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FDA Opening Remarks

Psychopharmacologic Drugs Advisory Committee Meeting
November 4, 2021

Intranasal carbetocin (LV-101) for the treatment of hyperphagia associated with Prader-Willi syndrome

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Prader-Willi Syndrome

- Rare and serious genetic disorder with cognitive, behavioral, and endocrine symptoms and characteristic physical features
- Caused by loss of expression of paternally derived genes on chromosome 15q11-13

Prader-Willi Syndrome

- Multiple nutritional phases (hyperphagia onset phase 3)
- Hyperphagia characterized by profound lack of satiety, constant preoccupation with food, and food-seeking behavior
- Obesity results from hyperphagia and decreased resting energy expenditure
- Shortened life expectancy appears related mainly to hyperphagia and obesity, including cardiopulmonary and gastrointestinal complications

Prader-Willi Syndrome

- Management of hyperphagia consists of a restricted calorie diet and strict environmental controls
- No available medication effective for treating hyperphagia
- Management has significant impact on quality of life

Prader-Willi Syndrome

- In addition to food-related behavioral and emotional difficulties, individuals with Prader-Willi syndrome (PWS) may experience symptoms such as anxiety, obsessive thoughts and compulsive behaviors, difficulty with change in routine, mood lability, skin picking

Intranasal (IN) carbetocin (LV-101)

- Synthetic neuroendocrine peptide analogue of oxytocin binds selectively with oxytocin receptors, attenuated binding to vasopressin receptors
- Administered three times daily via nasal spray pump
- Proposed indication: treatment of hyperphagia, anxiety, and distress behaviors associated with PWS

Substantial Evidence

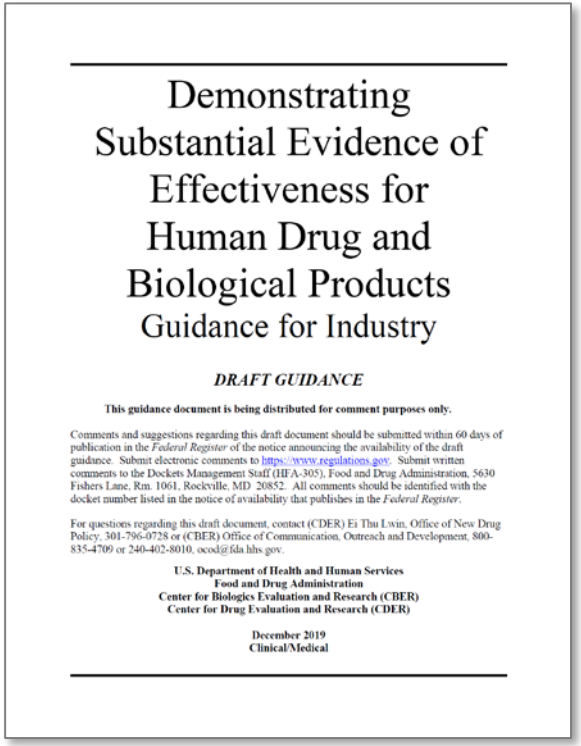
- Statutory standard*:

  "…evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

*FD&C Act section 505(d) (21 U.S.C. § 355(d))

Substantial Evidence

- At least two adequate and well-controlled clinical investigations
- Under certain circumstances:
  - One large multicenter trial that has certain characteristics to satisfy the legal requirement for substantial evidence
  - One adequate and well-controlled clinical investigation plus confirmatory evidence



Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ei Thu Lwin, Office of New Drug Policy, 301-796-0728 or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010, ocod@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)

December 2019
Clinical/Medical

Applicant's Submission

- Study 114
  - Proof-of-concept
  - Carbetocin 9.6 mg three times daily (TID) vs placebo
  - Change from baseline to Day 15 on hyperphagia
- Study LV-101-3-01
  - Phase 3 adequate and well-controlled study
  - Examined two different doses of carbetocin—9.6 mg or 3.2 mg TID—vs placebo
  - Change from baseline to Week 8 on hyperphagia and obsessive-compulsive symptoms
  - Primary analysis evaluated 9.6 mg vs placebo—no difference detected
  - Secondary analysis considered *post hoc* (prespecified analysis plan stopped when primary negative) suggests difference between 3.2 mg and placebo
- Long-term follow-up
  - Compared 9.6 mg and 3.2 mg
  - No placebo arm
  - Provides long-term safety data

Purpose of Meeting

- Question for the Committee:
  - Has the Applicant provided substantial evidence of effectiveness for carbetocin nasal spray (LV-101) in the treatment of hyperphagia associated with Prader Willi syndrome?

Intranasal carbetocin (LV-101) for the treatment of hyperphagia associated with Prader-Willi syndrome

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Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Outline

- Relevant Regulatory History
- Efficacy
  - Study 000114 (Study 114)
  - Study LV-101-3-01 (Study 301)
- Safety
- Statistical Assessment
- Conclusion

Regulatory History

- Carbetocin has not been approved or marketed in the United States
- Applicant acquired a license to develop intranasal (IN) carbetocin in August 2017
- Agency and Applicant have had multiple interactions regarding the completed phase 2 study (Study 114) and phase 3 study (Study LV-101-3-01)

Relevant Agency Guidance

- At the May 2018 End-Of-Phase 2 meeting, the Agency:
  - Provided feedback on the phase 3 study primary and secondary endpoints and other design elements
  - Recommended a dose-finding study
  - Noted that a longer-term safety study would be required prior to approval
- Provided statistical comments on Study LV-101-3-01

