COBENFY™

(xanomeline and trospium chloride) capsules

50mg/20mg, 100mg/20mg, 125mg/30mg

Value Proposition

This presentation contains healthcare economic information (HCEI) and is approved for use with payers, formulary committees, or other similar entities with knowledge and expertise in the area of healthcare economic analysis, carrying out their responsibilities for the selection of drugs for coverage and reimbursement.

INDICATION

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

SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

COBENFY™ is contraindicated in patients with: urinary retention; moderate or severe (Child-Pugh Class B or C) hepatic impairment; gastric retention; history of hypersensitivity to COBENFY or trospium chloride—angioedema has been reported with COBENFY and trospium chloride; and untreated narrow-angle glaucoma.

Please see additional Important Safety Information throughout and U.S. Full Prescribing Information, including Patient Information here.

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SCHIZOPHRENIA OVERVIEW

Introduction

Schizophrenia is a psychotic disorder characterized by disturbances in thinking (cognition), emotional responsiveness, and behavior, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[1]

It is a complex condition comprising 3 primary symptom domains: positive, negative, and cognitive symptoms, all of which can impact the lives of patients.[2,3]

In One Study, Hospitalized Patients Experienced Symptoms Despite D_2 Treatment[2-5]

73% of patients reported **positive symptoms**[a]

eg, hallucinations, delusions, agitation, aggression

82% of patients reported **negative symptoms**[a]

eg, apathy, social withdrawal, flat affect

73% of patients reported **cognitive symptoms**[a]

eg, memory issues, concentration difficulties, decision-making challenges

[a]12,442 people with schizophrenia reported positive, negative, and cognitive symptoms while taking antipsychotics, often in combination with antidepressants, mood stabilizers, benzodiazepines, or anxiolytics. Based on data from NeuroBlu, a Holmusk real-word behavioral health Electronic Health Record (EHR) dataset.[5,6]

D_2 treatment=D_2 receptor-binding treatment.

HOME ▶

Epidemiology and Disease State Background

Schizophrenia is one of the top 18 leading causes of disability worldwide[7]:

- **~3.7M people** in the United States are living with schizophrenia[8a]
- **~30 years** reduced life expectancy in the US[9]

Schizophrenia may increase the risk of costly comorbidities[10]:

- The **risk for obesity is estimated to be 4x greater** for people with schizophrenia than in the general population[11]
- **Type 2 diabetes** is **2 to 3 times more** prevalent in patients with schizophrenia than in the general population[12]
- It's estimated that **up to one third** of people with multi-episode schizophrenia **have metabolic syndrome[11]**
- Multiple side effects of antipsychotic drugs, including obesity, hypercholesterolemia, and dyslipidemia, put patients with schizophrenia at greater risk of cardiovascular disease[12]
- Tardive dyskinesia **impacts ~25% of patients** with schizophrenia taking antipsychotic drugs[13]

Schizophrenia and its treatment can have a serious impact on an individual's quality of life[14]:

- In a survey, patients prescribed oral antipsychotics reported that the side effects negatively impacted their work, social functioning, and treatment adherence[14b]

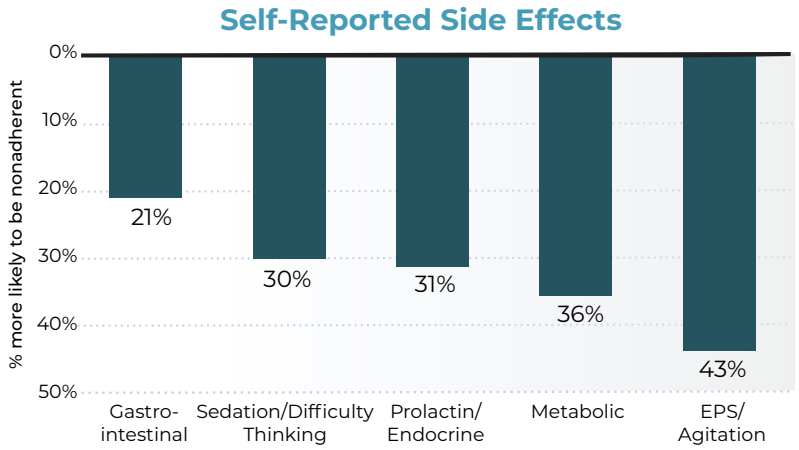
Reported very/extremely bothersome side effects[14b]

[a]Prevalence was estimated to affect 1.1% of the total 2020 US population.[8]
[b]A cross-sectional, observational online survey of 200 adults with self-reported physician-diagnosed schizophrenia who received oral antipsychotics within a year prior. The survey was conducted between December 14, 2018 and January 15, 2019.[14]

HOME

Adherence to D_2 Treatments Can Be a Challenge for Patients Living With Schizophrenia[15,16]

Side effects may increase the likelihood of nonadherence, according to a survey of patients with schizophrenia on D_2 treatments[15]



~74%

A double-blind, active-control clinical trial of D_2 treatments found that 74% of patients with schizophrenia assigned to a D_2 treatment discontinued treatment in the first 18 months[16a]

STUDY DESIGNS AND LIMITATIONS

DIBONAVENTURA ET AL[15]

Study Design:

Cross-sectional survey of 876 adults with self-reported physician-diagnosed schizophrenia currently taking a prescription medication (December 2007–February 2008). Of the 628 patients surveyed who were taking an antipsychotic, associations between self-reported side effects and medication adherence (assessed by the Morisky Medication Adherence Scale) were evaluated using logistical regression adjusted for demographics and comorbidities. Side effects were defined as those the patient reported as at least "somewhat bothered." Adherence was defined as a score of zero on the Morisky Medication Adherence Scale. The Morisky Medication Adherence Scale measures: forgetting to take medication, careless at times about taking medication, stopping medication when feeling better, stopping medication when feeling worse.

Study Limitations:

All data were self-reported; therefore, diagnoses, treatments, adherence levels, and healthcare resource utilization were not confirmed by clinicians, patient records, or administrative claims data. Cross-sectional designs prevent robust ascertainment of causality. Unobserved confounding may have influenced the observed results. Limited information was available with respect to the number of non-antipsychotic medications, thus the greater the number of medications, the more difficult it may be for patients to determine which side effects are due to which treatments. The use of a convenience sample may not be generalizable to the community-dwelling population of patients with schizophrenia.

LIEBERMAN ET AL[16]

Study Design:

In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, a total of 1493 adult patients diagnosed with schizophrenia were recruited at 57 US sites and randomly assigned to receive one of five D_2 treatments: olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone for up to 18 months. This double-blind, active-control trial was conducted (January 2001–December 2004) to compare the effectiveness of first-generation and second-generation antipsychotic drugs in the study population. The primary outcome measure was the discontinuation of treatment for any cause. Kaplan-Meier survival curves were used to estimate the time to the discontinuation of treatment.

Study Limitations:

Reported discontinuation rates may have been increased by the fact that patients were participating in a blinded, controlled trial. Across all medications administered, the medication dose could have impacted the therapeutic performance of the medications, as dose adjustments for treatment-related side effects were made. The FDA-approved dose ranges for quetiapine and ziprasidone may be lower than their respective optimal therapeutic doses. The recommended dosage of risperidone, which aimed to minimize extrapyramidal symptoms, may not reflect the complete therapeutic range of the medication. Additionally, the perphenazine dosage was also selected to reduce the likelihood of extrapyramidal symptoms, which could bias comparisons between first- and second-generation drugs.

[a]Seventy-four percent of patients (n=1061) in the intention-to-treat analysis (N=1432) discontinued their assigned treatment in phase 1 before 18 months.[16]

EPS=extrapyramidal symptoms.

HOME

Emergency Room Visits, Hospitalizations, and Readmissions Contribute to the Burden of Schizophrenia in Medicare Patients[17]

In a study of fee-for-service Medicare patients with schizophrenia (~86% dual-eligible for Medicaid), all-cause events reported included[17ab]

~47%

visited the emergency room (ER) at least once in a 12-month period

~28% **were hospitalized at least once in a 12-month period**

OF WHICH

~27% **were readmitted within 30 days after hospitalization**

STUDY DESIGN AND LIMITATIONS

LI ET AL[17]

Study Design:

This study was a cross-sectional descriptive study of Medicare claims data[c] from 2019 for 314,888 beneficiaries who were aged 18 years or older with continuous Medicare fee-for-service and stand-alone Part D prescription plan coverage. Participants had ≥1 inpatient claim and/or ≥2 outpatient claims on different days with a diagnosis of schizophrenia (ICD-10-CM: F20.XX, F21, and F25.X) and did not have ≥1 inpatient claim and/or ≥2 outpatient claims on different days with a diagnosis (ICD-10-CM: F31.XX) for bipolar disorder in any position. Participants were also proven to reside in one of the 50 states plus D.C. and were identified by a state code (ie, Federal Information Processing Standard code). The study used the Chronic Conditions Data Warehouse (CCW) 100% Medicare files for 2019. These files contain data on all fee-for-service Medicare beneficiaries in the US.[c]

About 91% used any AP (20% used an LAI and 14% used a SGA LAI).

Study Limitations:

This study had several limitations. First, the sample included Medicare beneficiaries with fee-for-service coverage and hence the findings may not be generalizable to those with Medicare Advantage (ie, Medicare beneficiaries covered by managed care plans). Future research should be conducted in this population. Second, there were limitations commonly associated with claims databases which depend on correct diagnosis, procedure, drug and billing codes. The coding inaccuracies may lead to case misidentification. Third, this was a cross-sectional study using 2019 data. The study could not determine causality between the observed measures (for example, between AP utilization and HRU measures). Furthermore, the sample selection requirement that beneficiaries have ≥1 inpatient claim and/or ≥2 outpatient claims on different days with a diagnosis for schizophrenia during the calendar year of 2019 may underestimate the number of beneficiaries with schizophrenia (ie, beneficiaries with a single outpatient diagnosis in the study year but another one in the previous or next year will be excluded). Finally, due to CMS reporting requirements, measures for some counties were not reported due to small sample sizes.

An initial literature review was conducted and recent studies capturing both hospitalization and readmission rates in the last decade for commercially insured schizophrenia patients were not found.

[a]Analysis also included patients with schizoaffective disorder and schizotypal disorder.

[b]Based on an analysis of 2019 Medicare files including 314,888 fee-for-service Medicare beneficiaries with schizophrenia across the 50 states plus D.C. ER visits and hospitalization rates reflected are all-cause, but the vast majority of ER visits (94.7%) were related to mental health.

[c]Beneficiaries residing in Puerto Rico, US Virgin Islands and Guam were not included.

AP=antipsychotic; CMS=Centers for Medicare and Medicaid Services; HRU=Healthcare Resource Utilization; ICD=The International Classification of Diseases; LAI=long-acting injectable antipsychotic; SGA=second-generation antipsychotic.

HOME ▶

Relapse is a Driver of Hospitalization Costs in Schizophrenia

A 2017 database analysis estimates that

US hospitalization costs for patients with schizophrenia who relapsed ranged from[18a]

$6,383 to $22,909[b]

over a 12- to 15-month period[c]

STUDY DESIGN AND LIMITATIONS

PENNINGTON ET AL[18]

Study Design:

A structured and comprehensive literature search of MEDLINE, Embase, and PsycINFO was undertaken to identify articles published before January 2017. A search of Health Management Information Consortium (HMIC) was also undertaken to identify articles published before November 2016 for Health Management. These searches identified 6 conference abstracts and 57 papers as providing relevant data on the cost of relapse in schizophrenia. Costs included were not always clearly stated, but all studies appeared to include inpatient, outpatient, and drug costs. Most studies limited hospitalizations to episodes associated with a diagnosis of schizophrenia, although some studies included all mental health-related hospitalizations, and 2 studies limited reporting of cost data to all-cause hospitalizations. A regression analysis was done to explore the influence of potential cost drivers on the cost of relapse and the cost of hospitalization for relapse. Cost drivers examined were price year, per capita GDP for the country of origin, and whether or not the study originated in the US. Costs were adjusted to 2015 US dollars.

Study Limitations:

A limited number of databases were searched, and a double review of articles retrieved by the initial search did not occur, which may have resulted in the exclusion of relevant studies. The authors did not undertake a formal assessment of the quality of the studies. Such an assessment may not reflect the relative merit of the cost estimates, which was frequently not the primary objective of the article.

One of the US studies included in the analysis included hospitalizations for patients with diagnoses including schizoaffective or schizophreniform disorder in addition to schizophrenia.

[a]One study in the analysis included hospitalizations for patients with diagnoses including schizoaffective or schizophreniform disorder in addition to schizophrenia.
[b]Based on data from articles published before 2017, with all cited costs adjusted to 2015 dollars. Most studies limited hospitalizations to episodes associated with a diagnosis of schizophrenia, although some studies included all mental health-related hospitalizations, and 2 studies limited reporting of cost data to all-cause hospitalizations.
[c]Represents the length of time that the US-based studies analyzed in Pennington et al reported the costs of hospitalizations related to relapse.

GDP=gross domestic product.

HOME ▶

In Addition to Positive Symptoms, Negative Symptoms and Cognitive Impairment Can Drive Unfavorable Hospital Outcomes[10,19,20a]

Negative Symptoms were associated with:

UP TO 50% MORE hospital admissions[19,20]

- 5.2 vs. 4.2 (N=242,586) admissions[19bc]
- 6.8 vs 4.5 (N=16,804) admissions[20d]

~1 week LONGER hospitalization[20]

- 74.6 vs 66.3 days (N=16,804)[bd]

21% GREATER inpatient stay costs[19]

- $15,492 vs $12,824 (N=242,586)[bce]

Cognitive Impairment was associated with:

64% MORE hospitalizations (since diagnosis)[10]

- 1.8 vs. 1.1 (N=443) admissions[bef]

2x AS MANY relapse-related hospitalizations[10]

- 0.6 vs 0.3 (N=821)[bef]

~2x LONGER relapse-related hospitalizations[10]

- 3.4 vs. 1.8 days (N=781)[bef]

Study Design and Limitations on page 10

[a]"Cognitive impairment" includes deficits in the main cognitive domains, especially executive function, working memory, and processing speed.[21]
[b]Comparative data presented are mean results.[10,19,20]
[c]Retrospective all-payer claims database analysis (study period 1/1/2016–9/30/2022) that estimated HCRU and healthcare costs among patients with (N=5691) and without (N=236,895) a diagnosis code of residual negative symptoms over a 12-month follow-up period. Adolescent and adult (age ≥13 years) patients with ≥1 inpatient or ≥2 outpatient diagnosis claims for schizophrenia (ICD-10-CM=F20.XX) were eligible for inclusion. The mean age of the with RNS study arm was 50.0 and the mean age of the without RNS arm was 47.7.[19]
[d]Retrospective database analysis (study period 2014–2017) that investigated HCRU and costs of patients with vs without negative symptoms of schizophrenia (N=16,804, 1:1 matched sample).[20]
[e]Schizophrenia-related events.[10,19,20]
[f]Adelphi Schizophrenia Disease Specific Programme, a point-in-time survey collecting data from psychiatrists and their patients in the US from July to October 2019 (N=124 physicians reporting on N=651 patients) with no/mild cognitive impairment and N=484 patients with moderate/severe cognitive impairment.[10]
HCRU=healthcare resource utilization; RNS=residual negative symptoms.

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Study Designs and Limitations

SEMWAL ET AL[19]

Study Design:

This retrospective longitudinal observational study estimated healthcare resource utilization and healthcare costs of patients diagnosed with and without residual negative symptoms (RNS) among patients with schizophrenia in the United States. The study used de-identified administrative all-payer claims data from STATinMED RWD Insights from patients with ≥1 inpatient or ≥2 outpatient diagnosis claims for schizophrenia (ICD-10-CM=F20.XX) from January 1, 2016 through September 30, 2022. Outcomes included prevalence of RNS during the study period as well as all-cause, Mental-Health (MH)-related, and schizophrenia-related HCRU and costs per patient per year (PPPY) during the follow-up period. Analyses were adjusted to account for differences between groups.

Study Limitations:

Administrative claims data are subject to data coding limitations and data entry error, which may result in missing or erroneous data. Residual Negative Symptoms diagnosis code may be under-utilized in clinical practice; thus this analysis may underestimate patients presenting as such. Results may not be generalizable to uninsured individuals or those with other insurance types. Due to the large sample sizes typically available in claims-based studies, some differences identified between cohorts may be statistically significant but not clinically meaningful. Even after adjusting for covariates, residual confounding may persist due to unmeasured or imperfectly measured factors.

LAVALLEE ET AL[20]

Study Design:

This study investigated if negative symptoms of schizophrenia (NSS) patients utilize more healthcare services and are more expensive to treat than non-negative symptoms of schizophrenia (NNSS) patients. This study used data from the Decision Resources Group (DRG) Real World Evidence Data Repository US database. DSM-IV/ICD-9 for Schizophrenia Residual Type or with the specifier "With Prominent Negative Symptoms" was used to identify patients. Between 2014 and 2017, patients with negative symptoms of schizophrenia (NSS) had to have 2 or more negative symptom codes and patients with non-negative symptoms of schizophrenia (NNSS) had to have no negative symptoms. NSS and NNSS patients were age and gender matched. Univariate and multivariate analyses estimated healthcare use and cost, and gamma log-link models were adjusted for demographic and clinical factors.

Study Limitations:

Administrative claims data are subject to data coding limitations and data entry error, which may result in missing or erroneous data. Diagnosis codes used to identify patients with negative symptoms may be under-utilized in clinical practice; this analysis may underestimate patients presenting as such. Results may not be generalizable to uninsured individuals or those with other insurance types. Due to the large sample sizes typically available in claims-based studies, some differences identified between cohorts may be statistically significant but not clinically meaningful. Even after matching, residual confounding may persist due to unmeasured or imperfectly measured factors.

KADAKIA ET AL[10]

Study Design:

The study evaluated the association of moderate/severe vs no/mild cognitive impairment and healthcare resource utilization (HCRU), employment status, housing circumstances and quality of life (QoL) of adults with a physician-confirmed diagnosis of schizophrenia who had visited their psychiatrist and were not currently taking part in a clinical trial. The study used data from the Adelphi Schizophrenia Disease Specific Programme (DSP)™ point-in-time survey to collect data from psychiatrists and their patients in the US between July 2019 and October 2019. Differences between patient characteristics for the RNS and non-RNS cohorts were tested using the standardized difference. Significance of HCRU and cost results was defined as *P* value <0.05.

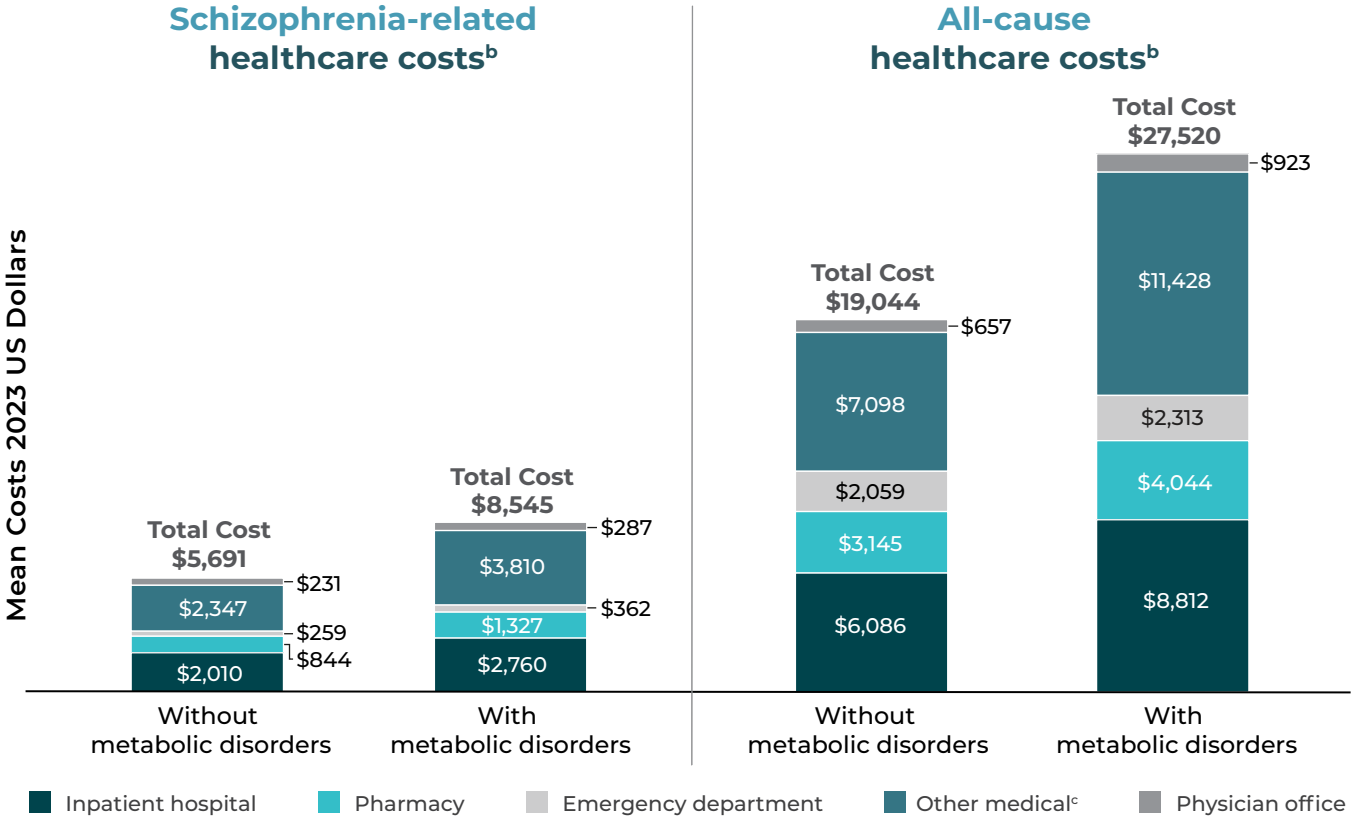
Study Limitations:

Severity of cognitive impairment was based on psychiatrists' judgments of their patients and not confirmed using a validated assessment of cognitive performance. The survey was not based on a random sample and the patients in this analysis may not reflect the general schizophrenia patient population. Recall bias was also possible for the physician-reported HCRU outcomes and patient-reported QoL outcomes. The QoL results for the moderate/severe patients may be a conservative estimate as the participation rate for patient self-completion questionnaires was lower than patients with no/mild schizophrenia. Lastly, causal relationships between cognitive impairment among patients with schizophrenia and patient outcomes could not be tested due to the survey's point-in-time cross-sectional design.

