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Managed Care Considerations for COBENFY™ (xanomeline and trospium chloride): A First-in-Class M₁/M₄ Muscarinic Agonist for the Treatment of Adults With Schizophrenia*

Estimated to affect 1.1% of the population, there were approximately 2.8 million adults with schizophrenia in the US in 2020, with an estimated 40% being untreated in any given year.^{1,‡} A complex condition, schizophrenia has 3 primary symptom domains: positive symptoms, negative symptoms, and cognitive symptoms.² Positive symptoms (eg, hallucinations, delusions, and disorganized thinking) are characterized by an excess of normal mental functions. Negative symptoms (eg, social withdrawal, reduced emotional expression, and diminished motivation) reflect a decline in normal mental and behavioral capacities. Cognitive symptoms (eg, deficits in memory, attention, and executive functioning) affect the ability to organize thoughts, make decisions, and sustain attention.²

Schizophrenia and its treatment can have a serious impact on an individual's quality of life (QOL).^{3,‡} Results from a double-blind comparative study conducted from January 2001 to December 2004 and involving 1432 patients who received at least 1 dose of an oral antipsychotic (intention-to-treat) showed that 1061 patients (74%) discontinued their assigned treatment before 18 months elapsed.^{4,‡} Additionally in a cross-sectional, observational online survey conducted from December 14, 2018,

‡Analyses discussed above were conducted prior to the availability of COBENFY and therefore do not capture adverse events specific to treatment with COBENFY.

*COBENFY is a combination of xanomeline, a muscarinic agonist, and trospium chloride, a muscarinic antagonist, indicated for the treatment of schizophrenia in adults.

INDICATION

COBENFY™ (xanomeline and trospium chloride) is indicated for the treatment of schizophrenia in adults.

IMPORTANT SAFETY INFORMATION CONTRAINDICATIONS

COBENFY is contraindicated in patients with:

- urinary retention
- moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment
- gastric retention
- history of hypersensitivity to COBENFY or trospium chloride. Angioedema has been reported with COBENFY and trospium chloride.
- untreated narrow-angle glaucoma

FOUNDER
Mike Hennessy Sr | 1960-2021

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Table 1. Estimated Cost of Select Comorbidities Associated With Schizophrenia and Tardive Dyskinesia^{7-11 a,b,‡}

Comorbidity	Cost per patient per year
Diabetes	\$12,238 ^{7,c}
Metabolic syndrome	\$1799 ^{8,d}
Cardiovascular disease	\$20,382 ^{9,d,e}
Adverse Event	Cost per patient per year
Tardive dyskinesia	\$32,117 ^{10,f,g}

CVD, cardiovascular disease; PPPY, per patient per year; VMAT2, vesicular monoamine transporter type 2.

^aThe individual studies were not focused specifically on schizophrenia as applied to these comorbidities. As such, the study data may overly estimate the relationship between schizophrenia and these costs.

^bIn patients with the conditions above, values represent the average difference in the PPPY total costs, adjusted to the 2024 USD for inflation.

^cBased on the results of a study estimating the 2022 economic burden of diagnosed diabetes in the US using a Cost of Diabetes Economic Model with data from national surveys (2015–2020 or most recent available), Medicare standard analytic files (2020), and administrative claims data from 2018 to 2021 for a large commercially insured population in the US. Direct medical costs for diabetes reached \$306.6 billion, with \$106.3 billion in indirect costs, totaling \$412.9 billion. People with diabetes incurred average annual medical expenses of \$19,736, which was 2.6 times higher than for those without diabetes. Glucose-lowering drugs and supplies accounted for 17% of direct costs, while productivity losses, disability, and premature mortality contributed significantly to indirect costs. Limitations included omitted costs, small sample sizes, outdated data, and potential biases, which may affect the accuracy of the diabetes economic burden estimates.⁷

^dBased on the results of a study of 170,648 men and women (21–87 years), who were continuously enrolled in 1 of 3 integrated delivery systems during July 1, 2003, to June 30, 2005. Health care resource utilization and costs were compared between individuals with and without metabolic syndrome. Participants with metabolic syndrome (n = 98,091) had significantly (P < .001) higher costs than those without it (n = 72,557); average annual costs for those with metabolic syndrome were 1.6 times greater overall and represented a 24% increase per additional risk factor (P < .001). Stratified by diabetes status, annual costs remained consistently higher for those with metabolic syndrome. Specific risk factor combinations like diabetes with weight risk, dyslipidemia, and hypertension nearly doubled costs compared to prediabetes with similar factors. Limitations include its observational design, reliance on health plan data, and limited generalizability beyond the study population.⁸

