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ACP-101 Clinical Development Program in Prader-Willi Syndrome

This letter is provided in response to your specific request for information regarding the ACP-101 clinical development program in Prader-Willi syndrome (PWS). ACP-101 (carbetocin nasal spray) is an investigational agent, and its safety and efficacy for the treatment of hyperphagia in PWS have not been established and approved by the FDA.

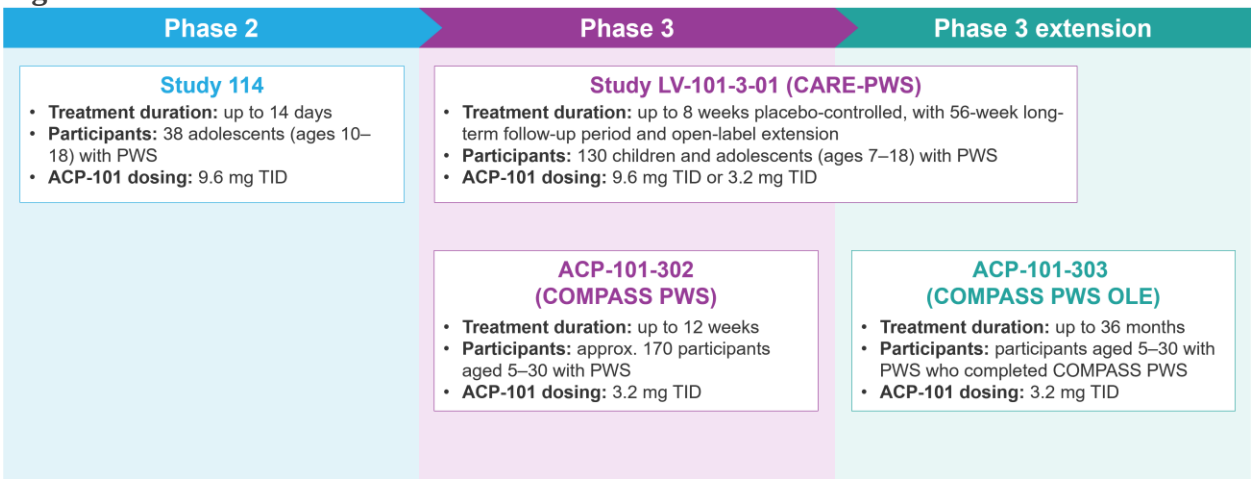
Summary

- ACP-101 9.6 mg three times daily (TID) was evaluated as a treatment for hyperphagia in a 14-day, Phase 2 study (**Study 114**) in 38 participants aged 10 to 18 years with PWS.[1]
  - A statistically significant improvement over placebo was demonstrated for ACP-101 9.6 mg for the primary endpoint, change from baseline to Day 15 in the Hyperphagia in PWS Questionnaire-Responsiveness (HPWSQ-R) total score.[1]
  - The most common treatment-emergent adverse event (TEAE) was headache, reported in 5 of 17 (29.4%) participants treated with ACP-101 9.6 mg and 6 of 20 (30.0%) participants receiving placebo.[1]
- Two doses of ACP-101 (9.6 mg and 3.2 mg TID) were assessed in an 8-week, Phase 3 study (**CARE-PWS**) as a treatment for hyperphagia and obsessive-compulsive symptoms in 130 participants aged 7 to 18 years with PWS.[2]
  - The change from baseline to Week 8 in the two primary endpoints (Hyperphagia Questionnaire for Clinical Trials [HQ-CT] total score and the Children's Yale-Brown Obsessive-Compulsive Scale [CY-BOCS] total score) for ACP-101 9.6 mg vs. placebo did not reach statistical significance.[2]
  - In a secondary analysis, ACP-101 3.2 mg showed nominally significant improvements in symptoms of hyperphagia, as measured by the HQ-CT total score.[2]
  - The most frequently reported TEAE was flushing, reported in 9 of 44 (20.5%) participants in the 9.6-mg arm, 6 of 43 (14.0%) participants in the 3.2-mg arm, and no participants in the placebo arm.[2]
- An ongoing Phase 3 study, **COMPASS PWS**, is assessing ACP-101 3.2 mg TID for the treatment of hyperphagia in approximately 170 participants aged 5 to 30 years with PWS.[3]
- Participants who complete COMPASS PWS will be eligible to enroll in an open-label, long-term extension study, **COMPASS PWS OLE**.[4]