HOME ▶

Metabolic Disorders Among Oral D_2-Treated Patients With Schizophrenia Can Increase Healthcare Resource Utilization and Costs[22a]

Metabolic disorders were associated with 1.5x higher annual healthcare costs in an administrative claims database study of patients with schizophrenia (N=45,528)



! Metabolic disorders included: diabetes, obesity, hyperlipidemia, and metabolic syndrome

i Study Design and Limitations on page 12

[a]In a study of patients with schizophrenia, with and without metabolic disorders, there were a total of 4497 matched pairs included in the analysis.
[b]During 12-month post-index period.
[c]The other medical category included all costs not captured as inpatient hospital, emergency department, physician office visits, and outpatient pharmacy such as laboratory, radiology and other imaging, durable medical equipment, hospice, skilled nursing facilities, and home health.

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Study Designs and Limitations

TZACK ET AL[22]

Study Design:

Patients with metabolic disorders compared to those without had increased schizophrenia-related utilization. This was an observational, retrospective analysis of de-identified administrative claims data examining the development of metabolic disorders among individuals with schizophrenia initiating OAP medications. The analysis utilized the Inovalon MORE^2 Registry of Closed Claims from 1/1/2016 to 9/30/2023 and the 100% Medicare FFS database from 1/1/2016 to 12/31/2022. The MORE^2 Registry includes de-identified, primary source medical and pharmacy claims covering all major US payers (commercial, Medicare Advantage, and Managed Medicaid). The 100% Medicare FFS database includes all Part A and Part B encounters in addition to all Part D claims for Medicare beneficiaries.

Key eligibility criteria included: diagnosis of schizophrenia (at least 1 inpatient claim or at least 2 outpatient claims); no evidence of oral antipsychotics or metabolic disorders in 12-month baseline period; new initiation of oral antipsychotics (at least 2 prescription claims separated by no more than 180 days in the 12 months following schizophrenia diagnosis); exclusion of patients receiving long-acting injectables (LAI); continuous database enrollment throughout baseline and follow-up periods. Individuals with metabolic disorders were identified with the presence of at least 2 non-diagnostic claims with an ICD-10-CM diagnosis code.

Study Limitations:

Results may not be generalizable to uninsured individuals or those with other insurance types. Moreover, administrative claims data are subject to data coding limitations and data entry error, which may result in missing or erroneous data. However, in adjudicated claims databases coding errors are thought to be minimal as accurate information is needed for claims to be adjudicated and paid. The objective of this study was to capture incident metabolic disorders, which was accomplished through requiring a pre-index metabolic naive period. However, incidence may be overestimated if individuals had a history of metabolic disorders prior to the start of the study period. As the incidence analysis was purely descriptive and did not include a control group of individuals without schizophrenia or those with schizophrenia not receiving OAP medications, it cannot be discerned to what degree OAP medications contribute additional risk of developing metabolic disorders among this already at-risk patient population. The study period coincides with the COVID-19 pandemic, which resulted in a restriction in access to care in the US for a period, and healthcare utilization during this time may be under-representative of typical care.

The study was funded by Bristol Myers Squibb. Some of the authors of the publication have received consideration from, or have an affiliation with, BMS.

FFS=fee for service; OAP=other antipsychotic medications.

HOME ▶

Extrapyramidal Symptoms (EPS) From Atypical Antipsychotics Can Result In Increased Healthcare Resource Utilization and Costs[23,24a]

Medicaid Beneficiaries[23]

53% MORE ED visits and costs

- Patients with an ED visit 25.5% vs 16.7% (N=7902)
- Mean $197 vs $118 (N=7902)

74% MORE hospital admissions

- Patients with an admission 22.5% vs 12.9% (N=7902)

2x GREATER inpatient stay costs

- Mean $4,675 vs $2,248 (N=7902)

Commercial and Medicare Patients[24]

~2.5x MORE ED visits and costs

- Patients with an ED visit 11.5% vs 4.7% (N=2170)
- Mean $189 vs $68 (N=2170)

2x AS MANY hospital admissions

- Patients with an admission 19.1% vs 9.5% (N=2170)

3x GREATER inpatient stay costs

- Mean $4,896 vs $1,536 (N=2170)

Atypical antipsychotics are associated with varying levels of extrapyramidal symptoms including acute dystonia, akathisia, parkinsonism, and tardive dyskinesia[23-25]

Study Designs and Limitations on page 14

[a]In patients with schizophrenia, those with EPS compared to those without had increased schizophrenia-related healthcare utilization.[23,24]
ED=emergency department.

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Study Designs and Limitations

KADAKIA ET AL *J Med Econ*[23]

Study Design:

Patients with schizophrenia initiating second-generation antipsychotics (SGAs) were identified in the MarketScan Multi-state Medicaid database from January 1, 2012 to December 31, 2018. Incidence of extrapyramidal symptoms (EPS) identified via ICD-9/ICD-10 diagnoses and medications were assessed during the 12 months following SGA initiation. Multivariate models examined all-cause and schizophrenia-related hospitalizations and total costs in the 12 months following the first EPS claim.

Study Limitations:

The study was limited to Medicaid beneficiaries and the results may not be generalizable to individuals with other types of insurance or the uninsured. The study relied on administrative claims, which has the potential for misclassification of covariates and the data are subject to coding limitations and data entry errors. Claims data are limited in scope to information relevant to reimbursement; therefore, analyses could not control for important clinical variables such as disease severity or specific symptoms of EPS. Medication utilization measures were based on medication administration and filled prescriptions, assuming patients were adherent. The risk of EPS for oral antipsychotics vs long-acting injectables was not examined separately. Systematic differences may exist between the study groups beyond the baseline covariates included in the models that account for differences in healthcare costs and utilization.

KADAKIA ET AL *Am J Manag Care*[24]

Study Design:

Patients with schizophrenia initiating atypical antipsychotics (AAPs) with no prior EPS were identified in the MarketScan Commercial and Medicare Supplemental databases from January 1, 2012 to December 31, 2018. Incidence of EPS (diagnosis or medication use) was assessed in the year following AAP initiation. Annual all-cause and schizophrenia-related healthcare resource utilization and costs were assessed in cohorts who did or did not develop EPS in the year following first EPS claim (EPS cohort) or randomly assigned index date (non-EPS cohort). Multivariate regression was used to compare all-cause and schizophrenia-related total healthcare costs and inpatient admissions between cohorts.

Study Limitations:

The clinical information was derived from adjudicated claims collected for billing and may be subject to misclassification or miscoding. Patients experiencing EPS who did not seek medical intervention would not be identifiable in the databases. Clinician assessments of schizophrenia severity were not available; thus, severity may differ between cohorts. The sample also included patients with prevalent schizophrenia; therefore, the chronicity of the disorder and prior disease history remain unknown. The patient sample had commercial or Medicare supplemental insurance and the findings may not be generalizable to individuals with other types of insurance or the uninsured. Individuals with antipsychotic use in the 6-month preindex period were excluded; however, it is possible that patients had earlier, unidentified use of antipsychotics. Multivariate modeling was used to control for differences in baseline demographic and clinical characteristics; however, these adjustments were limited to factors measurable in claims. Medication utilization was assessed through outpatient pharmacy prescription fills with no way to confirm adherence.

PATEL ET AL[25]

Study Design:

An observational, retrospective analysis of de-identified claims data from the Marketscan Medicaid (MM) and PharMetrics Plus (PMP) databases between January 1, 2014 through December 31, 2022, and January 1, 2009 through September 30, 2023, respectively. Outcomes were analyzed overall, and by the presence or absence of TD determined as 1. no evidence of TD: No VMAT-2 inhibitor use and no TD diagnosis or 2. with evidence of TD: VMAT-2 inhibitor use or TD diagnosis. VMAT-2 inhibitors included in the analysis were valbenazine, deutetrabenazine, and tetrabenazine. The 2 groups were matched using a 1:5 propensity score matching method.

Study Limitations:

Administrative claims data are subject to data coding limitations and data entry error, which may result in missing or erroneous data. Results may not be generalizable to uninsured individuals or those with other insurance types. Due to the large sample sizes typically available in claims-based studies, some differences identified between cohorts may be statistically significant but not clinically meaningful. This study did not include a comparison group of patients who did not receive antipsychotic (AP) treatment; therefore, study results are only generalizable to patients that received an AP at some point following their schizophrenia diagnosis. The study period coincides with the COVID-19 pandemic, during which there were restrictions in access to care in the US for a period of time, and healthcare utilization during this time may be under representative of typical care. Tetrabenazine was one of the VMAT-2 inhibitors analyzed in this study and it is not FDA approved for TD.

TD=tardive dyskinesia; VMAT-2=vesicular monoamine transporter 2.

HOME ▶

Comorbidities Associated With Schizophrenia Treatment Can Increase Total Cost of Care[26-30]

Comorbidity Costs (PPPY)[ab]

Diabetes

▲ $12,238[26]

Metabolic Syndrome

▲ $1,799[27]

Cardiovascular Disease

▲ $20,382[27,28]

Tardive Dyskinesia Costs (PPPY)[25c]

Median cost from 2 claims databases

Marketscan Medicaid

$32,465

- $37,780 TD with VMAT-2 inhibitors
- $29,207 TD without VMAT-2 inhibitors

PharMetrics Plus

$33,039

- $51,383 TD with VMAT-2 inhibitors
- $28,044 TD without VMAT-2 inhibitors

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[a]The 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.[25]
[b]Values represent the average difference in the PPPY total costs, adjusted to 2024 USD for inflation, in patients with the respective comorbidities vs those without.[25]
[c]An observational, retrospective analysis was performed with de-identified claims data from the MM and PMP databases.[25]

PPPY=per patient per year; USD=US dollars; VMAT-2=vesicular monoamine transporter 2.

Study Designs and Limitations

PARKER ET AL[26]

Study Design:

Using 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, the study estimated the 2022 economic cost of diabetes. Similar to previous studies on diabetes burden of illness sponsored by the American Diabetes Association, the study estimated the prevalence of diagnosed diabetes, health-care use, and costs at the state and national levels.

Study Limitations:

Due to data limitations, the potential increases in the use of over-the-counter medications and optometry, dental, and mental health services were omitted from this analysis. Expenditures for prevention programs targeted to people with diabetes, research activities, and health administration costs were also omitted, so the full medical costs associated with diabetes were underestimated. Time and costs associated with traveling to health-care visits and other medical emergencies were omitted, which may have resulted in underestimation of the indirect costs associated with diabetes.

BOUDREAU ET AL[27]

Study Design:

The study investigated the prevalent health-care utilization and costs for persons with and without metabolic syndrome and the independent associations of the factors that make up metabolic syndrome. A total of 170,648 men and women 21 to 87 years old, who were continuously enrolled in 1 of 3 integrated delivery systems between July 1, 2003 and June 30, 2005, were included.

Study Limitations:

The study was a cross-sectional design where exposure and outcome were measured during the same period. This endogeneity may result in higher costs and utilization because the measures used in defining the risk factors were tied to health-care utilization. Economic consequences by incident disease or duration of disease were not examined. Because the study evaluated a subset of patients that had all 5 clinical values used to identify metabolic syndrome risk factors, the prevalence of metabolic syndrome in the general population could not be estimated. As subjects were from 3 health plans in the western region of the United States, results may not be generalizable to care delivered and/or financed in other types of health-care systems and other regions of the United States.

NICHOLS ET AL[28]

Study Design:

An observational, longitudinal cohort study was conducted 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 (HMO). Patients were observed until they died or left the health plan for other reasons or until June 30, 2008, whichever came first.

Study Limitations:

The study assessed clinical characteristics at baseline and then observed patients for several years without reassessing those characteristics. Therefore, the extent to which the cost differences reported account for improvements in risk factors cannot be determined. The requirement for patients to remain enrolled for at least 6 months following registry entry generates survival bias that could have affected the results. The unique structure of the HMO may limit the generalizability of the findings.

PATEL ET AL[25]

Study Design:

An observational, retrospective analysis of de-identified claims data from the Marketscan Medicaid (MM) and PharMetrics Plus (PMP) databases between January 1, 2014 through December 31, 2022, and January 1, 2009 through September 30, 2023, respectively. Outcomes were analyzed overall, and by the presence or absence of TD determined as 1. no evidence of TD: No VMAT-2 inhibitor use and no TD diagnosis or 2. with evidence of TD: VMAT-2 inhibitor use or TD diagnosis. VMAT-2 inhibitors included in the analysis were valbenazine, deutetrabenazine, and tetrabenazine. The 2 groups were matched using a 1:5 propensity score matching method.

Study Limitations:

Administrative claims data are subject to data coding limitations and data entry error, which may result in missing or erroneous data. Results may not be generalizable to uninsured individuals or those with other insurance types. Due to the large sample sizes typically available in claims-based studies, some differences identified between cohorts may be statistically significant but not clinically meaningful. This study did not include a comparison group of patients who did not receive antipsychotic (AP) treatment; therefore, study results are only generalizable to patients that received an AP at some point following their schizophrenia diagnosis. The study period coincides with the COVID-19 pandemic, during which there were restrictions in access to care in the US for a period of time, and healthcare utilization during this time may be under representative of typical care. Tetrabenazine was one of the VMAT-2 inhibitors analyzed in this study and it is not FDA approved for TD.

CVD=cardiovascular disease.

HOME ▶

MECHANISM OF ACTION (MOA)

First-in-Class M_1/M_4 Muscarinic Agonist for Adults With Schizophrenia[2,31,33,34a]

COBENFY is a Unique Combination of[2,31,33]:

Xanomeline — A muscarinic receptor agonist

+

Trospium Chloride — A peripheral muscarinic receptor antagonist

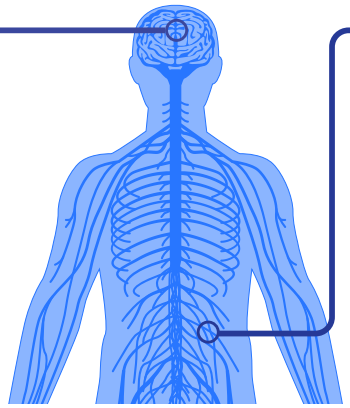
BRAIN

Xanomeline | Trospium Chloride

Selective, targeted M_1/M_4 activity in the CNS[2,31a]

Minimal trospium chloride activity in the CNS[31,35]

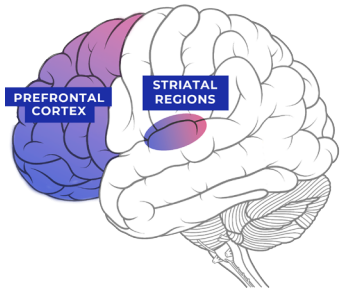
M_1 receptor M_4 receptor



PERIPHERY

Xanomeline | **Trospium Chloride**

Trospium chloride reduces peripheral adverse effects of xanomeline[2,31]



Selective M_1 and M_4 Receptor Activation in the CNS is Believed to Modulate Dopamine Release[2,36b]

M_1 and M_4 receptors are **highly expressed** in regions associated with **symptoms of schizophrenia[32]**

These receptors are **not highly expressed** in areas associated with **motor control and hormone regulation[2,35]**

! COBENFY does not target dopamine D_2 receptors[34]

- COBENFY is the first antipsychotic drug approved to treat schizophrenia that targets muscarinic receptors. COBENFY does not bind to dopamine receptors.[31,37]
- The mechanism of action of xanomeline in the treatment of schizophrenia is unclear[31]
- However, its efficacy is thought to be due to its agonist activity at M_1 and M_4 muscarinic acetylcholine receptors in the central nervous system[31]

[a]The muscarinic acetylcholine receptor family consists of 5 members located throughout the nervous system.[2]
[b]Xanomeline binds to muscarinic receptors M_1 to M_5 with comparable affinity and exhibits higher agonist activity at the M_1 and M_4 receptors.[31]
CNS=central nervous system.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

COBENFY™ is contraindicated in patients with: urinary retention; moderate or severe (Child-Pugh Class B or C) hepatic impairment; gastric retention; history of hypersensitivity to COBENFY or trospium chloride—angioedema has been reported with COBENFY and trospium chloride; and untreated narrow-angle glaucoma.

Please see additional Important Safety Information throughout and U.S. Full Prescribing Information, including Patient Information here.

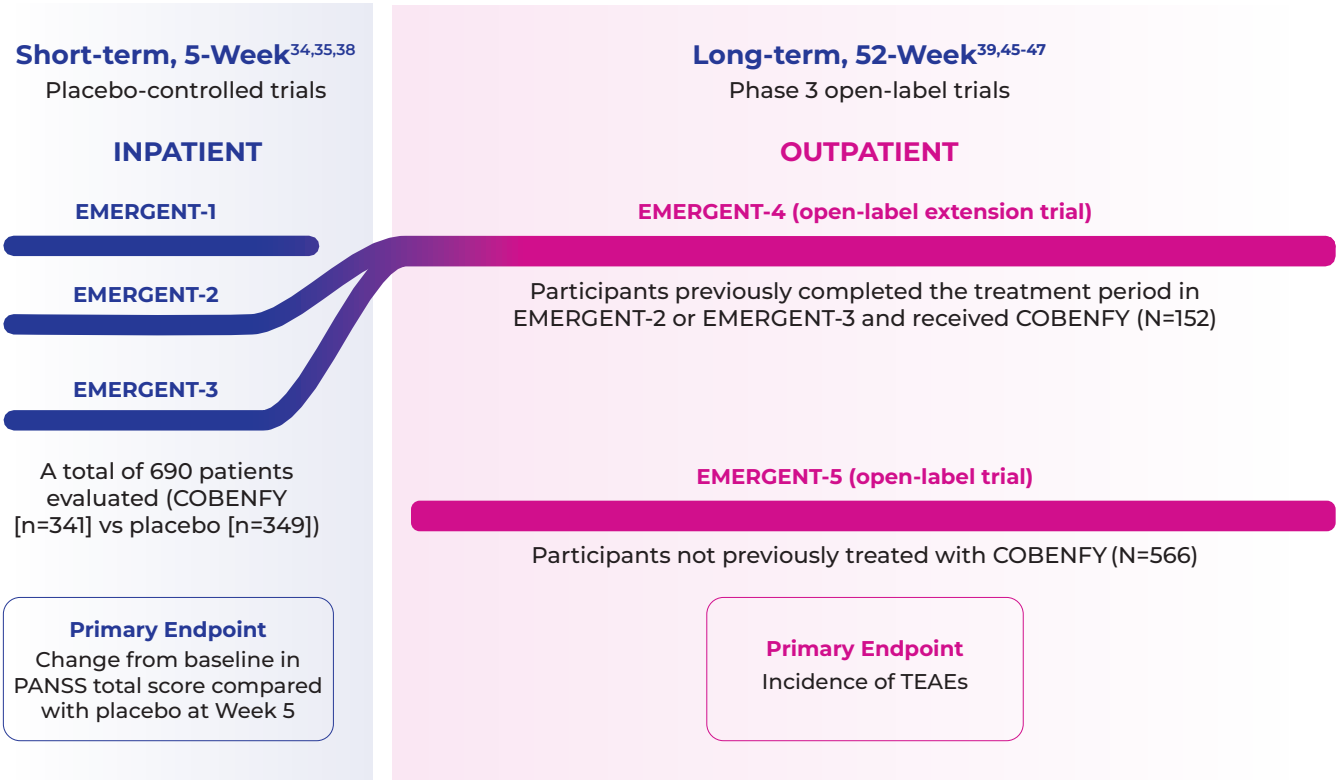
COBENFY™
(xanomeline and trospium chloride) capsules
50mg/20mg, 100mg/20mg, 125mg/30mg

SHORT-TERM DATA (INPATIENT)

The COBENFY Clinical Trial Program Evaluated More Than 1250 Patients Across 5 Clinical Trials[33,35,38-45]

Three 5-week inpatient studies evaluated mean change in PANSS total score in adult patients with schizophrenia experiencing acute psychosis[a]

- EMERGENT-1 (phase 2), EMERGENT-2, and EMERGENT-3 (phase 3) were randomized, double-blind, placebo-controlled, inpatient trials.[34,35,38]
- EMERGENT-4 and EMERGENT-5 were open-label, outpatient trials. EMERGENT-4 was an outpatient extension of phase 3 inpatient trials[39,45]



Short-term, 5-week trial n values are randomized patients.
Long-term, 52-week trial N values are safety analysis population.