^eBased on the results of an observational longitudinal cohort study to estimate the annual direct medical costs incurred by 12,278 patients over follow-up of up to 7 years following entry into the CVD registry of a health maintenance organization. Patients were observed until they died or left the health plan for other reasons or until June 30, 2008, whichever came first. The primary outcome was direct medical costs, with secondary outcomes including incidence rates of secondary CVD hospitalization and all-cause mortality. Results showed a mean annual direct medical cost of \$18,953 per patient with significant cost increases associated with secondary CVD hospitalizations and comorbidities such as diabetes, chronic kidney disease, and depression. Limitations include potential survival bias and the study's setting within a single health care system, which may affect generalizability.⁹

^fA retrospective analysis using Truven MarketScan claims data evaluated 1668 matched patients with and without TD; it focused on individuals with commercial or private Medicare supplemental insurance. Adult patients were included in the TD group if they had the first TD diagnosis (index date) between January 1, 2008, and September 30, 2014, with ≥ 1 inpatient or ≥ 2 outpatient nondiagnostic claims for TD. Among 834 matched patients with TD and 834 non-TD controls, both cohorts were demographically similar, but TD patients showed significantly (P < .001) higher use of certain atypical antipsychotics (paliperidone, risperidone, ziprasidone) and other medications (anticholinergics, metoclopramide, amantadine) while having a higher prevalence of diabetes. Limitations included reliance on administrative data prone to coding errors and omissions, which could affect the accuracy of clinical details.¹⁰

^gTardive dyskinesia costs do not consider the cost of VMAT2s and therefore likely underestimate the associated cost burden.

to January 15, 2019, of 200 adults with self-reported, physician-diagnosed schizophrenia who had received oral antipsychotics in the prior year, patients reported that AEs related to treatment negatively affected their work, social functioning, and treatment adherence.^{5,‡} These self-reported AEs included weight gain, sexual dysfunction, trouble concentrating, feeling *zombie-like*, drowsiness, anxiety, restlessness, lack of emotion, and involuntary spasms.

Schizophrenia is associated with an increased risk of comorbidities.^{6,‡} The comorbidities diabetes, metabolic syndrome, and cardiovascular disease, as well as the treatment-related AE, tardive dyskinesia, are associated with high health care costs (Table 1).^{7-11,‡}

In 2019, the economic burden of schizophrenia in the US was estimated to be \$343 billion.^{12,‡} Relapse is a driver of cost increases in schizophrenia management. A structured and comprehensive literature review of studies published prior to January 2017 (N = 63 studies) focused on the cost of relapse among patients with schizophrenia in the United States.^{13,‡} The results indicated that the excess cost of relapse ranged from \$8013 to \$43,501 over 12 to 15 months (adjusted from 2015 US\$ to 2024 US\$).^{11,13,‡} Excess cost of relapse was calculated as the difference between the costs for patients who relapsed and patients who did not. Where costs were reported for patients who relapsed and patients who did not, the excess cost of relapse was calculated as the difference between the 2 costs.^{13,‡}

‡Analyses discussed above were conducted prior to the availability of COBENFY™ (xanomeline and trospium chloride) and therefore do not capture adverse events specific to treatment with COBENFY.

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS

Risk of Urinary Retention: COBENFY can cause urinary retention. Geriatric patients and patients with clinically significant bladder outlet obstruction and incomplete bladder emptying (e.g., patients with benign prostatic hyperplasia (BPH), diabetic cystopathy) may be at increased risk of urinary retention.

COBENFY is contraindicated in patients with pre-existing urinary retention and is not recommended in patients with moderate or severe renal impairment.

In patients taking COBENFY, monitor for symptoms of urinary retention, including urinary hesitancy, weak stream, incomplete bladder emptying, and dysuria. Instruct patients to be aware of the risk and promptly report symptoms of urinary retention to their healthcare provider. Urinary retention is a known risk factor for urinary tract infections. In patients with symptoms of urinary retention, consider reducing the dose of COBENFY, discontinuing COBENFY, or referring patients for urologic evaluation as clinically indicated.

ABOUT COBENFY™ (XANOMELINE AND TROSPIUM CHLORIDE)

When COBENFY™ (xanomeline and trospium chloride; Bristol Myers Squibb) was approved by the FDA on September 26, 2024, it was the first medication with a different mechanism of action to be authorized for the treatment of adults with schizophrenia in over 30 years.^{14,15}

A unique combination of xanomeline (an M₁/M₄ muscarinic agonist) and trospium chloride (a muscarinic antagonist), COBENFY is the first and only M₁/M₄ muscarinic agonist approved for use in adults with schizophrenia.¹⁵⁻¹⁷ The mechanism of action of xanomeline in the treatment of schizophrenia is unclear; however, its efficacy is thought to be due to its agonist activity at M₁ and M₄ muscarinic acetylcholine receptors in the central nervous system.^{15,18} M₁ and M₄ are thought to be highly expressed in regions of the brain associated with symptoms of schizophrenia but not in areas associated with motor control and hormone regulation.¹⁷⁻²⁰ The specific mechanisms of each component are illustrated in (Figure 1).^{15-19,21}