Relevant Agency Guidance

- At the November 2020 pre-NDA meeting, the Agency:
  - Discussed the results of Study 114 and Study LV-101-3-01
  - Expressed concern that, based on the prespecified primary analysis, Study LV-101-3-01 was not a positive study
  - Noted that conflicting results between Studies 114 and LV-101-3-01 are difficult to reconcile

Phase 2 and 3 Studies

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Study 114

Study 114: Design & Population

- Phase 2, randomized, double-blind, placebo-controlled, multicenter, proof-of-concept study of IN carbetocin 9.6 mg three times daily versus placebo
- 14-day treatment period with follow-up call on Day 19
- 38 planned subjects ages 10 to 18 years
  - genetically confirmed PWS
  - in nutritional phase 3
  - baseline Hyperphagia in PWS Questionnaire-Responsiveness (HPWSQ-R) score > 13
  - stable psychotropic medications doses for ≥ 6 months before screening

Study 114: Primary Endpoint

- Change from baseline (Day 1) to end-of-treatment (Day 15) on the HPWSQ-R total score
  - 11-item observer-reported outcome measure
  - Hyperphagia, drive, and severity domains
  - Agency agreed with use in exploratory phase 2 study, though noted that the scale may be limited in its ability to detect change

Study 114: Secondary Endpoints

- Clinical Global Impression-Improvement (CGI-I) at Day 15
- Change from baseline to Day 15 on the:
  - Domain scores for the HPWSQ-R
  - HPWSQ-R-Clinician total score and domain scores
- Change from screening to Day 15 on the:
  - Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) score
    - Clinician-administered, 10-item severity scale
  - Food Domain of the Reiss Profile

Study 114: Statistical Design

- 38 patients provided
  - At least 80% power to detect a treatment difference of 5 points with a standard deviation of 6
  - At a one-sided alpha level = 0.1
- No pre-specified plan to control type I error rate for multiple comparisons over the primary and secondary endpoints
- Primary analysis:
  - Analysis of Covariance (ANCOVA) model with treatment and site as fixed effects and HPWSQ-R baseline score as a covariate

Study 114: Analysis Set

- 38 subjects randomized
  - One screen failure subject randomized in error
- 37 dosed subjects in Full Analysis Set (FAS)
  - 17 IN carbetocin 9.6 mg
  - 20 placebo
- One placebo subject discontinued (for adverse events [AEs])

Study 114: Demographics

- Mean age 13.7 years
- 62% female and 38% male
- 97% White
- 97% Not Hispanic or Latino

- Baseline HPWSQ-R
  - Mean = 35.6 IN carbetocin
  - Mean = 39.7 placebo
- Baseline CY-BOCS
  - Mean = 15.4 IN carbetocin
  - Mean = 16.0 placebo

Study 114: Inspection Findings
Primary Endpoint

- During FDA inspection of a study site, Agency investigator noted discrepancy between paper source and study database for one placebo subject on the HPWSQ-R Day 15 results
- Applicant re-analyzed Study 114 using the corrected data

Study 114: Primary Endpoint

Primary endpoint HPWSQ-R total score	IN carbetocin 9.6 mg - original (N=17)	Placebo - original (N=20)	IN carbetocin 9.6 mg - updated (N=17)	Placebo - updated (N=20)
Baseline mean (SD)	35.6 (7.20)	39.7 (7.62)	35.6 (7.20)	39.7 (7.62)
CFB to Day 15				
LS mean (SE)	-15.6 (3.06)	-8.9 (2.61)	-15.7 (3.05)	-8.8 (2.60)
LS mean difference versus placebo	-6.7		-6.9	
Upper limit of 90% CI	-2.2		-2.5	
95% CI	-13.2, 0.10		-13.4, -0.11	
One-sided p-value	0.0290		0.0244	
Two-sided p-value	0.0580		0.0488	

- Source: Adapted from Study 000114 Clinical Study Report, Table 9-1; verified by Statistical Reviewer
- CI = confidence interval, LS = least squares, SD = standard deviation, SE = standard error
- Note: For placebo Subject 101-003, the Day 8 assessment was imputed for invalid values at Day 15, because it was an early termination visit after discontinuation for an adverse event.

Study 114: Secondary Endpoints

Secondary endpoint	IN carbetocin 9.6 mg (N=16) versus Placebo (N=19)
CGI-I Day 15	
LS mean difference versus placebo	-0.8
Upper limit of 90% CI	-0.3
95% CI	-1.62, -0.12
One-sided p-value	0.0233
CY-BOCS change from Baseline to Day 15	
LS mean difference versus placebo	-6.2
Upper limit of 90% CI	-3.3
95% CI	-10.4, -1.67
One-sided p-value	0.0047

- Source: Adapted from Study 000114 Clinical Study Report, Tables 9-4 and 9-6; verified by Statistical Reviewer
- CGI-I = Clinical Global Impression-Improvement, CI = confidence interval, CY-BOCS = Children's Yale-Brown Obsessive-Compulsive Scale, LS = least squares
- Note: One subject in each treatment group did not have valid Day 15 results; both were excluded

Study 114: Efficacy Highlights

- Provides preliminary evidence for effect of 9.6 mg of carbetocin on hyperphagia
- Clinical meaningfulness of observed treatment effect unclear
- Study duration insufficient to evaluate chronic disease needing lifelong treatment
- Promising proof-of-concept results