Select Secondary Outcome Measures and Previous D_2 Treatment Use for EMERGENT-1, -2, -3 on page 21

Select Secondary Endpoints for EMERGENT-4, -5 on page 33

PANSS=Positive and Negative Syndrome Scale; TEAE=treatment-emergent adverse event.

[a]Patients who were newly diagnosed or were experiencing their first treated episode of schizophrenia were excluded.[48]

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.

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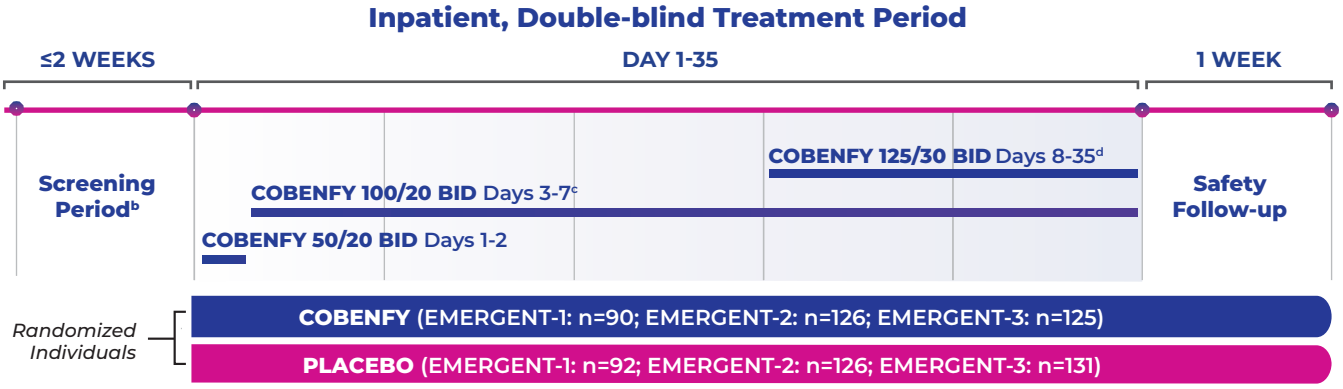
EMERGENT-1, EMERGENT-2, and EMERGENT-3 Study Designs[34,35,38]

Three randomized, double-blind, placebo-controlled, flexible-dose, 5-week, inpatient trials[a]



Primary Endpoint[34,35,38]

- Change from baseline in PANSS total score compared with placebo at Week 5

Select Secondary Outcome Measures[34,35,38]

- Change from baseline in PANSS positive, negative, and Marder negative factor subscales compared with placebo at Week 5
- CGI-S score at Week 5
- EMERGENT-2, EMERGENT-3: Percentage of PANSS responders (≥30% change in PANSS total score) at Week 5

Prior D_2 Treatment Use[49]

Of the 89% of enrolled patients who reported prior D_2 treatment use, the most commonly used were:

- Quetiapine (28%)
- Risperidone (28%)
- Olanzapine (16%)
- Aripiprazole (13%)

COBENFY dose is expressed as xanomeline/trospium chloride (mg/mg).

[a]EMERGENT-1 was a phase 2, randomized, double-blind, placebo-controlled, inpatient study. EMERGENT-2 and -3 were phase 3, randomized, double-blind, placebo-controlled, inpatient studies.[34,35,38]
[b]Screening period included a washout period in which oral D_2 treatments and certain other treatments were not permitted.[34,35,48]
[c]Optional increase in dose from 100 mg/20 mg, beginning at Day 8, based on clinical response and tolerability determined by a clinician.[34,35,38]
[d]Dose reduction to 100 mg/20 mg BID was permitted as necessary based on clinical response and tolerability.[34,35,38]

BID=twice a day; CGI-S=Clinical Global Impression Scale.

WARNINGS AND PRECAUTIONS

Risk of Urinary Retention (cont.): 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.

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EMERGENT-1, EMERGENT-2, and EMERGENT-3 Inclusion and Exclusion Criteria[34,35,38,48,50a]

Select Inclusion Criteria

- **EMERGENT-1:** 18-60 years of age
- **EMERGENT-2/EMERGENT-3:** 18-65 years of age
- DSM-5 confirmed primary diagnosis of schizophrenia and experiencing symptoms of psychosis
- Acute exacerbation or relapse of symptoms requiring hospitalization, with onset <2 months before screening
- PANSS total score between 80 and 120, with a score of ≥4 on ≥2 of the following: delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution
- No change in PANSS total score of ≥20% between screening and baseline
- CGI-S score ≥4 (moderately ill) at screening and baseline
- Off lithium for ≥2 weeks before baseline; no oral APs for ≥5 half-lives/1 week, whichever is longer, before baseline
- No LAI doses for ≥12 weeks (24 weeks for INVEGA TRINZA) before baseline

Select Exclusion Criteria

- No primary DSM-5 disorder other than schizophrenia within 12 months of screening
- Psychiatric hospitalization(s) ≥30 cumulative days in the 90 days before screening
- History of resistance to schizophrenia medications (failure to respond to 2 courses of pharmacotherapy) or required clozapine within the last 12 months
- Newly diagnosed or experiencing a first-treated episode of schizophrenia
- Risk for suicidal behavior during the study, determined by the investigator's clinical assessment and Columbia-Suicide Severity Rating Scale (C-SSRS)
- Prior exposure to COBENFY or any adverse effects due to xanomeline or trospium
- History or presence of clinically significant disease or condition that, in the opinion of the investigator, would jeopardize the safety of the subject or the validity of the study results

[a] Not full list of inclusion and exclusion criteria.

WARNINGS AND PRECAUTIONS

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.

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Baseline Demographics and Characteristics[34,35,38]

CHARACTERISTIC	EMERGENT-1[38] COBENFY (n=90)	EMERGENT-1[38] Placebo (n=92)	EMERGENT-2[35] COBENFY (n=126)	EMERGENT-2[35] Placebo (n=126)	EMERGENT-3[34] COBENFY (n=125)	EMERGENT-3[34] Placebo (n=131)
Age, years, mean ±SD	43.4±10.1	41.6±10.1	45.6±10.4	46.2±10.8	43.6±11.4	42.6±12.2
Sex, n (%)						
Male	72 (80.0)	68 (74.0)	95 (75)	95 (75)	87 (69.6)	104 (79.4)
Female	18 (20.0)	24 (26.0)	31 (25)	31 (25)	38 (30.4)	27 (20.6)
Race, n (%)						
Asian[35]	NA	NA	2 (2)	1 (1)	1 (0.8)	0
Black or African American	67 (74.0)	70 (76.0)	97 (77)	92 (73)	79 (63.2)	77 (58.8)
Caucasian	20 (22.0)	17 (18.0)	26 (21)	31 (25)	45 (36.0)	53 (40.5)
Other[35]	3 (3)	5 (5)	1 (1)	2 (2)	0	0
Not reported[35]	NA	NA	0	0	0	1 (0.8)
PANSS total score, mean ±SD[a]	97.7±9.7	96.6±8.3	98.3±8.9	97.9±9.7	97.3±8.9	96.7±8.9
PANSS positive subscale score, mean ±SD[b]	26.4±3.4	26.3±3.2	26.8±3.7	26.7±4.0	26.9±3.7	26.4±3.3
PANSS negative subscale score, mean ±SD[c]	22.6±4.4	22.8±4.6	22.9±4.0	22.9±3.8	22.6±3.2	22.0±3.7
PANSS Marder negative factor score, mean ±SD[d]	22.3±4.7	22.3±5.0	22.9±5.0	22.5±4.7	22.0±3.7	21.8±4.2
CGI-S score, mean ±SD	5.0±0.6	4.9±0.6	5.1±0.6	5.1±0.6	5.1±0.6	5.0±0.6

Trial Population Disposition[34,35,38]

CHARACTERISTIC	EMERGENT-1[38] COBENFY	EMERGENT-1[38] Placebo	EMERGENT-2[35] COBENFY	EMERGENT-2[35] Placebo	EMERGENT-3[34] COBENFY	EMERGENT-3[34] Placebo
Randomized, n	90	92	126	126	125	131
Completed, n (%)	72 (80.0)	73 (79.3)	94 (74.6)	100 (79.4)	79 (63.2)	93 (71.0)
Discontinued, n (%)	18 (20.0)	19 (20.7)	32 (25.4)	26 (20.6)	46 (36.8)	38 (29.0)
Reason for discontinuation, n (%)						
Consent withdrawal	14 (15.6)	14 (15.2)	13 (10.3)	12 (9.5)	35 (28.0)	22 (16.8)
Adverse event	3 (3.3)	2 (2.2)	10 (7.9)	6 (4.8)	8 (6.4)	7 (5.3)
Progressive event	NA	NA	NA	1 (0.8)	0	4 (3.1)
Protocol nonadherence	NA	NA	NA	0	2 (1.6)	2 (1.5)
Changes in participant's condition[e]	NA	NA	NA	NA	1 (0.8)	0
Suicidal or assault behavior	NA	NA	NA	0	0	2 (1.5)
Investigator decision	1 (1.1)	1 (1.1)	NA	NA	NA	NA
Lost to follow-up	0	1 (1.1)	NA	NA	NA	NA
Other	0	1 (1.1)	9 (7.1)	7 (5.6)	0	1 (0.8)[f]

[a] PANSS total score includes 30 items; score range: 30-210.[38]
[b] Positive subscale includes 7 items; score range: 7-49.[38]
[c] Negative subscale includes 7 items; score range: 7-49 [38]
[d] PANSS Marder negative factor includes 7 items; score range: 7-49.[38]
[e] Assessed in EMERGENT-3 only.[34]
[f] Due to COVID-19.[34]
NA=not applicable; SD=standard deviation.

WARNINGS AND PRECAUTIONS

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.

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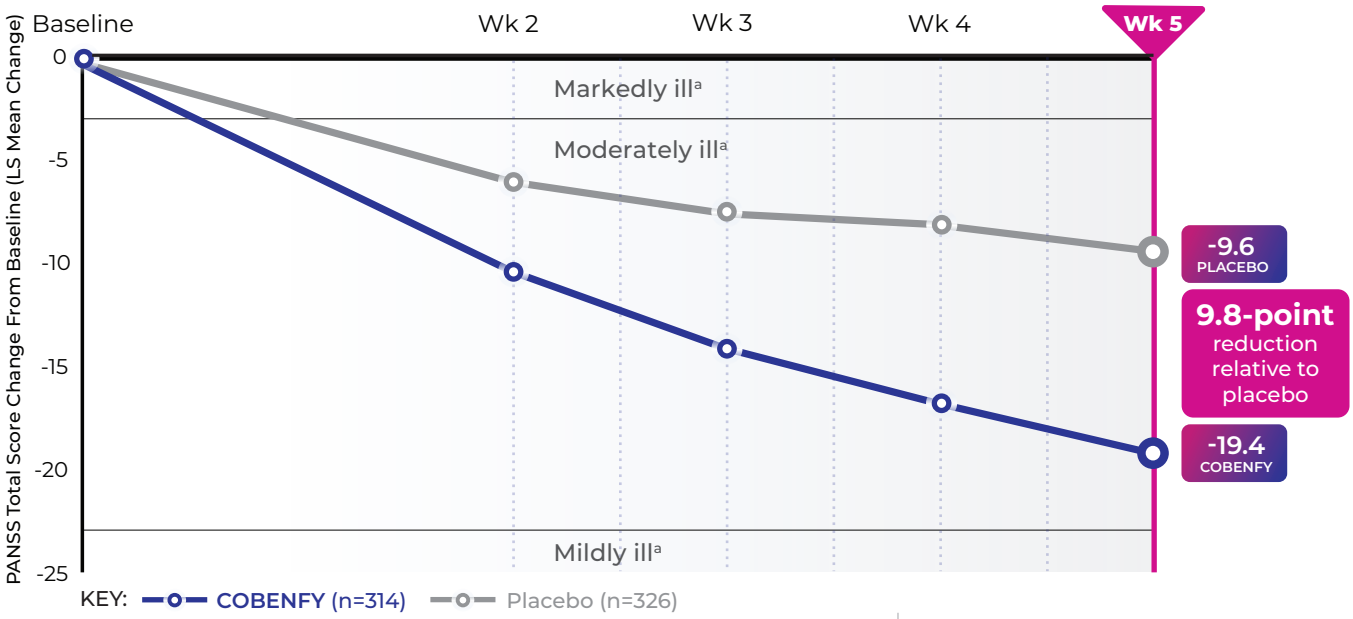
50mg/20mg, 100mg/20mg, 125mg/30mg

COBENFY Achieved Significant Symptom Improvement in PANSS Total Score at Week 5[33]

Post hoc analysis: Change in PANSS total score vs placebo from baseline to Week 5



EMERGENT-2[35]	
COBENFY (n=117)	Placebo (n=119)
-21.2	-11.6

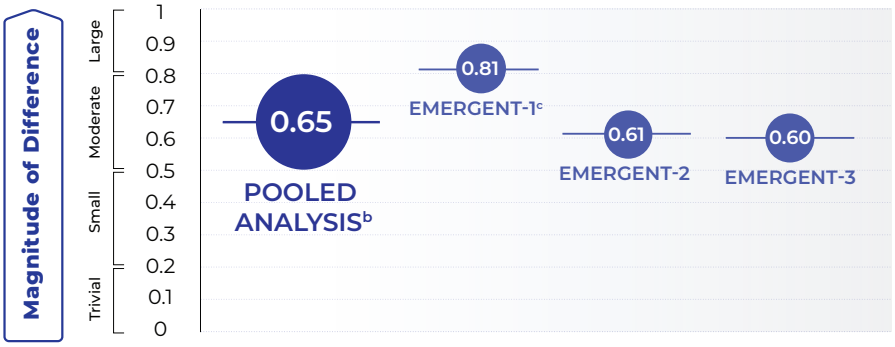
P<0.0001

EMERGENT-3[34,50]	
COBENFY (n=114)	Placebo (n=120)
-20.6	-12.2

P<0.0001

EMERGENT-1[38]	
COBENFY (n=83)	Placebo (n=87)
-17.4	-5.9

Effect Size of COBENFY (Total PANSS Reduction) Across 5-Week, Short-term Trials[33-35]



Effect Size[51]:

- Reflects the **magnitude of difference** in outcomes between an experimental arm and a control arm

Pooled endpoints and effect size were analyzed descriptively and are considered exploratory.

[a]Markedly Ill: Intrusive symptoms that distinctly impair social/occupational function or cause intrusive levels of distress. Approximately corresponds to a PANSS total score of 95. Moderately Ill: Overt symptoms causing noticeable, but modest, functional impairment or distress; symptom level may warrant medication. Approximately corresponds to a PANSS total score of 75. Mildly Ill: Clearly established symptoms with minimal, if any, distress or difficulty in social and occupational function. Approximately corresponds to a PANSS total score of 58.[52,53]

[b]Includes three 5-week EMERGENT clinical trials.[33]

[c]This updated effect size is calculated from a revised methodology based on mixed model for repeated measures (MMRM), and is consistent with calculations performed for EMERGENT-2 and -3.[33-35,38]

LS=least squares; Wk=week.

PANSS definition on page 27

WARNINGS AND PRECAUTIONS

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.

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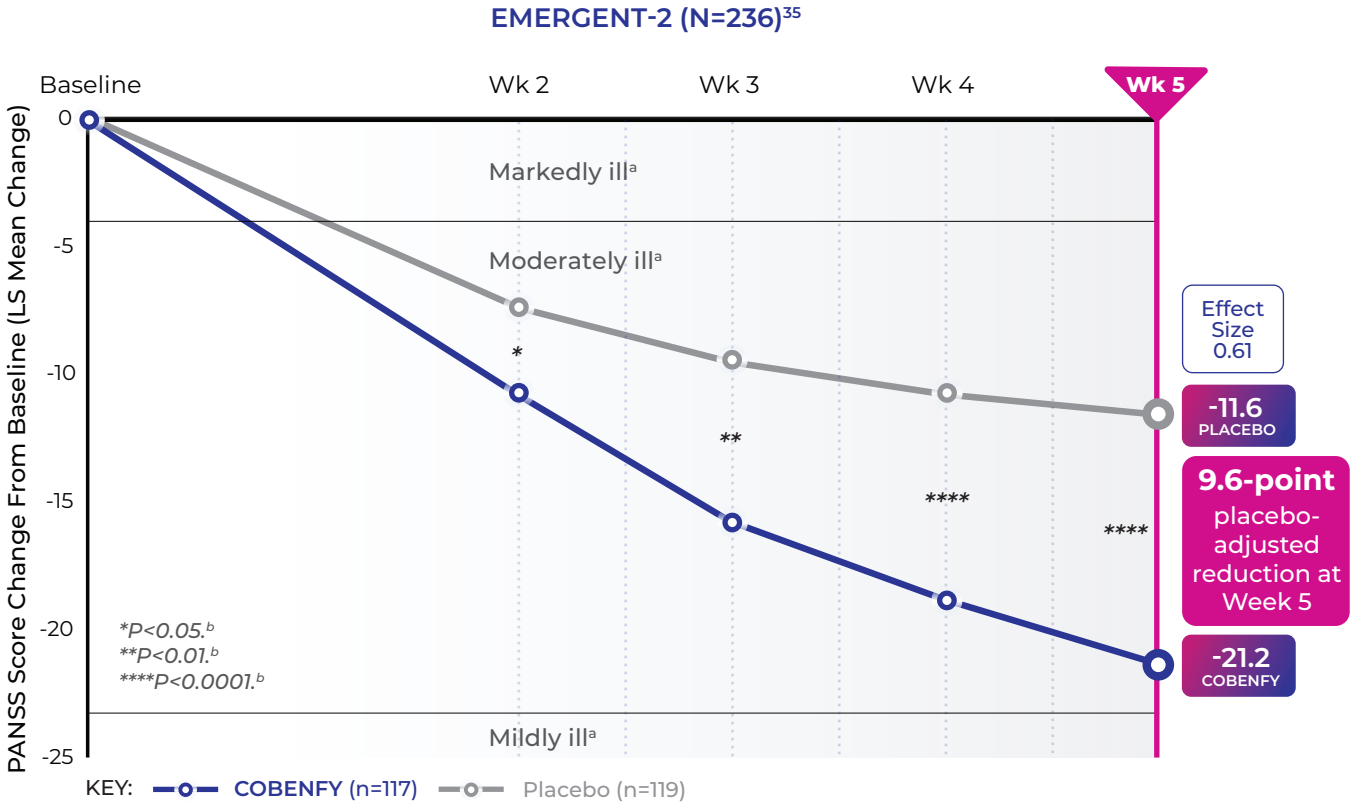
COBENFY Demonstrated Significant Improvement in PANSS Total Symptoms Score Across Each Short-term, Phase 3 Study: EMERGENT-2[35]



EMERGENT-1, a phase 2 trial, showed similar efficacy at Week 5[38] (PANSS: -17.4 COBENFY [n=83] vs -5.9 placebo [n=87])

Week 2-4 data were not prespecified clinical endpoints. *P* values are nominal. It is unknown if the statistically significant differences observed at time points earlier than Week 5 represent clinically relevant treatment effects.

[a]Markedly Ill: Intrusive symptoms that distinctly impair social/occupational function or cause intrusive levels of distress. Approximately corresponds to a PANSS total score of 95. Moderately Ill: Overt symptoms causing noticeable, but modest, functional impairment or distress; symptom level may warrant medication. Approximately corresponds to a PANSS total score of 75. Mildly Ill: Clearly established symptoms with minimal, if any, distress or difficulty in social and occupational function. Approximately corresponds to a PANSS total score of 58.[52,53]

[b]*P* values are nominal. It is unknown if the statistical difference observed at time points earlier than Week 5 represent clinically relevant treatment effects.[35]

WARNINGS AND PRECAUTIONS

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.