Clinical Studies in PWS

The efficacy and safety of ACP-101 in participants with PWS have been evaluated in one Phase 2 study assessing a 9.6 mg dose for the treatment of hyperphagia, and one Phase 3 study assessing two doses (9.6 mg and 3.2 mg) for the treatment of hyperphagia and obsessive-compulsive symptoms (**Figure 1**).[1,2] A second Phase 3 trial, COMPASS PWS, is ongoing to assess the 3.2 mg TID dose for the treatment of hyperphagia,[3] and an open-label, long-term extension study will enroll participants who complete COMPASS PWS.[4]

Figure 1. ACP-101 Studies in PWS[1-4]

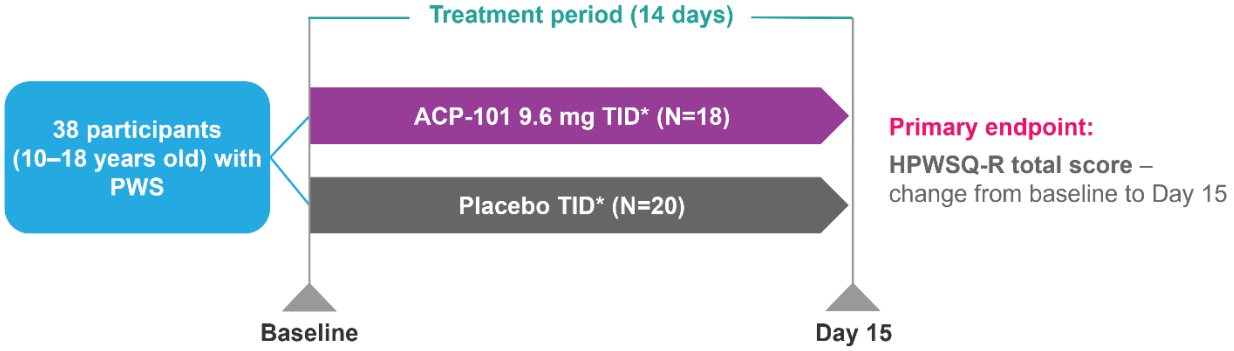


Abbreviations: PWS=Prader-Willi syndrome; TID=three times daily.

Study 114

This was a multicenter, randomized, double-blind, placebo-controlled, Phase 2 study to evaluate the efficacy and safety of ACP-101 9.6 mg vs. placebo as a targeted treatment for symptoms of hyperphagia in 38 participants with PWS for up to 14 days (**Figure 2**). The primary endpoint was the change from baseline to Day 15 in the caregiver-rated HPWSQ-R total score. Eligible participants had a genetically confirmed diagnosis of PWS, were PWS Nutritional Phase 3 (i.e., hyperphagia), and had a HPWSQ-R total score >13 at screening.[1]

Figure 2. Study 114 Design[1]



**Intranasal doses were administered 3 times daily, prior to meals, and according to prespecified time intervals (morning dose: 6:00 to 9:00 am; midday dose: 11:00 am to 1:00 pm; evening dose: 4:30 to 6:00 pm). A single dose consisted of 3 sprays in each nostril.*
Abbreviations: HPWSQ-R=Hyperphagia in PWS Questionnaire–Responsiveness; PWS=Prader-Willi syndrome; TID=three times a day.

Baseline Characteristics

Demographics and baseline characteristics were generally similar between the 2 treatment groups (**Table 1**).[1] Mean (standard deviation [SD]) baseline HPWSQ-R total scores were 35.6 (7.2) for the ACP-101 group and 39.7 (7.6) for the placebo group.[5]

Table 1. Selected Baseline Demographics and Clinical Characteristics (Study 114; Full Analysis Set)[1]

	ACP-101 9.6 mg (N=17)	Placebo (N=20)	Overall (N=37)
Female sex, n (%)	**11 (64.7)**	**12 (60.0)**	**23 (62.2)**
Age, years			
Mean ± SD	13.9 (2.4)	13.6 (2.5)	13.7 (2.5)
Range	10.0–18.0	10.0–18.0	10.0–18.0
Race, n (%)			
Black/African American	0	1 (5)	1 (2.7)
White/European descent	17 (100)	19 (95)	36 (97.3)
BMI, kg/m^2 (mean ± SD)	**25.7 (5.9)**	**25.7 (7.5)**	**25.7 (6.8)**

Abbreviations: BMI=body mass index; SD=standard deviation.

