CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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CAPLYTA is indicated in adults for the treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate.[1]

Phase 3 studies

Study 404[2] is a 6-week, randomized, double-blind, placebo-controlled, multi-center study that assessed the efficacy and safety of CAPLYTA 42 mg monotherapy in the treatment of patients with MDEs associated with bipolar I or bipolar II disorder.

- In the mITT population, CAPLYTA 42 mg (n=188) showed a statistical improvement in MADRS total score compared to placebo (n=188) at day 43.
  - LS mean change (SE): −16.7 (0.69) vs −12.1 (0.68); LSMD: − 4.6, (95% CI: −6.34 to −2.83; ES=−0.56; *P*<0.0001).
- The most common TEAEs (≥2% in the CAPLYTA 42 mg group) were headache, somnolence and nausea. Most TEAEs were mild or moderate in severity.

Study 402[3] is a 6-week randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of CAPLYTA 42 mg as adjunctive treatment to lithium or valproate in patients with MDEs associated with BPD.

- At day 43, CAPLYTA 42 mg (n=174) adjunctive to lithium or valproate showed a statistical improvement in MADRS total score compared to adjunctive placebo (n=174).
  - LS mean change (SE): −16.9 (0.81) vs −14.5; LSMD: −2.4, (95% CI: −4.42 to −0.37; ES: −0.27; *P*=0.021).
- The most common TEAEs (≥5% in the CAPLYTA 42 mg adjunctive to lithium or valproate group and more than twice that in the placebo group) were somnolence, dizziness, and nausea. Most TEAEs (>99%) were mild or moderate in severity.

Abbreviations: BPD, bipolar depression; CI, confidence interval; ES, effect size; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episodes; mITT, modified intent-to-treat; SE, standard error; TEAE, treatment-emergent adverse event.

CAPLYTA® (lumateperone)
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Phase 3 studies

Study 401[4] is 6-week, randomized, double-blind, placebo-controlled, outpatient, multicenter study that assessed the efficacy and safety of CAPLYTA in patients with MDEs associated with bipolar disorder I and II. A 6-month OLE period of study 401 evaluated long-term safety of CAPLYTA 42 mg in patients with MDEs associated with bipolar disorder.[5]

- **Part A**
  - At day 43, CAPLYTA 42 mg (n=166) showed a decrease in MADRS total score compared to placebo (n=177) in the ITT population. LS mean change (SE): −20.7 (1.16) vs -19.7 (1.11); LSMD: -1 (95% CI: −3.73 to 1.79).
  - The most common TEAEs (in ≥5% and at least twice the rate of the placebo group) for patients treated with CAPLYTA 42 mg were headache, dry mouth, dizziness, nausea, somnolence, diarrhea, and vomiting. Most TEAEs were mild or moderate in severity.
- **Part B**
  - In the OLE period, 42.5% of treated patients experienced drug-related TEAE and the most common TEAEs in ≥5% for patients treated with CAPLYTA 42 mg were headache (20.5%), dry mouth (11.8%), dizziness (10.2%), and nausea (10.2%). Most TEAEs were mild or moderate in severity, and CAPLYTA 42 mg was well-tolerated during the 6-month treatment period.[5]
  - CAPLYTA 42 mg demonstrated a reduction in MADRS total score compared to baseline in this OLE study with mean change (SE) from baseline in MADRS total score (−8.9 [1.25]; *P*<0.0001), at day 175.[6]

Study 403[7] is a 6-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of CAPLYTA 42 mg in patients with MDEs associated with MDD/BPD with mixed features.

- In patients with combined MDD/BPD with mixed features, CAPLYTA 42 mg (n=192) met the primary endpoint and showed improvement in MADRS total score from baseline at day 43 compared with placebo (n=191).
  - LS mean change (SE): −18.1 (0.71) vs −12.4 (0.7); LSMD: −5.7, (95% CI: −7.60 to −3.84; ES: −0.64; *P*<0.0001).
- The most common TEAEs (≥5% in the CAPLYTA 42 mg group and more than twice that of the placebo group) were somnolence, dizziness, and nausea. Most TEAEs (≥99%) were mild or moderate in severity.[7]

Abbreviations: BPD, bipolar depression; CI, confidence interval; ES, effect size; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episodes; OLE, open-label extension; SE, standard error; TEAE, treatment-emergent adverse event.

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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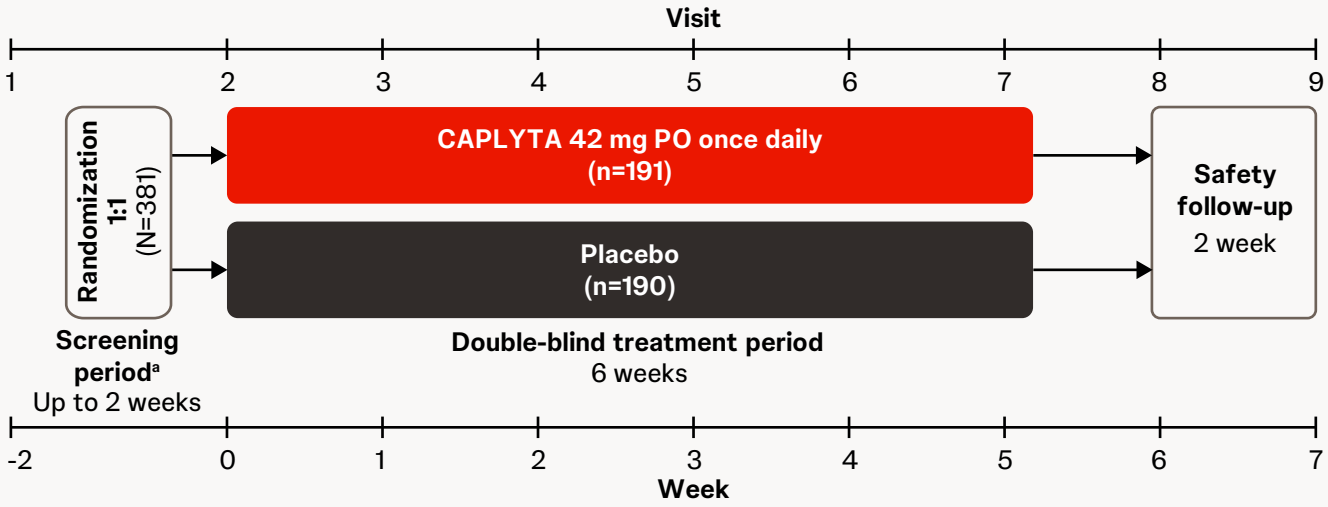
- **Study 404**[2] (NCT03249376) is a randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of CAPLYTA 42 mg monotherapy in the treatment of patients with MDEs associated with bipolar I or bipolar II disorder conducted globally.

Study design[7]



- Key inclusion criteria[2,8]:
  - Adults (18-75 years old), inclusive at the start of screening, with a diagnosis of bipolar I or bipolar II disorder experiencing MDE
  - Body mass index (BMI) of 19–35 kg/m^2
  - Meeting the DSM-5 criteria for bipolar I or bipolar II disorder, as confirmed by the investigator or sponsor-approved rater by a MINI International Neuropsychiatric Interview and met all the following 5 criteria:
    - The start of the current MDE was at least 2 weeks but no more than 6 months prior to screening visit
    - Were at least moderately ill as measured by MADRS total score ≥20 and CGI-BP-S score ≥4 at screening and baseline
    - Had a lifetime history of at least 1 bipolar manic episode or mixed episode (for bipolar I) or hypomanic episode (for bipolar II)
    - Had a rater-administered YMRS total score ≤12 at screening and at baseline
    - Had sufficient history and/or independent report verifying that the current MDE was causing clinically significant distress or impairment in social, occupational, or other important areas of functioning
- **Primary endpoint:** change in MADRS total score from baseline to day 43.
- **Key secondary endpoint:** change in CGI-BP-S score from baseline to day 43.

[a]Patients eligible for participation discontinued their current antidepressant or other psychotropic treatment during a screening period of up to 2 weeks.

