A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Pimavanserin as Adjunctive Treatment for the Negative Symptoms of Schizophrenia (ADVANCE-2)

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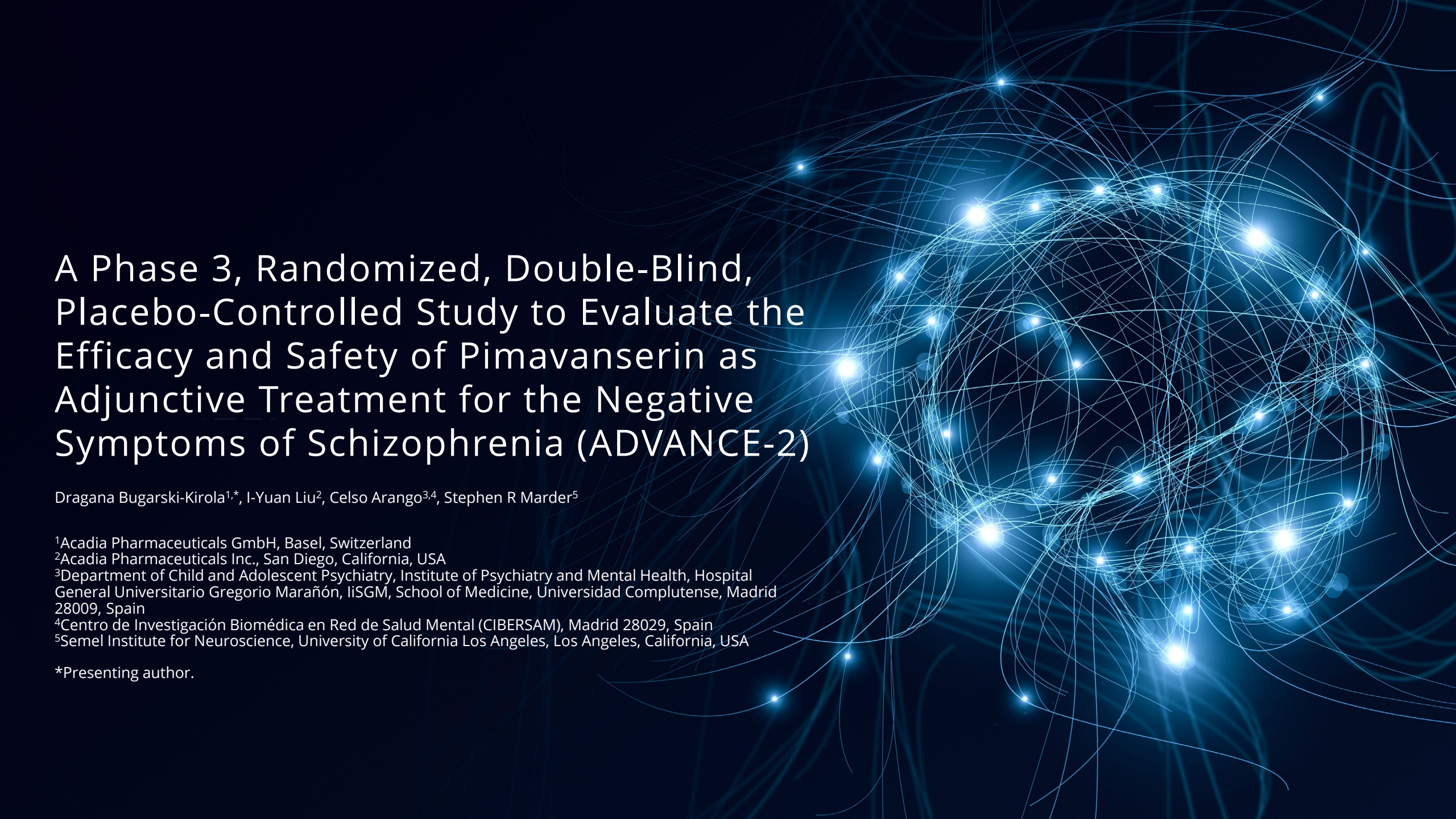
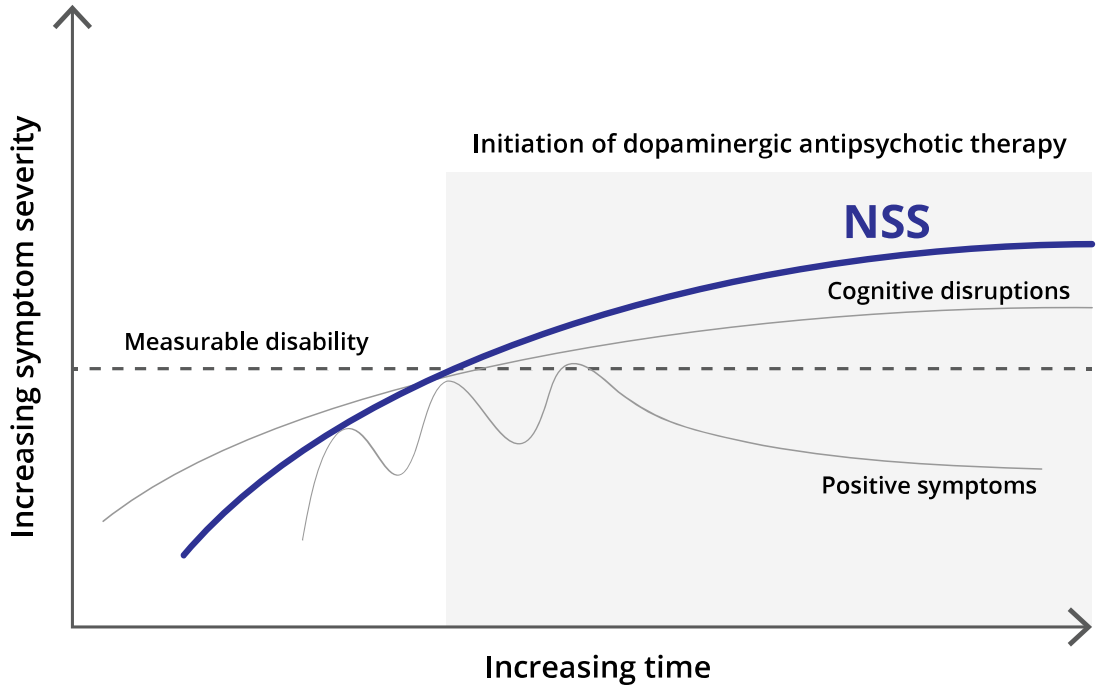
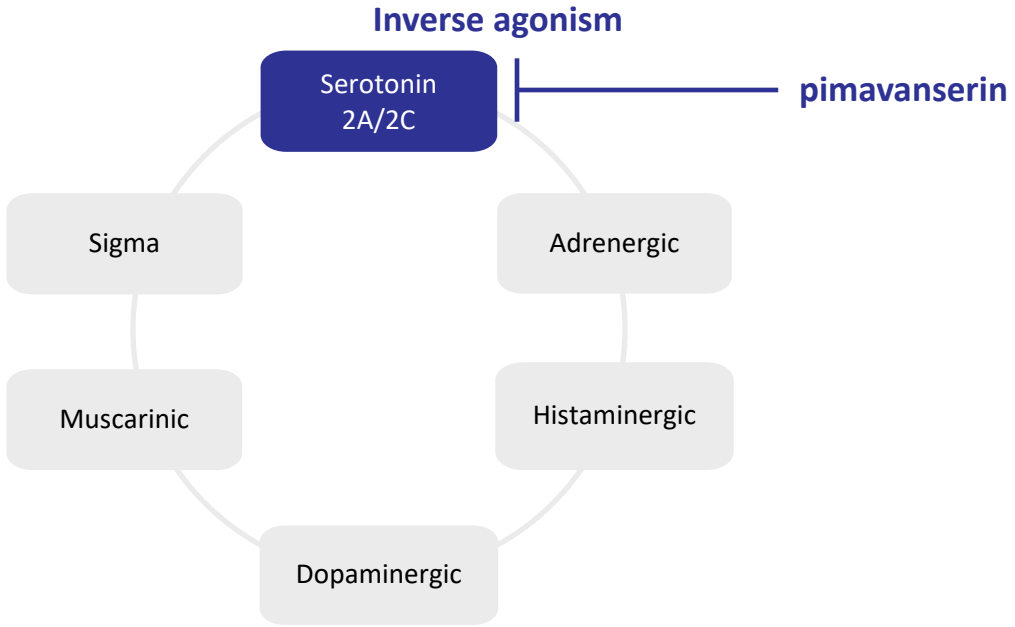


