Cobenfy™ (xanomeline and trospium chloride) oral capsules

Note: The purpose of this document is to provide the clinical information regarding Cobenfy™ (xanomeline and trospium chloride) as requested; it is not intended to be used for any other purpose. This document contains relevant information for Cobenfy, which may or may not be included in the US prescribing information. BMS does not suggest or recommend the use of Cobenfy in any manner other than as described in the US prescribing information.

Indication: Cobenfy is a first-in-class oral combination of xanomeline (M_1/M_4-preferring muscarinic agonist) and trospium chloride (muscarinic antagonist) indicated for treatment of schizophrenia in adults.[1]

Warnings/Precautions with Cobenfy include decreased GI motility, HR increase, CNS effects, anticholinergic AEs in pts with renal impairment, risks of urinary retention or angioedema, and risks of use in pts with biliary disease, hepatic impairment or narrow-angle glaucoma. Cobenfy has no boxed warning, nor warnings/precautions related to metabolic changes nor movement disorders.[1]

Long-term safety & efficacy analyses:

EMERGENT-4 and -5 were 52-wk open-label, outpt, phase 3 studies evaluating the safety and efficacy of X/T in adults with schizophrenia. All pts initiated BID oral X/T 50 mg/ 20 mg and titrated up to a maximum dose of 100/20mg or 125/30 mg. Safety analyses were performed in pts who received ≥1 X/T dose; efficacy analyses were conducted in the mITT population (pts who received ≥1 X/T dose and had ≥1 post-BL PANSS assessment).[2,3]

EMERGENT-4 was an extension study evaluating pts in either the X/T or PBO arm who completed the treatment period of the registrational 5-wk (acute) randomized, double-blind EMERGENT-2 and -3 studies, resided in a stable living situation, and had a reliable informant/ caregiver.

Safety (N = 152)[2]

- TEAEs occurred in 53.3% of pts, treatment-related TEAEs in 35.5% of pts, treatment-related SAEs in 1.3% of pts and TEAEs leading to treatment discontinuation in 10.5% of pts. [2]
- The majority of treatment-related TEAEs were GI, mild-moderate intensity, did not lead to treatment discontinuation and resolved with continued treatment. The most common treatment-related TEAEs (≥ 2% of pts) were nausea (9.2%), vomiting (7.9%), dyspepsia (5.9%), dry mouth (5.3%), hypertension (5.3%), constipation (3.3%), wt increased (3.3%), diarrhea (2.6%), gastroesophageal reflux disease (2.6%), dizziness (2.6%), headache (2.0%) and somnolence (2.0%).[2]
- At OLE wk 52 vs acute study (EMERGENT 2/3) BL, X/T was associated with[2]
  - A decrease in body wt with a mean Δ (SD) of -1.9 (4.7) kg. The mean Δ (SD) in BMI and prolactin were -0.6 (1.5) kg/m^2 and -11.3 (38.1) µg/L, respectively.
  - No clinically meaningful changes in movement disorder scale scores with mean Δ (SD) in SAS, BARS, and AIMS total scores of -0.4(1.1), -0.3(1.3) and -0.1(0.4), respectively. No TEAEs of akathisia or tardive dyskinesia were reported.
  - Increases in BP (SBP: +1.9 mmHg; DBP: +0.7 mmHg) and HR (3.9 bpm), which peaked ≤ 2 wks of the OLE and partially attenuated with repeated dosing.

Efficacy (N =111)[2]

- From acute study BL through OLE wk 52, continued improvements (mean Δ) in the primary endpoint, PANSS total score (-32.6), and secondary endpoints, CGI-S (-1.7), PANSS positive subscale (-10.7), and PANSS negative subscale (-6.0) scores were observed with XT overall. [2]
  - Mean Δ from acute study BL to wk 52 in PANSS total score was -33.8 vs -31.3 in pts with (X/T_X/T) vs without (PBO_X/T) prior X/T exposure, respectively[2]
  - By OLE wk 2, the PBO_X/T vs X/T_X/T subgroup demonstrated significantly greater improvement in the primary endpoint; no clinically meaningful differences were observed across the primary and secondary endpoints by OLE wk 4 through wk 52[2]
- At OLE wk 52, 68.6%) of pts achieved a ≥ 30% decline from acute study BL in floor-adjusted PANSS total score with X/T overall. [2]

EMERGENT-5 evaluated pts without prior X/T exposure who had stable symptoms of schizophrenia, PANSS total score ≤ 80 and CGI-S ≤ 4.