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Study LV-101-3-01

Study LV-101-3-01: Design

- Phase 3, randomized, double-blind, placebo-controlled, multicenter study of IN carbetocin 9.6 mg or 3.2 mg three times daily versus placebo
- 8-week, double-blind, placebo-controlled treatment period followed by 56-week Long-Term Follow-Up (LTFU) period, with option for extension
  - LTFU was unblinded to active drug, blinded to dose
- Subjects randomized 1:1:1 to
  - 9.6mg carbetocin, 3.2mg carbetocin, or Placebo
  - At baseline, placebo subjects further randomized at 1:1 to switch to either 9.6 mg or 3.2 mg in the LTFU

Study LV-101-3-01: Population

- 175 planned subjects ages 7 to 18 years with genetically-confirmed PWS in nutritional phase 3
- Screening and baseline Hyperphagia Questionnaire for Clinical Trials (HQ-CT) score ≥ 13, CY-BOCS ≥ 9
- No new food-related interventions (including environment or dietary restrictions) within 1 month of screening (or during study)
- Stable doses of permitted chronic concomitant medications for ≥ 3 months before and expected during study

Study LV-101-3-01: Primary Endpoints

- Change from Baseline to Week 8 for the HQ-CT total score in the 9.6 mg arm
  - 9-item observer-reported outcome measure, revision of HPWSQ-R
  - Assesses hyperphagia-related behaviors
- Change from Baseline to Week 8 in CY-BOCS Severity Rating total score in the 9.6 mg arm
  - Clinician-administered, 10-item severity scale

Study LV-101-3-01: Secondary Endpoints

- First Secondary: Change from Baseline to Week 8 in HQ-CT and CY-BOCS in the 3.2 mg arm
- Other secondary endpoints in both the 9.6 mg and 3.2 mg arms:
  - Change from Baseline to Week 8 on the PWS Anxiety and Distress Behaviors Questionnaire (PADQ) score
    - Agency disagreed with adequacy as an observer-reported outcome
  - CGI-Change (CGI-C) score at Week 8
  - Change from Baseline to Week 8 on an HQ-CT subset (items 1, 2, 5, 6, 8, and 9) and on HQ-CT item 9
    - Agency disagreed with use of HQ-CT subsets

Study LV-101-3-01: Pre-specified Statistical Analysis

- Overall type I error specified at alpha = 0.05
- Pre-specified control for multiple comparisons:
  - Combined Hochberg procedure and hierarchical testing procedure
- Applicant proposed 175 subjects would provide 90% for the HQ-CT and 99% power for the CY-BOCS assuming phase 2 results held in phase 3
  - HQ-CT: 5.5 mean difference with standard deviation = 8.5
  - CY-BOCS: 5.7 mean difference with standard deviation = 6.4
- Constrained Longitudinal Data Analysis (cLDA) model for primary endpoint
  - LS means estimates for treatment effects

Potentially Clinically Meaningful Within-Patient Change on the HQ-CT

- 2016 psychometric validation report suggest a 7.7 point improvement as within-patient responder threshold
- Subjects in each arm of Study LV-101-3-01 with 8 points or better improvement:
  - Placebo: 5 of 40 (12.5%)
  - 3.2 mg: 13 of 39 (33.3%)
  - 9.6 mg: 9 of 40 (22.5%)

Study LV-101-3-01: Analysis Sets

- Because of the COVID-19 pandemic, Applicant held enrollment on March 12, 2020, and defined two analysis sets:
  - Primary Analysis Set (PAS): 119 randomized subjects who received ≥ 1 dose of IN carbetocin and completed either Week 2 or 8 visits before March 1, 2020
    - Only observations before March 1, 2020, were used in the primary analysis
  - Full Analysis Set (FAS): 130 randomized subjects who received ≥ 1 dose of IN carbetocin

Study LV-101-3-01: Analysis Sets

	IN carbetocin 3.2 mg (N=43) n (%)	IN carbetocin 9.6 mg (N=44) n (%)	Placebo (N=43) n (%)	Total (N=130) n (%)
Safety Analysis Set[a]	43 (100.0)	44 (100.0)	43 (100.0)	130 (100)
Full Analysis Set[b]	43 (100.0)	44 (100.0)	43 (100.0)	130 (100)
Primary Analysis Set[c]	39 (90.7)	40 (90.9)	40 (93.0)	119 (91.5)
Per-Protocol Analysis Set[d]	36 (83.7)	33 (75.0)	36 (83.7)	105 (80.7)