Conflict of interest disclosure

Affiliation / Financial interest	Commercial company
Grants/research support:	
Honoraria or consultation fees:	
Participation in a company sponsored bureau:	
Stock shareholder:	Acadia Pharmaceuticals Inc.
Spouse / partner:	
Other support / potential conflict of interest:	Employee of Acadia Pharmaceuticals Inc.

Background: negative symptoms of schizophrenia (NSS)





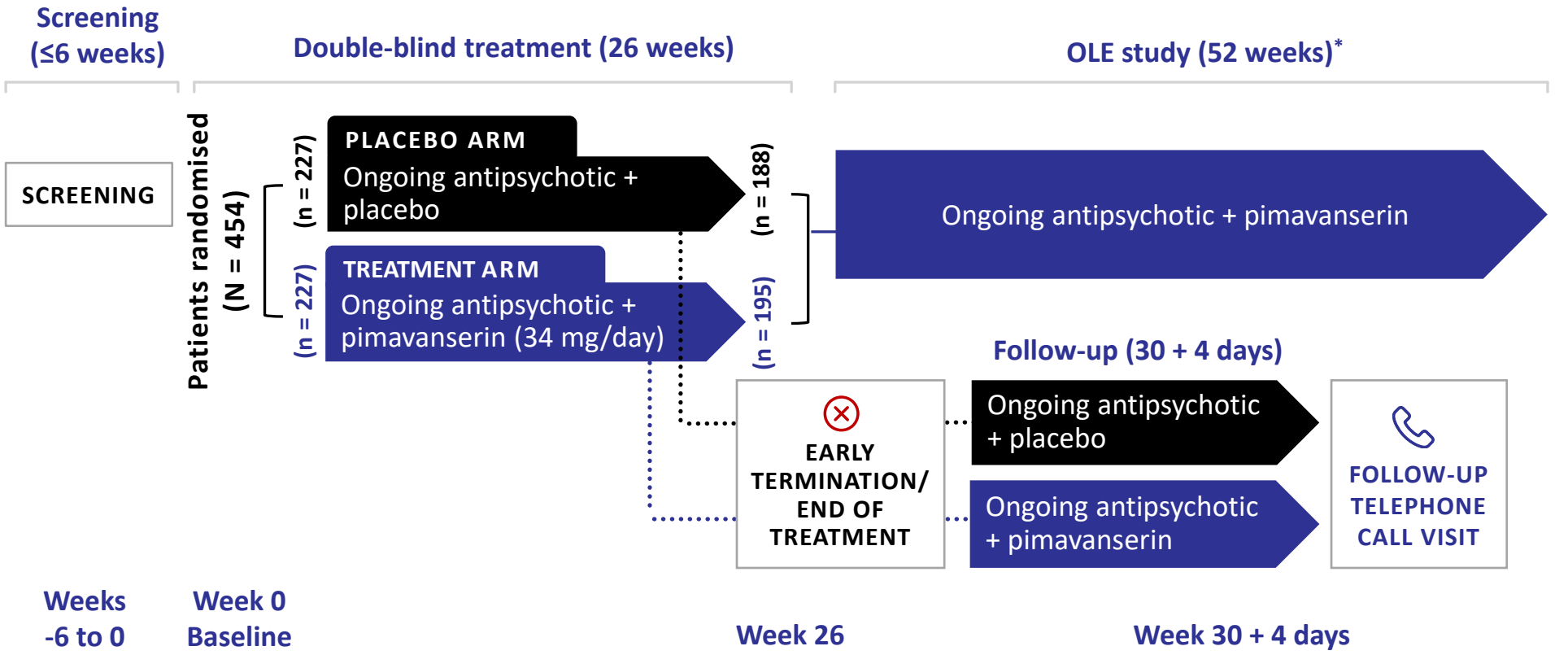
- NSS have substantial burden and adverse clinical outcomes; few treatments are effective[1]