Safety (N = 566)[3]

- TEAEs occurred in 82.3% of pts, treatment-related TEAEs in 67.1% of pts, treatment-related SAEs in 1.6% of pts and TEAEs leading to treatment discontinuation in 17.7% of pts. [3]
- The majority of treatment-related TEAEs were GI, mild-moderate intensity, and did not lead to treatment discontinuation; the most common treatment-related TEAEs (≥ 5% of pts) were nausea (21.4%), vomiting (17.8%), constipation (16.8%), dry mouth (9.0%), diarrhea (6.7%), dyspepsia (6.5%), dizziness (7.8%), hypertension (6.5%) and somnolence (5.8%).[3]
- At wk 52 vs BL, X/T was associated with[3]
  - A decrease in body wt with a mean Δ (SD) of -2.2 (6.3) kg. Mean Δs (SD) in BMI and prolactin were -0.7 (2.1) kg/m^2 and -2.5 (11.8) µg/L, respectively.
  - No clinically meaningful changes in movement disorder scales with mean Δs (SD) in SAS, BARS, and AIMS of -0.3(1.0), -0.2(1.0) and -0.1(0.8), respectively. TEAEs of akathisia and tardive dyskinesia were reported in 1.2% and 0.4% of pts, respectively.
  - X/T was associated with increases in BP (SBP: +1.8 mmHg; DBP: +1.5 mmHg) and HR (+2.4 bpm), which peaked at wks 1 and 2, respectively, and partially attenuated with repeated dosing.

Efficacy (N= 558) [3]

- From BL through wk 52, continued improvements (mean Δ) in the primary endpoint, PANSS total score (-5.5), and secondary endpoints, CGI-S (-0.4), PANSS positive subscale (-1.9), and PANSS negative subscale (-0.8) scores were observed with X/T. [3]
- At wk 52, 30.0% of pts achieved a ≥ 30% decline from acute study BL in floor-adjusted PANSS total score with X/T. [3]

Qualitative interview-based sub-studies of EMERGENT-5 (N = 70) evaluated perceived Δ in symptoms and QoL in pts with schizophrenia treated with X/T and consisted of 2 semi-structured interviews conducted by an independent research team at 6 wks (T1, n = 70) and ~6 months (T2, n = 47) post-initiation of X/T monotherapy.[4,5]

Symptoms: At BL, the most commonly reported ongoing symptoms were auditory hallucinations (81.4%), concentration/focus (72.9%), disorganized thinking (65.7%), persecutory delusions (65.7%), avolition (61.4%) and visual hallucinations (44.3%).[4]

- Across the noted symptoms, ≥ ~52.2% and 80.0% of impacted pts reported improvement at T1 and T2, respectively, and ≤ 6.1% reported worsening by T2.

Abbreviations: Δ, change; BID, twice daily; BL, baseline; GI, gastrointestinal; HR, heart rate; CNS, central nervous system, AE, adverse event; pts, patients; wk, week; X/T, xanomeline/ trospium chloride; PBO, placebo, mITT, modified intent-to-treat; PANSS, Positive and Negative Syndrome Scale; TEAEs, treatment-emergent adverse event, SAE, serious adverse event, BMI, body mass index; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; SAS, Simpson-Angus Scale; wt, weight; OLE, open-label extension, BP, blood pressure, SBP, systolic blood pressure; DBP, diastolic blood pressure; QoL, quality of life; EPS, extrapyramidal symptoms; NMA, network meta-analysis; CGI-S, Clinical Global Impressions - Severity; CrI, credible interval; MD, mean difference

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QoL: At BL, the majority of pts reported QoL impacts to physical (95.7%), social (85.7%), emotional (74.3%) and role functioning (80.7%); the most common problems in each domain were energy level and sleep, communication and active social withdrawal, anger/agitation and depression/sadness, as well as activities of daily living and employment, respectively.[5]

- Across the noted problems for all domains, ≥ 44.8% and 68.0% of impacted pts reported improvement at T1 and T2, respectively, and ≤ 10.3% reported worsening by T2.
- The majority of impacted pts (85.7%) reported improvements in their QoL in ≥ 1 domain by T1 (12.9% unchanged, 1.4% worsened).

Pooled interim safety analyses of the EMERGENT-4 and -5 studies (data cutoff: August 18, 2023, N = 718) further characterized the long-term EPS and metabolic outcomes with X/T in pts with schizophrenia.[6,7] At 52 wks,

EPS[6]

- EPS TEAEs overall occurred in a 3.5% of pts; akathisia was the most common (1.3%). Treatment-related EPS TEAEs occurred in 0.7% of pts and included akathisia (0.6%) and dyskinesia (0.1%); no treatment-related cases of dystonia or extrapyramidal disorders were reported.
- The incidence of EPS TEAEs overall was not associated with clinically meaningful changes in movement disorder scale total scores [mean Δ from BL (SD), SAS: −0.2(0.92); BARS: 0.0(0.91); AIMS: −0.1(0.58)]

Metabolic effects[7]