Source: Adapted from Study LV-101-3-01 Clinical Study Report, Table 12

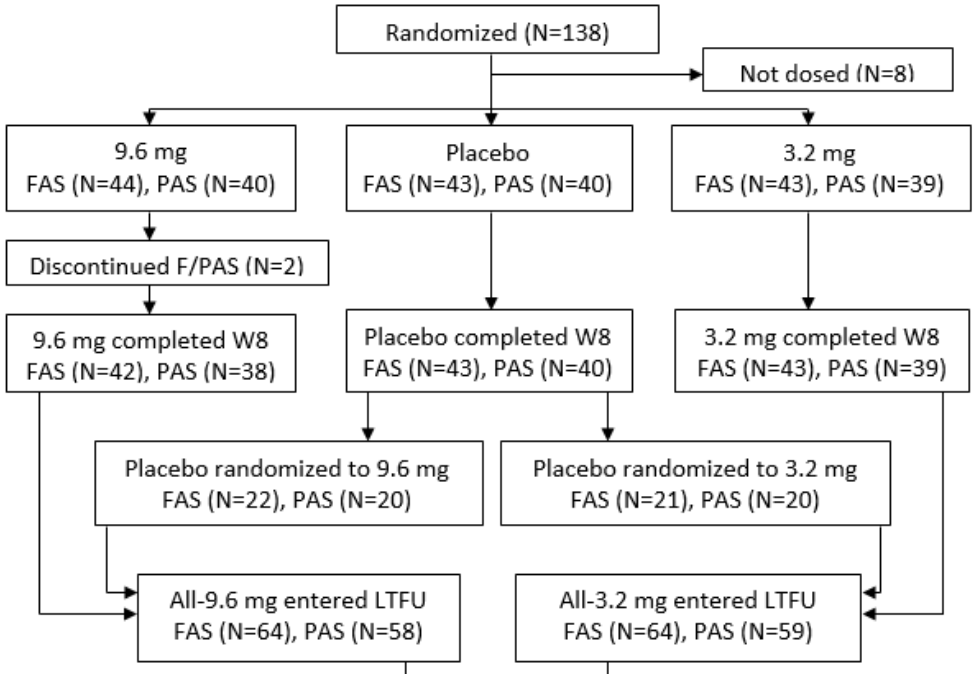
[a] The Safety Analysis Set included all subjects who received at last one dose of investigational product. Counts are based on treatment received.

[b] The Full Analysis Set included subjects who were both randomized and dosed. Counts are based on randomized treatment.

[c] The Primary Analysis Set included all subjects in the FAS with at least one post-Baseline visit completed prior to March 1, 2020. Counts are based on randomized treatment.

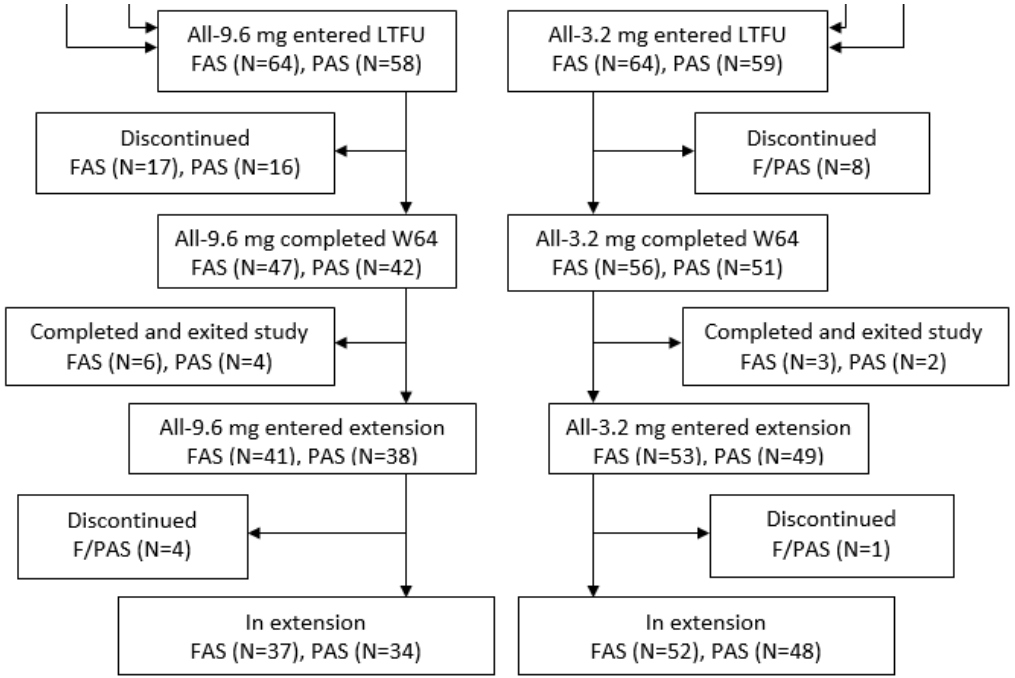
[d] The Per-Protocol Analysis Set included subjects in the PAS who did not meet criteria for PPS exclusion as outline in the Statistical Analysis Plan. Counts are based on randomized treatment.

Subject Disposition Through Start of LTFU



Source: Clinical reviewer-created from 120-day safety update, Table 14.1A.2, and ADSL dataset
FAS = Full Analysis Set, LTFU = Long-Term Follow-Up, PAS = Primary Analysis Set, W8 = Week 8

Subject Disposition Through Ongoing Extension



Source: Clinical reviewer-created from 120-day safety update, Table 14.1A.2, and ADSL dataset
FAS = Full Analysis Set, LTFU = Long-Term Follow-Up, PAS = Primary Analysis Set, W64 = Week 64

Note: In-extension and discontinuations during extension numbers current as of June 18, 2021 data cutoff.