THE EMERGENT CLINICAL STUDY PROGRAM

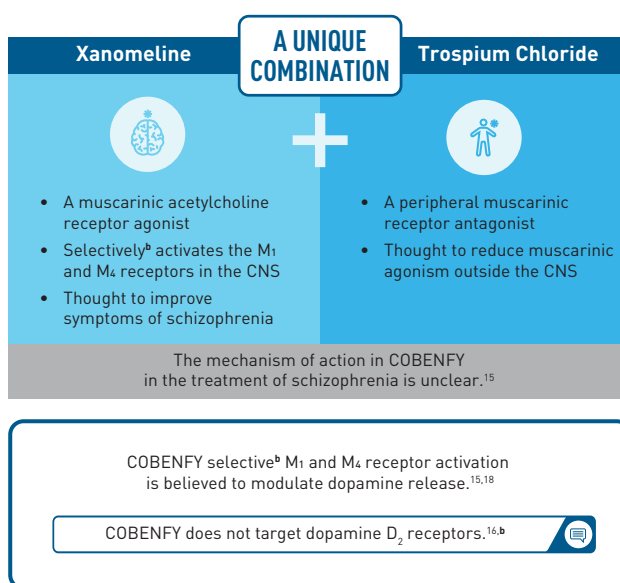
The safety and efficacy of COBENFY was evaluated in the EMERGENT clinical study program (Figure 2).^{16,19,22-25} The EMERGENT clinical study program includes the EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), EMERGENT-3 (NCT04738123), EMERGENT-4 (NCT04659174), and EMERGENT-5 (NCT04820309) studies.^{16,19,22,26,27} EMERGENT-1 (phase 2), EMERGENT-2 (phase 3), and EMERGENT-3 (phase 3) were short-term, 5-week, randomized, double-blind placebo-controlled, inpatient studies, whereas EMERGENT-4 was a phase 3, 52-week, outpatient open-label extension trial, and EMERGENT-5 was a phase 3 long-term, 52-week, outpatient open-label trial.^{16,19,22,26,27} Throughout the EMERGENT clinical study program, standardized assessment tools including the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity (CGI-S), and the PANSS Marder negative factor score were used as key evaluation measures for trial participants.^{16,19,22,26,27}

The PANSS is a 30-item, 7-point rating tool used to measure the severity of schizophrenia symptoms. It is divided into 3 scales: positive (7 items), negative (7 items), and general psychopathology (16 items).

Each item is rated from 1 (absent) to 7 (extreme), based on detailed criteria. Scores are summed across items to assess symptom severity and provide a comprehensive view of the patient's condition.²⁸

The PANSS Marder negative factor score, also called the negative symptoms factor, includes 7 PANSS items: blunted affect, emotional withdrawal, poor rapport, passive/apathetic withdrawal, motor retardation, active social avoidance, and lack of spontaneity in conversation. The PANSS Marder negative factor score provides a more precise representation of negative symptoms.²⁹

Figure 1. Mechanism of Action of Xanomeline and Trospium Chloride Combination Therapy^{15-19,21,a,b}



CNS, central nervous system; D₂, dopamine type 2.

^aCOBENFY is a combination of xanomeline (a muscarinic agonist) and trospium chloride (a muscarinic antagonist) indicated for the treatment of schizophrenia in adults.¹⁵

^bXanomeline binds to muscarinic receptors M₁ to M₅ with comparable affinity and exhibits higher agonist activity at the M₁ and M₄ receptors.

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Risk of Use in Patients with Hepatic Impairment: Patients with hepatic impairment have higher systemic exposures of xanomeline, a component of COBENFY, compared to patients with normal hepatic function, which may result in increased incidence of COBENFY-related adverse reactions.

COBENFY is contraindicated in patients with moderate or severe hepatic impairment. COBENFY is not recommended in patients with mild hepatic impairment.

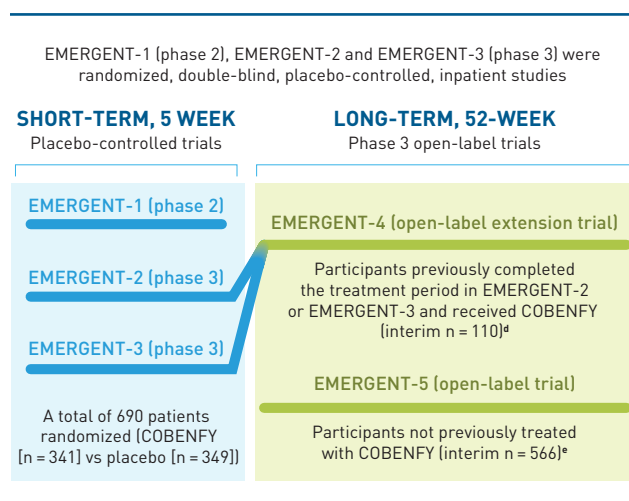
Assess liver enzymes prior to initiating COBENFY and as clinically indicated during treatment.