Efficacy Results

In the primary efficacy endpoint analysis, patients who received ACP-101 9.6 mg had statistically significant reductions from baseline in the HPWSQ-R total score at Day 15 compared with those who received placebo: least squares mean (LSM) change of -15.6 vs. -8.9 (p=0.029).[1]

Safety Results

The incidence of TEAEs occurring in ≥5% of either treatment is shown in **Table 2**. In the ACP-101 9.6 mg group, 7 participants (41.2%) reported TEAEs, of which 96% were categorized as mild (1 TEAE was moderate). In the placebo group, 8 (40%) participants reported TEAEs, of which 86% were categorized as mild (4 TEAEs were moderate). One participant in the placebo group was withdrawn from the study because of moderate TEAEs that included agitation, increased aggression, and hyperphagia related to a broken distal ulnar. The most common TEAE in both treatment groups was headache, reported in 29.7% of participants overall.[1]

Table 2. TEAEs ≥5% in Either Treatment Group (Study 114; Safety Population)[1]

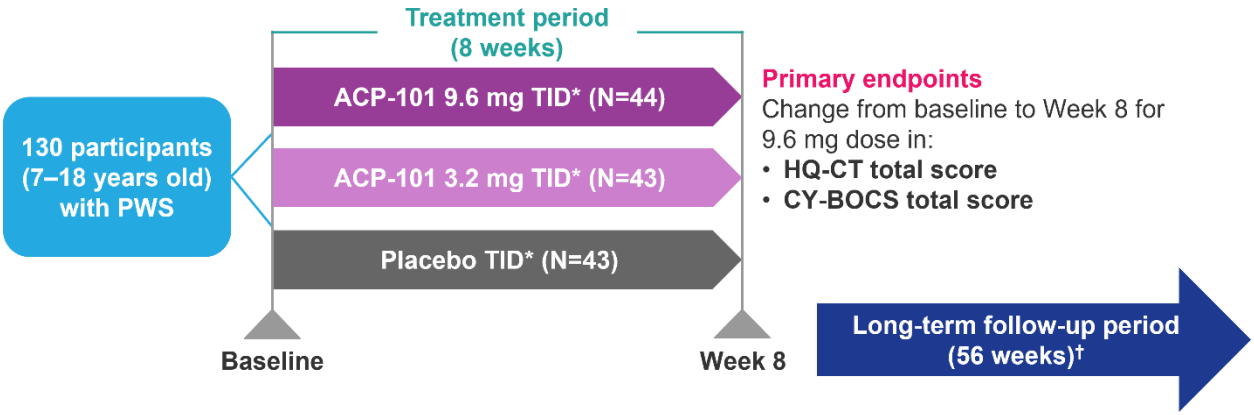
	ACP-101 9.6 mg (N=17) n (%)	Placebo (N=20) n (%)	Overall (N=37) n (%)
Any TEAE	**7 (41.2)**	**8 (40.0)**	**15 (40.5)**
Headache	5 (29.4)	6 (30.0)	11 (29.7)
Medication error	1 (5.9)	2 (10.0)	3 (8.1)
Abdominal pain upper	1 (5.9)	1 (5.0)	2 (5.4)
Conjunctivitis infective	1 (5.9)	0 (0)	1 (2.7)
Diarrhea	1 (5.9)	0 (0)	1 (2.7)
Dysgeusia	1 (5.9)	0 (0)	1 (2.7)
Aggression	0 (0)	1 (5.0)	1 (2.7)
Hyperphagia	0 (0)	1 (5.0)	1 (2.7)
Procedural pain	0 (0)	1 (5.0)	1 (2.7)
Sinusitis	0 (0)	1 (5.0)	1 (2.7)
Ulna fracture	0 (0)	1 (5.0)	1 (2.7)
Urine analysis abnormal	0 (0)	1 (5.0)	1 (2.7)

Abbreviation: TEAE-treatment-emergent adverse event.

