

# Administration of xanomeline and trospium chloride

**ICD-10 Coordination and Maintenance Committee Update**

**March 2025**

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# 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

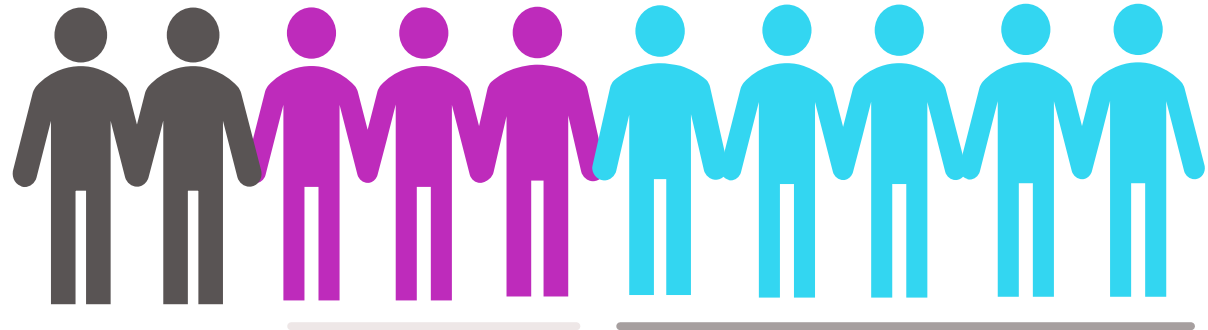
Estimated **potential life lost is ~30 years** compared to general population; this is partially attributed to cardiovascular and metabolic comorbidities and an increased suicide rate

~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

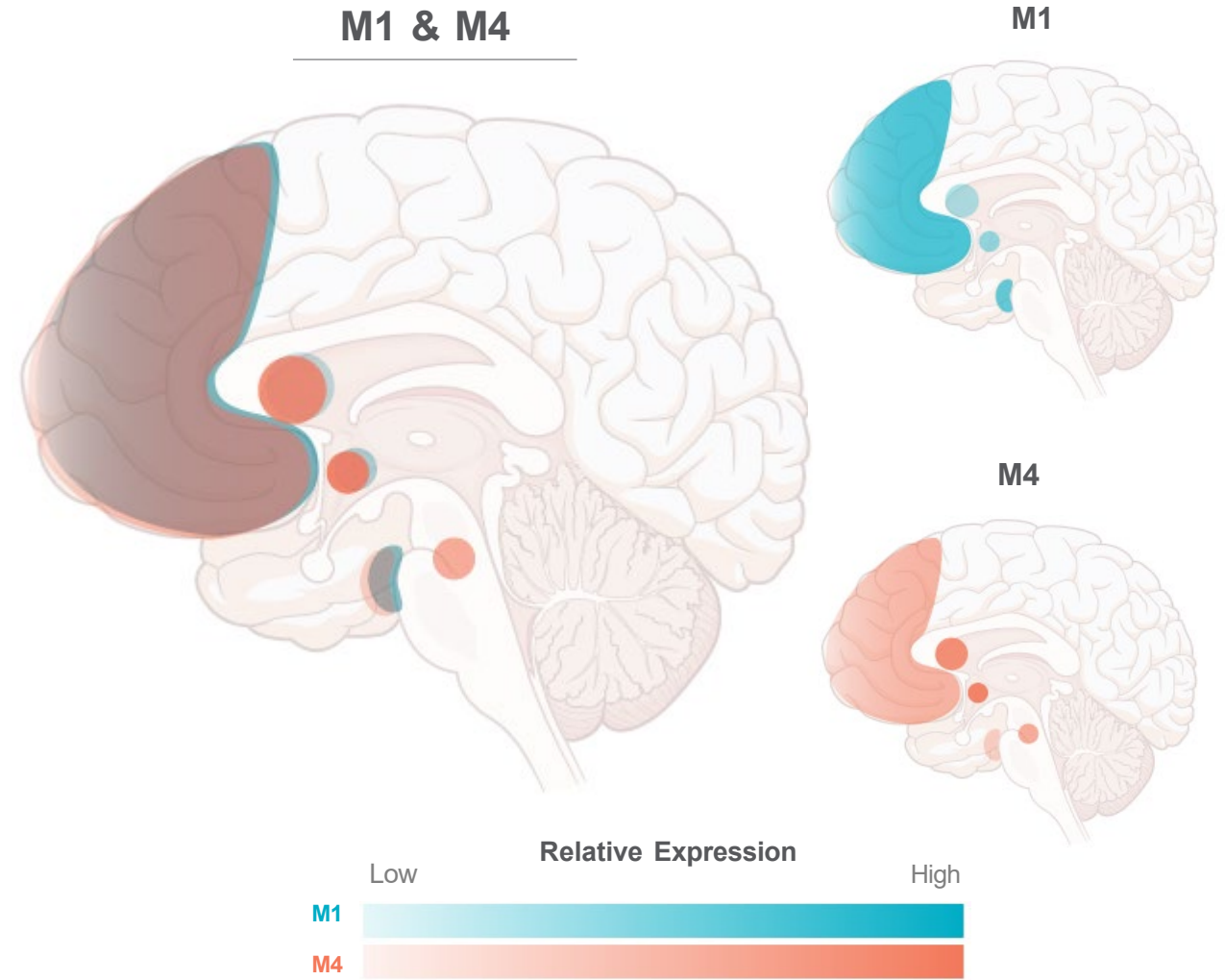
# COBENFY: A new pharmacological approach for treating schizophrenia