The CGI-S is a clinician-administered tool that rates the current severity of a patient's mental illness on a scale ranging from 1 point (normal, not at all ill) to 7 points (among the most extremely ill). It is a brief rating scale which quantifies and tracks clinical progress over time. It assesses the current severity of the patient's symptoms with the same condition (eg, schizophrenia).³⁰

EMERGENT-1, EMERGENT-2, AND EMERGENT-3

The phase 2 EMERGENT-1 and phase 3 EMERGENT-2 and EMERGENT-3 studies were randomized, double-blind, placebo-controlled, flexible-dose, 5-week inpatient trials designed to assess the efficacy and safety of COBENFY™ (xanomeline and trospium chloride) in the treatment of schizophrenia in adults (Figure 3).^{15,16,19,22}

Figure 2. EMERGENT Clinical Trial Program^{16,19,22-25,a,b,c}



^aEMERGENT-1, -2, -3 PANSS total score between 80 and 120 as part of patient inclusion.

^bEMERGENT-4 patients must have completed EMERGENT-2 or -3.

^cEMERGENT-5 PANSS total score ≤ 80 and CGI-S ≤ 4 at baseline as part of patient inclusion.

^dmITT population

^eSafety population

The select inclusion criteria for EMERGENT-1, EMERGENT-2, and EMERGENT-3 required participants to have a primary diagnosis of schizophrenia—as confirmed by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*—with symptoms of psychosis and an acute exacerbation or relapse requiring hospitalization and onset occurring less than 2 months before screening.^{16,19,22,31,32} Participants needed a PANSS total score between 80 and 120, with a score of 4 or higher on at least 2 of the following items: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), and suspiciousness/persecution (P6).^{16,19,22,28}

Additionally, patients had to show no more than 20% improvement in the PANSS total score between screening and baseline and a CGI-S score of at least 4 points (moderately ill) at both time points.^{16,19,22,31,33} Participants were required to meet medication requirements including being off lithium for at least 2 weeks before baseline, oral antipsychotics for at least 5 half-lives or 1 week (whichever was longer) before baseline, and long-acting injectable antipsychotics for at least 12 weeks (24 weeks for paliperidone palmitate extended-release injectable suspension) before baseline.³¹⁻³³ Participants had to be aged 18 to 60 years for EMERGENT-1 and 18 to 65 years for EMERGENT-2 and EMERGENT-3.^{16,19,22} (Please see published studies for full inclusion criteria.^{16,19,22})

Select exclusion criteria for the EMERGENT-1, EMERGENT-2, and EMERGENT-3 trials included diagnosis with any primary DSM-5 disorder other than schizophrenia within 12 months of screening, evidence of psychiatric hospitalizations totaling 30 or more days in the 90 days before screening, or history of treatment resistance to schizophrenia medications (defined as failure to respond to 2 pharmacotherapy courses or requiring clozapine within the previous year).^{16,19,22,31-33} Additionally, those with newly diagnosed schizophrenia or those experiencing a first-treated episode, those deemed at risk for suicidal behavior (based on clinical assessment and the Columbia-Suicide Severity Rating Scale [C-SSRS]), and those who had prior exposure to COBENFY or who experienced AEs from xanomeline or trospium also were excluded.³¹⁻³³ Participants with any clinically significant disease or condition that could compromise their safety or the study's validity (as determined by the investigator) were also ineligible.³¹⁻³³ (Please see published studies for full exclusion criteria.^{16,19,22})

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Risk of Use in Patients with Biliary Disease: In clinical studies with COBENFY, transient increases in liver enzymes with rapid decline occurred, consistent with transient biliary obstruction due to biliary contraction and possible gallstone passage.

COBENFY is not recommended for patients with active biliary disease such as symptomatic gallstones. Assess liver enzymes and bilirubin prior to initiating COBENFY and as clinically indicated during treatment. The occurrence of symptoms such as dyspepsia, nausea, vomiting, or upper abdominal pain should prompt assessment for gallbladder disorders, biliary disorders, and pancreatitis, as clinically indicated.

Discontinue COBENFY in the presence of signs or symptoms of substantial liver injury such as jaundice, pruritus, or alanine aminotransferase levels more than five times the upper limit of normal or five times baseline values.