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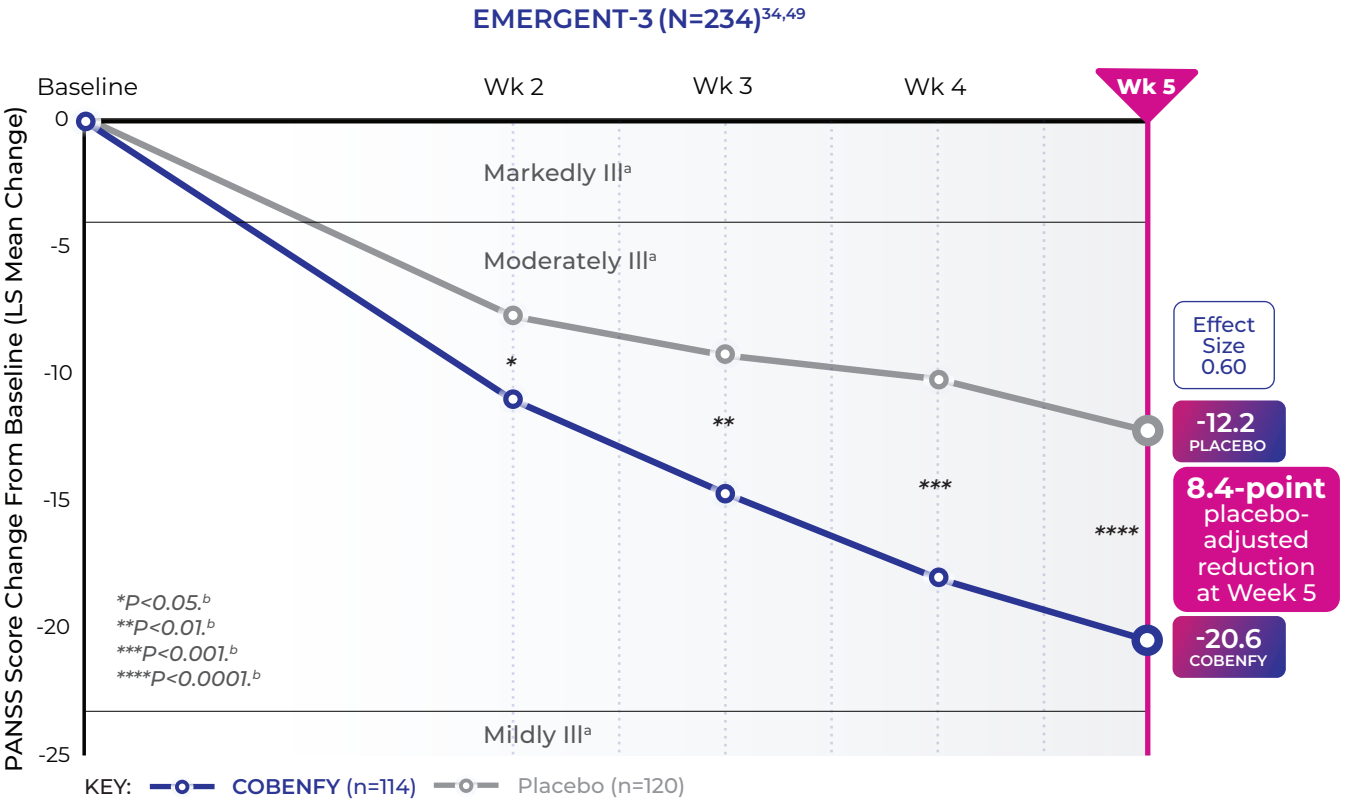
50mg/20mg, 100mg/20mg, 125mg/30mg

COBENFY Demonstrated Significant Improvement in PANSS Total Symptoms Score Across Each Short-term, Phase 3 Study: EMERGENT-3[34,49]



EMERGENT-1, a phase 2 trial, showed similar efficacy at Week 5[38] (PANSS: -17.4 COBENFY [n=83] vs -5.9 placebo [n=87])

Week 2-4 data were not prespecified clinical endpoints. *P* values are nominal. It is unknown if the statistically significant differences observed at time points earlier than Week 5 represent clinically relevant treatment effects.

[a]Markedly Ill: Intrusive symptoms that distinctly impair social/occupational function or cause intrusive levels of distress. Approximately corresponds to a PANSS total score of 95. Moderately Ill: Overt symptoms causing noticeable, but modest, functional impairment or distress; symptom level may warrant medication. Approximately corresponds to a PANSS total score of 75. Mildly Ill: Clearly established symptoms with minimal, if any, distress or difficulty in social and occupational function. Approximately corresponds to a PANSS total score of 58.[52,53]

[b]*P* values are nominal. It is unknown if the statistical difference observed at time points earlier than Week 5 represent clinically relevant treatment effects.[35]

WARNINGS AND PRECAUTIONS

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.

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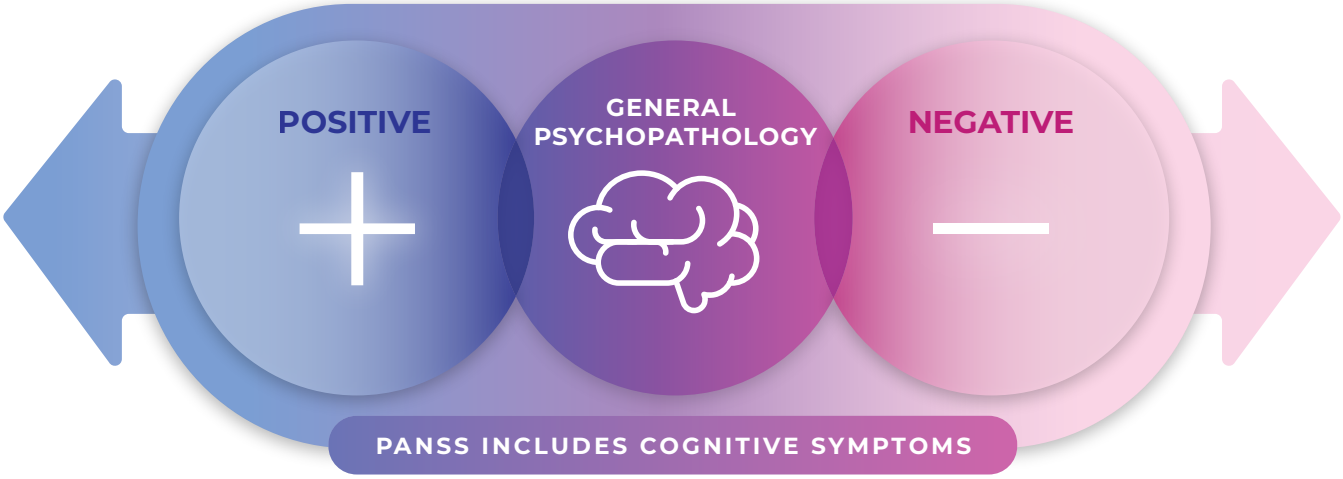
The PANSS Scale Measures Severity Across Positive Symptoms, Negative Symptoms, and General Psychopathology[52,54]



PANSS Scale Calculation[52,54]

Positive (~25%)

1. Delusions
2. Conceptual disorganization
3. Hallucinatory behavior
4. Excitement
5. Grandiosity
6. Suspiciousness/persecution
7. Hostility

Negative (~25%)

1. Blunted affect
2. Emotional withdrawal
3. Poor rapport
4. Passive/apathetic and social withdrawal
5. Difficulty in abstract thinking
6. Lack of spontaneity and flow of conversation
7. Stereotyped thinking

General Psychopathology (~50%)

1. Somatic concern
2. Anxiety
3. Guilt feelings
4. Tension
5. Mannerism and posturing
6. Depression
7. Motor retardation
8. Uncooperativeness
9. Unusual thought content
10. Disorientation
11. Poor attention
12. Lack of judgment and insight
13. Disturbance of volition
14. Poor impulse control
15. Preoccupation
16. Active social avoidance

Interpreting PANSS Total Score[52a]

210

95 to <116
markedly ill

75 to <95
moderately ill

58 to <75
mildly ill

30

[a]When interpreting the PANSS total score, "severely ill" corresponds to a score of 116 or higher.
Each subscale item is worth a maximum of 7 points. The maximum PANSS score across all 3 domains is 210 points.[52]

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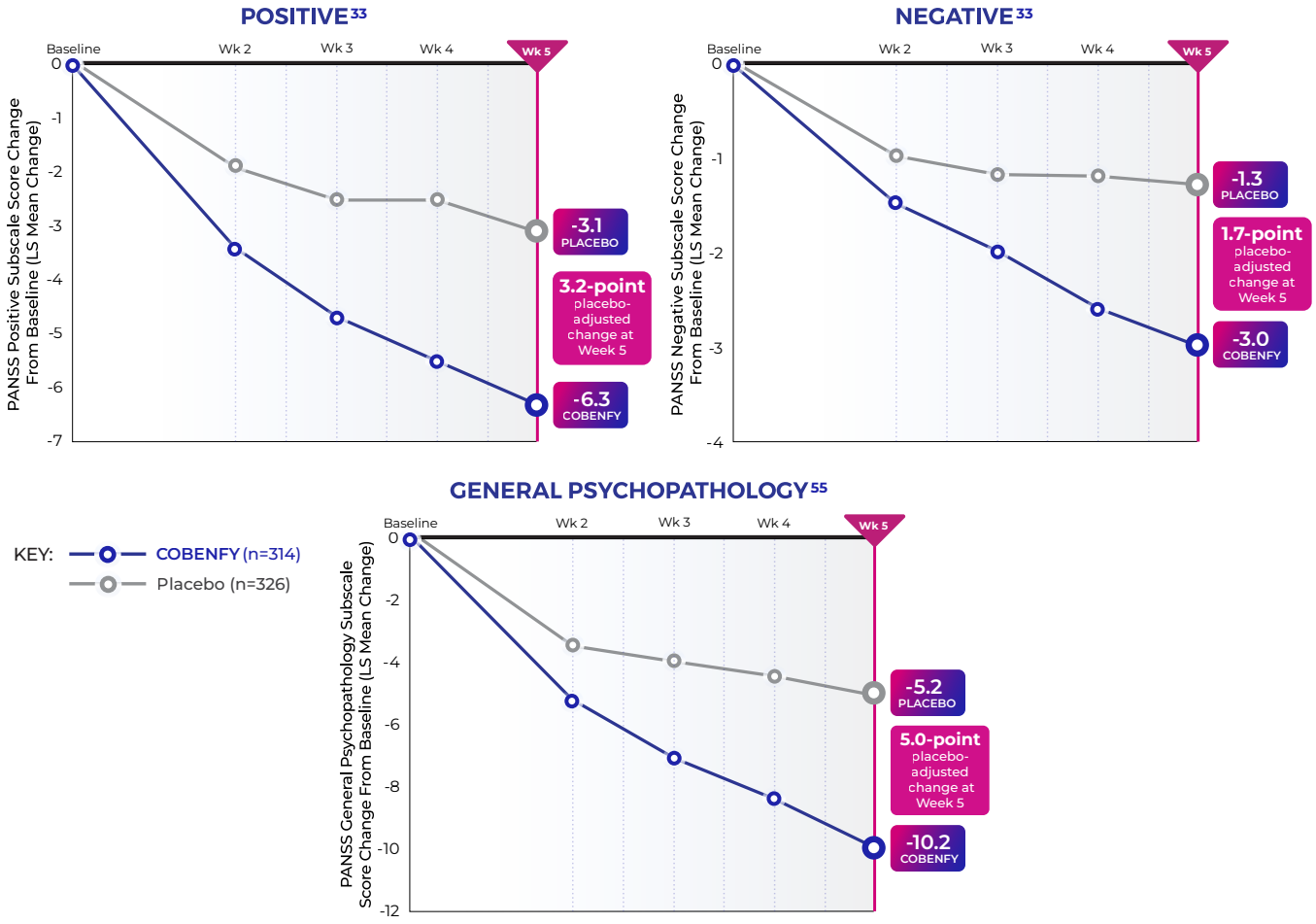
Change in Positive, Negative, and GPS Subscales at Week 5



	POSITIVE	NEGATIVE	GENERAL PSYCHOPATHOLOGY
EMERGENT-2[35,42]	**-6.8 COBENFY** -3.9 Placebo	**-3.4 COBENFY** -1.6 Placebo	**-11.6 COBENFY** -6.5 Placebo
EMERGENT-3[34,43,50]	**-7.1 COBENFY** -3.6 Placebo	**-2.7 COBENFY** -1.8 Placebo	**-10.5 COBENFY** -6.5 Placebo
EMERGENT-1[38,44]	**-5.6 COBENFY** -2.4 Placebo	**-3.2 COBENFY** -0.9 Placebo	**-9.4 COBENFY** -3.4 Placebo

- **Pooled data above is from a post hoc analysis of 3 short-term clinical trials[33]**
- **In EMERGENT trials, positive and negative subscales were prespecified; the GPS subscale was not. These results are exploratory due to the study design. Interpret individual subscale data with caution[35]**

GPS=general psychopathology scale.

WARNINGS AND PRECAUTIONS

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

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Derived from PANSS, the Marder Factor Model Established 5 Dimensions to Evaluate Change in Schizophrenia Symptoms and Severity[56,57]

Factor-analytic studies of PANSS reorganized and expanded symptom subscales of schizophrenia

Positive Symptoms
- Delusions
- Hallucinatory behavior
- Grandiosity
- Suspiciousness
- Stereotyped thinking
- Somatic concern
- Unusual thought content
- Lack of judgment and insight

Negative Symptoms
- Blunted affect
- Emotional withdrawal
- Poor rapport
- Passive social withdrawal
- Lack of spontaneity
- Motor retardation
- Active social avoidance

Prespecified endpoint

Uncontrolled Hostility/ Excitement
- Excitement
- Hostility
- Uncooperativeness
- Poor impulse control

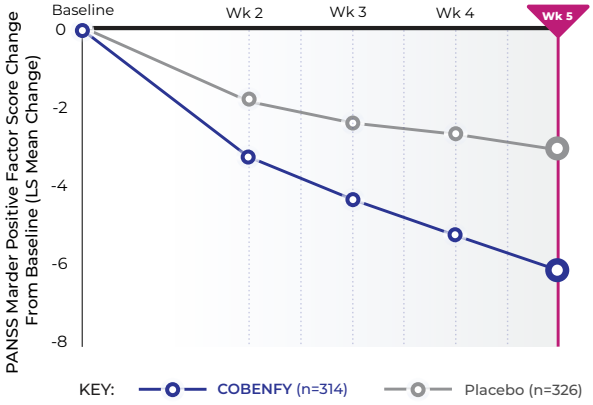
Disorganized Thought
- Conceptual disorganization
- Difficulty in abstract thinking
- Mannerisms and posturing
- Poor attention
- Disturbance of volition
- Preoccupation
- Disorientation

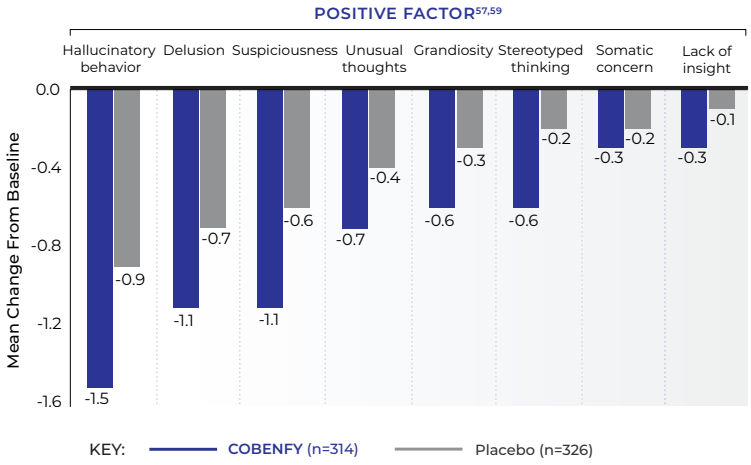
Anxiety/ Depression
- Anxiety
- Guilt
- Tension
- Depression

Each subscale item is worth a maximum of 7 points. Similar to PANSS, a higher score indicates greater symptom severity.[57]

PANSS Marder Factor Results: Positive[58]

Post hoc analysis of pooled data from EMERGENT-1, -2, and -3





Efficacy analyses performed using the mITT analysis set, defined as all randomized individuals who received ≥1 dose of trial medication and ≥1 postbaseline PANSS assessment (COBENFY n=314, placebo n=326).[60]

- **PANSS Marder positive factor score was not a prespecified endpoint in the EMERGENT clinical trials**
- **Pooled endpoints were analyzed descriptively and are considered exploratory. The trials were not designed to assess changes in individual symptoms**

mITT=modified intent-to-treat.

WARNINGS AND PRECAUTIONS

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).

Please see additional Important Safety Information throughout and U.S. Full Prescribing Information, including Patient Information here.

COBENFY™
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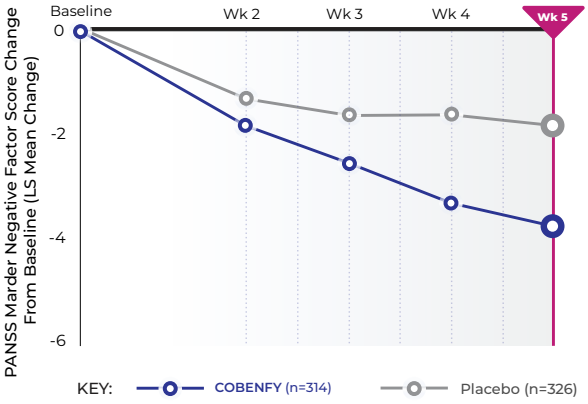
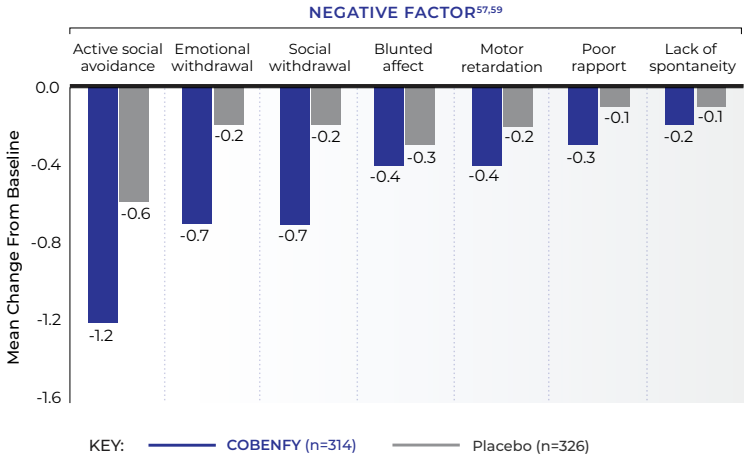
PANSS Marder Factor Results[58]

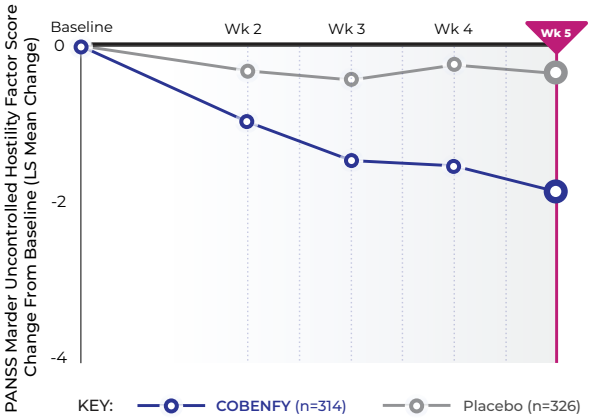
Post hoc analysis of pooled data from EMERGENT-1, -2, and -3

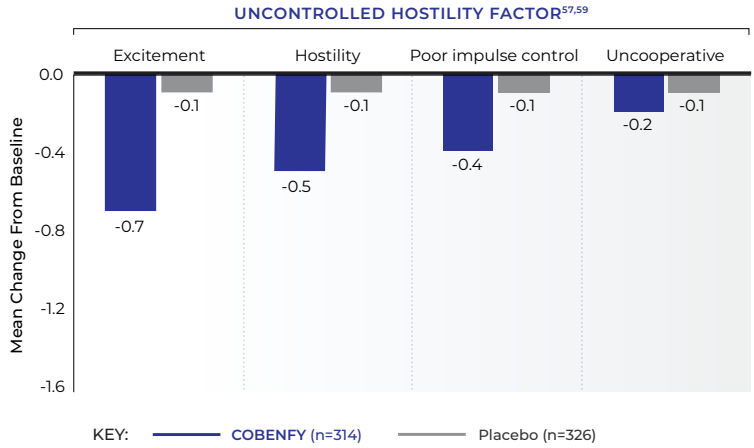
Negative[58]





Uncontrolled Hostility[58]





Efficacy analyses performed using the mITT analysis set, defined as all randomized individuals who received ≥1 dose of trial medication and ≥1 postbaseline PANSS assessment (COBENFY n=314, placebo n=326).[60]

- **PANSS Marder negative factor score was a prespecified endpoint and PANSS Marder uncontrolled hostility factor score was not a prespecified endpoint in the EMERGENT clinical trials**
- **Pooled endpoints were analyzed descriptively and are considered exploratory. The trials were not designed to assess changes in individual symptoms**

WARNINGS AND PRECAUTIONS

Anticholinergic Adverse Reactions in Patients with Renal Impairment (cont.): 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.