CARE-PWS (LV-101-3-01)

This was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy, safety, and tolerability of two different doses of ACP-101 (9.6 mg or 3.2 mg) vs. placebo in 130 participants with PWS for up to 8 weeks (**Figure 3**). The primary endpoints assessed the efficacy of ACP-101 9.6 mg vs. placebo in improving hyperphagia and obsessive-compulsive symptoms, measured by change from baseline in total scores on the caregiver-rated HQ-CT and clinician-rated CY-BOCS, respectively. HQ-CT total score and CY-BOCS total score were assessed for the 3.2-mg dose as secondary endpoints.[2]

Figure 3. CARE-PWS Study Design[2]



**Intranasal doses were administered 3 times daily with meals, with a minimum of 2.5 hours between doses. A single dose consisted of 2 sprays in each nostril.*
†Participants randomized to placebo for the 8-week period were further randomized to receive ACP-101 9.6 mg or 3.2 mg for the 56-week follow-up period. Participants initially randomized to ACP-101 continued the same dose they were receiving in the double-blind period.
Abbreviations: CY-BOCS=Children's Yale-Brown Obsessive-Compulsive Scale; HQ-CT=Hyperphagia Questionnaire for Clinical Trials; PWS=Prader-Willi syndrome; TID=three times a day.

Eligible participants had a genetically confirmed diagnosis of PWS, were PWS Nutritional Phase 3 (i.e., hyperphagia), and had a HQ-CT total score ≥13 and CY-BOCS total score ≥9 at screening.[2,6] Participants who completed the 8-week, placebo-controlled period were given the option to continue to a long-term follow-up portion of the trial, and subsequent open-label extension. Trial enrollment was closed prematurely before the target enrollment number of 175 participants because of the impact of COVID-19.[2]

Baseline Characteristics

Treatment arms were generally well-balanced with respect to baseline demographics and clinical characteristics (**Table 3**).[2]

Table 3. Selected Baseline Demographics and Clinical Characteristics (LV-101-3-01; Primary Analysis Set)[2]

	ACP-101 3.2 mg (N=39)	ACP-101 9.6 mg (N=40)	Placebo (N=40)
Age, years (mean ± SD)	12.3 ± 3.12	11.7 ± 3.45	11.8 ± 3.52
Female sex, n (%)	24 (61.5)	19 (47.5)	23 (57.5)
Race, n (%)			
American Indian/Alaska Native	0	1 (2.5)	0
Asian	2 (5.1)	2 (5.0)	0
Black/African American	2 (5.1)	1 (2.5)	1 (2.5)
White	33 (84.6)	33 (82.5)	35 (87.5)
Other	2 (5.1)	3 (7.5)	4 (10.0)
Ethnicity, n (%)			
Not Hispanic or Latino	34 (87.2)	37 (92.5)	37 (92.5)
BMI, kg/m^2 (mean ± SD)	26.43 ± 8.3	26.30 ± 9.2	24.35 ± 8.8
Baseline total scores, mean ± SD			
HQ-CT	22.1 ± 5.1	23.4 ± 5.7	22.4 ± 4.7
CY-BOCS	25.5 ± 4.1	28.4 ± 4.0	27.8 ± 6.0

Abbreviations: BMI=body mass index; CY-BOCS=Children's Yale-Brown Obsessive-Compulsive Scale; HQ-CT=Hyperphagia Questionnaire for Clinical Trials; SD=standard deviation.

Efficacy Results

The two primary endpoints assessing change in HQ-CT total score and CY-BOCS total score for ACP-101 9.6 mg vs. placebo did not reach statistical significance (**Table 4**). Therefore, the trial did not meet its primary endpoint and all other statistical analyses are considered nominal. Results for ACP-101 3.2 mg showed nominally significant improvements in symptoms of hyperphagia, as measured by the HQ-CT total score (LSM difference vs. placebo of -3.1; nominal p=0.016).[2]

Table 4. Change from Baseline to Week 8 in HQ-CT and CY-BOCS Total Scores (LV-101-3-01; Primary Analysis Set)[2]