Study LV-101-3-01: Demographics

- Mean age = 12 years across all arms
- 85% White
- 91% Not Hispanic or Latino across all arms
- Sex:
  - 9.6 mg 48% female, 53% male
  - 3.2 mg 62% female, 39% male
  - Placebo 58% female, 43% male

Study LV-101-3-01: Baseline Scores (PAS)

	IN carbetocin 3.2 mg (N=39)	IN carbetocin 9.6 mg (N=40)	Placebo (N=40)	Total (N=119)
HQ-CT				
Mean (SD)	22.1 (5.1)	23.4 (5.7)	22.4 (4.7)	22.6 (5.2)
Median	22.0	24.0	21.0	22.0
Min, Max	13, 31	13, 35	15, 34	13, 35
CY-BOCS				
Mean (SD)	25.2 (4.5)	27.9 (5.1)	27.8 (6.0)	27.0 (5.3)
Median	26.0	28.5	27.5	27.0
Min, Max	13, 33	8, 35	15, 40	8, 40

Source: Statistical Reviewer Analysis; adsl.xpt

CY-BOCS = Children's Yale-Brown Obsessive-Compulsive Scale, HQ-CT = Hyperphagia Questionnaire for Clinical Trials, Min = minimum, Max = maximum, PAS = Primary Analysis Set, SD = standard deviation

Study LV-101-3-01: Key Results

9.6 mg Carbetocin

- HQ-CT
  - Treatment difference of -1.2
  - P-value = 0.3493
- CY-BOCS
  - Treatment difference of -0.6
  - P-value = 0.6001
- No evidence of efficacy on either endpoint

3.2 mg Carbetocin

- HQ-CT
  - Treatment difference of -3.1
  - P-value = 0.0162
- CY-BOCS
  - Treatment difference of -0.8
  - P-value = 0.5143
- Potential efficacy signal for HQ-CT

Study LV-101-3-01: Primary Endpoints (9.6 mg dose; Primary Analysis Set)

Endpoint	Visit		IN carbetocin 9.6 mg (N = 40)	Placebo (N = 40)
HQ-CT	Baseline	Mean[a] (SE)	22.22 (0.730)	
	Week 2	LS mean CFB (SE)	-3.402 (0.905)	-2.977 (0.894)
		LS mean difference vs. placebo	-0.4250	--
		(95% CI of LS mean differences)	(-2.821, 1.971)	--
		Two-sided p-value	--	--
	Week 8	LS mean CFB (SE)	-3.439 (0.946)	-2.237 (0.943)
		LS mean difference vs. placebo	-1.202	--
		(95% CI of LS mean differences)	(-3.729, 1.324)	--
		Two-sided p-value	0.3493	--
CY-BOCS	Baseline	Mean (SE)	27.33 (0.632)	
	Week 2	LS mean CFB (SE)	-2.571 (0.824)	-1.220 (0.810)
		LS mean difference vs. placebo	-1.351	--
		(95% CI of LS mean differences)	(-3.514, 0.811)	--
		Two-sided p-value	--	--
	Week 8	LS mean CFB (SE)	-2.968 (0.862)	-2.360 (0.855)
		LS mean difference vs. placebo	-0.608	--
		(95% CI of LS mean differences)	(-2.890, 1.674)	--
		Two-sided p-value	0.6001	--

Source: Statistical Reviewer; adef.xpt
CFB = change from baseline, CI = confidence interval, CY-BOCS = Children's Yale-Brown Obsessive-Compulsive Scale, HQ-CT = Hyperphagia Questionnaire for Clinical Trials, LS = least squares, SE = standard error
[a] Baseline mean is estimated from the cLDA primary analysis model

Study LV-101-3-01: Secondary Endpoints (3.2 mg dose; Primary Analysis Set)

Endpoint	Visit		IN carbetocin 3.2 mg (N = 39)	Placebo (N = 40)
HQ-CT	Baseline	Mean[a] (SE)	22.22 (0.730)	
	Week 2	LS mean CFB (SE)	-5.983 (0.907)	-2.977 (0.894)
		LS mean difference vs. placebo	-3.006	--
		(95% CI of LS mean differences)	(-5.410, -0.602)	--
		Two-sided p-value	--	--
	Week 8	LS mean CFB (SE)	-5.372 (0.957)	-2.237 (0.943)
		LS mean difference vs. placebo	-3.136	--
		(95% CI of LS mean differences)	(-5.685, -0.586)	--
		Two-sided p-value	0.0162	--
CY-BOCS	Baseline	Mean (SE)	27.33 (0.632)	
	Week 2	LS mean CFB (SE)	-3.037 (0.826)	-1.220 (0.810)
		LS mean difference vs. placebo	-1.818	--
		(95% CI of LS mean differences)	(-3.990, 0.353)	--
		Two-sided p-value	--	--
	Week 8	LS mean CFB (SE)	-3.123 (0.873)	-2.360 (0.855)
		LS mean difference vs. placebo	-0.764	--
		(95% CI of LS mean differences)	(-3.068, 1.541)	--
		Two-sided p-value	0.5143	--

Source: Statistical Reviewer; adef.xpt
CFB = change from baseline, CI = confidence interval, CY-BOCS = Children's Yale-Brown Obsessive-Compulsive Scale, HQ-CT = Hyperphagia Questionnaire for Clinical Trials, LS = least squares, SE = standard error
[a] Baseline mean is estimated from the cLDA primary analysis model

Study LV-101-3-01: Other Secondary Endpoints

- 9.6 mg dose (change from Baseline to Week 8)
  - None showed signal of improvement compared to placebo
- 3.2 mg dose (change from Baseline to Week 8)
  - Many showed potential signal of improvement compared to placebo
  - PADQ total score nominal *p*-value of 0.027
  - CGI-C at Week 8 nominal *p*-value of 0.027
  - HQ-CT subset nominal *p*-value 0.011
  - HQ-CT item 9 nominal *p*-value 0.114