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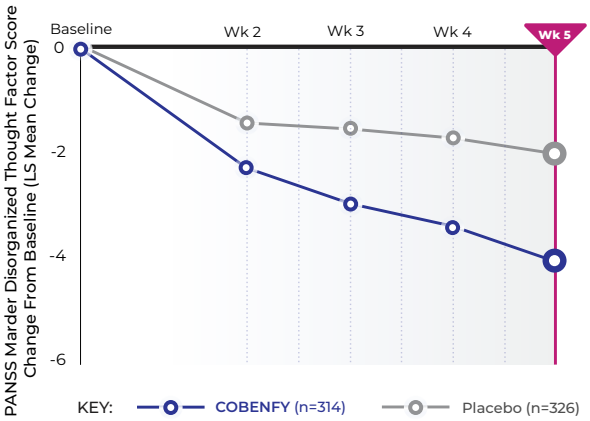
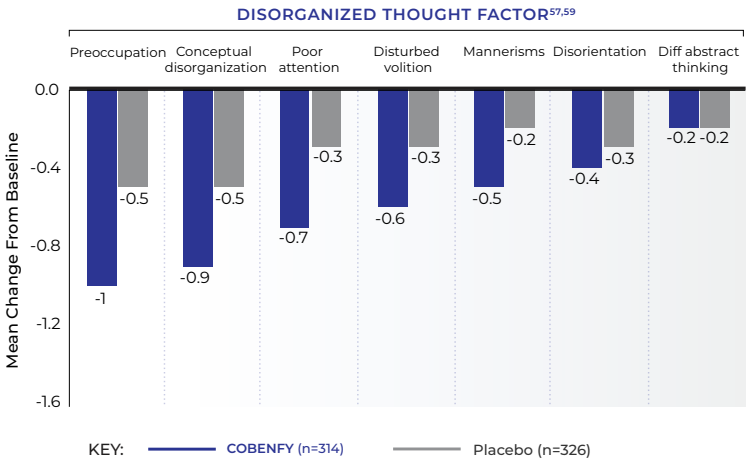
PANSS Marder Factor Results[58]

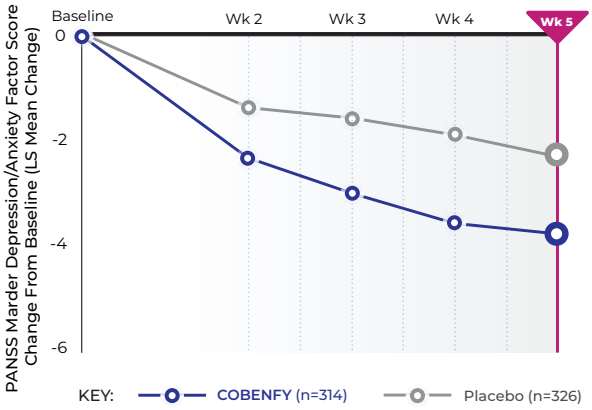
Post hoc analysis of pooled data from EMERGENT-1, -2, and -3

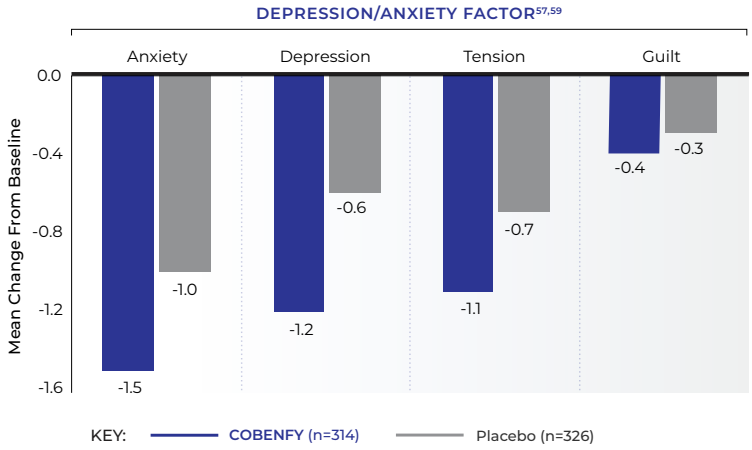
Disorganized Thought[58]





Depression/Anxiety[58]





Efficacy analyses performed using the mITT analysis set, defined as all randomized individuals who received ≥1 dose of trial medication and ≥1 postbaseline PANSS assessment (COBENFY n=314, placebo n=326).[60]

- **PANSS Marder disorganized thought and depression/anxiety factor scores were not prespecified endpoints in the EMERGENT clinical trials**
- **Pooled endpoints were analyzed descriptively and are considered exploratory. The trials were not designed to assess changes in individual symptoms**

Diff=difficulty.

WARNINGS AND PRECAUTIONS

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.

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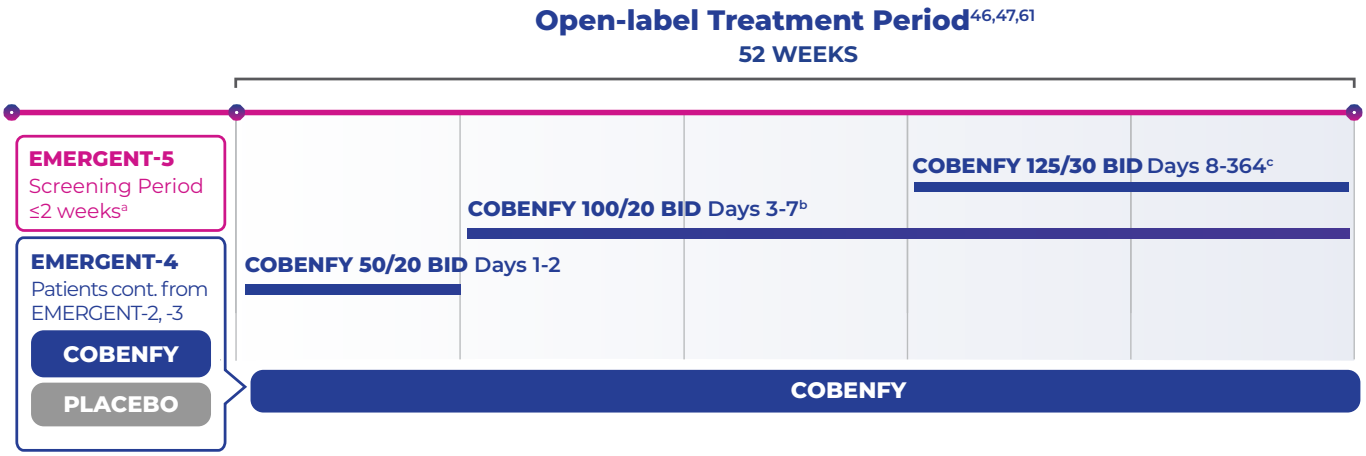
50mg/20mg, 100mg/20mg, 125mg/30mg

LONG-TERM DATA (OUTPATIENT)

EMERGENT-4 and EMERGENT-5 Study Designs[46,47,61]

Two open-label trials evaluating the long-term efficacy, safety, and tolerability of COBENFY



Primary Endpoint[46,47]

- Incidence of TEAEs

Select Secondary Outcome Measures[46,47]

- Incidence of serious TEAEs
- Incidence of TEAEs leading to withdrawal
- Change from baseline in PANSS total score; positive, negative, and Marder negative factor subscale; and CGI-S scores at Week 52
- Percentage of PANSS responders (≥30% change in PANSS total score) at Week 52

EMERGENT-2 and EMERGENT-3 patients transitioned from inpatient to outpatient and both the COBENFY arm and placebo arm were retitrated on COBENFY for EMERGENT-4[61]

COBENFY dose is expressed as xanomeline/trospium chloride (mg/mg).

[a]Screening period included a washout period in which oral D_2 treatments and certain other treatments were not permitted.[62]

[b]Optional increase in dose from 100 mg/20 mg, beginning at Day 8, based on clinical response and tolerability determined by a clinician.[46,47]

[c]Dose reduction to 100 mg/20 mg BID was permitted as necessary based on clinical response and tolerability.[46,47]

WARNINGS AND PRECAUTIONS

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

Use in Specific Populations:

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

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EMERGENT-4 and EMERGENT-5 Inclusion and Exclusion Criteria[46,47a]

Select Inclusion Criteria

- **EMERGENT-4 ONLY:** Completed the EMERGENT-2 and EMERGENT-3 5-week, double-blind, placebo-controlled efficacy and safety studies
- **EMERGENT-5 ONLY:**
  - PANSS total score ≤80 at screening
  - CGI-S score ≤4 at screening and baseline

- 18 to 65 years of age at screening
- Receiving an oral antipsychotic medication daily as maintenance therapy at screening

Select Exclusion Criteria

- **EMERGENT-4 ONLY:** Any clinically significant abnormality at the end of treatment visits in the EMERGENT-2 and EMERGENT-3 trials that, in the opinion of the investigator, in consultation with the medical monitor, would jeopardize the safety of the subject

- Psychiatric hospitalization, acute crisis intervention, or other increase in level of care due to symptom exacerbation within 8 weeks of screening and is psychiatrically unstable, in investigator's opinion
- Risk for suicidal behavior during the study, determined by the investigator's clinical assessment and Columbia-Suicide Severity Rating Scale (C-SSRS)
- Subject is unsuitable for enrollment in the study or has any finding that, in the view of the investigator (and/or sponsor), may compromise the safety of the subject or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements

[a]Not full list of inclusion and exclusion criteria. EMERGENT-4 eligibility included completed treatment period in EMERGENT-2 or EMERGENT-3.

WARNINGS AND PRECAUTIONS

Pregnancy and Lactation: There is a pregnancy exposure registry that monitors outcomes in women exposed to psychiatric medications, including COBENFY, during pregnancy. Healthcare providers are encouraged to advise patients to register by calling 1-866-961-2388 or visiting https://womensmentalhealth.org/research/pregnancyregistry/atypicalantipsychotic/.

There are no available data on COBENFY use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Additionally, there are no data on the presence of xanomeline or trospium in human milk, the effects on the breastfed infant, or the effects on milk production. However, xanomeline and trospium are present in animal milk, suggesting they may also be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COBENFY and any potential adverse effects on the breastfed infant from COBENFY or the underlying maternal condition.

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

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Baseline Characteristics and Trial Population[61,62]

Pooled EMERGENT-4 and EMERGENT-5

CHARACTERISTIC	COBENFY (N=718)
Age, years, mean ±SD	46.9±11.8
Sex, n (%)	
Male	489 (68.1)
Female	229 (31.9)
Race, n (%)	
American Indian or Alaskan Native	1 (0.1)
Asian	6 (0.8)
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
Completed, n (%)	337 (46.9)
Discontinued, n (%)	381 (53.1)
Reason for discontinuation, n (%)	
Consent withdrawn	134 (18.7)
Adverse events	107 (14.9)
Lost to follow-up	59 (8.2)
Participant failed to adhere to protocol requirement	53 (7.4)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

COBENFY™ is contraindicated in patients with: urinary retention; moderate or severe (Child-Pugh Class B or C) hepatic impairment; gastric retention; history of hypersensitivity to COBENFY or trospium chloride—angioedema has been reported with COBENFY and trospium chloride; and untreated narrow-angle glaucoma.

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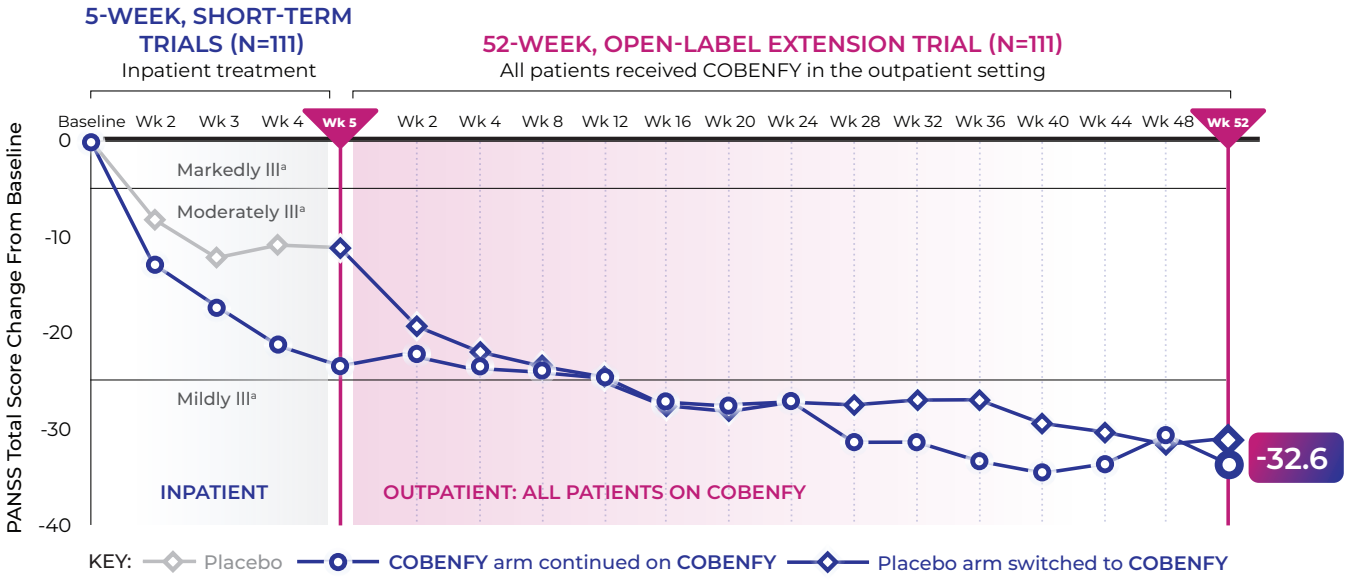
EMERGENT-4

Continued Symptom Improvement Over 52 Weeks[63]

Reductions from baseline of 23.2 points at Week 5 and 32.6 points at Week 52 in PANSS total score[64]



69% of patients achieved ≥30% improvement in PANSS total score[63,64]

- **Endpoints in the open-label extension trial were analyzed descriptively**
- **Patients who completed the EMERGENT-2 or EMERGENT-3 COBENFY treatment arms were retitrated on COBENFY at the start of EMERGENT-4[63]**

[a]Markedly Ill: Intrusive symptoms that distinctly impair social/occupational function or cause intrusive levels of distress. Approximately corresponds to a PANSS total score of 95. Moderately Ill: Overt symptoms causing noticeable, but modest, functional impairment or distress; symptom level may warrant medication. Approximately corresponds to a PANSS total score of 75. Mildly Ill: Clearly established symptoms with minimal, if any, distress or difficulty in social and occupational function. Approximately corresponds to a PANSS total score of 58.[52,53]

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.

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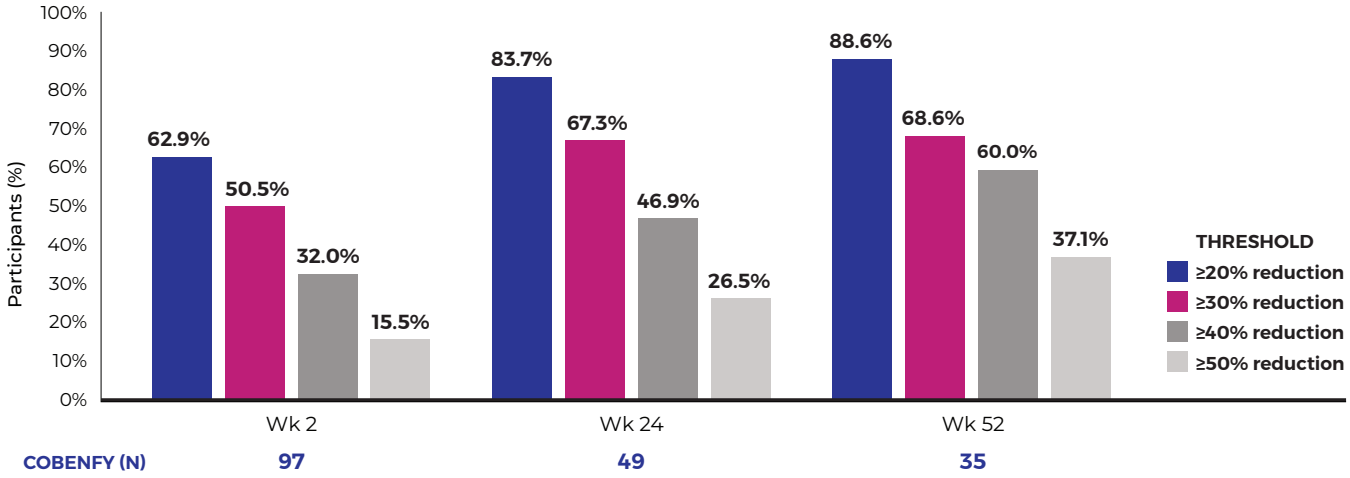
Responder Analyses in the EMERGENT-4 Study Evaluated the Long-term Efficacy of COBENFY[63]

Post hoc analyses of EMERGENT-4 long-term, phase 3, open-label study

Change in PANSS Total Score From Short-term Trial Baseline (N=111)



37% of participants achieved a ≥50% reduction in floor-adjusted PANSS score from short-term baseline at 52 weeks[a]

- Endpoints in the open-label extension trial were analyzed descriptively
- PANSS responders were defined as a proportion of participants with ≥30% reduction in floor-adjusted PANSS total score from short-term baseline at Week 52. Our results are exploratory due to the design of the study
- Results of EMERGENT-4 may reflect benefit patients received in PANSS score reductions relative to the acute trial baseline due to participation in EMERGENT-2 and EMERGENT-3 trials
- Data at Weeks 1-4 were not prespecified efficacy endpoints in the EMERGENT-2 and EMERGENT-3 trials[39]

[a]The floor-adjusted total score is the total PANSS score minus 30. When a significant proportion of participant scores are concentrated at the lower end of the scale range, floor adjusting spreads the scores out to show greater response variability.[65,66]

WARNINGS AND PRECAUTIONS

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.

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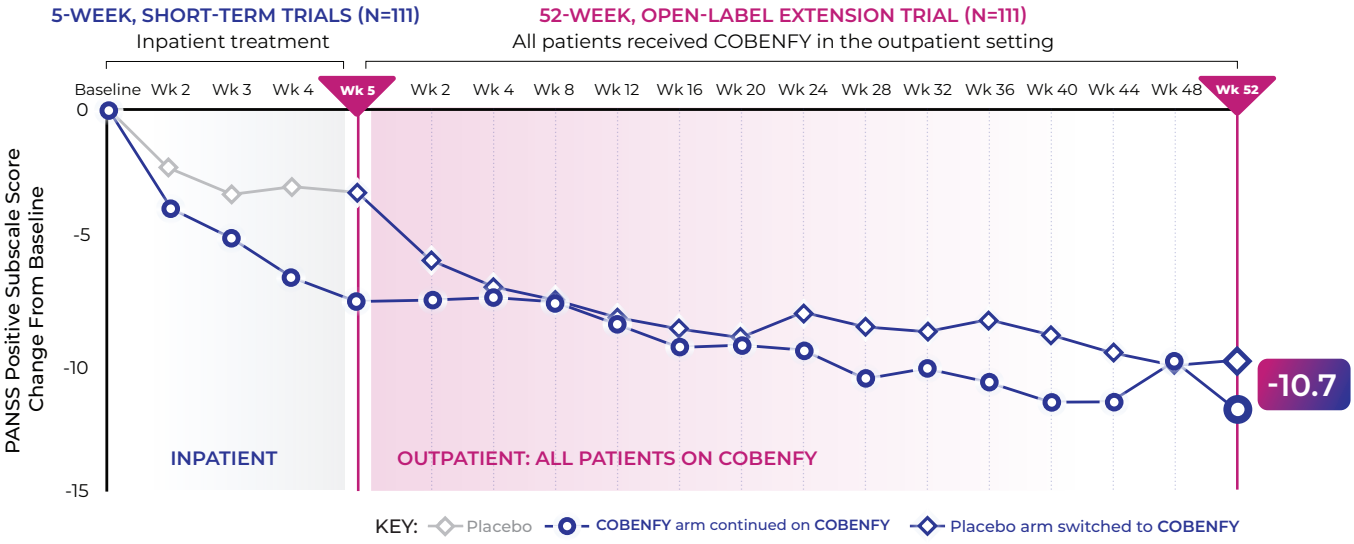
EMERGENT-4

PANSS Positive Subscale Results[39,64]

Secondary endpoint: Change in mean PANSS positive subscale score overall from baseline to Week 52



After the 5-week trials, all participants received COBENFY for up to 52 weeks.[39]

- In EMERGENT trials, positive and negative subscales were prespecified; the GPS subscale was not. These results are exploratory due to the study design. Interpret individual subscale data with caution
- Patients who completed the EMERGENT-2 or EMERGENT-3 COBENFY treatment arms were retitrated on COBENFY at the start of EMERGENT-4[39]

WARNINGS AND PRECAUTIONS

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.

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.

Please see additional Important Safety Information throughout and U.S. Full Prescribing Information, including Patient Information here.