A total of 690 patients were randomized across the 3 trials (COBENFY [n = 341] vs placebo [n = 349]), with 182 participants in EMERGENT-1, 252 participants in EMERGENT-2, and 256 participants in EMERGENT-3.^{16,19,22} The baseline characteristics for the EMERGENT-1, EMERGENT-2, and EMERGENT-3 trials were similar between the COBENFY and placebo groups. Across the 3 trials, the age of participants was approximately 42 to 46 years old and 89% reported prior antipsychotic use. Approximately 20.0% to 30.4% of participants identified as female, 58.8% to 77% identified as Black or African American, and 18% to 40.5% identified as Caucasian. The mean baseline PANSS total scores were approximately 97.5, which is defined as “markedly ill”; the positive subscale scores averaged approximately 27 and negative subscale scores averaged approximately 23.^{16,19,22,34} The Marder negative factor scores were consistent across groups, with the average ranging from 21.8 to 22.9.^{16,19,22} The mean CGI-S scores were uniform across all 3 studies, averaging approximately 5.

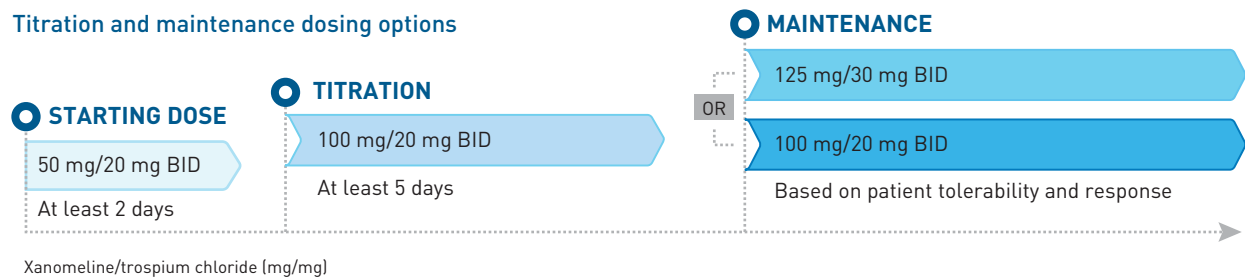
The primary end point of these studies was the change in PANSS total score from baseline at week 5 versus placebo. Secondary outcome measures were the change from baseline in PANSS positive, PANSS negative, and PANSS Marder negative factor subscales at the same time point. Additional secondary outcome measures in EMERGENT-1, EMERGENT-2, and EMERGENT-3 included the CGI-S score at week 5

and the percentage of PANSS responders, defined as patients showing at least a 30% change in PANSS total score at week 5 (EMERGENT-2 and EMERGENT-3 only).^{16,19,22}

In the phase 2 EMERGENT-1 trial, the modified intention-to-treat (mITT) analysis included 83 patients given COBENFY and 87 patients given placebo. At week 5, participants in the COBENFY group achieved greater reductions in the PANSS total score compared to the placebo group (-17.4 vs -5.9 points) (LS mean difference, -11.6 points; 95% confidence interval [CI], -16.1 to -7.1 points).²²

The results from the 2 phase 3 clinical trials, EMERGENT-2 and EMERGENT-3, highlight the efficacy of COBENFY in reducing PANSS total symptom scores.^{16,19} In the EMERGENT-2 study, patients in the COBENFY group achieved a least-squares mean reduction of 21.2 points from baseline in PANSS total score by week 5, compared with an 11.6-point reduction in the placebo group, corresponding to a placebo-adjusted difference of 9.6 points (P < .0001).¹⁹ Similarly, in the EMERGENT-3 trial, patients in the COBENFY group achieved a least-squares mean reduction of 20.6 points from baseline in PANSS total score at week 5, compared with a 12.2-point reduction in the placebo group, yielding a placebo-adjusted difference of 8.4 points (P < .001).¹⁶ These findings are consistent with prior results from the EMERGENT-1 phase 2 study, in which patients in the COBENFY group

Figure 3. COBENFY™ (xanomeline and trospium chloride) Dosing Considerations^{15,a}



BID, twice a day.

^aRecommended maintenance dose is 100 mg/20 mg or 125 mg/30 mg given orally 2 times a day based on patient tolerability and response.

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Decreased Gastrointestinal Motility: COBENFY contains trospium chloride. Trospium chloride, like other antimuscarinic agents, may decrease gastrointestinal motility. Administer COBENFY with caution in patients with gastrointestinal obstructive disorders because of the risk of gastric retention. Use COBENFY with caution in patients with conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis.