Study 114 versus Study LV-101-3-01

Study 114

- Preliminary evidence of efficacy on primary endpoint result on HPWSQ-R for 9.6 mg dose
  - Clinical meaningfulness unclear, brief duration for chronic illness
- Preliminary evidence of efficacy on secondary endpoint results on CGI-I and CY-BOCS
  - Secondary endpoints not controlled for multiplicity

Study LV-101-3-01

- Negative on the primary endpoints of HQ-CT and CY-BOCS for 9.6 mg dose
  - Also negative at Week 2 (exploratory), inconsistent with Study 114
- Descriptive findings for secondary endpoints in 3.2 mg arm:
  - Positive for HQ-CT
  - Negative for CY-BOCS

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Study LV-101-3-01 Long-Term Follow-Up

Study LV-101-3-01: LTFU Design

- In LTFU, placebo subjects randomized to 3.2 mg or 9.6 mg (unblinded to active drug, blinded to dose)
- Assessments were collected at Weeks 8, 10, 16, 28, 40, 52, 64, and early termination if applicable
- Subjects could continue in an optional open-label extension following the LTFU completion of Week 64

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Safety Assessment

Safety

- No deaths or other serious adverse events (SAEs) during Study 114 or placebo-controlled period of Study LV-101-3-01
- Discontinuations for AEs:
  - Study 114: one placebo subject for agitation, increased aggression, increased hyperphagia, and broken distal ulna
  - Study LV-101-3-01 placebo-controlled period:
    - Two 9.6 mg subjects for impulsive behavior and tachycardia (one each)
    - One 9.6 mg subject's AE of hypersexuality led to discontinuation in LTFU

Safety

- Most common AEs: ≥ 5% incidence ≥ 2x rate with placebo:
  - Study 114: none occurred in > 1 subject
  - Study LV-101-3-01 placebo-controlled period:
    - 3.2 mg arm: headache (16.3%), flushing (14.0%), diarrhea (9.3%), abdominal pain + abdominal pain upper (7.0%), pyrexia (7.0%), fatigue (7.0%), nasal discomfort (7.0%)
    - 9.6 mg arm: flushing (20.5%), epistaxis (13.6%), headache (9.1%)
- No findings for nasal examinations, vital signs, or laboratory assessments suggesting a safety signal

Safety: LTFU and Extension AEs

- 17 SAEs in 16 subjects (no deaths)
  - Occurring in > 1 subject: scoliosis surgery (four subjects), pneumonia (two subjects)
- Nine AEs led to discontinuation in 8 subjects
  - Occurring in > 1 subject: emotional disorder (two subjects)
  - Primarily psychiatric (in addition, one subject each for aggression, agitation, behavior disorder, and obsessive thoughts and separation anxiety disorder)
  - More discontinuations for AEs in 9.6 mg versus 3.2 mg (five versus three subjects)

Safety: LTFU and Extension AEs

- AEs in ≥ 5% of subjects:
  - 3.2 mg arm: headache (13.0%), pyrexia (8.3%), epistaxis (8.3%), diarrhea (7.4%), nasopharyngitis (7.4%), constipation (5.6%), anxiety (5.6%)
  - 9.6 mg arm: nasopharyngitis (12.5%), epistaxis (10.9%), headache (7.8%), pyrexia (6.3%), anxiety (6.3%)

Dose-Response

- Applicant hypothesized higher dose (at longer duration in Study LV-101-3-01 than Study 114) was associated with more off-target vasopressin effects, leading to psychiatric AEs that counteract treatment effect
- Overall number of discontinuations for psychiatric AEs was small, no placebo control in LTFU or extension for comparison, and overlap with symptoms seen in PWS

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Statistical Assessment

Key Statistical Findings

Study 114

- Acceptable as a short proof-of-concept study

Study LV-101-3-01

- Negative on both primary endpoints—HQ-CT and CY-BOCS in 9.6 mg dose arm
  - Interpretation of the findings on the 3.2 mg dose arm becomes post hoc
  - Challenging to interpret finding in the 3.2 mg dose

Study LV-101-3-01: Primary Endpoints (9.6 mg dose; Primary Analysis Set)

Endpoint	Visit		IN carbetocin 9.6 mg (N = 40)	Placebo (N = 40)
HQ-CT	Baseline	LS Mean[a]	22.2	
	Week 2	LS mean CFB	-3.4	-3.0
		LS mean difference vs. placebo	-0.4	--
		(95% CI of LS mean differences)	(-2.8, 2.0)	--
		Two-sided p-value	--	--
	Week 8	LS mean CFB	-3.4	-2.2
		LS mean difference vs. placebo	-1.2	--
		(95% CI of LS mean differences)	(-3.7, 1.3)	--
		Two-sided p-value	0.3493	--
CY-BOCS	Baseline	LS Mean[a]	27.3	
	Week 2	LS mean CFB	-2.6	-1.2
		LS mean difference vs. placebo	-1.4	--
		(95% CI of LS mean differences)	(-3.5, 0.8)	--
		Two-sided p-value	--	--
	Week 8	LS mean CFB	-3.0	-2.7
		LS mean difference vs. placebo	-0.6	--
		(95% CI of LS mean differences)	(-2.9, 1.7)	--
		Two-sided p-value	0.6001	--