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

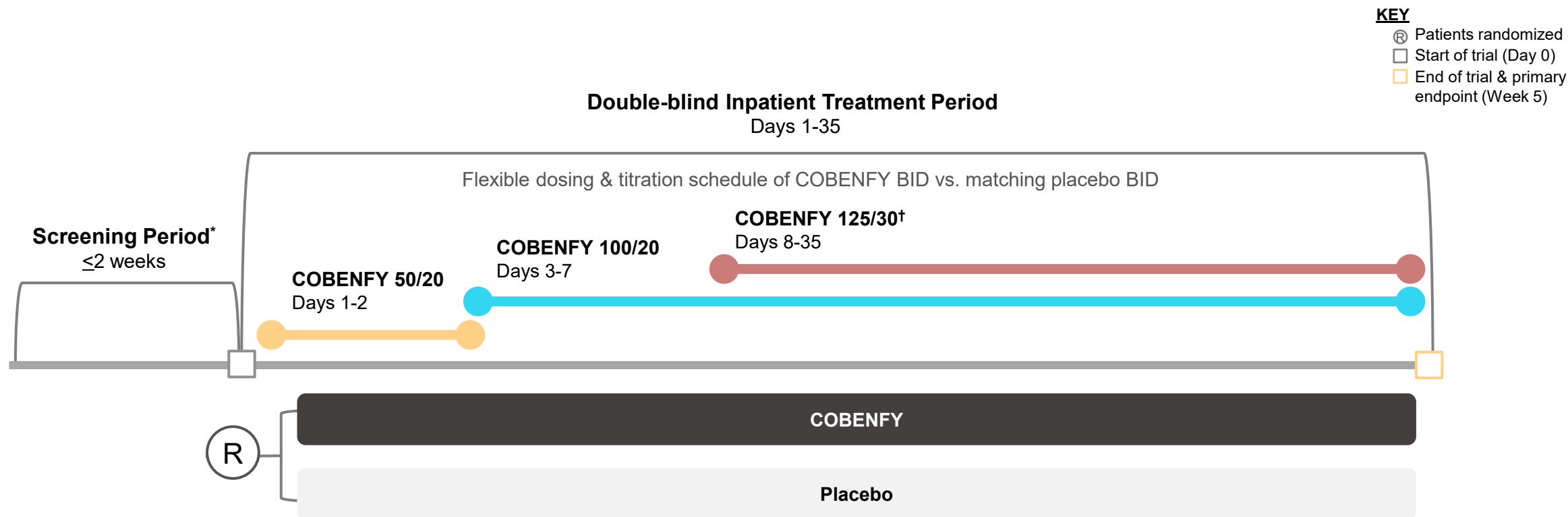
COBENFY **does not directly modulate dopamine or serotonin receptors**, providing a clear rationale for the lack of dopamine- and serotonin-related side effects

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<sup>^</sup> years of age
- Confirmed diagnosis of schizophrenia and experiencing symptoms of psychosis
- PANSS total score between 80 and 120
- CGI-S  $\geq 4$  at baseline