Risk of Angioedema: Angioedema of the face, lips, tongue, and/or larynx has been reported with COBENFY and trospium chloride, a component of COBENFY. In one case, angioedema occurred after the first dose of trospium chloride. Angioedema associated with upper airway swelling may be life-threatening. If involvement of the tongue, hypopharynx, or larynx occurs, discontinue COBENFY and initiate appropriate therapy and/or measures necessary to ensure a patent airway. COBENFY is contraindicated in patients with a history of hypersensitivity to trospium chloride.

showed a 17.4-point reduction from baseline in PANSS total score at week 5, compared with a 5.9-point reduction in the placebo group.²²

The results of a pooled analysis of EMERGENT-1, EMERGENT-2, and EMERGENT-3 data showed that patients taking COBENFY™ (xanomeline and trospium chloride) achieved a least-squares mean reduction of 19.4 points from baseline in PANSS total score by week 5, compared with a 9.6-point reduction in the placebo group, corresponding to 9.9-point reduction relative to placebo ($P < .0001$). **In the pooled analysis, end point data were analyzed descriptively, and the results are considered exploratory.**³⁵

The phase 3 study data demonstrated that patients treated with COBENFY also achieved improvements in PANSS positive subscale scores by week 5. In the EMERGENT-2 study, patients in the COBENFY group had a 6.8-point least-squares mean reduction from baseline compared with a 3.9-point reduction in the placebo group, with a placebo-adjusted difference of 2.9 points ($P < .0001$).¹⁹ In the EMERGENT-3 study, patients in the COBENFY group achieved a 7.1-point reduction compared with a 3.6-point reduction in the placebo group, with a placebo-adjusted difference of 3.5 points ($P < .001$).¹⁶ Similar efficacy was observed in the EMERGENT-1 phase 2 trial, where patients in the COBENFY group achieved a 5.6-point reduction compared with a 2.4-point reduction in the placebo group, for a placebo-adjusted difference of 3.5 points ($P < .001$).²²

Across the 3 trials, patients treated with COBENFY also achieved reductions in PANSS negative subscale scores by week 5. In the EMERGENT-2 study, patients in the COBENFY group had a 3.4-point least-squares mean reduction from baseline compared with a 1.6-point reduction with placebo, yielding a 1.8-point placebo-adjusted difference.¹⁹ In the EMERGENT-3 study, patients in the COBENFY group had a 2.7-point reduction compared with 1.8 points for placebo, yielding a placebo-adjusted difference of 0.8 points, though this difference was not statistically significant.³² In the phase 2 EMERGENT-1 trial, COBENFY reduced negative symptoms by 3.2 points compared with 0.9 points with placebo, yielding a 2.3-point placebo-adjusted difference.²² The most common adverse reactions (occurring in $\geq 5\%$ of patients and at least twice placebo) included nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, and gastroesophageal reflux disease.³⁶ Additional safety data are provided in subsequent sections.

EMERGENT-4 AND EMERGENT-5

The EMERGENT-4 and EMERGENT-5 open-label studies evaluated the safety and efficacy of COBENFY over a 52-week period. EMERGENT-4 was a phase 3, multicenter, 52-week, outpatient, open-label extension study designed to evaluate the long-term safety, tolerability, and efficacy of COBENFY in individuals with schizophrenia who previously completed the treatment period of either the EMERGENT-2 or EMERGENT-3 studies.²⁶ EMERGENT-5 was a phase 3, 52-week, open-label study that assessed the same outcomes in individuals with schizophrenia.²⁷

The primary end point for EMERGENT-4 and EMERGENT-5 was the incidence of treatment-emergent AEs (TEAEs). Secondary outcome measures included the incidence of serious TEAEs and of TEAEs leading to study drug discontinuation; the change from baseline to week 52 in PANSS total score, PANSS positive subscale score, PANSS negative subscale score, PANSS Marder negative factor score, and CGI-S score; and the percentage of PANSS responders (those with at least a 30% reduction in PANSS total score).^{26,27}

The inclusion criteria for both EMERGENT-4 and EMERGENT-5 required participants to be between the ages of 18 to 65 years.^{26,27} Eligible participants in EMERGENT-5 also were required to have a PANSS total score of 80 points or less and a CGI-S score of no more than 4 points at both screening and baseline, as well as be on daily oral antipsychotic medication consistent with drug label as maintenance therapy at the time of screening or within 30 days prior.²⁷ Participants in EMERGENT-4 were required to have completed the 5-week treatment period of EMERGENT-2 or EMERGENT-3.²⁶ Participants stopped their prior oral antipsychotic therapy before starting COBENFY.^{26,27} (*Please see ClinicalTrials.gov for full inclusion criteria.*^{26,27})

EMERGENT-4 excluded participants with any clinically significant abnormality at the end of treatment visits in the EMERGENT-2 and EMERGENT-3 acute trials that, in the investigator's opinion and in consultation with the medical monitor, could jeopardize the subject's safety.²⁶ For EMERGENT-4 and EMERGENT-5, participants were excluded if they had a psychiatric hospitalization, an acute crisis intervention, or an increase in the level of care due to symptom exacerbation within 8 weeks of screening or if they were considered psychiatrically unstable by the investigator.^{26,27} Additionally, both

IMPORTANT SAFETY INFORMATION (*Continued*) WARNINGS AND PRECAUTIONS (*Continued*)

Risk of Use in Patients with Narrow-angle Glaucoma: Pupillary dilation may occur due to the anticholinergic effects of COBENFY. This may trigger an acute angle closure attack in patients with anatomically narrow angles. In patients known to have anatomically narrow angles, COBENFY should only be used if the potential benefits outweigh the risks and with careful monitoring.