- 5-HT_{2A} inverse agonism has shown promise to treat NSS
- Pimavanserin selectively targets 5-$HT_{2A/2C}$

The phase 3 ADVANCE-2 trial evaluated the efficacy and safety of adjunctive pimavanserin to treat patients with predominant NSS

5-HT, 5-hydroxytryptamine; NSS, negative symptoms of schizophrenia.
Correll, C.U., et al., *Neuropsychiatr Dis Treat*. 2020:519-534.

ADVANCE-2 study design and patients



PRIMARY ENDPOINT

Change from Baseline to week 26 in the NSA-16 total score

KEY SECONDARY ENDPOINT

Change from Baseline to week 26 for the CGI-SCH-S negative symptom score

ADVANCE-2 (NCT04531982) was a 26-week, phase 3, randomized, double-blind, placebo-controlled, multicenter, multinational, outpatient study of pimavanserin in patients with schizophrenia and predominant NS

*Participants who complete the 26-week treatment period were eligible to enroll in a 52-week, open-label extension study (Study ACP-103-035). Patients entering the OLE did not complete a follow-up telephone call visit as were immediately enrolled in the OLE study.
Note: Patients were randomized 1:1 and were stratified by geographic region (Europe, Rest of world). The ongoing antipsychotic list included commonly prescribed atypical antipsychotics, including long acting injectables and did not include clozapine.
CGI-SCH-S, Clinical Global Impression of Schizophrenia Scale–Severity; OLE, open label extension; NSA-16, Negative Symptom Assessment–16; NS, negative symptoms.