	ACP-101 3.2 mg (N=39)	ACP-101 9.6 mg (N=40)	All placebo (N=40)
HQ-CT total score			
LSM (SE)	-5.4 (0.96)	-3.4 (0.95)	-2.2 (0.94)
LSM difference vs. placebo	-3.1	-1.2	—
(95% CI of LSM differences)	(-5.7 to -0.6)	(-3.7 to 1.3)	—
Two-sided p-value vs placebo	0.016*	0.349	—
CY-BOCS total score			
LSM (SE)	-3.1 (0.87)	-3.0 (0.86)	-2.4 (0.86)
LSM difference vs. placebo	-0.8	-0.6	—
(95% CI of LSM differences)	(-3.1 to 1.5)	(-2.9 to 1.7)	—
Two-sided p-value vs. placebo	0.514*	0.600	—

**Nominal p-value.*

Abbreviations: CI=confidence interval; CY-BOCS=Children's Yale-Brown Obsessive-Compulsive Scale; HQ-CT=Hyperphagia Questionnaire for Clinical Trials; LSM=least squares mean; SE=standard error.

Safety Results: 8-Week, Placebo-controlled Period

In the 8-week, placebo-controlled period, 63.2% of participants receiving ACP-101 (both doses) reported at least 1 TEAE, compared with 55.8% of participants in the placebo arm (**Table 5**).

The most frequently reported TEAE was flushing, reported in 14.0% of participants in the 3.2-mg arm, 20.5% of participants in the 9.6-mg arm, and no participants in the placebo arm. In all participants, flushing was transient, mild in intensity, not serious, and self-limited (generally resolving spontaneously within 30 minutes).[2]

Table 5. TEAEs Reported During the 8-week, Placebo-Controlled Period by ≥5% of Participants in Any Treatment Group (LV-101-3-01; Safety Analysis Set)[2]

	ACP-101 3.2 mg (N=43) n (%)	ACP-101 9.6 mg (N=44) n (%)	All ACP-101 (N=87) n (%)	All placebo (N=43) n (%)
At least 1 TEAE	**26 (60.5)**	**29 (65.9)**	**55 (63.2)**	**24 (55.8)**
Flushing	6 (14.0)	9 (20.5)	15 (17.2)	0
Headache	7 (16.3)	4 (9.1)	11 (12.6)	3 (7.0)
Epistaxis	1 (2.3)	6 (13.6)	7 (8.0)	1 (2.3)
Diarrhea	4 (9.3)	2 (4.5)	6 (6.9)	1 (2.3)
Upper respiratory tract infection	3 (7.0)	2 (4.5)	5 (5.7)	2 (4.7)
Nasal discomfort	3 (7.0)	2 (4.5)	5 (5.7)	1 (2.3)
Fatigue	3 (7.0)	1 (2.3)	4 (4.6)	0
Pyrexia	3 (7.0)	0	3 (3.4)	0
Nasopharyngitis	0	1 (2.3)	1 (1.1)	3 (7.0)

Abbreviation: TEAE-treatment-emergent adverse event.

No deaths or serious TEAEs were reported, and no study drug discontinuations were reported by participants in the placebo arm or the 3.2-mg arm. A total of 3 participants (6.8%) in the 9.6-mg arm reported TEAEs that led to trial discontinuation.[2]