## Primary Endpoint:

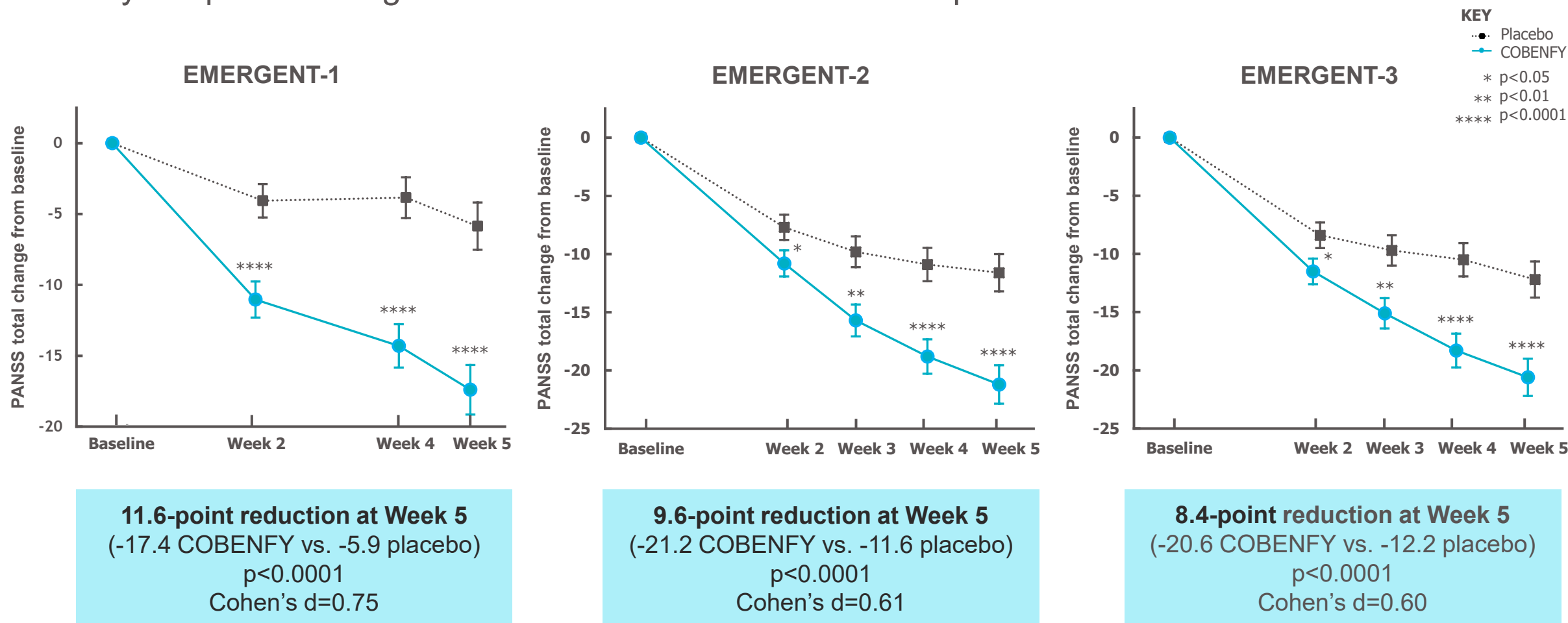
- CFB in PANSS total score compared to placebo at Week 5

## Prespecified Secondary Outcome Measures:

- CFB in PANSS positive, PANSS negative, PANSS negative Marder factor subscales, CGI-S<sup>‡</sup> 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

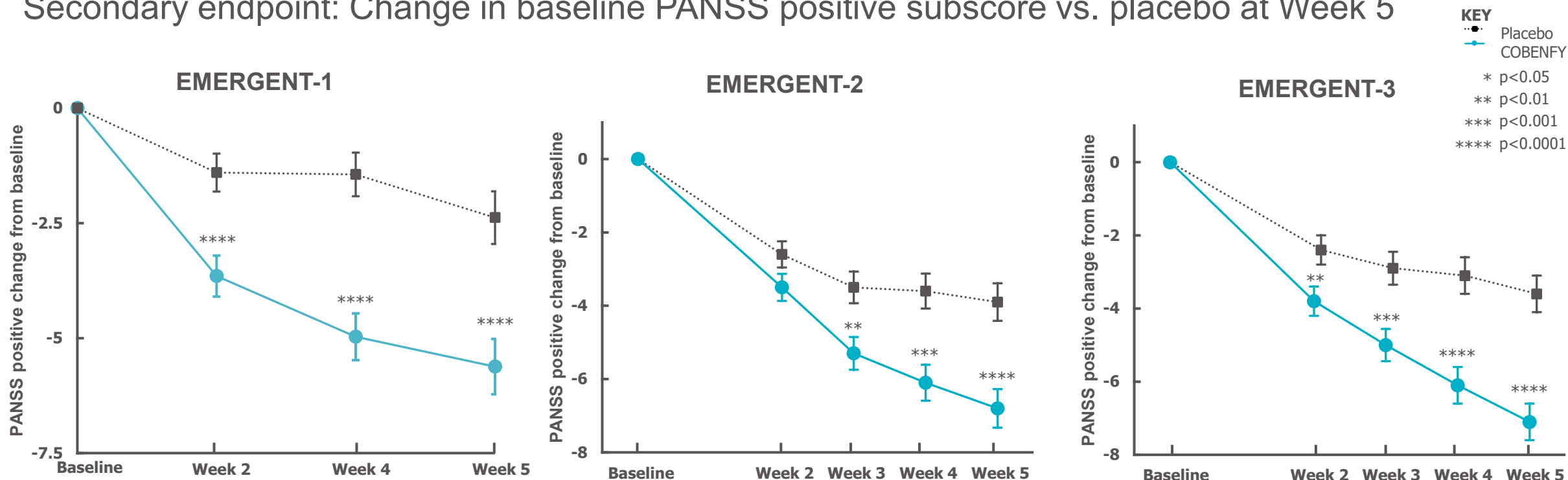


All efficacy analyses performed using the modified intent-to-treat (mITT) analysis set, defined as all randomized participants who received at least one dose of study medication at baseline and at least one post-baseline PANSS assessment (EMERGENT-1: COBENFY  $n=83$ , placebo  $n=87$ ; EMERGENT-2: COBENFY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