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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- Demographic and baseline characteristics were comparable between both treatment groups.[2]
- Majority of patients were White (~91%) with a mean age of 46 years.[2]

Select baseline and disease characteristics[2]

	CAPLYTA 42 mg (n=188)	Placebo (n=189)
Age, years, mean (SD)	46 (14.1)	44 (12.9)
Bipolar I disorder	150 (79.8)	151 (79.9)
Bipolar II disorder	38 (20.2)	38 (20.1)
Age at first diagnosis, mean (SD), years	33.2 (11.97)	32 (11.5)
No. of lifetime MDEs, n (%)		
1–9	166 (88.3)	168 (88.9)
10–20	21 (11.2)	19 (10.1)
>20	1 (0.5)	2 (1.1)
MADRS total score, mean (SD)	30.8 (4.92)	30.2 (4.65)
CGI-BP-S total score, mean (SD)	10.3 (1.12)	10.2 (1.08)
CGI-BP-S mania score, mean (SD)	1.1 (0.25)	1.1 (0.28)
CGI-BP-S depression score, mean (SD)	4.6 (0.56)	4.6 (0.52)
CGI-BP-S overall bipolar illness score, mean (SD)	4.6 (0.55)	4.5 (0.52)
Q-LES-Q-SF percent score, mean (SD)	37 (12.53)	38.6 (12.25)

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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- In the ITT set, CAPLYTA 42 mg met the primary endpoint and demonstrated statistically significant reduction in MADRS total score at day 43 compared with placebo.[2]

Change in efficacy parameters at day 43 in BPD subgroups—MMRM (mITT set)[2,a]

Measure	CAPLYTA 42 mg (n=188)	Placebo (n=188)
MADRS total score, change from baseline to day 43		
LS mean (SE)	−16.7 (0.69)	−12.1 (0.68)
LSMD (95% CI), ES, *P*-value	−4.6 (−6.34, −2.83), −0.56, <0.0001	-
CGI-BP-S total score, change from baseline to day 43		
CGI-BP-S total score, LS mean (SE)	−3.5 (0.17)	−2.5 (0.17)
LSMD (95% CI), ES, *P*-value	−0.9 (−1.37, −0.51), −0.46, <0.0001	-
CGI-BP-S mania subscore, LS mean (SE)	0 (0.02)	0 (0.02)
LSMD (95% CI), ES, *P*-value[b]	−0 (−0.08, 0.04), −0.08, 0.448	-
CGI-BP-S depression subscore, LS mean (SE)	−1.8 (0.09)	−1.3 (0.09)
LSMD (95% CI), ES, *P*-value[b]	−0.5 (−0.75, −0.30), −0.50, <0.0001	-
CGI-BP-S overall bipolar illness subscore, LS mean (SE)	−1.7 (0.08)	−1.3 (0.08)
LSMD (95% CI), ES, *P*-value[b]	−0.4 (−0.65, −0.22), −0.43, <0.0001	-
MADRS response, n (%)	96 (51.1)	69 (36.7)
OR (95% CI), *P*-value[b]	2.98 (1.747, 5.078), <0.001	-
MADRS remission, n (%)	75 (39.9)	63 (33.5)
OR (95% CI), *P*-value[b]	1.91 (1.119, 3.255), 0.018	-

[a]Response was defined as a decrease ≥50% in MADRS score, and remission was defined as a MADRS score ≤12.
[b]These endpoints were not adjusted for multiple comparisons. Therefore, the *P*-values displayed are nominal, and statistical significance has not been established.

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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Summary of AEs (safety analysis set)[8]

Event, n (%)	CAPLYTA 42 mg (n=188)	Placebo (n=189)
Patients with ≥1 TEAE	103 (54.8)	95 (50.3)
Patients with drug-related TEAEs	78 (41.5)	59 (31.2)
Patients who discontinued due to TEAEs	11 (5.9)	4 (2.1)
Patients who discontinued due to drug-related TEAEs	9 (4.8)	2 (1.1)
Patients with SAEs[a]	1 (0.5)	0
Patients with drug-related SAE	0	0
Patients who discontinued due to SAEs	1 (0.5)	0
Patients who discontinued due to drug-related SAEs	0	0
Patients who died	0	0
Patients with TEAEs in ≥2% in the CAPLYTA 42 mg group[b]		
Headache	33 (17.6)	19 (10.1)
Somnolence	16 (8.5)	2 (1.1)
Nausea	12 (6.4)	4 (2.1)

[a]SAE was unrelated to the study drug.
[b]The most frequently reported TEAEs in the placebo group were headache (10.1%) and dizziness (5.3%).

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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McIntyre et al[9] conducted a post hoc analysis of Study 404 to evaluate the efficacy of CAPLYTA 42 mg in patients with MDE associated with bipolar I or bipolar II disorder with mixed features (YMRS score ≥4 and ≤12) or without mixed features (YMRS score <4).

- CAPLYTA (n=191) reduced MADRS total score from baseline at day 43 compared with placebo (n=190).
  - MADRS total score (CAPLYTA 42 mg vs placebo):
    - Patients with mixed features: LS mean change (SE), −19.2 (1.24) vs −14.8 (1.2) [LSMD, −4.4; 95% CI: −7.26 to −1.52; ES: −0.52; *P*<0.01[a]].
    - Patients without mixed features: LS mean change (SE), −15.3 (0.87) vs −11.3 (0.9) [LSMD, −4.2; 95% CI: −6.46 to −1.92; ES: −0.53; *P*<0.001[a]].
  - CGI-BP-S score (CAPLYTA 42 mg vs placebo):
    - Patients with mixed features: LS mean change (SE), −3.7 (0.31) vs −2.9 (0.3) [LSMD, −0.7; 95% CI: −1.43 to −0.05; ES: −0.37; *P*<0.05[a]].
    - Patients without mixed features: LS mean change (SE), −3.3 (0.22) vs −2.2 (0.23) [LSMD, −1; 95% CI: −1.62 to −0.47; ES: −0.52; *P*<0.001[a]].
- The rate of TEAEs were similar in patients between CAPLYTA 42 mg and placebo groups who received ≥1 dose of study drug (with mixed features: 54.8% vs 51.8% and without mixed features: 54.8% vs 49.1%). Majority of cases were of mild to moderate severity.

McIntyre et al[10] conducted a prespecified secondary and post hoc analysis of Study 404 to evaluate the efficacy of CAPLYTA 42 mg in patients with bipolar disorder experiencing a current MDE. Patients were evaluated with bipolar disorder I subgroup (CAPLYTA 42 mg, n=150; placebo, n=150) and bipolar disorder II subgroup (CAPLYTA 42 mg, n=38; placebo, n=38).

- In the mITT bipolar disorder subgroups, CAPLYTA 42 mg improved MADRS total score from baseline to day 43 compared with placebo.
  - MADRS total score (CAPLYTA 42 mg vs placebo):
    - Patients with bipolar disorder I: LSMD (−4; [95% CI: −5.92 to −1.99]; ES: −0.48; *P*<0.0001[a]).
    - Patients with bipolar disorder II: LSMD (−7; [95% CI: −10.92 to −3.16]; ES: −0.85; *P*<0.001[a]).
  - MADRS anhedonia factor (CAPLYTA 42 mg vs placebo):
    - Patients with bipolar disorder I: LSMD (−1.8; [95% CI: −3.03 to −0.62]; ES: −0.36; *P*<0.01[a]).
    - Patients with bipolar disorder II: LSMD (−4.5; [95% CI, −6.87 to −2.1; ES: −0.90; *P*<0.001[a]).

[a]These endpoints were not adjusted for multiple comparisons. Therefore, the *P*-values displayed are nominal, and statistical significance has not been established.

CAPLYTA® (lumateperone)
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Edwards et al[11] conducted a pos-hoc analysis of Study 404 to evaluate the effects of CAPLYTA 42 mg on functional disability and QoL as measured using the secondary outcome measure, the Q-LES-Q-SF in patients with MDE associated with BPD.