Safety Results: Long-term Follow-up

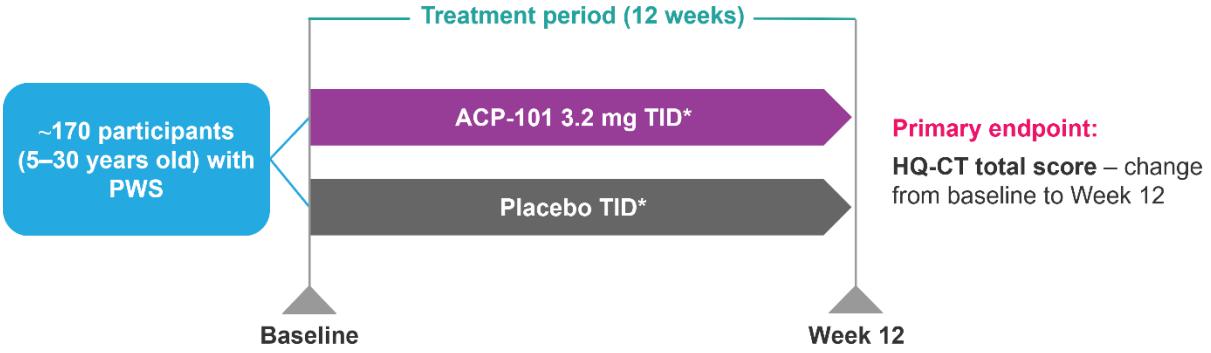
The most frequently reported TEAEs during the long-term follow-up and extension periods were nasopharyngitis (10.9% of all participants, including 9.4% and 12.1% of participants in the 3.2-mg and the 9.6-mg arms, respectively), headache (11.7% of all participants, including 15.6% and 7.8% of participants in the 3.2-mg and 9.6-mg arms, respectively), and epistaxis (10.9% of all participants and for both dose arms).[2]

COMPASS PWS (ACP-101-302)

This is an ongoing multicenter, randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of ACP-101 (3.2 mg TID) vs. placebo in approximately 170 participants with PWS (ages 5-30) for up to 12 weeks (**Figure 4**). The primary efficacy endpoint is the change from baseline in the caregiver-rated HQ-CT at Week 12.[3]

Eligible participants have PWS with a documented disease-causing mutation and increased appetite with decreased satiety accompanied by food seeking (consistent with PWS Nutritional Phase 3). Participants are also required to have a HQ-CT total score ≥13 and Clinical Global Impression-Severity (CGI-S) score for hyperphagia in PWS of ≥4 at screening and baseline.[3]

Figure 4. ACP-101-302 Study Design[3]

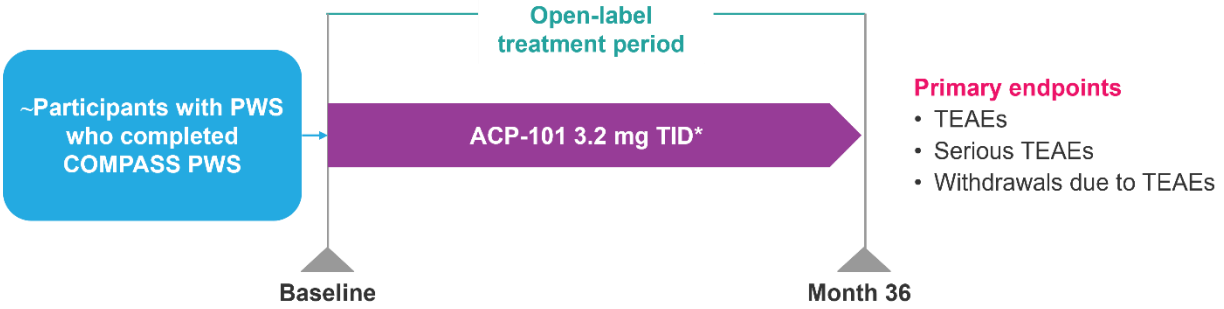


**Intranasal doses will be administered 3 times daily at mealtimes (if possible), with a minimum of 2.5 hours between doses. A single dose consists of 2 sprays in each nostril.[7]*
Abbreviations: HQ-CT=Hyperphagia Questionnaire for Clinical Trials; PWS=Prader-Willi syndrome; TID=three times a day.

COMPASS PWS OLE (ACP-101-303)

This is a planned multi-center, open-label, long-term study (up to 36 months) to evaluate long-term safety and tolerability of ACP-101 (3.2 mg TID) in participants with PWS (**Figure 5**). Participants who complete the antecedent double-blind study (COMPASS PWS) will be invited to participate in the open-label extension study. The primary objective of this study is to investigate the safety and tolerability of long-term treatment with ACP-101 for the treatment of hyperphagia in PWS.[4]

Figure 5. ACP-101-303 Study Design[4]



**Intranasal doses will be administered 3 times daily at mealtimes (if possible), with a minimum of 2.5 hours between doses. A single dose consists of 2 sprays in each nostril.*
Abbreviations: PWS=Prader-Willi syndrome; TEAE=treatment-emergent adverse event; TID=three times a day.

References

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