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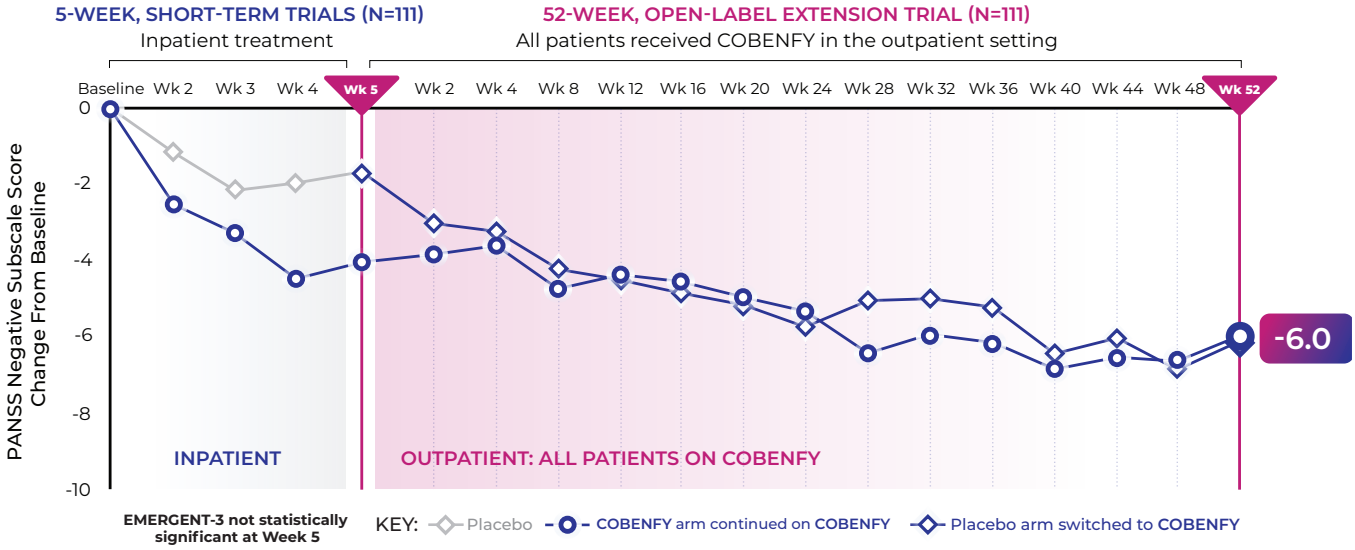
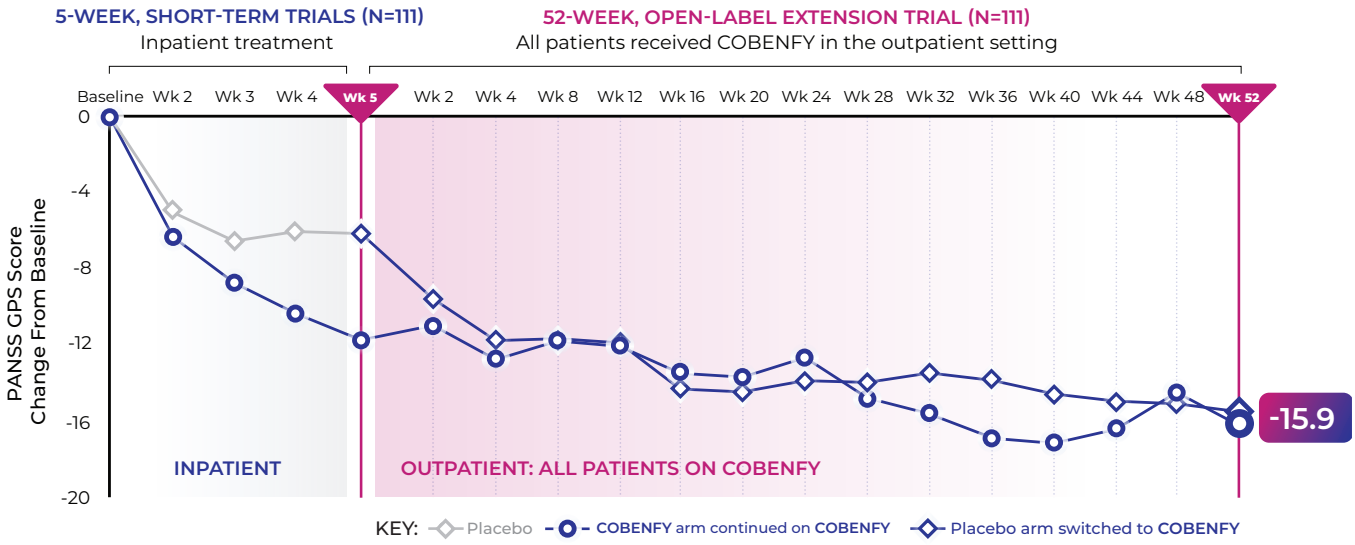
PANSS Negative Subscale Results[39,64]

Secondary endpoint: Change in mean PANSS negative subscale score overall from baseline to Week 52



PANSS General Psychopathology Scale Results[40,41]

Exploratory endpoint: Change in mean PANSS GPS score overall from baseline to Week 52



- In EMERGENT trials, positive and negative subscales were prespecified; the GPS subscale was not. These results are exploratory due to the study design. Interpret individual subscale data with caution
- Patients who completed the EMERGENT-2 or EMERGENT-3 COBENFY treatment arms were retitrated on COBENFY at the start of EMERGENT-4[39]

WARNINGS AND PRECAUTIONS

Decreased Gastrointestinal Motility (cont.): Use COBENFY with caution in patients with conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis.

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SAFETY AND TOLERABILITY

UNIQUE SAFETY PROFILE

Demonstrated In Over 1250 Patients Across 5 Clinical Trials

NO WARNINGS OR PRECAUTIONS FOR[31]:

Metabolic changes, including weight gain

Tardive dyskinesia

Orthostatic hypotension or syncope

QTc prolongation

Hyperprolactinemia

NO BOXED WARNING[31]

COBENFY has warnings and precautions for[31]:

- Risk of urinary retention
- Risk of use in patients with hepatic impairment
- Risk of use in patients with biliary disease
- Decreased gastrointestinal motility
- Risk of angioedema
- Risk of use in patients with narrow-angle glaucoma
- Increases in heart rate
- Anticholinergic adverse reactions in patients with renal impairment
- Central nervous system effects

QTc=heart-rate corrected QT interval.

WARNINGS AND PRECAUTIONS

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.

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Unique Safety Profile[31]

Demonstrated Safety and Tolerability Profile for COBENFY

Adverse Reactions Reported in ≥2% of COBENFY-Treated Patients and Greater Than Rate of Placebo in the Phase 3 Trials (EMERGENT-2, -3)[31]

ADVERSE REACTIONS	COBENFY (n=251)	Placebo (n=253)
Nausea	19%	4%
Dyspepsia[a]	18%	5%
Constipation	17%	7%
Vomiting	15%	1%
Hypertension[b]	11%	2%
Abdominal pain[c]	8%	4%
Diarrhea	6%	2%
Tachycardia[d]	5%	2%
Dizziness	5%	2%
Gastroesophageal reflux disease	5%	<1%
Dry mouth	4%	2%
Somnolence	3%	2%
Vision blurred	3%	0%
Salivary hypersecretion	2%	0%
Orthostatic hypotension	2%	1%
Cough[e]	2%	1%
Extrapyramidal symptoms, non-akathisia[f]	2%	<1%

Overall discontinuation rates due to adverse reactions were similar between COBENFY (6%) and placebo (4%)[31]

[a]Dyspepsia includes dyspepsia and esophageal discomfort.
[b]Hypertension includes hypertension, blood pressure increased, labile hypertension, and orthostatic hypertension.
[c]Abdominal pain includes abdominal discomfort, abdominal pain upper, abdominal pain, abdominal pain lower, and abdominal tenderness.
[d]Tachycardia includes tachycardia, heart rate increased, and sinus tachycardia.
[e]Cough includes cough and productive cough.
[f]EPS (non-akathisia) includes dyskinesia, drooling, dystonia, extrapyramidal disorder, muscle contraction involuntary, and muscle spasms.

WARNINGS AND PRECAUTIONS

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.

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Metabolic Data From Short-term and Long-term Trials

In short-term studies, the incidence of certain metabolic side effects was low. In long-term studies over 52 weeks, the majority of patients did not experience clinically significant weight gain.[67,68]

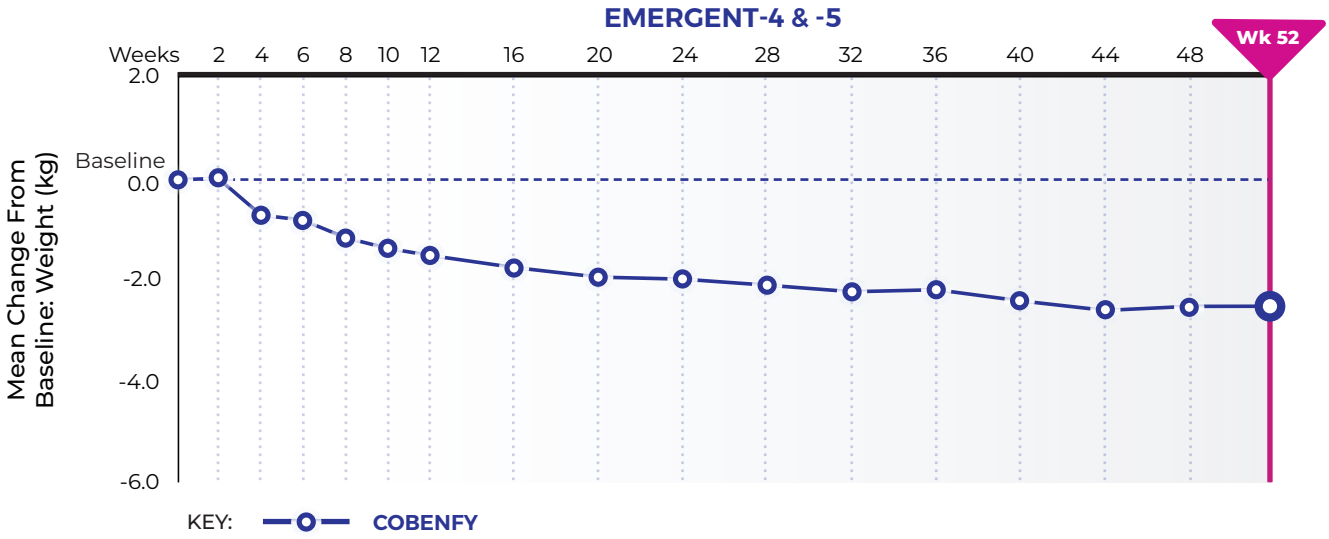
Shifts From Baseline to Endpoint in EMERGENT-1, -2, & -3 (pooled data)[67]

Fasting glucose	From normal to impaired: 1.8% vs 1.7% for placebo	Proportion of metabolic shifts was similar to placebo
Total cholesterol	From borderline to high: 6.8% vs 5.1% for placebo	
Fasting triglycerides	From borderline to high: 0.7% vs 1.7% for placebo	
Prolactin	+0.75 µg/L vs -1.38 µg/L for placebo	No meaningful increase in mean levels

Patients had a mean decrease in prolactin levels of -3.1+/-0.88 µg/L from baseline to Week 52 in EMERGENT-4 and -5[67]

~96% of patients did not experience clinically significant weight gain (≥7%)[68]

Weight Change Over the 52-Week Treatment Period (pooled long-term data)[68]



On average, patients lost 4.7 lbs in the year-long, open-label trials.[68]

- 17.6% of patients had a decrease in body weight of ≥7%
- 4.1% of patients had an increase in body weight of ≥7%

WARNINGS AND PRECAUTIONS

Anticholinergic Adverse Reactions in Patients with Renal Impairment: Trospium chloride, a component of COBENFY, is substantially excreted by the kidney.

Please see additional Important Safety Information throughout and U.S. Full Prescribing Information, including Patient Information here.

COBENFY™
(xanomeline and trospium chloride) capsules
50mg/20mg, 100mg/20mg, 125mg/30mg

Movement Disorder Data From Short-term and Long-term Trials

Data From Short-term and Long-term Trial[69,70]

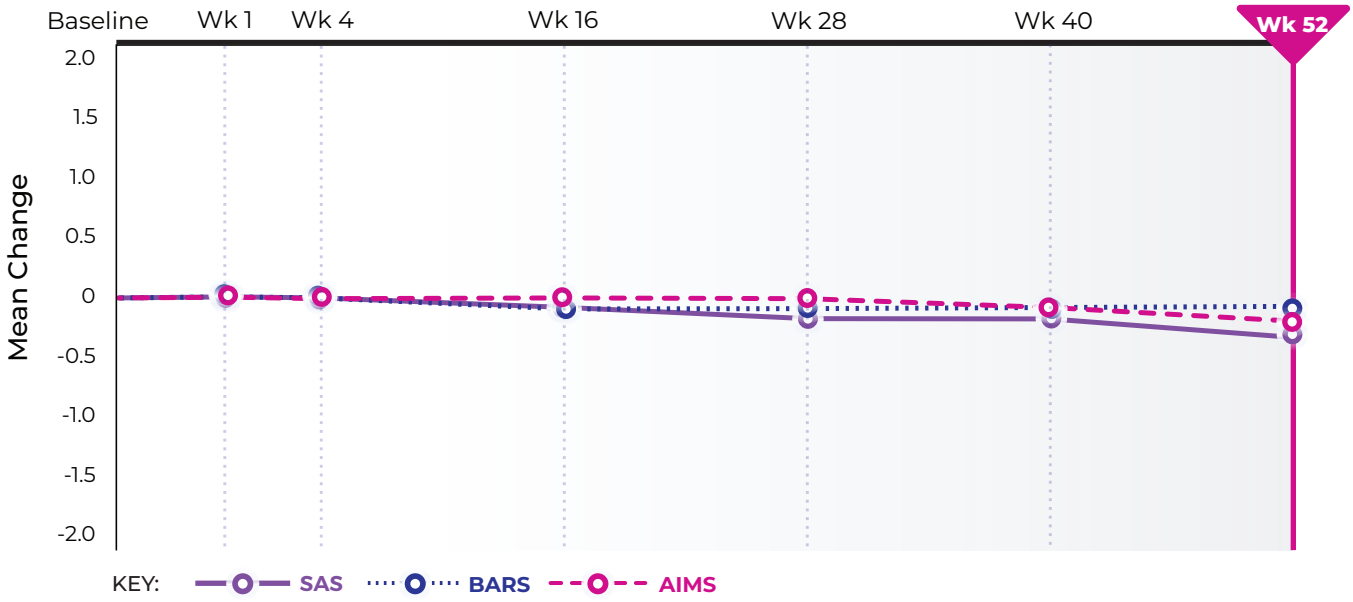
EPS REPORTED AS TEAEs[a]	COBENFY 5-week (N=340)	Placebo 5-week (N=343)	COBENFY 52-week (N=718)
≥1 EPS events	3.8%	1.5%	3.2%
Akathisia	2.4%	0.9%	1.0%
Drooling	0.3%	0%	0.6%
Tremor	0%	0%	0.4%
Restlessness	0%	0.3%	0.6%
Tardive dyskinesia	0%	0%	0.3%
Dyskinesia	0.3%	0%	0.1%
Muscle spasms	0.3%	0%	0.3%
Extrapyramidal disorder	0.3%	0%	0%
Dystonia	0.3%	0%	0%

<4% reported ≥1 EPS TEAEs

Mean change across movement disorder scales (AIMS, BARS, SAS) was -0.2; **<1% discontinued** due to EPS[69,70]

Movement Disorders With COBENFY (Pooled Long-term Data)[71-73]

EMERGENT-4 & -5



Movement scales assessing movement disorders were stable over 52 weeks.[74]

[a]The data table above does not include EPS events that had an incidence of less than 0.3% at 5 and 52 weeks.[69]

AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; msec=milliseconds; SAS=Simpson-Angus Scale.

WARNINGS AND PRECAUTIONS

Anticholinergic Adverse Reactions in Patients with Renal Impairment (cont.): 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.

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50mg/20mg, 100mg/20mg, 125mg/30mg

Cardiovascular Data From Short-term and Long-term Trials

Pooled Cardiovascular TEAE Incidence From EMERGENT-2 & -3[31,67]

VARIABLE		COBENFY (n=251)	Placebo (n=253)
BLOOD PRESSURE	Any hypertension TEAE[a]	11%	2%
	Hypertension	8%	1%
	Blood pressure increased	2%	<0.5%
	Labile hypertension	1%	0%
	Orthostatic hypertension	0%	<0.5%
	Orthostatic hypotension	2%	1%

- In two phase 3, short-term trials, COBENFY was associated with a mean increase from baseline of 1.5 mmHg SBP and 2.3 mmHg DBP at Week 5[75]
- In two 52-week studies, the average change in SBP and DBP from baseline to 52 weeks was +0.9 mmHg and +1.4 mmHg, respectively[67]
- **In two phase 3, short-term trials, no syncope events were reported in any subjects[67]**
- **In two 52-week studies, syncope events were reported by patients treated with COBENFY 4 times (0.47)[67]**

HEART RATE	Any tachycardia TEAE[b]	5%	2%
	Tachycardia	2%	1%
	Heart rate increased	3%	1%
	Sinus tachycardia	<0.5%	0%

- In two phase 3, short-term trials, COBENFY was associated with an increase in heart rate of 5.9 BPM vs placebo[31c]
- In two 52-week studies, the average change in heart rate from baseline to 52 weeks was +1.7 BPM[67]
- **In two phase 3, short-term trials, at the maximum recommended dosage of 125 mg/30 mg twice daily, COBENFY did not prolong the QT interval to any clinically relevant extent[34,35]**

[a]Hypertension includes hypertension, blood pressure increased, labile hypertension, and orthostatic hypertension.[31]
[b]Tachycardia includes tachycardia, heart rate increased, and sinus tachycardia.[31]
[c]Assess heart rate at baseline and as clinically indicated during treatment.[31]
BPM=beats per minute; DBP=diastolic blood pressure; mmHg=millimeters of mercury; SBP=systolic blood pressure.

WARNINGS AND PRECAUTIONS

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.

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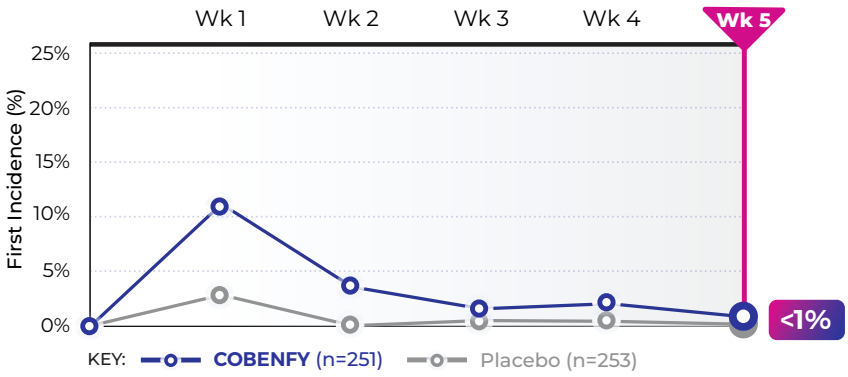
Initial Onset of Nausea and Vomiting Was Transient[76,77a]

Nausea[76]

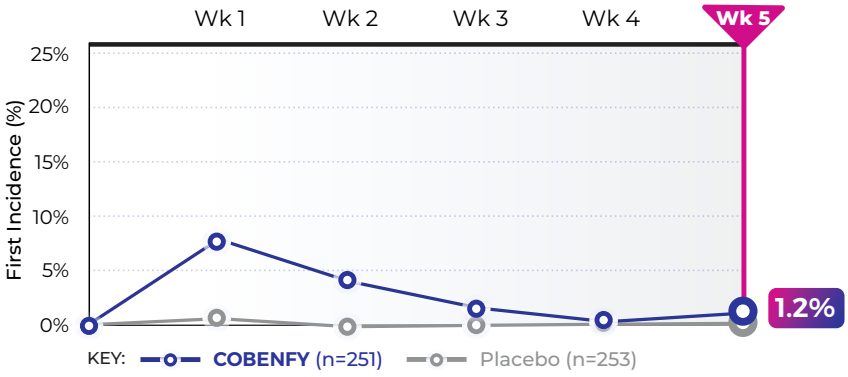
(EMERGENT-2 & -3)



- Mean duration was 12.9 days vs 5.6 for placebo[77]
- Discontinuation rate was 2% vs 0% for placebo[78]

Vomiting[76]

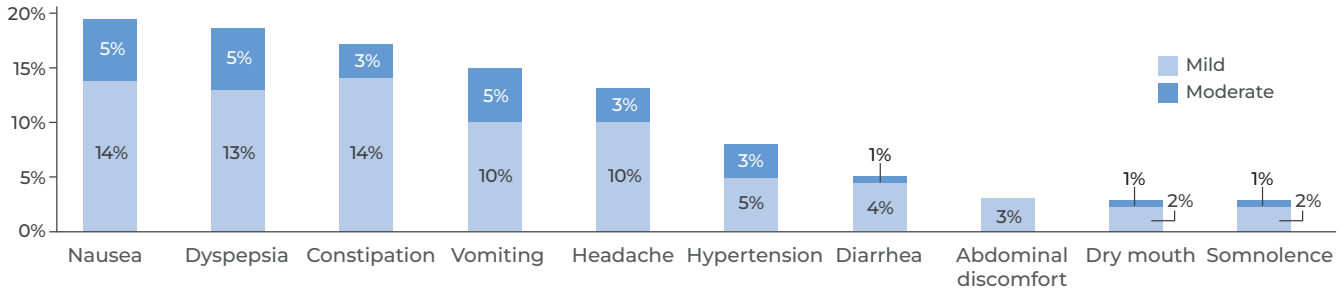
(EMERGENT-2 & -3)



- Mean duration was 2.5 days vs 6.5 for placebo[77]
- Discontinuation rate was 1.2% vs 0% for placebo[78]

The Majority of Cholinergic Adverse Events Were Characterized as Mild[79]

Intensity of Common Cholinergic Adverse Events in EMERGENT-2 & -3 (n=251)



Antiemetics were allowed across clinical trials; 4% of patients in the short-term trials used antiemetics (mostly ondansetron)[80]

[a]Safety population defined as all participants who received ≥1 dose of trial medication.