Increases in Heart Rate: COBENFY can increase heart rate. Assess heart rate at baseline and as clinically indicated during treatment with COBENFY.

studies excluded individuals at risk for suicidal behavior as determined by the investigator's clinical assessment and the C-SSRS or those deemed unsuitable for enrollment due to safety concerns or an inability to adhere to the protocol visit schedule and requirements.^{26,27} (Please see *ClinicalTrials.gov* for full exclusion criteria.^{26,27})

The pooled baseline characteristic and trial population data for EMERGENT-4 and EMERGENT-5 are shown in **Table 2**.^{23,24} In the EMERGENT-4 open label extension trial, over 75% of participants in the mITT group achieved a 30% or greater improvement in PANSS total score by week 52.²⁵ The average reduction in PANSS score was 33.3 points from baseline. Additionally, participants experienced a mean reduction of 10.7 points in the PANSS positive subscale score

and a mean reduction of 6.2 points in the PANSS negative subscale score from baseline by week 52. **End point data from the open-label extension trials were analyzed descriptively.**²⁵

Safety Results

The safety profile of COBENFY™ (xanomeline and trospium chloride) was evaluated in the EMERGENT clinical study program trials.³⁶ Adverse reactions reported in at least 2% of patients treated with COBENFY across the phase 3 trials are included in **Table 3**.^{15,36} A mild adverse reaction was defined as an event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities, whereas a moderate adverse reaction was defined as an event sufficiently

Table 2. Pooled EMERGENT-4 and EMERGENT-5 Baseline Characteristics and Trial Population^{23,24,a}

Characteristic	COBENFY (N = 718)	Characteristic	COBENFY (N = 718)
Age, years, mean (SD)	46.9 (11.8)	Completed, n (%)	337 (46.9)
Sex, n (%)		Discontinued (%)	381 (53.1)
Male	489 (68.1)	Reason for discontinuation, n (%)	
Female	229 (31.9)	Consent withdrawn	134 (18.7)
Race, n (%)		Adverse events	107 (14.9)
American Indian or Alaskan Native	1 (0.1)	Lost to follow-up	59 (8.2)
Asian ²³	6 (0.8)	Participant failed to adhere to protocol	53 (7.4)
Black or African American	482 (67.1)		
Native Hawaiian or Other Pacific Islander	2 (0.3)		
White	220 (30.6)		
Other/not reported/missing/unknown	7 (0.9)		
Weight, kg, mean (SD)	88.1 (18.5)		
Body mass index, kg/m ² , mean (SD)	29.5 (5.6)		
Most common prior antipsychotic medications, n			
Quetiapine	238		
Risperidone	197		
Aripiprazole	129		
Olanzapine	122		

^aInterim results as of April 2023.

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Anticholinergic Adverse Reactions in Patients with Renal Impairment: Trospium chloride, a component of COBENFY, is substantially excreted by the kidney. COBENFY is not recommended in patients with moderate or severe renal impairment (estimated glomerular filtration rate (eGFR) <60 mL/min). Systemic exposure of trospium chloride is higher in patients with moderate and severe renal impairment. Therefore, anticholinergic adverse reactions (including dry mouth, constipation, dyspepsia, urinary tract infection, and urinary retention) are expected to be greater in patients with moderate and severe renal impairment.

Table 3. Adverse Reactions Reported in $\geq 2\%$ of Patients Treated With COBENFY™ (xanomeline and trospium chloride) vs Placebo Across Phase 3 Trials^{15,a}

Adverse Reactions	COBENFY (n = 251)	Placebo (n = 253)
Nausea	19%	4%
Dyspepsia ^b	18%	5%
Constipation	17%	7%
Vomiting	15%	1%
Hypertension ^c	11%	2%
Abdominal pain ^d	8%	4%
Diarrhea	6%	2%
Tachycardia ^e	5%	2%
Dizziness	5%	2%
GERD	5%	<1%
Dry mouth	4%	2%
Somnolence	3%	2%
Vision blurred	3%	0%
Salivary hypersecretion	2%	0%
Orthostatic hypotension	2%	1%
Cough ^f	2%	1%
EPS, nonakathisia ^g	2%	<1%

AR, adverse reactions; EPS, extrapyramidal symptoms; GERD, gastroesophageal reflux disease.