Source: Statistical Reviewer; adef.xpt
CFB = change from baseline, CI = confidence interval, CY-BOCS = Children's Yale-Brown Obsessive-Compulsive Scale, HQ-CT = Hyperphagia Questionnaire for Clinical Trials, LS = least squares, SE = standard error
[a] Baseline mean is estimated from the cLDA primary analysis model

Study LV-101-3-01: Secondary Endpoints (3.2 mg dose; Primary Analysis Set)

Endpoint	Visit		IN carbetocin 3.2 mg (N = 39)	Placebo (N = 40)
HQ-CT	Baseline	LS Mean[a]	22.2	
	Week 2	LS mean CFB	-6.0	-3.0
		LS mean difference vs. placebo	-3.0	--
		(95% CI of LS mean differences)	(-5.4, -0.6)	--
		Two-sided p-value	--	--
	Week 8	LS mean CFB	-5.4	-2.2
		LS mean difference vs. placebo	-3.1	--
		(95% CI of LS mean differences)	(-5.7, -0.6)	--
		Two-sided p-value	0.0162	--
CY-BOCS	Baseline	LS Mean[a]	27.3	
	Week 2	LS mean CFB	-3.0	-1.2
		LS mean difference vs. placebo	-1.8	--
		(95% CI of LS mean differences)	(-4.0, 0.4)	--
		Two-sided p-value	--	--
	Week 8	LS mean CFB	-3.1	-2.4
		LS mean difference vs. placebo	-0.8	--
		(95% CI of LS mean differences)	(-3.1, 1.5)	--
		Two-sided p-value	0.5143	--

Source: Statistical Reviewer; adef.xpt
CFB = change from baseline, CI = confidence interval, CY-BOCS = Children's Yale-Brown Obsessive-Compulsive Scale, HQ-CT = Hyperphagia Questionnaire for Clinical Trials, LS = least squares, SE = standard error
[a] Baseline mean is estimated from the cLDA primary analysis model

Study LV-101-3-01: Results of the Pre-Specified Statistical Testing Plan

- First, test the 9.6 mg dose arm endpoints:
  - Use the two p-values for the 9.6 mg:
    - HQ-CT: 0.3493
    - CY-BOCS: 0.6001
  - Both p-values are greater than 0.05
  - Testing STOPS
- Interpretation of findings on the 3.2 mg dose becomes *post hoc*

Study LV-101-3-01: Details of Pre-specified Statistical Testing Plan

- Controls for multiple comparisons over four endpoints
- Use combination of Hochberg's Procedure and hierarchical testing
  - First: test 9.6 mg HQ-CT and CY-BOCS using Hochberg's Procedure
    - If positive on either 9.6 mg endpoint, then proceed to second step
  - Second: test 3.2 mg HQ-CT and CY-BOCS using Hochberg's Procedure
  - All other secondary endpoints tested in a fixed sequence hierarchy
- FDA Comments:
  - The pre-specified testing plan may inflate the overall Type I error rate
  - To control the overall Type I error rate, tests on both 9.6 mg endpoints need to be rejected before proceeding to test both 3.2 mg endpoints
  - Statistical Analysis Plan was first submitted to FDA with NDA submission

Study LV-101-3-01: Evaluation of the Primary Analysis

- Pre-specified primary analysis - constrained longitudinal data analysis
  - Analyzes Baseline, Week 2, and Week 8 observations in placebo, 3.2 mg dose, and 9.6 mg dose arms
  - Treatment differences estimated by least squares means
  - Constraint that all three treatment arms have the same baseline mean
  - Assumes that all observations within a subject have the same covariance
    - Compound symmetry (CS) covariance matrix
    - May not be met in a clinical trial
    - Violations of CS may underestimate the standard errors causing overly optimistic p-values
    - Sandwich estimator and unstructured covariance matrix commonly used to prevent underestimated standard errors

Study LV-101-3-01: Sensitivity Analyses of CS Covariance Assumption in 3.2 mg dose for HQ-CT

Covariance Structure	Adjustment	Equal Variance between Arms	Treatment Difference	95% CI	Nominal p-value
Compound Symmetry[a]	Kenward Rogers degrees of freedom	Yes	-3.14	-5.69 to -0.58	0.0162
Compound Symmetry	Sandwich Estimator	Yes	-3.14	-6.24 to -0.03	0.048
Unstructured	None	Yes	-3.29	-6.28 to -0.30	0.0314
Unstructured	Kenward Rogers degrees of freedom	Yes	-3.29	-6.31 to -0.26	0.0335
Unstructured	None	No	-3.21	-6.36 to -0.058	0.044
Unstructured	Kenward Rogers degrees of freedom	No	-3.21	-6.46 to 0.044	0.0531

- [a] Results in this row equivalent to the pre-specified primary analysis.
- Source: Statistical Reviewer Analysis; adef.xpt, CI = confidence interval

Study LV-101-3-01: Statistical Conclusions for Placebo Controlled Period

- Lack of evidence for 9.6 mg dose
  - At both Week 2 and Week 8
  - On all primary and secondary endpoints
  - Contradicts results of Study 114
- Suggestion of efficacy signal for 3.2 mg dose
  - Statistical inferences about 3.2 mg dose are *post hoc*
  - Sensitivity analyses raise additional uncertainty on these exploratory results
- Challenging to interpret finding in the 3.2 mg dose because of lack of evidence for 9.6 mg dose