WARNINGS AND PRECAUTIONS

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

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The Safety and Tolerability Profile of COBENFY Remained Consistent Over 52 Weeks[39]

EMERGENT-4 was an open-label extension of EMERGENT-2 & -3 involving patients from both the COBENFY and placebo groups[39]

TEAE Incidence From EMERGENT-4[39]

ADVERSE EVENT[a]	COBENFY-naïve (n=84)	COBENFY-experienced (n=68)
Any TEAE	54%	**53%**
Nausea	10%	**9%**
Vomiting	12%	**3%**
Dyspepsia[b]	6%	**6%**
Dry mouth	6%	**4%**
Hypertension[c]	6%	**4%**
Constipation	2%	**4%**
Weight increased	4%	**3%**
Diarrhea	2%	**3%**
Gastroesophageal reflux disease	2%	**3%**
Dizziness	2%	**3%**
Headache	2%	**2%**
Somnolence	1%	**3%**

TEAEs led to discontinuation in <15% of participants in this long-term, open-label trial[39]

[a] Adverse event severity was determined by the investigator's clinical judgment, as specified in the clinical trial protocol.[41]
[b] Dyspepsia includes dyspepsia and esophageal discomfort.[31]
[c] Hypertension includes hypertension, blood pressure increased, labile hypertension, and orthostatic hypertension.[31]

WARNINGS AND PRECAUTIONS

Use in Specific Populations:

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

Pregnancy and Lactation: There is a pregnancy exposure registry that monitors outcomes in women exposed to psychiatric medications, including COBENFY, during pregnancy. Healthcare providers are encouraged to advise patients to register by calling 1-866-961-2388 or visiting https://womensmentalhealth.org/research/pregnancyregistry/atypicalantipsychotic/.

There are no available data on COBENFY use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Additionally, there are no data on the presence of xanomeline or trospium in human milk, the effects on the breastfed infant, or the effects on milk production. However, xanomeline and trospium are present in animal milk, suggesting they may also be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COBENFY and any potential adverse effects on the breastfed infant from COBENFY or the underlying maternal condition.

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PRODUCT PROFILE

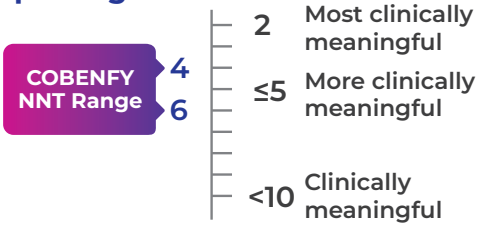
Post Hoc Analysis of EMERGENT Trials-1, -2, & -3

COBENFY Number Needed to Treat (NNT) Range: 4-6[81-83ab]

Importance of NNT[84]

- NNT helps the clinician assess the clinical relevance of a statistically significant result
- NNT reflects the number of people needed to be treated with Intervention A vs Intervention B before one additional positive outcome of interest is encountered, such as a therapeutic response

Interpreting NNT[81-83c]



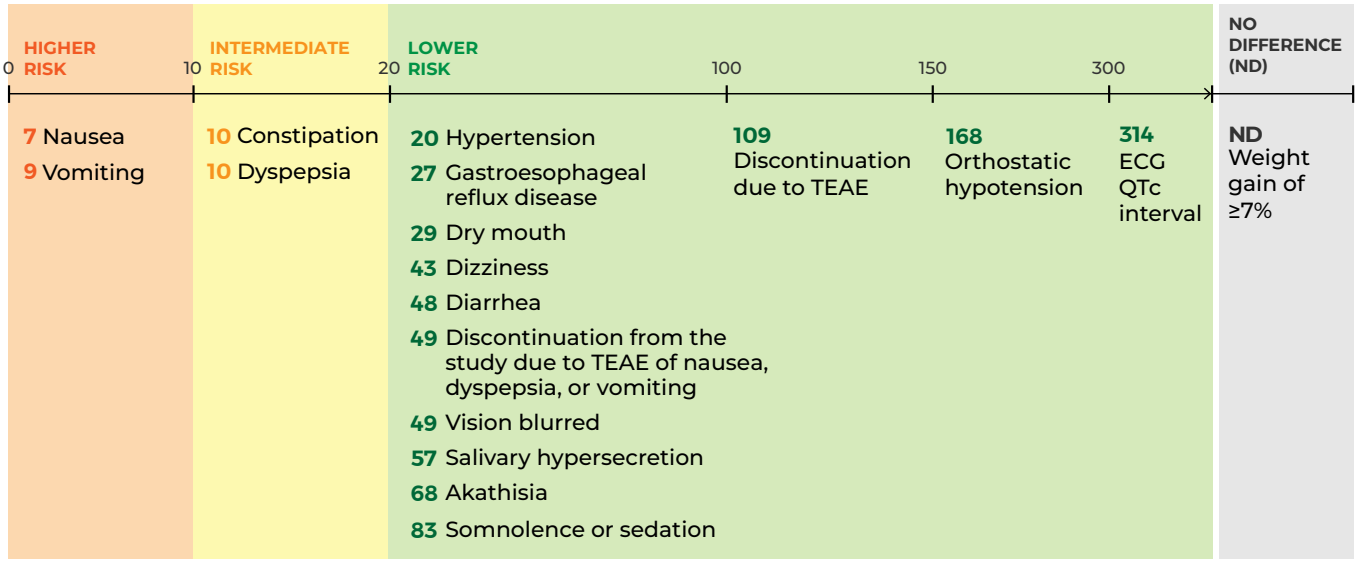
- A smaller NNT means fewer patients need to be treated for one patient to benefit[84]

COBENFY Number Needed to Harm (NNH) Due to Discontinuation From a Treatment-Emergent Adverse Event (TEAE): 109[85,86d]

Importance of NNH

- NNH helps the clinician assess the clinical relevance of tolerability-related outcomes[86,87]
- NNH reflects the number of patients who must be treated with Intervention A instead of Intervention B to encounter one additional adverse outcome of interest[85]

COBENFY NNH risk of an undesirable outcome[85,86e]



Post hoc analysis to investigate the efficacy and tolerability of COBENFY in adults with an acute exacerbation of schizophrenia using the metrics of NNT, NNH and likelihood to be helped or harmed (LHH).

[a]Value range across EMERGENT-1, -2, and -3 total PANSS score. NNT: EMERGENT-1 (4), EMERGENT-2 (6), EMERGENT-3 (6).[86]
[b]For the outcome of ≥30% reduction from baseline on the total PANSS score. The NNTs were ≤10 at endpoint for most other efficacy outcomes.[85]
[c]Scale provided as general interpretation only. Multiple factors and clinical contexts can impact the clinical meaningfulness of reported NNTs.[85]
[d]NNH estimates for most TEAEs were ≥10. NNH estimates for nausea and vomiting were <10; however, the NNH estimate based on discontinuation due to a TEAE of nausea, dyspepsia, or vomiting was 49, and the NNH estimate based on dose reductions due to the same TEAEs was 170 and non-significant compared with placebo. NNH estimates based on metabolic and clinical laboratory outcomes either exceeded 10 or the event rate was higher with placebo than with COBENFY, resulting in negative NNH values.[85]
[e]The short duration (5 weeks) prevents examining of NNH for TEAEs that manifest after prolonged treatment. Applicability of these results beyond the research environment is uncertain; individuals living with schizophrenia in the general population typically differ from those individuals who meet the strict inclusion and exclusion criteria for participation in clinical trials; also, participants discontinue clinical trials for myriad and complex reasons and, as such, the NNH estimates of discontinuation due to TEAEs may not accurately reflect tolerability in a clinical setting.[85]
ECG=electrocardiogram.

WARNINGS AND PRECAUTIONS

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

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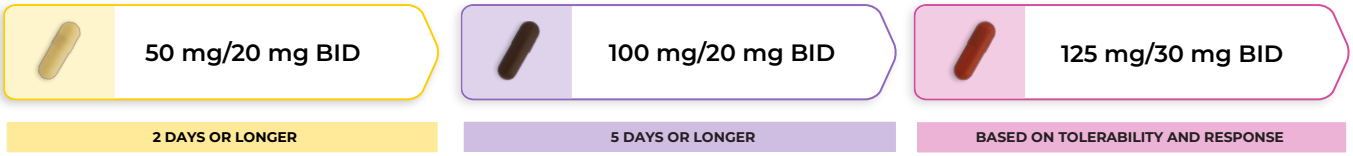
COBENFY™
(xanomeline and trospium chloride) capsules
50mg/20mg, 100mg/20mg, 125mg/30mg

A Therapeutic Dose for COBENFY Can Be Achieved By Day 3[31]

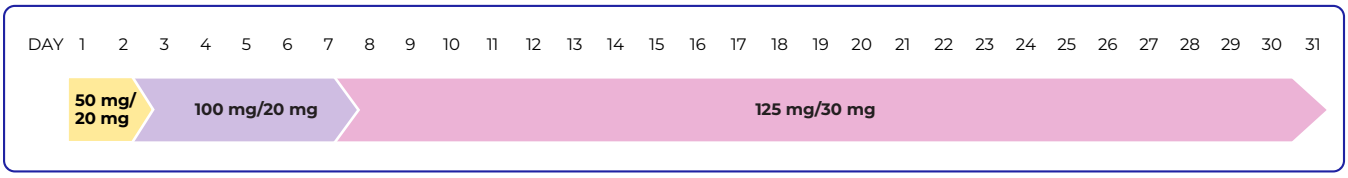
Starting dosage

Therapeutic dosages



- 50 mg/20 mg is not a therapeutic dose.
- COBENFY is taken orally and dose is expressed as mg xanomeline/mg trospium chloride.
- Capsules not shown at actual size.

STUDY TITRATION[a]



Dosing in geriatric patients: The recommended starting dosage of COBENFY is 50 mg/20 mg orally BID. Consider a slower titration for geriatric patients. The maximum recommended dosage in geriatric patients is 100 mg/20 mg BID.[31]

Recommended testing and monitoring: Assess liver enzymes, bilirubin, and heart rate before starting COBENFY and as clinically indicated.[31]

Titration considerations:

Only 100 mg/20 mg and 125 mg/30 mg are therapeutic doses

Initial onset of nausea and vomiting generally declined with **continued titration to 125 mg/30 mg[88ab]**

91% of patients who completed the 5-week EMERGENT trials **were on 125 mg/30 mg[89c]**

COBENFY Initiation, Special Populations, and Drug Interactions Information on pages 54-55

The approach to initiating should be individualized based on the patient's regimen and guided by the clinician's judgment.

[a]Patients must be on the 50 mg/20 mg dose for a minimum of 2 days and the 100 mg/20 mg for a minimum of 5 days.[31]

[b]Percent of patients with first occurrence of nausea or vomiting by week, respectively: Week 1: 11.2% and 8.0%; Week 2: 3.6% and 4.0%; Week 3: 1.6% and 1.6%; Week 4: 2.0% and 0.4%; Week 5: 0.8% and 1.2%.[76]

[c]In EMERGENT-1, -2, & -3, 245 of 314 COBENFY patients finished the trials; 222 patients completed the trials at 125 mg/30 mg. Among those who increased to 125 mg/30 mg BID, 5% reduced their dosage back down to 100 mg/20 mg BID.[67, 89, 90]

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

COBENFY™ is contraindicated in patients with: urinary retention; moderate or severe (Child-Pugh Class B or C) hepatic impairment; gastric retention; history of hypersensitivity to COBENFY or trospium chloride—angioedema has been reported with COBENFY and trospium chloride; and untreated narrow-angle glaucoma.

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50mg/20mg, 100mg/20mg, 125mg/30mg

Patients Can Start and End Their Day With COBENFY:

COBENFY should be dosed BID on an empty stomach[31]

To do so, patients can take[31]:

1 capsule 1 hour before breakfast or snack is served

1 capsule 2 hours after dinner or snack is served

- Do not open capsules
- BID dosing important due to half-life of components (5-6 hours)
- Taking COBENFY with food could increase the likelihood of procholinergic side effects[31,91]

Nausea and vomiting may occur with COBENFY. Consider taking proactive measures by:

Planning dosing around delivered **meals and snacks**

Communicating about meals and dosing during **shift changes**

Prescribing antiemetics **prophylactically**[86a]

[a]Ondansetron was the antiemetic most used in COBENFY clinical trials. 4% of patients were prescribed ondansetron, as needed in EMERGENT-1, -2, & -3 clinical trials (pooled data).[80]

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.

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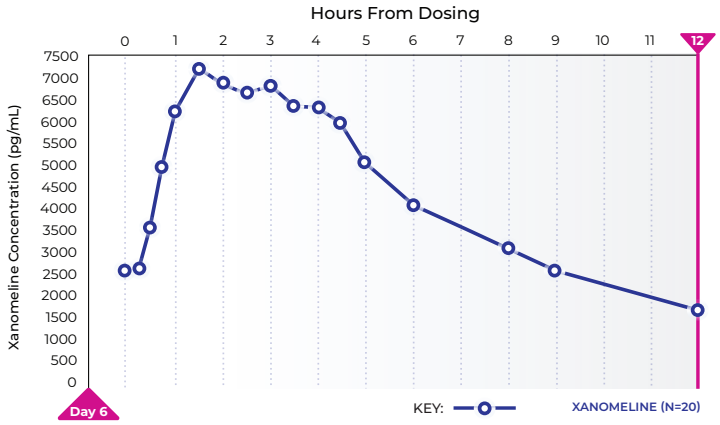
50mg/20mg, 100mg/20mg, 125mg/30mg

COBENFY Reaches Maximum Systemic Concentrations Within 2 Hours[31]

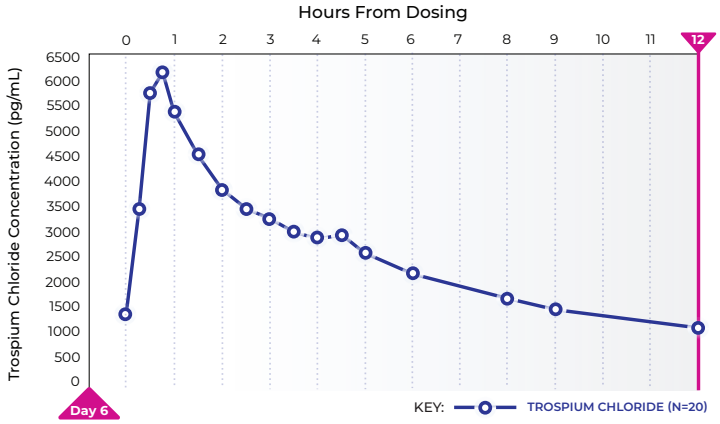
Geometric mean plasma concentration of xanomeline and trospium chloride[92a]

Xanomeline Plasma Concentration Following Multiple Doses of COBENFY



Effective half-life 5 hours

Trospium Chloride Plasma Concentration Following Multiple Doses of COBENFY



Effective half-life 6 hours

The time to steady-state plasma concentration: 3 to 5 days[31]

Time to reach the maximum concentration (T_{max}): xanomeline, 2 hours; trospium chloride, 1 hour.[31]
The prespecified efficacy endpoints in the COBENFY short-term trials were assessed at Week 5.[34,35]
Pharmacokinetic (PK) data should not be used to draw conclusions regarding clinical outcomes.[31]

[a]Concentrations for both graphs are following multiple doses of 50 mg/20 mg COBENFY twice daily on Days 1-2 and 100 mg/20 mg COBENFY twice daily on Days 3-5 and morning of Day 6.[92]

pg/mL=picograms per milliliter.

WARNINGS AND PRECAUTIONS

Risk of Urinary Retention (cont.): 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.

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Pharmacokinetic (PK) Study Design[31,92]

- Open-label, randomized PK study
- 6-sequence crossover study of 20 completed COBENFY (N=20) male and female healthy patients
- Multiple doses of xanomeline 50 mg and trospium 20 mg twice daily on Days 1 through 2 and xanomeline 100 mg and trospium 20 mg twice daily on Days 3 through 5 and morning of Day 6
- Serial pharmacokinetic samples collected hourly from pre-morning-dose through 12 hours post-morning-dose on Days 1 and 6. Additional PK samples were collected on Days 4 and 5 pre-morning-dose only
- Safety was monitored throughout the study
- Xanomeline (muscarinic acetylcholine receptor agonist) crosses the blood-brain barrier while trospium chloride (peripheral muscarinic receptor antagonist) does not appreciably cross the blood-brain barrier
- Xanomeline is heavily metabolized before entering the systemic circulation, and hence has low bioavailability

WARNINGS AND PRECAUTIONS

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.

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Considerations Before Starting COBENFY[31]

Recommended Testing and Monitoring Prior to Initiation and During Treatment

- Assess liver enzymes and bilirubin prior to initiating COBENFY and as clinically indicated during treatment.
- Assess heart rate at baseline and as clinically indicated during treatment.

Dosage Recommendations in Geriatric Patients

- The recommended starting dosage of COBENFY in geriatric patients is one 50 mg/20 mg capsule orally twice daily. Consider a slower titration for geriatric patients. The maximum recommended dosage in geriatric patients is one 100 mg/20 mg capsule twice daily.

Recommendations for Special Populations

Pregnancy

- There is a pregnancy exposure registry that monitors outcomes in women exposed to psychiatric medications, including COBENFY, during pregnancy. Healthcare providers are encouraged to advise patients to register by calling 1-866-961-2388 or visiting online at https://womensmentalhealth.org/research/pregnancyregistry/atypicalantipsychotic/.
- There are no available data on COBENFY use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Lactation

- There are no data on the presence of xanomeline or trospium in human milk, the effects on the breastfed infant, or the effects on milk production. Xanomeline and trospium are present in animal milk.

Pediatric Use

- The safety and effectiveness of COBENFY in pediatric patients have not been established.

Geriatric Use

- Controlled clinical studies of COBENFY did not include patients older than 65 years of age to determine whether they respond differently from younger adult patients.
- Because COBENFY can increase the risk of urinary retention in geriatric patients, including older males with bladder outlet obstruction due to benign prostatic hyperplasia (BPH), a slower titration and lower maximum dosage is recommended in geriatric patients.

Renal Impairment

- Use of COBENFY is not recommended in patients with moderate or severe renal impairment (eGFR<60 mL/min).

Hepatic Impairment

- Use of COBENFY is contraindicated in patients moderate or severe hepatic impairment. It is not recommended in patients with mild hepatic impairment.

eGFR=epidermal growth factor receptor.

WARNINGS AND PRECAUTIONS

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.

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Check for Clinically Relevant Drug Interactions Before and During Treatment With COBENFY[31]

COBENFY has no contraindicated medications[31]

Antimuscarinic drugs in combination with COBENFY may increase frequency and/or severity of anticholinergic side effects[31,93,94]

Examples of commonly used drugs:

- Benztropine
- Diphenhydramine
- Hydroxyzine

COBENFY is contraindicated in patients with urinary retention, moderate or severe hepatic impairment, gastric retention, history of hypersensitivity to COBENFY or trospium chloride, and untreated narrow-angle glaucoma.[31]

Strong Inhibitors of CYP2D6[95]

Examples:
fluoxetine
paroxetine
bupropion
terbinafine

Drugs Eliminated by Active Tubular Secretion[96,97]

Examples:
metformin
hydrochlorothiazide
furosemide

May increase plasma concentration and frequency and/or severity of side effects of:

Xanomeline

Trospium chloride or other drug administered

COBENFY may increase plasma concentration and frequency and/or severity of side effects of[27,95,98-101]:

Sensitive Substrates of CYP3A4

Examples:
buspirone
eletriptan

Narrow Therapeutic Index Substrates of P-glycoprotein

Examples:
digoxin
colchicine
apixaban

Effects On Absorption of Drugs[31]

COBENFY may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. Dosage adjustment of concomitant medications may be necessary based on clinical response and tolerability.