- In the ITT population, in patients with MDEs associated with BPD, treatment with CAPLYTA 42 mg (n=188) improved QoL and functional impairment compared with placebo (n=188).
- CAPLYTA 42 mg improved MADRS and Q-LES-Q-SF total score change from baseline to day 43 compared with placebo.
  - MADRS total score: LSMD (−4.585; [95% CI: −6.344 to −2.826]; ES: −0.56; *P*<.0001[a]).
  - Q-LES-Q-SF total score: LSMD (2.9; [95% CI: 1.15 to 4.59]; *P*<.001[a]).
- By day 43, CAPLYTA 42 mg treatment significantly improved 8 of the 14 items in the Q-LESQ- SF (*P*<0.05[a]).

[a]These endpoints were not adjusted for multiple comparisons. Therefore, the *P*-values displayed are nominal, and statistical significance has not been established.

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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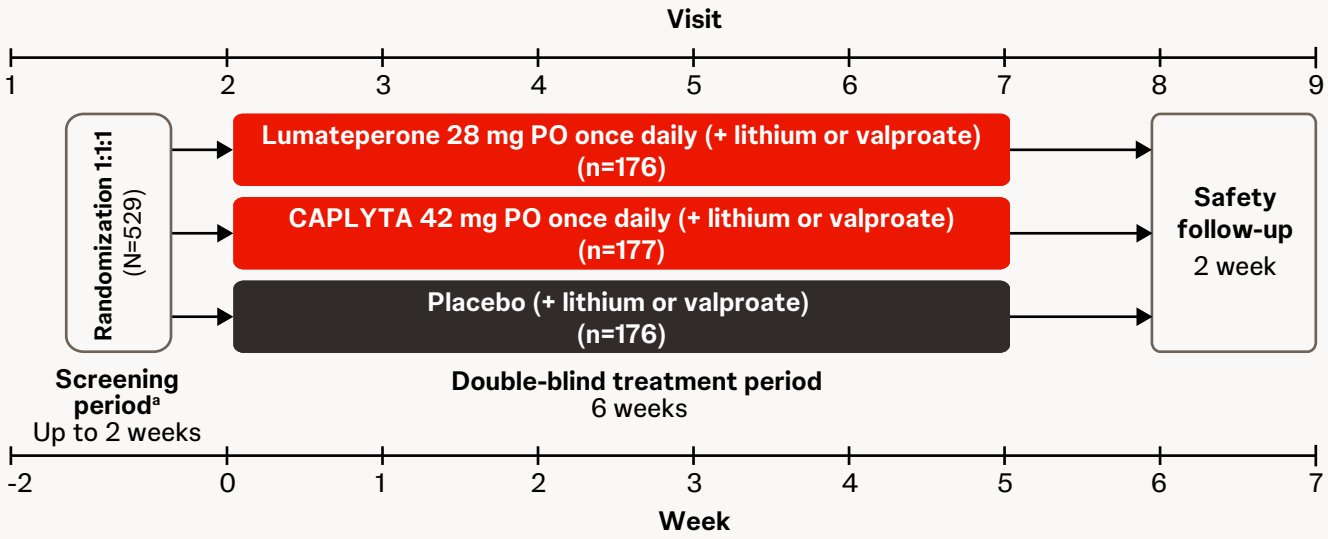
- **Study 402**[3] (NCT02600507) is a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of lumateperone 28 mg or CAPLYTA 42 mg adjunctive to lithium or valproate in the treatment of patients with MDEs associated with bipolar I or bipolar II disorder.

Study design[3]



- Key inclusion criteria[3]:
  - Adults (18-75 years old) with a diagnosis of bipolar I or bipolar II disorder per DSM-5 criteria, as confirmed by Structured Clinical Interview for DSM-5 Disorders—Clinical Trials Version or MINI
  - The start of the current MDE was at least 2 weeks but no more than 6 months prior to screening and must have caused clinically significant distress or functional impairment
  - At least moderate-to-severe depression with MADRS total score ≥20 and CGI-BP-S depression subscores of ≥4 and overall bipolar illness at the screening and baseline visits
  - YMRS total score of ≤12 at the screening and baseline visits
  - A minimum of 28 days of treatment with either lithium[b] or valproate[c] and inadequate response of depressive symptoms
- **Primary endpoint:** mean change in MADRS total score from baseline to day 43.
- **Key secondary endpoint:** mean change in CGI-BP-S score from baseline to day 43.

[a]Patients eligible for participation discontinued their current antidepressant or other psychotropic treatment during a screening period of up to 2 weeks, but continued treatment with lithium or valproate during the study.
[b]In addition to 0.4 to 1.5 mEq/L blood level at screening.
[c]In addition to 25 µg/mL blood level minimum at screening.

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Select baseline and disease characteristics (safety population)[3]

	Lumateperone 28 mg (n=176)	CAPLYTA 42 mg (n=177)	Placebo (n=175)
Age, years, mean (range)	44 (19-74)	45 (18-70)	45 (18-70)
Female, n (%)	101 (57.4)	109 (61.6)	98 (56)
Bipolar I disorder, n (%)	146 (83)	148 (83.6)	146 (83.4)
Bipolar II disorder, n (%)	30 (17)	29 (16.4)	29 (16.6)
Lithium adjunctive treatment, n (%)	50 (28.4)	51 (28.8)	50 (28.6)
Valproate adjunctive treatment, n (%)	126 (71.6)	126 (71.2)	125 (71.4)
Age at first bipolar diagnosis, mean (SD), years	32 (11.4)	32 (11.4)	32 (11.7)
No. of lifetime MDEs, n (%)			
1–9	145 (87.3)	140 (80.5)	143 (85.1)
10–20	18 (10.8)	28 (16.1)	22 (13.1)
>20	3 (1.8)	6 (3.4)	3 (1.8)
MADRS total score, mean (SD)	32.5 (5.6)	32.3 (5)	32.2 (5.2)
CGI-BP-S total score, mean (SD)			
Depression score	4.7 (0.6)	4.7 (0.6)	4.6 (0.5)
Overall bipolar illness subscore	4.7 (0.6)	4.7 (0.6)	4.6 (0.5)
Q-LES-Q-SF percent score, mean (SD)	36.3 (12)	37.9 (12.5)	38.6 (12.6)

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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- CAPLYTA 42 mg as adjunctive therapy to lithium or valproate showed significant improvement in the MADRS total score compared with placebo + lithium or valproate on day 43.[3]

Change in efficacy parameters at day 43 (ITT population)[3]

Parameters	Lumateperone 28 mg (n=171)	CAPLYTA 42 mg (n=174)	Placebo (n=174)
MADRS Total score (MMRM), LS mean change (SE)	−16.2 (0.79)	−16.9 (0.81)	−14.5 (0.79)
LSMD (95% CI), *P*-value	−1.7 (−3.65, 0.32), 0.099[a]	−2.4 (−4.42, −0.37), 0.021[a]	-
CGI-BP-S depression subscore (MMRM), LS mean change (SE)	−1.7 (0.09)	−1.8 (0.10)	−1.5 (0.09)
LSMD (95% CI), *P*-value	−0.3 (−0.5, −0.01), 0.040[a]	−0.3 (−0.59, −0.09), 0.008[a]	-
CGI-BP-S overall bipolar illness subscore (MMRM), LS mean change (SE)	−1.7 (0.09)	−1.8 (0.1)	−1.5 (0.09)
LSMD (95% CI)	−0.3 (−0.5, −0.01)	−0.3 (−0.58, −0.08)	-
Q-LES-Q-SF, percent score (MMRM)[b], LS mean change (SE)	17.9 (1.45)	19.5 (1.5)	15.4 (1.47)
LSMD (95% CI)	2.5 (−0.95, 5.94)	4.1 (0.53, 7.58)	-
MADRS Total score response (logistic regression), n (%)	85 (49.7)	78 (44.8)	68 (39.1)
OR (95% CI)	1.55 (1.006, 2.381)	1.27 (0.825, 1.948)	-
MADRS Total score remission (logistic regression), n (%)	53 (31)	49 (28.2)	54 (31)
OR (95% CI)	1 (0.633, 1.579)	0.87 (0.549, 1.381)	-

[a]*P*-values for the primary and key secondary analyses in the CAPLYTA 42-mg group were controlled for multiple comparisons.
[b]Q-LES-Q-SF is a 14-item questionnaire in which a higher score indicates a better QoL.