^aEMERGENT-2 and -3 were phase 3, randomized, double-blind, placebo-controlled, inpatient studies. In the 5-week placebo-controlled studies, 6% of patients treated with COBENFY and 4% of placebo-treated patients discontinued participation due to ARs. ARs that led to study discontinuation in $\geq 1\%$ of patients treated with COBENFY included nausea (2%) and vomiting (1%).

^bDyspepsia includes dyspepsia, esophageal discomfort.

^cHypertension includes hypertension, blood pressure increased, labile hypertension, orthostatic hypertension.

^dAbdominal pain includes abdominal discomfort, abdominal pain upper, abdominal pain, abdominal pain lower, abdominal tenderness.

^eTachycardia includes tachycardia, heart rate increased, sinus tachycardia.

^fCough includes cough, productive cough.

^gEPS (nonakathisia) includes dyskinesia, drooling, dystonia, extrapyramidal disorder, muscle contraction involuntary, muscle spasms.

discomforting to interfere with—but not prevent—normal everyday activities.³⁷ Approximately 14.1% and 4.4% of patients treated with COBENFY experienced mild or moderate nausea, respectively, whereas 9.1% and 4.4% experienced mild or moderate vomiting, respectively.³⁶ No patients experienced severe nausea or vomiting. The mean duration of nausea and vomiting was less than 2 weeks.³⁷ The mean duration of nausea was 12.9 days for patients taking COBENFY compared with 5.6 days for patients taking placebo; 2% of patients in the COBENFY group and 0% of patients in the placebo group discontinued due to nausea.^{36,37} For vomiting, the mean duration was 2.5 days for patients taking COBENFY and 6.5 days for patients taking placebo; 1.2% of patients in the COBENFY group and 0% of patients in the placebo group discontinued due to vomiting.^{36,37} Antiemetics, mainly ondansetron, were used by 4% of patients in the trials.³⁷

Throughout the 52-week period, the incidences of clinically significant weight gain, certain metabolic side effects, and movement disorders were low in the safety populations.^{24,37,38} Treatment with COBENFY was not associated with weight gain in approximately 96% of participants in the EMERGENT-4 and EMERGENT-5 trials.²³ Pooled results from EMERGENT-4 and EMERGENT-5 showed that patients taking COBENFY lost an average of 5.6 pounds, with 17.6% experiencing a weight decrease of 7% or more, and 4.1% experiencing a weight increase of 7% or more.²⁴ There were no clinically meaningful changes in total cholesterol and triglyceride levels among participants. The proportion of metabolic shifts was similar to placebo.³⁷ Pooled data from EMERGENT-1, EMERGENT-2, and EMERGENT-3 showed that total cholesterol increased from 'borderline' to 'high' in 6.8% of patients compared to 5.1% with placebo, whereas fasting triglycerides showed a similar shift in 0.7% of patients compared to 1.7% with placebo. Additionally, fasting glucose increased from 'normal' to 'impaired' in 1.8% of patients compared to 1.7% with placebo. In EMERGENT-5, hemoglobin A_{1c} (HbA_{1c}) levels remained stable throughout treatment, and fewer participants had elevated HbA_{1c} at the final assessment compared with baseline.²⁴ There were no clinically meaningful changes in movement disorder scale scores, or significant changes related to prolactin.²³ Over the 52-week period, changes in movement disorder scale scores were as follows: Simpson-Angus Scale score (-0.2 ± 0.04), Barnes Akathisia Rating Scale score (0.0 ± 0.04), and Abnormal Involuntary Movement Scale score (0.1 ± 0.02).

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Central Nervous System Effects: Trospium chloride, a component of COBENFY, is associated with anticholinergic central nervous system (CNS) effects. A variety of CNS anticholinergic effects have been reported with trospium chloride, including dizziness, confusion, hallucinations, and somnolence. Monitor patients for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise patients not to drive or operate heavy machinery until they know how COBENFY affects them. If a patient experiences anticholinergic CNS effects, consider dose reduction or drug discontinuation.

Most Common Adverse Reactions ($\geq 5\%$ and at least twice placebo): nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, and gastroesophageal reflux disease.

CONCLUSIONS

Schizophrenia can have a serious impact on quality of life, and significant costs are associated with the disease and its management. COBENFY™ (xanomeline and trospium chloride) is a first-in-class treatment that selectively activates M₁ and M₄ receptors, which may modulate dopamine release. Patients treated with COBENFY demonstrated significant improvements in PANSS total scores in the phase 3 short-term trials. The availability of COBENFY expands the range of treatment options available for patients. •

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IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Use in Specific Populations:

- Moderate or Severe Renal Impairment: Not recommended
- Mild Hepatic Impairment: Not recommended

COBENFY (xanomeline and trospium chloride) is available in 50mg/20mg, 100mg/20mg, and 125mg/30mg capsules.

Please see U.S. [Full Prescribing Information](#), including [Patient Information at \[cobenfyhcp.com\]\(https://cobenfyhcp.com\)](#).