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Long-Term Follow-up Period

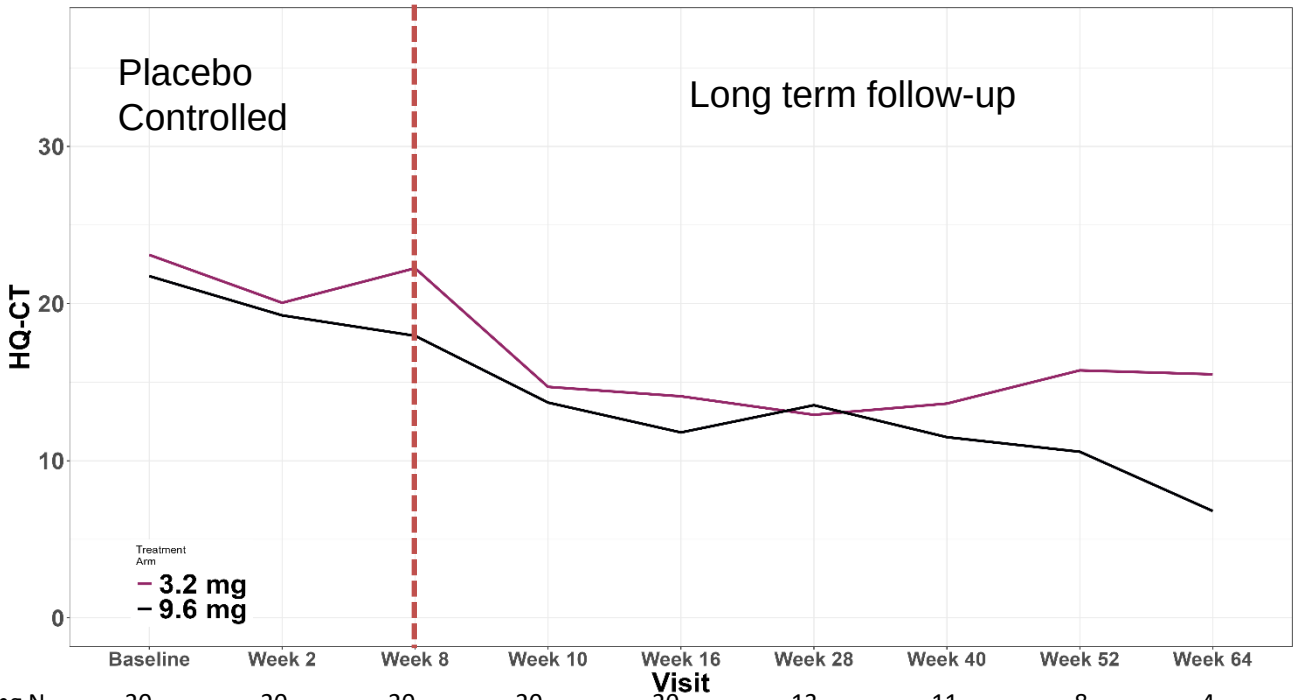
Study LV-101-3-01 LTFU: Placebo-Crossover Analysis of HQ-CT in 3.2 mg and 9.6 mg Carbetocin

- Exploratory placebo-crossover analysis compared
  - Change in HQ-CT from Study Baseline to Week 8 (Period 1)
  - Change in HQ-CT from Week 8 to Week 16 (Period 2)
  - Subjects randomized at study baseline to
    - Placebo followed by 3.2 mg
    - Placebo followed by 9.6 mg

IN Carbetocin Dose		Study Baseline to Week 8	Week 8 to Week 16
3.2 mg	LS mean CFB (SE) LS mean difference between period 2 and period 1 (95% CI of LS mean differences)	0.26 (1.37)	-9.06 (1.63) -9.32 -14.5 to -4.14
9.6 mg	LS mean CFB (SE) LS mean difference between period 2 and period 1 (95% CI of LS mean differences)	-4.76 (1.41)	-4.95 (1.69) -0.19 -5.52 to 5.14

Source: Applicant's Clinical Study Report; adef.xpt

Study LV-101-3-01 LTFU: HQ-CT Means over Time (PAS; Subjects starting on placebo)



Placebo/3.2 mg N	20	20	20	20	20	13	11	8	4
Placebo/9.6 mg N	20	20	20	20	20	15	10	7	5

Source: Statistical Reviewer Analysis; adef.xpt
HQ-CT = Hyperphagia Questionnaire for Clinical Trials

Study LV-101-3-01 LTFU: Evaluation of LTFU Period Analyses

- LTFU lacked placebo control
  - Subjects were not blinded to receiving active drug,
  - Blinded to which dose (9.6 mg or 3.2 mg)
- Randomization at study baseline leads to imbalance in placebo crossover subjects at Week 8
- LTFU analyses subject to confounding by potential expectation bias and other sources of bias
- Limited sample size later in LTFU period
  - Data cutoff dates and cumulative study discontinuations
  - Limits ability to draw conclusions
  - Subjects who withdrew may have done so for lack of efficacy, skewing results

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Overall Conclusions

Conclusions

- Study 114
  - Preliminary evidence of efficacy for 9.6 mg dose
  - Unclear clinical meaningfulness of the results given the 2-week duration in a chronic condition
- Study LV-101-3-01
  - Did not show efficacy for the 9.6 mg dose
  - Challenging to interpret 3.2 mg dose findings
  - Contradicts results of Study 114
  - LTFU data lacks placebo control and is subject to various sources of confounding, such as expectation bias and sample size degradation


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