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Summary of AEs[3]

Event, n (%)	Lumateperone 28 mg (n=176)	CAPLYTA 42 mg (n=177)	Placebo (n=175)
≥1 TEAE	80 (45.5)	88 (49.7)	78 (44.6)
Drug-related TEAEs	60 (34.1)	64 (36.2)	48 (27.4)
Treatment-emergent SAE	0	1 (0.6)	0
Drug-related treatment-emergent SAE	0	0	0
Treatment-emergent death	0	0	0
Study discontinuation			
Due to TEAEs	3 (1.7)	14 (7.9)	5 (2.9)
Due to drug-related TEAE	3 (1.7)	10 (5.6)	3 (1.7)
Due to drug-related SAEs[a]	0	1 (0.6)	0
Due to drug-related treatment-emergent SAE	0	0	0
Death	0	0	0
Most common TEAEs			
Headache	23 (13.1)	20 (11.3)	20 (11.4)
Somnolence	13 (7.4)	20 (11.3)	6 (3.4)
Dizziness	18 (10.2)	19 (10.7)	4 (2.3)
Nausea	10 (5.7)	15 (8.5)	7 (4)

[a]This SAE was attributed to lithium toxicity and not related to the study drug.

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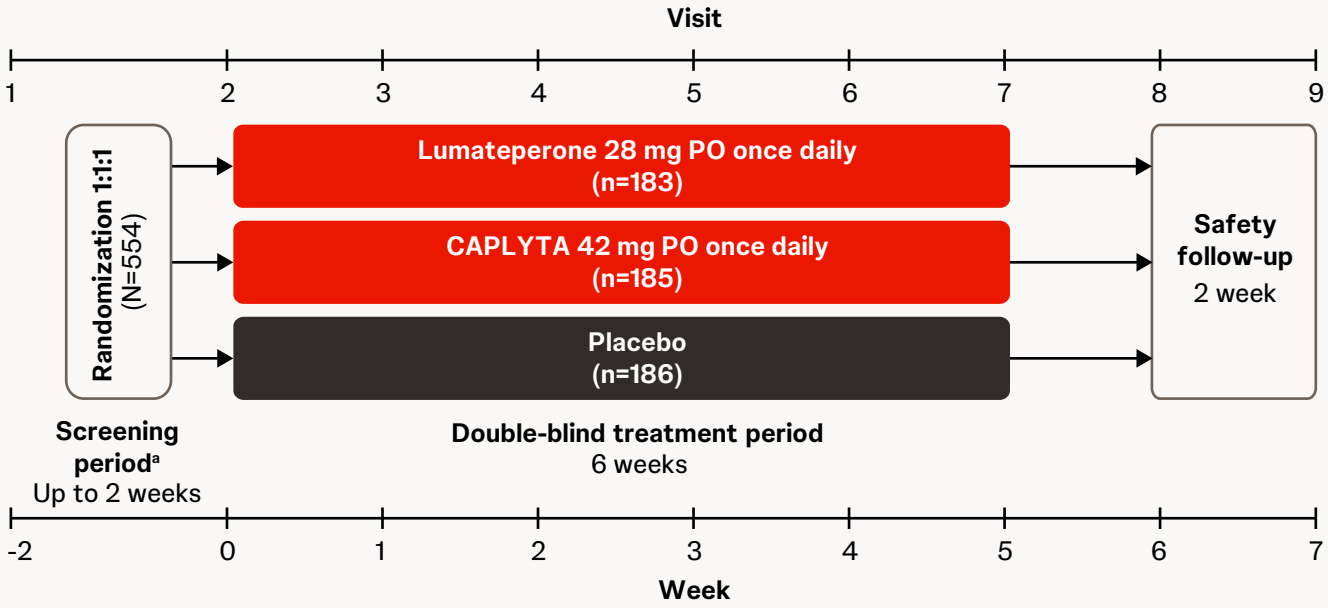
- **Study 401[4] Part A**, is a 6-week, phase 3, randomized, double-blind, placebo-controlled, outpatient, multicenter study to assess the efficacy and safety of lumateperone 28 mg and CAPLYTA 42 mg in patients with MDEs associated with bipolar I or bipolar II disorder.

Study design[4]



- Key inclusion criteria[4]:
  - Adults (18-75 years old) with a diagnosis of bipolar I or bipolar II disorder per DSM-5 criteria, and experiencing an MDE
  - The duration of MDE must be at least 2 weeks but no more than 6 months prior to screening and must have caused clinically significant distress or functional impairment
  - At least moderate depression with MADRS total score ≥20 and CGI-BP-S depression subscores of ≥4 and overall bipolar illness at the screening and baseline visits
  - YMRS total score of ≤12 at the screening and baseline visits
- **Primary endpoint:** mean change in MADRS total score from baseline to day 43.
- **Key secondary endpoint:** the time to first sustained response (≥50% reduction from baseline in MADRS Total score).

[a]Patients eligible for participation discontinued their current antidepressant or other psychotropic treatment during a screening period of up to 2 weeks.

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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- In the safety population, the majority were White (55.4%) with a mean age of 41.9 years.[4]

Select baseline and disease characteristics (safety population)[4]

	Lumateperone 28 mg (n=180)	CAPLYTA 42 mg (n=184)	Placebo (n=185)
Age, years, mean (SD)	40.5 (12.12)	42.7 (11.85)	42.3 (13.13)
Female, n (%)	109 (60.6)	111 (60.3)	114 (61.6)
Bipolar I disorder, n (%)	158 (87.8)	162 (88)	163 (88.1)
Bipolar II disorder, n (%)	22 (12.2)	22 (12)	22 (11.9)
Age at first bipolar diagnosis, mean (SD), years	26.3 (10.51)	29.4 (11.19)	28.2 (11.86)
No. of lifetime MDEs, n (%)			
1–9	85 (54.1)	90 (53.9)	80 (47.3)
10–20	61 (38.9)	65 (38.9)	71 (42)
>20	11 (7)	12 (7.2)	18 (10.7)
MADRS total score, mean (SD)	35.8 (6.08)	35.9 (5.79)	34.7 (5.84)
CGI-BP-S, mean (SD)			
Total score	11 (1.28)	10.9 (1.4)	10.6 (1.24)
Mania subscore	1.2 (0.47)	1.3 (0.55)	1.3 (0.53)
Depression score	4.9 (0.61)	4.8 (0.63)	4.7 (0.58)
Overall bipolar illness subscore	4.9 (0.61)	4.8 (0.63)	4.7 (0.58)
SDS total score, mean (SD)	20.2 (6.22)	20.7 (6.81)	20.4 (5.56)
Q-LES-Q-SF percent score, mean (SD)	34.2 (13.2)	35.2 (14.51)	37 (14.45)

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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- In the bipolar disorder subgroups, no statistically significant difference was observed in the mean change from baseline to day 43 in MADRS total score compared with placebo (lumateperone 28 mg vs CAPLYTA 42 mg vs placebo: −18.7 vs −20.7 vs −20.5 [for BPD I] and −22.2 vs −22.5 vs −15.4 [for BPD II]), respectively.[4]

Change from baseline to day 43 in MADRS and CGI-BP-S total score[12]

	Lumateperone 28 mg (n=172)	CAPLYTA 42 mg (n=166)	Placebo (n=177)
ITT Population			
Change from baseline to day 43 in MADRS total score, LS mean (SE)	−18.9 (1.11)	−20.7 (1.16)	−19.7 (1.11)
LSMD (95% CI)	0.9 (−1.83, 3.53)	−1 (−3.73, 1.79)	-
Change from baseline to day 43 in CGI-BP-S total score, LS mean (SE)	-3.5 (0.27)	-4.1 (0.28)	-3.9 (0.27)
LSMD (95% CI)	0.3 (−0.33, 1.01)	−0.3 (−0.94, 0.43)	-
Bipolar I			
Change from baseline to day 43 in MADRS total score in ITT population, LS mean (SE)	−18.7 (1.06)	−20.7 (1.11)	−20.5 (1.01)
LSMD (95% CI)	1.8 (−1.02, 4.65)	−0.2 (−3.13, 2.69)	-
Change from baseline to day 43 in CGI-BP-S total score in ITT population, LS mean (SE)	−3.4 (0.26)	−4 (0.28)	−4 (0.25)
LSMD (95% CI)	0.6 (−0.07, 1.33)	0.0 (−0.73, 0.72)	-