Key eligibility criteria

Inclusion

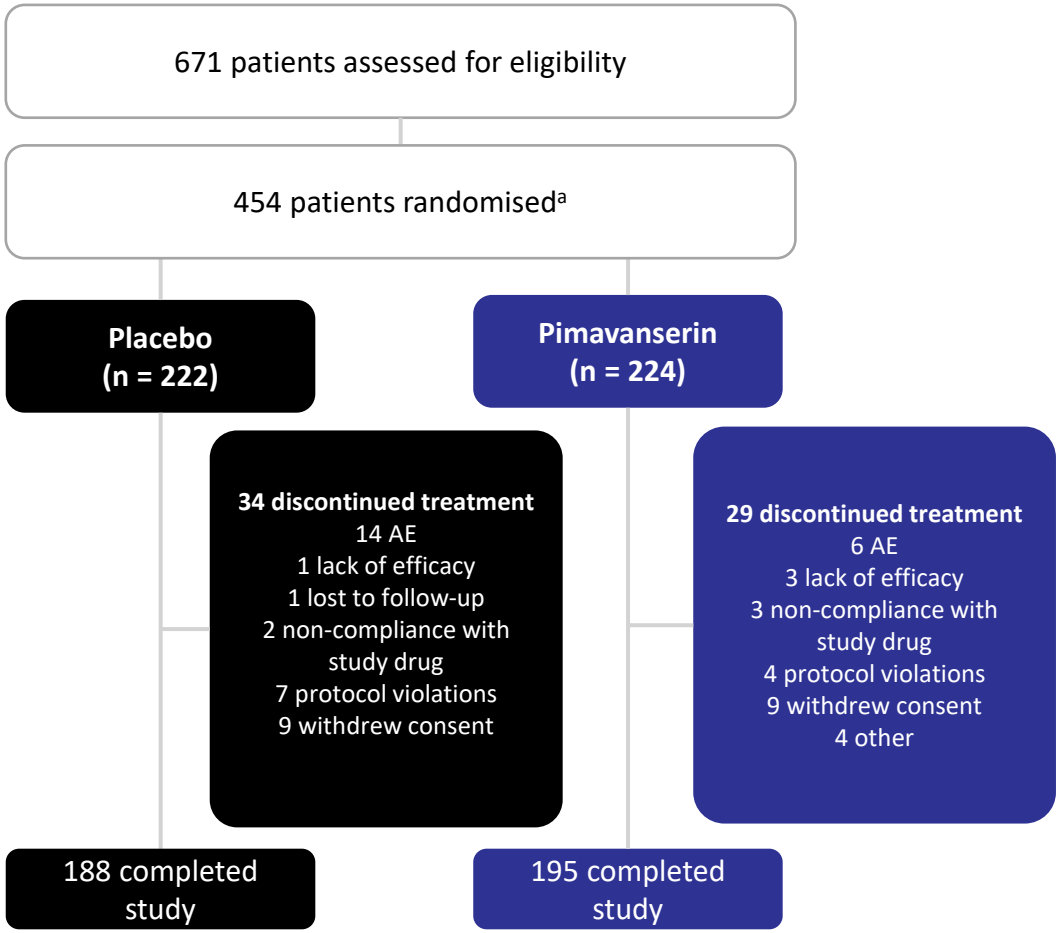
- Adults with schizophrenia (≥1 year prior to Screening) by DSM-5 and confirmed by SCID-5-CT
- Score ≥20 on sum of 7 PANSS NSF items at Screening and Baseline and Score ≥4 on at least 3, or ≥5 on at least 2 of the PANSS NSF items
- Score ≤ 22 on sum of 8 PANSS PSF items and where ≤2 of the following items have a score of 4
  - P1 (delusions)
  - P3 (hallucinatory behavior)
  - P4 (excitement)
  - P6 (suspiciousness/persecution)
  - P7 (hostility)
- Score ≥4 on CGI-SCH-S of negative symptoms (at least moderately ill)
- Access to a caregiver (study compliance)
- Stable (≥12 weeks prior to screening) on select adequately dosed antipsychotic

Exclusion

- PANSS PSF items P1, P3, P4, P6, or P7 ≥5 at Screening and Baseline
- Concurrent psychiatric diagnoses
- Movement
  - AIMS: Score ≥2 for two or more movements or a score of 3 or 4 for any single movement
  - BARS: Total score ≥2
  - SAS: Total score ≥5
- CDSS score ≥9 at both Screening and Baseline

AIMS, Abnormal Involuntary Movement scale; BARS, Barnes Akathisia Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI-SCH-S, Clinical Global Impression of Schizophrenia Scale–Severity; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; NSF, Marder negative factor; PANSS, Positive and Negative Syndrome Scale; PSF, Marder positive factor; SAS, Simpson-Angus Extrapyramidal Side Effects Scale; SCID-5-CT, Structured Clinical Interview for DSM-5, Clinical Trials Version.

