least two days.
- The dosage is increased to one 100mg/20mg capsule orally twice daily for at least five days
- The dose may be increased thereafter to one 125mg/30mg capsule orally twice daily based on patient tolerability and response.

Thank You!