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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Change from baseline to day 43 in MADRS and CGI-BP-S total score[12]

	Lumateperone 28 mg (n=172)	CAPLYTA 42 mg (n=166)	Placebo (n=177)
Bipolar II			
Change from baseline to day 43 in MADRS total score in ITT population, LS mean (SE)	−22.2 (2.8)	−22.5 (2.96)	−15.4 (3.05)
LSMD (95% CI)	−6.8 (−14.73, 1.17)	−7.1 (−15.43, 1.17)	-
Change from baseline to day 43 in CGI-BP-S total score in ITT population, LS mean (SE)	−4.5 (0.70)	−4.8 (0.73)	−2.4 (0.75)
LSMD (95% CI)	−2.1 (−4.09, −0.11)	−2.4 (−4.49, −0.37)	-

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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Summary of TEAEs[4]

Event, n (%)	Lumateperone 28 mg (n=180)	CAPLYTA 42 mg (n=184)	Placebo (n=185)
≥1 TEAE	109 (60.6)	106 (57.6)	82 (44.3)
Drug-related TEAEs	83 (46.1)	78 (42.4)	48 (25.9)
Treatment-emergent SAE	5 (2.8)	0	1 (0.5)
Drug-related treatment-emergent SAE	1 (0.6)	0	0
Treatment-emergent death	0	0	0
Study discontinuation			
Due to TEAEs	14 (7.8)	15 (8.2)	4 (2.2)
Due to drug-related TEAE	8 (4.4)	13 (7.1)	3 (1.6)
Due to drug-related treatment-emergent SAE	1 (0.6)	0	0
Death	0	0	1 (0.5)
Patients with TEAEs in ≥5% in the CAPLYTA 42 mg group and more than twice that of placebo			
Somnolence	21 (11.7), *P*=0.005	24 (13), *P*=0.001	7 (3.8)
Headache	35 (19.4), *P*<0.001	20 (10.9), NS	10 (5.4)
Nausea	12 (6.7), NS	16 (8.7), NS	7 (3.8)
Dizziness	10 (5.6), NS	15 (8.2), *P*=0.009	4 (2.2)
Dry mouth	13 (7.2), *P*=0.009	15 (8.2), *P*=0.004	3 (1.6)
Diarrhea	9 (5), NS	10 (5.4), NS	5 (2.7)
Vomiting	5 (2.8), *P*<0.05	10 (5.4), *P*<0.001	0

Note: *P* values in the TEAEs occurring in ≥5% and at least twice that of placebo in the CAPLYTA 42 mg group indicate whether patients were significantly more likely to experience the TEAE vs placebo.

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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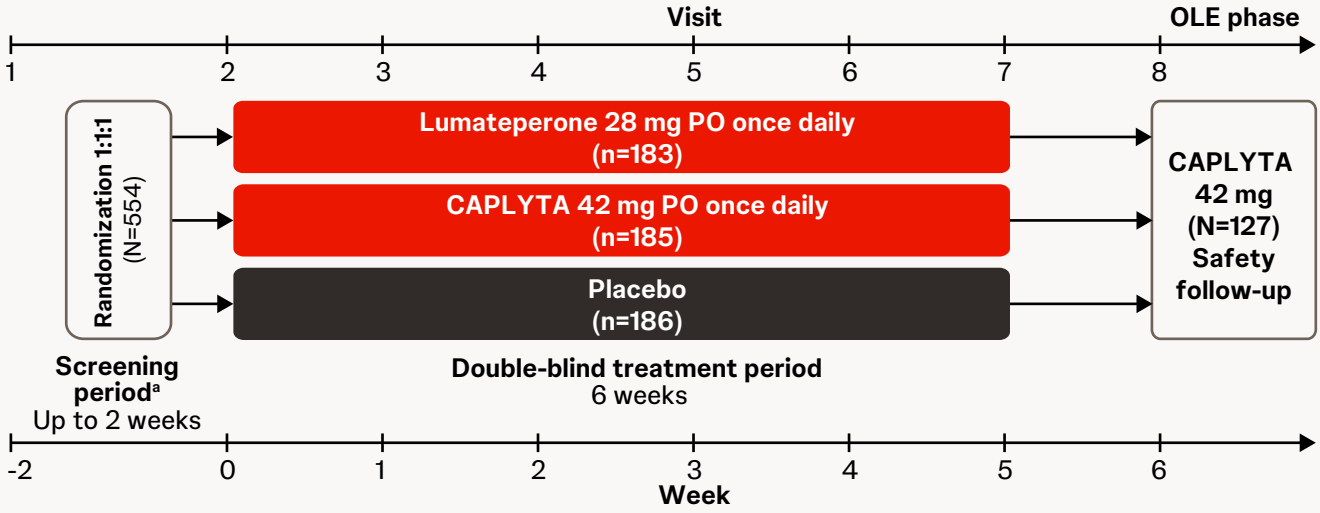
- **Study 401[5] Part B,** is a 6-month OLE period of 401 study that evaluated long-term safety of CAPLYTA 42 mg in patients with MDEs associated with BPD. Patients who completed the 6-week randomized controlled trial could choose to enter the OLE or not. Patients enrolling directly entered at Day 43 (Study Day 1), whereas those completing the short-term phase earlier were rescreened and enrolled after a gap between study phases.

Study design[5]



- Of the 127 patients receiving CAPLYTA 42 mg, 40 patients received lumateperone 28 mg, 43 patients received CAPLYTA 42 mg, and 44 patients received placebo in the randomized Part A of the study.
- Key inclusion criteria[5]:
  - Patients who completed 6-week, double-blind, randomized, placebo-controlled period of Study 401, which included lumateperone 28 mg, CAPLYTA 42 mg, or placebo
  - Adults (18-75 years old) with a diagnosis of bipolar I or bipolar II disorder per DSM-5 criteria
  - The start of the current MDE was at least 2 weeks but no more than 6 months prior to screening
  - At least moderate depression with MADRS total score ≥20 and CGI-BP-S depression subscores of ≥4 and overall bipolar illness at the screening and baseline visits
  - YMRS total score of ≤12 at the screening and baseline visits
- **Primary endpoint:** safety and tolerability of long-term CAPLYTA 42 mg treatment, as measured by AEs coded using the MedDRA version 20.1, clinical laboratory evaluations, ECGs, and vital sign measurements.
- **Secondary endpoints:** change from baseline in MADRS total score, CGI-BP-S total score, and Q-LES-Q-SF percent score.

[a]Patients eligible for participation discontinued their current antidepressant or other psychotropic treatment during a screening period of up to 2 weeks.

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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- The majority of patients were White (60.6%) and female (57.5%) with a mean age of 44.9 years.[5]

Select baseline and disease characteristics[5]

	CAPLYTA 42 mg (N=127)
Age, years, mean (SD)	44.9 (12.82)
Bipolar I disorder, n (%)	110 (86.6)
Bipolar II disorder, n (%)	17 (13.4)
Age at first bipolar diagnosis, mean (SD), years	30.1 (11.39)
No. of lifetime MDEs, n (%)	
1–9	42 (39.6)
10–20	53 (50)
>20	11 (10.4)
MADRS total score, mean (SD)	20.3 (12.73)
CGI-BP-S, mean (SD)	
Total score	8.1 (2.67)
Mania subscore	1.3 (0.61)
Depression score	3.4 (1.29)
Overall bipolar illness subscore	3.4 (1.29)
Q-LES-Q-SF percent score, mean (SD)	52.3 (17.10)

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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Summary of TEAEs[5]

Event, n (%)	CAPLYTA 42 mg (N=127)
≥1 TEAE	73 (57.5)
Drug-related TEAEs	54 (42.5)
Treatment-emergent SAE	4 (3.1)
Drug-related treatment-emergent SAE	1 (0.8)
Treatment-emergent death	0
Treatment discontinuation	
Due to TEAEs	12 (9.4)
Due to drug-related TEAE	8 (6.3)
Treatment-emergent SAE	3 (2.4)
Due to drug-related treatment-emergent SAE	1 (0.8)
Death	0
TEAEs reported in ≥10% patients	
Headache	26 (20.5)
Dry Mouth	15 (11.8)
Dizziness	13 (10.2)
Nausea	13 (10.2)

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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Change in efficacy parameters based on observed cases[6]

Parameters	CAPLYTA 42 mg (N=127)	
	Baseline, mean (SD)	Mean change at day 175 (SE)
	(n=127)	(n=74)
MADRS Total score	20.3 (12.73)	−8.9 (1.25)
	(n=127)	(n=71)
CGI-BP-S Total score	8.1 (2.67)	−2.3 (0.35)
CGI-BP-S depression subscore	3.4 (1.29)	−1.3 (0.16)
	(n=127)	(n=74)
Q-LES-Q-SF percent score	52.3 (17.1)	9 (1.92)

Note: *P*-value for all parameters is <0.0001 and all *P*-values are nominal. P-value is based on 1-sample t-test for mean change from baseline.