- Wt Δs reported included wt decreased (4.5%), wt increased (2.9%), obesity (0.7%) and BMI decrease (0.1%). The mean Δ (SE) in wt from BL was -2.56 (0.47), with wt loss ≥ 7% vs wt gain ≥ 7% observed in 17.6% vs 4.1% of pts, respectively.
- Metabolic and nutrition disorders/investigations reported occurred in ≤ 1% of pts and included hypertriglyceridemia (0.3%), blood triglyceride increased (0.3%), hyperlipidemia (0.3%), hypercholesteremia (0.1%), blood cholesterol increased (0.1%), and high-density lipoprotein decreased (0.1%). The mean Δs (SE) in total cholesterol and triglycerides from BL were 0.6 (0.07) mmol/L and -0.06 (0.05) mmol/L, with the incidence of pts with elevated total cholesterol (≥5.17 mmol/L) and triglycerides, respectively, decreasing from 33.7% and 15.3% (BL) to 29.7% and 12.8% (last on-treatment assessment)
- AEs related to hyperglycemia/new-onset diabetes occurred in ≤ 1% of pts and included HbA1c increased (0.6%), blood glucose increased (0.6%), type 2 diabetes mellitus (0.3%), glucose urine present (0.1%), urine ketone body present (0.1%). The mean Δ (SE) in HbA1c from BL (EMERGENT-5 study only) was 0.01 (0.05)%, with the incidence of pts with high HbA1c (≥ 6.5%) decreasing from 12.9% (BL) to 10.9% (last on-treatment assessment).

Health Economic and Outcomes Studies

Please note there are no head-to-head studies between X/T and other oral antipsychotics.

An **NMA** of randomized-controlled studies (n = 58) indirectly compared the efficacy and safety of XT with other oral antipsychotic therapies (aripiprazole, cariprazine, olanzapine, risperidone, brexpiprazole, quetiapine, clozapine, and lumateperone) for the acute treatment of schizophrenia in adult hospitalized pts. . Outcomes included Δ from BL in PANSS scores (total, positive sub-score, negative sub-score), percentage of pts with a ≥ 30% improvement in PANSS total score, Δ from BL CGI-S and response rates (CGI-S of 1 or 2), discontinuation rates due to all causes and AEs, percentage with > 7% increase from BL and Δ from BL wt and percentage that experienced somnolence/sedation. X/T was associated with[8]

- Significantly improved odds of PANSS response (≥ 30% improvement in PANSS total score) versus aripiprazole (odds ratio [OR]: 1.85; 95% credible interval [CrI]: 1.11, 3.11), brexpiprazole (OR: 2.23; 95% CrI: 1.34, 3.83), and cariprazine (OR: 2.05; 95% CrI: 1.19, 3.57).
- Significantly greater Δ from BL in PANSS positive score vs brexpiprazole (MD: -2.08; 95% CrI: -3.82, -0.35) and in CGI-S score compared with aripiprazole (MD: -0.33; 95% CrI: -0.57, -0.11), brexpiprazole (MD: -0.38; 95% CrI: -0.62, -0.15), cariprazine (MD: -0.37; 95% CrI: -0.62, -0.13), and olanzapine (MD: -0.28; 95% CrI: -0.52, -0.03).
- No significant differences in Δ from BL in PANSS total and negative score vs all active comparators.
- Significantly higher odds for all cause discontinuation vs. all active comparators except cariprazine (ORs ranged from 1.61 (95% CrI: 1.07, 2.51) vs brexpiprazole to 3.29 (95% CrI: 1.09, 10.06) vs clozapine).
- Significantly lower odds of clinically meaningful wt gain vs all active treatments (clozapine data unavailable) (ORs ranged from 0.08 (95% CrI: 0.03, 0.22) vs quetiapine to 0.21 (95% CrI: 0.08, 0.55) vs cariprazine).
- Significantly lower odds of Δ from BL wt compared to brexpiprazole (MD: -1.60; 95% CrI: -2.73, -0.47) , clozapine (MD: -3.82; 95% CrI: -6.52, -1.15) , olanzapine (MD: -3.02; 95% CrI: -4.10, -2.00), quetiapine (MD: -1.82; 95% CrI: -2.96, -0.68), and risperidone (MD: -2.01; 95% CrI: -3.07, -0.99)
- No significant differences in odds of sedation vs all active comparators.

Study Limitations:

- Substantial heterogeneity was present in NMAs for ≥ 30% improvement in PANSS total score, somnolence endpoints, CFB in PANSS scores (total, positive symptoms, negative symptoms), CGI-S score and wt, Potential reasons include: evidence inclusion for any treatment dose within FDA label ranges without consideration of potential dose–efficacy relationships, population differences related to race and placebo effect size variability between included studies.
- Lack of reported data precluded inclusion of clozapine in NMAs for several endpoints.

Please refer to Important Safety Information in the cover letter & accompanying full US prescribing information for more information.

References: 1. Cobenfy. Prescribing information. Bristol-Myers Squibb Company; 2024., 2. Kaul I, et al. Presented at: Psych Congress; October 29-November 2, 2024; Boston, MA. (Poster 65), 3. Kaul I, et al. Presented at: Psych Congress; October 29-November 2, 2024; Boston, MA. (Poster 62), 4. Novak K, et al. Presented at: ASCP; May 28-31, 2024; Miami Beach, Fl., 5. Claxton, A, et al. Presented at: SIRS; April 3-7, 2024; Florence, Italy., 6. Horan W, et al. Presented at: ASCP; May 28-31, 2024; Miami Beach, Fl., 7. Weiden PJ, et al. Presented at: Psych Congress; October 29-November 2, 2024; Boston, MA.,8. Hickey C, et al. Presented at: Psych Congress; October 29-November 2, 2024; Boston, MA.

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