This is not an exhaustive list of medications and is only used to show select examples from each category. For additional examples, visit FDA.gov.
The approach to initiating should be individualized based on the patient's current regimen and guided by the clinician's judgment.
CYP2D6=cytochrome P450 2D6; CYP3A4=cytochrome P450 3A4.

WARNINGS AND PRECAUTIONS

Risk of Use in Patients with Biliary Disease (cont.): 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.

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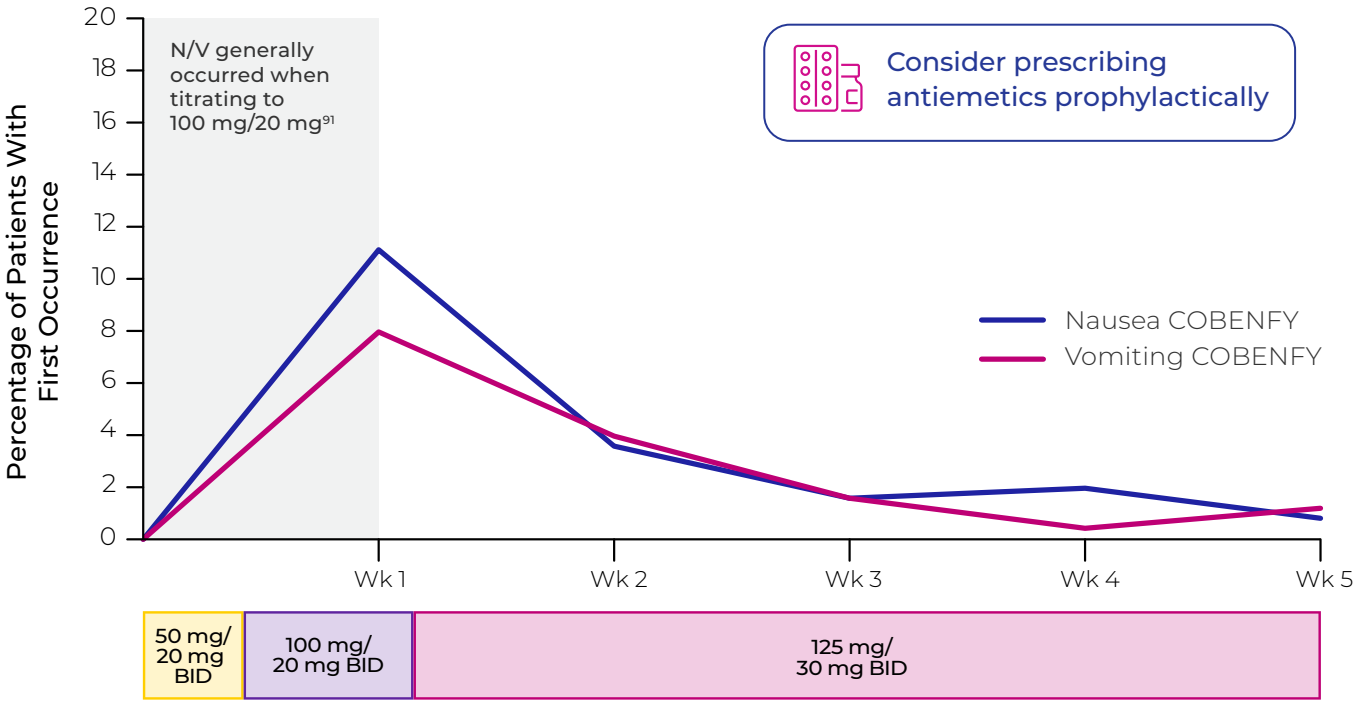
COBENFY™
(xanomeline and trospium chloride) capsules
50mg/20mg, 100mg/20mg, 125mg/30mg

Initial Onset of Nausea and Vomiting Were Mild to Moderate, Transient, and Generally Declined With Continued Titration to 125 mg/30 mg[76,77,79,91a-c]



Nausea and vomiting were reported by **19% and 15% of patients,** respectively[31]

~70% of nausea and vomiting were mild[79]

97% of patients **did not discontinue COBENFY** due to nausea or vomiting[78d]

Data from EMERGENT -2 & -3 trials[79]:

[a]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; a moderate adverse reaction was defined as an event that was sufficiently discomforting to interfere with—but not prevent—normal everyday activities.[102-104]

[b]In EMERGENT-2 & -3, 13.9% and 5.2% of patients treated with COBENFY had mild or moderate nausea, respectively, and 10.4% and 4.8% had mild or moderate vomiting, respectively. No patients had severe nausea or vomiting.[79]

[c]Ondansetron was the antiemetic most used in COBENFY clinical trials. 4% of patients were prescribed ondansetron, as needed in EMERGENT-1, -2, & -3 clinical trials (pooled data).[80]

[d]6% of patients treated with COBENFY and 4% of patients treated with placebo discontinued due to adverse reactions in the 5-week, placebo-controlled studies. In EMERGENT-2 & -3, adverse reactions that led to study discontinuation in ≥1% of patients treated with COBENFY included nausea (2%) and vomiting (1%).[33,78] In EMERGENT-1, -2, & -3, 87% of patients on COBENFY increased to 125 mg/30 mg BID, and 5% of patients reduced their maintenance dosage back down to 100 mg/20 mg BID.[90]

WARNINGS AND PRECAUTIONS

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.

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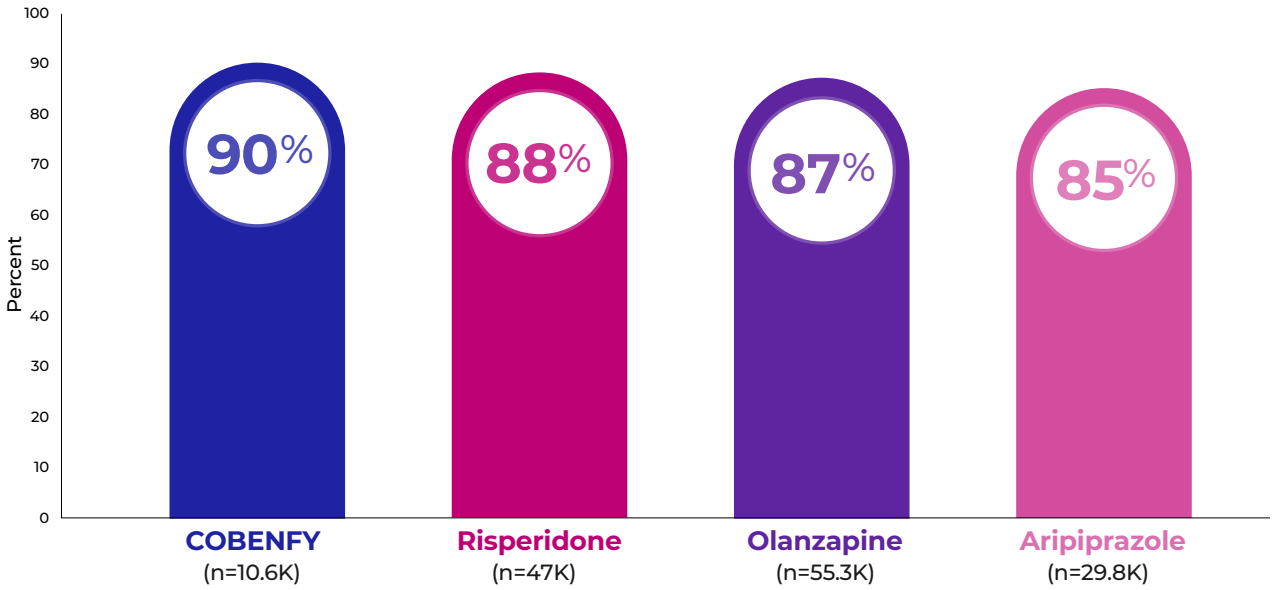
Outpatient Compliance in Clinical Trial and Real-World Patient Populations

97% On average, patients took **97% of their COBENFY twice-daily doses** for the duration of their enrollment in EMERGENT-5, a 52-week, long-term, outpatient study[45,105-107a]

Compliance rates for COBENFY and select common generic treatments over a 6-month period[108b-d]



[a]This represents patients who took at least 1 dose of COBENFY in the EMERGENT-5 clinical study. 566 patients were enrolled in EMERGENT-5, and 277 completed the 52-week outpatient trial. Patients included in this analysis may not have completed the 52-week outpatient trial. Compliance was ensured by study site personnel (during in-clinic visits) and by a digital compliance tool. Treatment compliance was calculated as number of doses taken compared to the number planned.[107]

[b]Includes select common generic atypical antipsychotics and COBENFY associated with ICD-10 codes F20, F20.8, and F20.9, based on patients who initiated treatment between November 2024 and May 2025. Patients under 18 were excluded.[108]

[c]Compliance is determined by comparing the total number of days a patient has medication available (days of supply) with the total length of their treatment period. This measure is based on prescription refill records, which reflect whether the medication was received by the patient, not whether it was actually taken.[108]

[d]These data reflect treatment patterns and compliance and are not intended to suggest clinical comparability or imply conclusions about safety or efficacy. They may not represent overall medication use across all approved indications or patient populations. Claims data may be subject to omissions, errors, or discrepancies in the billing and reimbursement practices of clinicians and insurance plans.[108]

WARNINGS AND PRECAUTIONS

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.

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COBENFY Is Committed to Patient Access

COBENFY is COVERED for **99%** of Medicare and Medicaid patients[a]

$0

9 out of **10** patients paid **$0** out of pocket for COBENFY[b]

90% of claims were approved for COBENFY[c]

Use the formulary lookup tool to verify coverage for COBENFY

[a]Formulary data are provided by Fingertip Formulary Data and are current as of 04/26. Because formularies change and many payers offer more than one formulary, please check directly with the payer to confirm coverage requirements and status for individual patients. Coverage and benefits are subject to change without notice. The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item. Bristol Myers Squibb does not endorse any individual health plans.

[b]Out-of-pocket distribution data cost averages are provided by IQVIA FIA and include prescriptions filled among Commercial, Medicare, and Medicaid patients, latest 4 weeks ending 12/26/25, and reflect any financial assistance that was used. "Commercially Insured Patients" is inclusive of commercially insured patients eligible and receiving assistance through the Co-Pay Assistance Program. "Medicare and Medicaid Patients" are not eligible for the Co-Pay Assistance Program, but may be eligible for other forms of third-party co-pay assistance. Some patients may pay more than the cost listed above.

[c]Claims approval data are provided by IQVIA FIA and include prescriptions filled among Commercial, Medicare, and Medicaid patients, latest 4 weeks ending 01/23/26.

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Provide Patient Support Before Hospital Discharge

COBENFY cares

Help patients and caregivers enroll via:

FAX

COBENFYCares.com

1-877-COBENFY
(1-877-262-3639)

"I look forward to my COBENFY Cares Champions calls.

Your help means more than you can understand. Thank you so much"

— COBENFY Patient

Access to COBENFY

Prior Authorization Support

- Electronic prior authorization (PA) submission support is available to help your patients access COBENFY
- Starting the access process early may help your patients leave the hospital with coverage in place

Voucher Program

- 30-day trial vouchers available to eligible patients post discharge
- See full terms and conditions at: https://www.COBENFY.com/hospital-discharge-voucher-program

Post-discharge support with COBENFY Cares™

COBENFY Cares Champions Provide:[a]

- **Patients and their care partners free, dedicated, 1-on-1 weekly support—available 24/7, 365 days a year**
- **Navigate their care journey** by reminding them of **key dates in their discharge plans**
- **Prepare for follow-up appointments** and offer support with pharmacy coordination
- **Set expectations** around dosing and adherence
- **Build routines** for taking their medication as prescribed
- **Connects to trusted local housing, transportation, and community support resources**

Financial Support

- Assists with navigating **financial conversations** and co-pay support (for eligible patients)[bc]

[a]COBENFY Cares Champions are available to provide support to patients who have been prescribed COBENFY. Champions do not provide medical advice or care; they are provided as a service by Bristol Myers Squibb. Patients should discuss any questions about their medical conditions and treatment options with their healthcare professionals.
[b]COBENFY Cares does not guarantee insurance coverage for COBENFY. Coverage is determined by your insurance provider.
[c]Eligible participants may pay as little as $0. If you have private or commercial health insurance, you may be eligible to pay as little as $0 per month through a co-pay savings offer.
[d]Certain terms and conditions apply. See full Terms and Conditions at www.cobenfy.com/co-pay-assistance-program.

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SUPPLY AND DISTRIBUTION

COBENFY Supply[31]

Designed for the hospital setting—from packaging through returns

Strength	Capsules Per Package	Package Configuration	NDC	COBENFY WAC Price[a]	COBENFY Price Per Day[a]
Hospital Unit-Dose 10 x 10 Blister Packs					
50 mg/20 mg	100	10 Blister Cards with 10 Capsules Each	0003-0050-98	$3,145.00	$62.90
100 mg/20 mg	100	10 Blister Cards with 10 Capsules Each	0003-1100-98	$3,145.00	$62.90
125 mg/30 mg	100	10 Blister Cards with 10 Capsules Each	0003-0125-98	$3,145.00	$62.90
30-Day Bottles					
50 mg/20 mg	60	Bottle	0003-0050-60	$1,887.00	$62.90
100 mg/20 mg	60	Bottle	0003-1100-60	$1,887.00	$62.90
125 mg/30 mg	60	Bottle	0003-0125-60	$1,887.00	$62.90
Starter Pack for 100 mg/20 mg Dose					
Starting Dose: 50 mg/20 mg (4) **Therapeutic Dose:** 100 mg/20 mg (52)	56	**1 Mixed Blister Wallet:** four (4) 50 mg/20 mg capsules and ten (10) 100 mg/20 mg capsules **3 Wallets:** fourteen (14) 100 mg/20 mg capsules in each wallet	0003-5200-56	$1,761.20	$62.90

Capsules not shown at actual size.

[a]WAC price current as of June 2026.

NDC=National Drug Code; WAC=Wholesale Acquisition Cost.

WARNINGS AND PRECAUTIONS

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.

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COBENFY Distribution[31]

Designed for the hospital setting—from packaging through returns

Distribution[31]

COBENFY is readily available for anyone who is prescribed it, supplied via an open distribution network through hospitals, mail-order pharmacies, specialty pharmacies, office-based physicians, and retail pharmacies including Genoa Healthcare for on-site service in care facilities.

Return Goods Policy

COBENFY is eligible for return goods credit under the BMS U.S. Pharmaceuticals Return Goods Policy, which applies to the U.S. and U.S. territories.

For hospitals, BMS offers a dedicated return goods program that provides credit for all COBENFY returns, regardless of expiry date or whether the product is in its original manufacturer container. No enrollment is required to request a return; simply follow the steps outlined in the BMS U.S. Pharmaceuticals Return Goods Policy. Eligibility is limited to hospital in-patient pharmacy class of trade only.

For complete details on terms, conditions, and return procedures, please contact your primary distributor.

Storage

Store at 68°F to 77°F (20°C to 25°C); excursions permitted to 59°F to 86°F (15°C to 30°C).

WARNINGS AND PRECAUTIONS

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

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.

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SUMMARY

COBENFY SUMMARY

COBENFY: A First-in-Class M_1/M_4 Muscarinic Agonist[2,31,32,34]

For the treatment of adults with schizophrenia[31]

1 FIRST-IN-CLASS & HIGHLY SELECTIVE[2,31,32,34ab]

- **First and only** M_1/M_4 muscarinic agonist for the treatment of schizophrenia[31,32,34]
- M_1/M_4 activation is **thought to modulate dopamine release**[2]
- Does not bind to **dopamine D_2 receptors**[34]

2 PROVEN EFFICACY ACROSS PANSS TOTAL[c]

- **Significant symptom improvement** in PANSS total score[33c]
- **PANSS total score** reflects the **full spectrum of schizophrenia symptoms**[33,55]
- **Continued symptom improvements** over 52 weeks[63]

3 UNIQUE SAFETY PROFILE

- **No warnings or precautions** for metabolic changes, including[31]:
  - Weight gain
  - Tardive dyskinesia
  - QTc prolongation
  - Orthostatic hypotension or syncope
  - Hyperprolactinemia
- **No new safety signals** were observed in the 52-week, outpatient trial (EM-4) compared with the 5-week trials (EM-1, -2, -3)[109]
- **No Boxed Warning**[31]

COBENFY has warnings and precautions for: risk of urinary retention; risk of use in patients with hepatic impairment; risk of use in patients with biliary disease; decreased gastrointestinal motility; risk of angioedema; risk of use in patients with narrow-angle glaucoma; increases in heart rate; anticholinergic adverse reactions in patients with renal impairment; and central nervous system effects.[31]

! Access to the first M_1/M_4 muscarinic agonist provides another treatment option for schizophrenia patients[2,31,32,34]

COBENFY is the first antipsychotic drug approved to treat schizophrenia that targets muscarinic receptors. COBENFY does not bind to dopamine receptors. The mechanism of action of COBENFY in the treatment of schizophrenia is unclear.[31,37]

[a]COBENFY is a combination of xanomeline, a muscarinic agonist, and trospium chloride, a muscarinic antagonist, indicated for the treatment of schizophrenia in adults.[31]
[b]Xanomeline binds to muscarinic receptors M_1-M_5 with comparable affinity and exhibits higher agonist activity at the M_1 and M_4 receptors.[31]
[c]As measured by the primary endpoint of PANSS total score change from baseline at Week 5 vs placebo (EMERGENT-2: −21.2 vs −11.6, $P<0.0001$; EMERGENT-3: −20.6 vs −12.2, $P<0.001$).[31]

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INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

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

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

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.

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.

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.

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.

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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.

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.

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 (≥5% and at least twice placebo): nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, and gastroesophageal reflux disease.

Use in Specific Populations:

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

Pregnancy and Lactation: There is a pregnancy exposure registry that monitors outcomes in women exposed to psychiatric medications, including COBENFY, during pregnancy. Healthcare providers are encouraged to advise patients to register by calling 1-866-961-2388 or visiting https://womensmentalhealth.org/research/pregnancyregistry/atypicalantipsychotic/.

There are no available data on COBENFY use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Additionally, there are no data on the presence of xanomeline or trospium in human milk, the effects on the breastfed infant, or the effects on milk production. However, xanomeline and trospium are present in animal milk, suggesting they may also be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COBENFY and any potential adverse effects on the breastfed infant from COBENFY or the underlying maternal condition.

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 here.

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Abbreviations

AAP: Atypical Antipsychotics
AIMS: Abnormal Involuntary Movement Scale
AP: Antipsychotics
BARS: Brief Adherence Rating Scale
BID: Twice a day
BPH: Benign Prostatic Hyperplasia
BPM: Beats Per Minute
CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness
CCW: Chronic Conditions Data Warehouse
CGI-S: Clinical Global Impressions Scale
CMS: Centers for Medicare & Medicaid Services
CNS: Central Nervous System
C-SSRS: Columbia-Suicide Severity Rating Scale
CVD: Cardiovascular Disease
CYP2D6: Cytochrome P450 2D6
CYP3A4: Cytochrome P450 3A4
DBP: Diastolic Blood Pressure
Diff: Difficulty
DRG: Decision Resources Group
DSM: Diagnostic and Statistical Manual of Mental Disorders
DSP: Disease Specific Programme
ECG: Electrocardiogram
ED: Emergency Department
eGFR: Estimated Glomerular Filtration Rate
EHR: Electronic Health Record
EPS: Extrapyramidal Symptoms
ER: Emergency Room
FFS: Fee-For-Service
GDP: Gross Domestic Product
GPS: General Psychopathology Scale
HCEI: Health Care Economic Information
HMIC: Health Management Information Consortium
HMO: Health Maintenance Organization
HRU/HCRU: Health Resource Utilization/Health Care Resource Utilization
ICD: International Classification of Diseases
LAI: Long-Acting Injectable
LHH: Likelihood To Be Helped or Harmed
LS: Least Squares
mITT: Modified Intent-To-Treat
MM: Marketscan Medicaid
mmHg: Millimeters of Mercury
NA: Not Applicable
ND: No Difference
NDC: National Drug Code
NNH: Number Needed to Harm
NNSS: Non-Negative Symptoms of Schizophrenia
NNT: Number Needed to Treat
NSS: Negative Symptoms of Schizophrenia
OAP: Oral Antipsychotic
PANSS: Positive and Negative Syndrome Scale
pg/mL: Picograms per Milliliter
PK: Pharmacokinetics
PMP: PharMetrics Plus
PPPY: Per Patient Per Year
QoL: Quality of Life
QTc: Corrected QT Interval
RNS: Residual Negative Symptoms
SAS: Simpson-Angus Scale
SBP: Systolic Blood Pressure
SD: Standard Deviation
SGA: Second-Generation Antipsychotic
TD: Tardive Dyskinesia
TEAE: Treatment-Emergent Adverse Event
USD: United States Dollar
VMAT: Vesicular Monoamine Transporter
WAC: Wholesale Acquisition Cost
Wk: Week