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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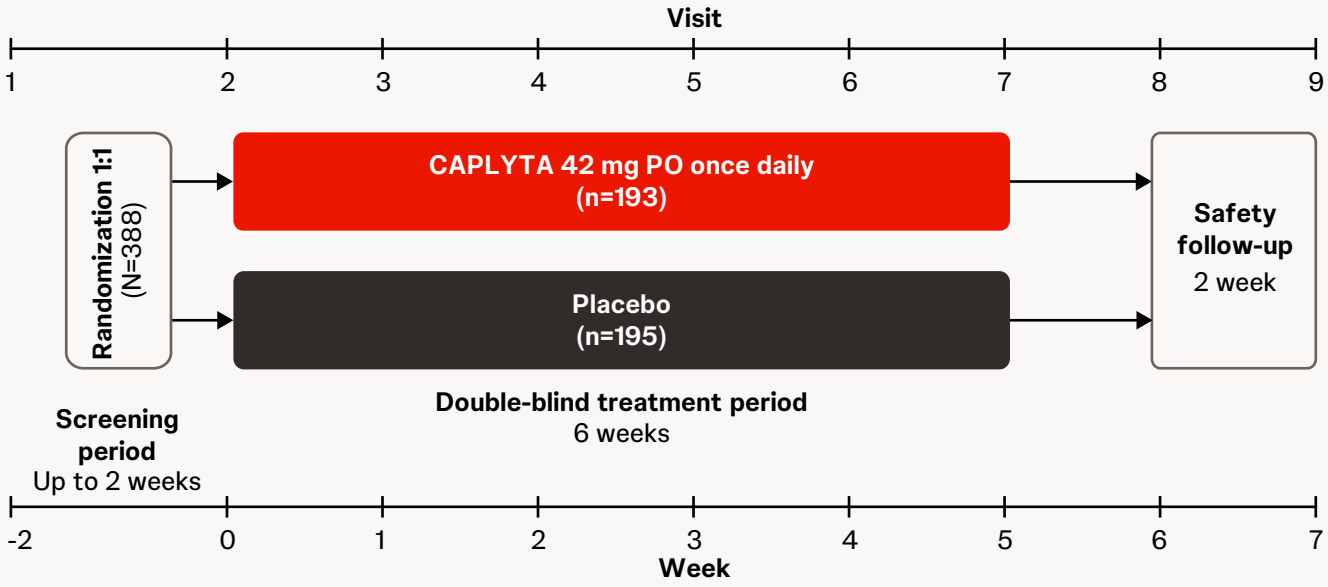
- **Study 403**[7] (NCT04285515) is a 6-week randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of CAPLYTA 42 mg for the treatment of patients with MDE associated with MDD or bipolar disorder (bipolar depression) with mixed features.

Study design[7,13]



- Key inclusion criteria[7,13]:
  - Adults (18-75 years old) with a diagnosis of MDD with mixed features or bipolar I or bipolar II disorder with mixed features
  - Body mass index (BMI) of 19–35 kg/m^2
  - Meeting the DSM-5 criteria for bipolar I and bipolar II disorder for mixed features, as confirmed by the investigator or sponsor-approved rater using the MINI and met all the following 4 criteria:
    - The start of the current MDE was at least 2 weeks but no more than 6 months prior to screening and causing clinically significant distress or functional impairment
    - A MADRS total score ≥24, at screening and baseline
    - A CGI-S score ≥4, at screening and baseline
    - A YMRS total score between 4 and 16 at screening and baseline
    - The patient had sufficient history and/or independent report verifying that the current MDE was causing clinically significant distress or impairment in social, occupational, or other important areas of functioning
- **Primary endpoint:** change in MADRS total score from baseline to day 43.
- **Key secondary endpoint:** change in CGI-S score from baseline to day 43.

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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- In the safety population, the majority were White (n=324; 84.2%) and female (n=238; 61.8%), with a mean age of 43 years.[7]
- Baseline characteristics were comparable across treatment groups and among patients in the combined MDD+BPD with mixed features group.[7]

Select baseline and disease characteristics[7]

	Combined MDD+BPD Group		BPD Group	
	CAPLYTA 42 mg (n=192)	Placebo (n=193)	CAPLYTA 42 mg (n=100)	Placebo (n=100)
Age, years, mean (SD)	43 (14.7)	43 (14)	42 (14.3)	41 (12.9)
Bipolar I disorder, n (%)	78 (40.6)	79 (40.9)	78 (78)	79 (79)
Bipolar II disorder, n (%)	22 (11.5)	21 (10.9)	22 (22)	21 (21)
MDD, n (%)	92 (47.9)	93 (48.2)	0	0
Age at first diagnosis, mean (SD), years	NA	NA	30 (12)	30 (10)
No. lifetime depressive episodes, n (%)				
1–9	NA	NA	86 (86)	85 (85)
10–20	NA	NA	9 (9)	13 (13)
>20	NA	NA	4 (4)	1 (1)
Baseline efficacy parameters, mITT population	n=192	n=191	n=100	n=99
MADRS total score, mean (SD)	31.3 (4.05)	31.1 (4.07)	31.8 (4.4)	31.1 (4.01)
CGI-S score, mean (SD)	4.5 (0.54)	4.5 (0.52)	4.6 (0.55)	4.6 (0.54)
YMRS total score, mean (SD)	9 (2.4)	9.2 (2.46)	8.7 (2.52)	9.1 (2.76)

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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- In the combined MDD/bipolar depression group, CAPLYTA 42 mg showed improvement in both MADRS total score and CGI-S score from baseline to day 43 compared with placebo.[7]

Change in MADRS total score and CGI-S score at day 43 (mITT population)[7,13]

	CAPLYTA 42 mg	Placebo
Combined MDD+BPD group	n=192	n=191
MADRS total score		
LS mean (SE) change	−18.1 (0.71)	−12.4 (0.7)
LSMD (95% CI; vs placebo)	−5.7 (−7.6 to −3.84)	-
Effect size; *P*-value	−0.64; *P*<0.0001	-
CGI-S score		
LS mean (SE) change	−1.8 (0.08)	−1.2 (0.08)
LSMD (95% CI; vs placebo)	−0.6 (−0.81 to −0.39)	-
Effect size; *P*-value	−0.59; *P*<0.0001	-
BPD group	n=100	n=99
MADRS total score		
LS mean (SE) change	−17.7 (1)	−12 (0.96)
LSMD (95% CI; vs placebo)	−5.7 (−8.29 to −3.05)	-
Effect size; unadjusted *P*-value	−0.64; *P*<0.0001[a]	-
CGI-S score		
LS mean (SE) change	−1.8 (0.11)	−1.2 (0.11)
LSMD (95% CI; vs placebo)	−0.6 (−0.91 to −0.31)	-
Effect size; unadjusted *P*-value	−0.61; *P*<0.0001[a]	-

[a]These endpoints were not adjusted for multiple comparisons. Therefore, the p-values displayed are nominal, and statistical significance has not been established.

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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- The most common TEAEs (≥5% in the CAPLYTA 42 mg group and more than twice that of the placebo group) were somnolence, dizziness, and nausea. Most TEAEs (>99%) were mild or moderate in severity.[7]

Summary of AEs[7]

Event, n (%)	Combined MDD+BPD Group		BPD Group	
	CAPLYTA 42 mg (n=192)	Placebo (n=193)	CAPLYTA 42 mg (n=100)	Placebo (n=100)
≥1 TEAE	104 (54.2)	72 (37.3)	57 (57)	42 (42)
Drug-related TEAEs	81 (42.2)	38 (19.7)	43 (43)	22 (22)
Treatment discontinuation due to AEs	9 (4.7)	3 (1.6)	7 (7)	2 (2)
Patients with SAEs	0	1 (0.5)	0	0
Patients who died	0	0	0	0
TEAEs in ≥5% in the CAPLYTA 42 mg group and more than twice that of placebo[a]				
Somnolence	24 (12.5)	3 (1.6)	13 (13)	2 (2)
Dizziness	23 (12)	4 (2.1)	12 (12)	0
Nausea	19 (9.9)	3 (1.6)	9 (9)	2 (2)

[a]For the bipolar depression population only, dry mouth (CAPLYTA 42 mg, 5 [5%] vs placebo 2 [2%]) and fatigue (CAPLYTA 42 mg, 5 [5%] vs placebo 1 [1%]) also met the criteria.

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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Bhagwagar et al[14] conducted a post hoc analysis of Study 403 to investigate the efficacy of CAPLYTA 42 mg in patients with MDD/BPD with mixed features and anxious distress.

- In the mITT population, 63.7% patients in the combined MDD/BPD population with mixed features (CAPLYTA 42 mg [n=123] vs placebo [n=121]) had anxious distress (with 54.3% in patients with BPD (CAPLYTA 42 mg [n=56] vs placebo [n=52]). CAPLYTA 42 mg showed improvement in MADRS and CGI-S scores from baseline at day 43 compared with placebo in patients with anxious distress:
  - MADRS total score: LSMD, −6.1 (95% CI: −8.52 to −3.71; ES: −0.67) in the MDD/BPD population and −5.5 (95% CI: −9.34 to −1.62; ES: −0.59) in the BPD population.
  - CGI-S score: LSMD, −0.5 (95% CI: −0.78 to −0.26; ES: −0.54) in the MDD/BPD population and −0.4 (95% CI: −0.82 to −0.05; ES: −0.48) in the BPD population.
  - Inner tension MADRS single-item score improved from baseline for both MDD/BPD or BPD populations at day 43.

Durgam et al[15] conducted a post hoc analysis in patients with MDD/BPD with mixed features to investigate efficacy of CAPLYTA 42 mg in improving anhedonia.

- CAPLYTA 42 mg showed improvement from baseline at day 43 compared with placebo in patients with combined MDD/BPD (CAPLYTA 42 mg [n=192] vs placebo [n=191]) and BPD (CAPLYTA 42 mg [n=100] vs placebo [n=99]) populations:
  - MADRS anhedonia factor score: LSMD, −3.4 (95% CI: −4.56 to −2.26; ES: −0.63) in the combined MDD/BPD population and −3.3 (95% CI: −4.89 to −1.67; ES: −0.61) in the BPD population.
  - In the combined MDD/BPD population, all MADRS items comprising the anhedonia factor score (apparent sadness, reported sadness, lassitude, and inability to feel) significantly improved with CAPLYTA 42 mg vs placebo at day 43.
  - In the combined MDD/BPD population, TEAEs were reported by 54.2% vs 37.3% in the CAPLYTA 42 mg vs placebo groups, respectively. The majority of TEAEs were mild to moderate in severity.

Durgam et al[16] conducted another post hoc analysis to define and measure response and remission based on reductions in both MADRS and YMRS scores in patients with MDEs with mixed features associated with MDD/BPD.

- At day 43, CAPLYTA 42 mg improved MADRS total score and YMRS total score compared with placebo in MDD/BPD population (CAPLYTA 42 mg [n=192] vs placebo [n=191]) and BPD population (CAPLYTA 42 mg [n=100] vs placebo [n=99]):
  - MADRS total score: combined MDD/BPD population (CAPLYTA 42 mg : LSMD, −18.1, ES: −0.64 vs placebo: LSMD, −12.4) and BPD population (CAPLYTA 42 mg : LSMD, −17.7, ES: −0.64 vs placebo: LSMD, −12).
  - YMRS total score: combined MDD/BPD population (CAPLYTA 42 mg : LSMD, −6, ES: −0.62 vs placebo: LSMD, −4.1) and BPD population (CAPLYTA 42 mg : LSMD, −5.6, ES: −0.51 vs placebo: LSMD, −4).

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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Study details	Study design	Efficacy outcomes	Safety outcomes
Durgam et al 2025[17] Efficacy of lumateperone in depression associated with bipolar II disorder: a pooled analysis of late-phase clinical trials	This post hoc analysis assessed the efficacy of CAPLYTA 42 mg in 3 pooled short term, Phase 3 studies in patients with MDE associated with bipolar II disorder, who were treated with CAPLYTA 42 mg monotherapy or adjunctive therapy. All 3 studies included 6-week of CAPLYTA 42 mg monotherapy or adjunctive therapy period followed by 2 weeks of safety follow-up. ITT population (CAPLYTA 42 mg, n=87 vs placebo, n=87) **Study endpoints:** • **Primary endpoint:** MADRS total score change from baseline to day 43. • **Secondary endpoints:** CGI-BP-S total and subscale scores change from baseline to day 43.	CAPLYTA 42 mg vs placebo: • LS mean change (SE) at day 43 in the ITT population: ◦ MADRS total score: −16.4 (1.19) vs −12.4 (1.17) ◦ CGI-BP-S total score: −3.4 (0.3) vs −2.4 (0.29) ◦ CGI-BP-S depression subscore: −1.7 (0.15) vs −1.3 (0.14) ◦ CGI-BP-S overall bipolar subscore: −1.7 (0.14) vs −1.2 (0.14) ◦ CGI-BP-S mania subscore: 0 (0.06) vs 0 (0.06) ◦ Q-LES-Q-SF percent scorea: 17.2 (1.91) vs 10.9 (1.88)	CAPLYTA 42 mg vs placebo: • Rate of TEAEs: 65.2% vs 48.3% • Drug-related TEAEs: 55.1% vs 30.3% • TEAEs (≥5% of patients and more than twice the rate of placebo): headache, 18% vs 6.7%; dizziness, 12.4% vs 5.6%; somnolence, 15.7% vs 2.2%; postural dizziness, 10% vs 1.1%; nausea, 10.1% vs 3.4%

[a]An increase in Q-LES-Q-SF percent score indicates improvement.

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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Study details	Study design	Safety outcomes
Escher et al 2022[18] Lumateperone in the treatment of major depressive episodes associated with bipolar I or bipolar II disorder: evaluation of extrapyramidal and motor symptoms in late-phase clinical trials	This pooled analysis assessed the incidence of EPS across three short-term studies and one long-term study of CAPLYTA 42 mg in patients with BPD. The short-term safety population comprised 746 patients from pooled monotherapy studies (CAPLYTA 42 mg, n=372; placebo, n=374) and 352 patients from adjunctive therapy with lithium or valproate studies (adjunctive CAPLYTA 42 mg, n=177; adjunctive placebo, n=175), and the long-term OLE safety population comprised 127 patients. **Study measures:** • Incidence and severity of EPS-related TEAEs. • EPS assessment scales (AIMS, BARS, and SAS).	• In the short-term studies, EPS-related TEAEs reported were mild dyskinesia with CAPLYTA monotherapy (n=1; 0.3%), mild akathisia with adjunctive CAPLYTA 42 mg (n=1; 0.6%), and severe akathisia with placebo in monotherapy trials (n=1; 0.3%). • AIMS, BARS, and SAS scores (mean change from baseline) were similar across groups for both monotherapy and adjunctive therapy studies. • In patients without SAS-assessed parkinsonism at baseline (SAS ≤3), SAS-confirmed incidences of parkinsonism (SAS >3) in monotherapy were (CAPLYTA 42 mg: n=2, 0.6%; placebo: n=1, 0.3%) and adjunctive therapy (CAPLYTA 42 mg: n=2, 1.2%; placebo: n=1, 0.6%). • In patients without BARS-assessed akathisia at baseline (BARS ≤2), BARS-confirmed akathisia (BARS >2) for monotherapy (CAPLYTA 42 mg: n=0, 0%; placebo: n=2, 0.6%) and adjunctive therapy (CAPLYTA 42 mg: n=2, 1.2%; placebo: n=2, 1.2%). • In the long-term study population, the EPS-related TEAE of akathisia (mild and moderate severity) was reported in 2 patients (1.6%).

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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Study details	Study design	Efficacy outcomes	Safety outcomes
Tohen et al 2022[19] Evaluation of mania and hypomania in late-phase clinical trials of lumateperone in the treatment of major depressive episodes associated with bipolar I or bipolar II disorder.	This analysis evaluated the incidence of mania and hypomania in patients with MDE associated with BPD who were treated with CAPLYTA 42 mg across short- and long-term studies. The short-term safety population comprised 746 patients from pooled monotherapy studies (CAPLYTA 42 mg, n=372; placebo, n=374) and 352 patients from adjunctive therapy with lithium or valproate studies (adjunctive CAPLYTA 42 mg, n=177; adjunctive placebo, n=175), and the long-term OLE safety population comprised 127 patients. Study endpoints: **Study measures:** • Incidence and severity of TEAEs of mania/ hypomania in the safety population. • YMRS Total score and CGI-BP-S mania subscore in the ITT population.	• ITT population: ◦ Mean change in the YMRS total score from baseline to day 43 was comparable between CAPLYTA 42 mg (n=354) and placebo (n=365) (LSMD, −0.5; 95% CI, −1 to 0.1; *P*=0.10). • Adjunctive treatment study: ◦ Mean change in the YMRS total score from baseline to day 43 was comparable between CAPLYTA 42 mg (n=174) and placebo (n=174; LSMD, −0.2; 95% CI, −0.8 to 0.4; *P*=0.56). • OLE safety population (N=127): ◦ The mean change in the YMRS score from baseline to the end of treatment was −0.5 (95% CI, −1.7 to 0.6; *P*=0.37).	• Safety population (pooled monotherapy groups): ◦ TEAEs of mania or hypomania of mild or moderate severity - CAPLYTA 42 mg group (n=372; 6 [1.6%]) vs placebo group (n=374; 5 [1.3%]). • Adjunctive therapy group: ◦ One patient each in the CAPLYTA 42 mg (n=177) and placebo (n=175) groups reported mania or hypomania. In the CAPLYTA 42 mg monotherapy group, 1 patient reported a serious TEAE of mania. • OLE safety population (N=127): ◦ One patient reported a TEAE of mild mania in the CAPLYTA 42 mg group.

CAPLYTA® (lumateperone)
Use in bipolar depression (bipolar disorder I and II)

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Study details	Study design	Safety outcomes
Correll et al 2023[20] Metabolic syndrome in bipolar depression with lumateperone (ITI-007): a post hoc analysis of 2 randomized, placebo-controlled trials	This post hoc pooled analysis of Study 401 and Study 404 compared rates of MetSya with CAPLYTA 42 mg and placebo in the treatment of BPD. **Analysis population:** CAPLYTA 42 mg, n=372 vs placebo, n=374 **Study measure:** • Rates of MetSy in safety population.	• Rates of MetSy: ◦ At baseline: 20.7% vs 22.2% ◦ At EOT: 21.8% vs 23.8% • CAPLYTA 42 mg vs placebo patients (36.4% vs 30.1%) improved from having MetSy at baseline to no longer meeting MetSy criteria at EOT. • BP for CAPLYTA 42 mg (46.8%) and glucose for placebo (43.2%) was the individual criteria that shifted the most from meeting MetSy criteria at baseline to no longer meeting criteria at EOT. • The rate of MetSy developed during treatment was comparable between CAPLYTA 42 mg and placebo (10.8% vs 10.7%) with nearly half of these patients (CAPLYTA 42 mg, 43.8%; placebo, 45.2%) shifting due to a change in ≥2 criteria.
Davis et al 2021[21] Metabolic profile of lumateperone (ITI-007) monotherapy in bipolar depression: a post hoc analysis of 2 randomized, placebo-controlled trials	This pooled safety analysis evaluated the metabolic profile of CAPLYTA 42 mg monotherapy in the treatment of BPD. The safety population comprised 746 patients from pooled monotherapy studies (CAPLYTA 42 mg, n=372; placebo, n=374). **Study measure:** • AEs, laboratory parameters, and vital signs.	• Mean change from baseline to the last on-treatment value (CAPLYTA 42 mg vs placebo): ◦ Weight: +0.06 kg vs +0.19 kg ◦ BMI: +0.02 kg/m2 vs +0.07 kg/m2 ◦ Waist circumference: 0.18 cm vs 0.03 cm ◦ Cholesterol: −0.6 mg/dL vs −1.1 mg/dL ◦ LDL-cholesterol: −0.7 mg/dL vs −0.6 mg/dL ◦ HDL-cholesterol: +0.4 mg/dL vs 0 mg/dL ◦ Triglycerides: −1.4 mg/dL vs −4 mg/dL ◦ Glucose: +0.1 mg/dL vs 0 mg/dL

[a]MetSy definition includes meeting 3 of the following 5 criteria: waist circumference >40 in (men) or >35 in (women), triglycerides ≥150 mg/dL, high density lipoprotein cholesterol <40 mg/dL (men) or <50 mg/dL (women), systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg, fasting glucose ≥100 mg/dL.

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Use in bipolar depression (bipolar disorder I and II)

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Study details	Study design	Safety outcomes
McElroy et al 2021[22] The safety and tolerability of lumateperone 42 mg for the treatment of bipolar depression: a pooled analysis of 2 randomized placebo-controlled trials	This pooled safety analysis evaluated the safety and tolerability profile of CAPLYTA 42 mg in patients with bipolar I or bipolar II disorder experiencing a MDE or BPD. The safety population comprised 746 patients from pooled studies (CAPLYTA 42 mg, n=372; placebo, n=374). **Study measure:** • AEs, laboratory parameters, vital signs, and changes in EPS scales.	• CAPLYTA 42 mg vs placebo: ◦ Rate of TEAEs: 56.2% vs 47.3% ◦ TEAEs (≥5%): ◦ Headache:14.2% vs 7.8% ◦ Somnolence: 13.2% vs 3.2% ◦ Rate of discontinuation due to AEs: 7% vs 2.1% ◦ TEAEs rates of mania/hypomania: 1.6% vs 1.3%

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AE	Adverse event	**ISBD**	International Society for Bipolar Disorders
AIMS	Abnormal Involuntary Movement Scale	**ITT**	Intent-to-treat
BARS	Barnes Akathisia Rating Scale	**LDL**	Low-density lipoprotein
BMI	Body mass index	**LS**	Least squares
BP	Blood pressure	**LSMD**	Least squares mean difference
BPD	Bipolar depression	**MADRS**	Montgomery-Åsberg Depression Rating Scale
CGI-BP-S	Clinical Global Impression Scale of Bipolar Disorder-Severity	**MDD**	Major depressive disorder
CGI-S	Clinical Global Impression-Severity Scale	**MDE**	Major depressive episodes
CI	Confidence interval	**MedDRA**	Medical Dictionary for Regulatory Activities
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition	**MetSy**	Metabolic syndrome
ECG	Electrocardiogram	**MINI**	Mini International Neuropsychiatric Interview
EOT	End of treatment	**mITT**	Modified intent-to-treat
EPS	Extrapyramidal symptoms	**MMRM**	Mixed-effects model for repeated measures
ES	Effect size	**NS**	Not significant
HDL	High-density Lipoprotein	**OLE**	Open-label expansion

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OR	Odds ratio	**SD**	Standard deviation
PO	Orally	**SDS**	Sheehan Disability Scale
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form	**SE**	Standard error
QoL	Quality of life	**TEAE**	Treatment-emergent adverse event
SAE	Serious adverse event	**YMRS**	Young Mania Rating Scale
SAS	Simpson Angus Scale		

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A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal/external databases) was conducted on 4 February 2026.

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Use in bipolar depression (bipolar disorder I and II)

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