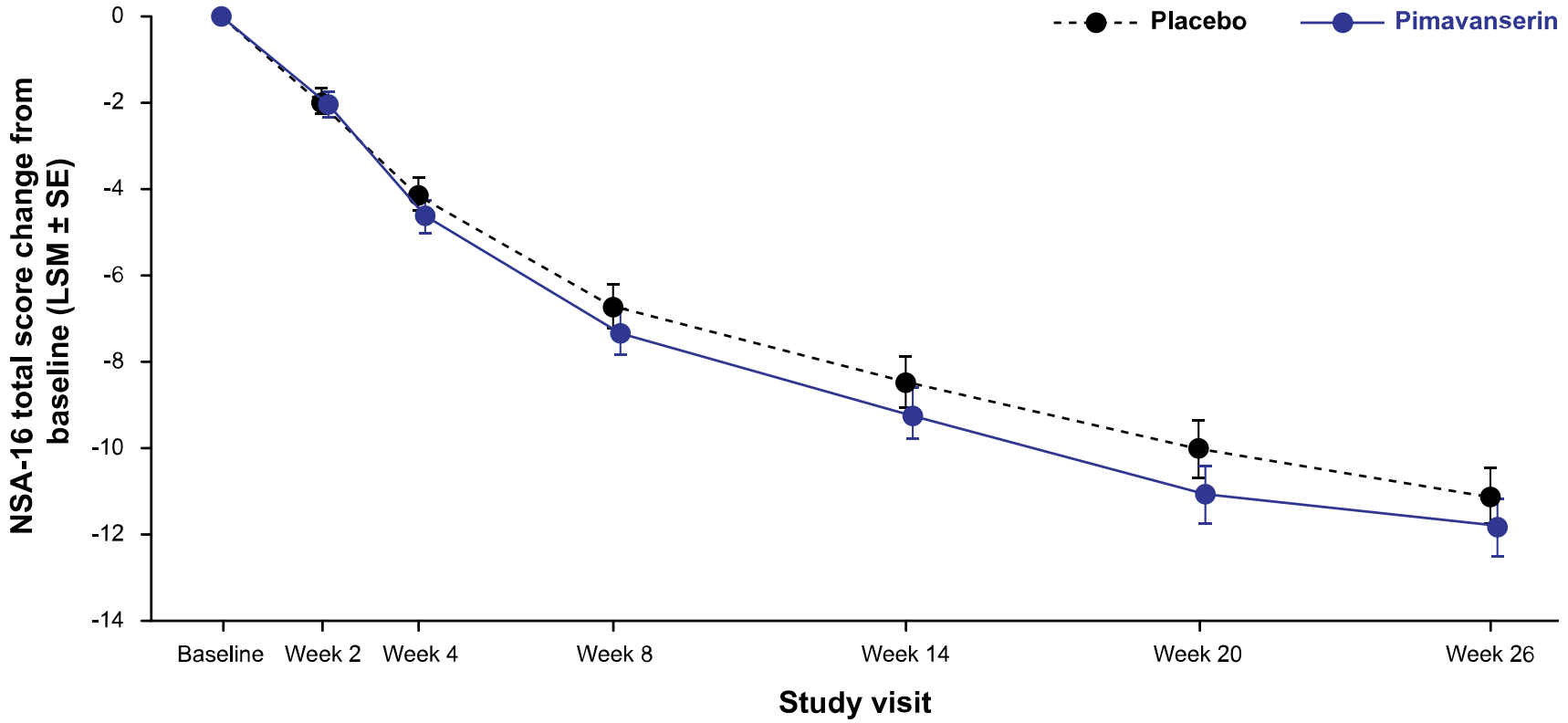
Patient disposition and baseline characteristics (FAS)



[a]Patients randomized (1:1) and stratified by geographical region. [b]Data are presented as mean (SE) unless indicated s otherwise.
[c]Includes long-acting injectable formulations.
AE, adverse event; CGI-SCH-S, Clinical Global Impression of Schizophrenia Scale–Severity; FAS, full analysis set; NSA-16, Negative Symptom Assessment–16; PSP, Personal and Social Performance scale.

Characteristic[b]	Placebo (n = 222)	Pimavanserin (n = 224)
Age at screening (years)	37.5 (0.7)	36.2 (0.6)
Sex, male, n (%)	134 (60.4)	131 (58.5)
Duration of schizophrenia (years)	12.5 (0.5)	11.5 (0.6)
Duration of negative symptoms, n (%)		
<1 year	24 (10.8)	13 (5.8)
1 to 5 years	104 (46.8)	117 (52.2)
>5 years	94 (42.3)	94 (42.0)
Background antipsychotic type, n (%)		
Aripiprazole[c]	55 (24.8)	57 (25.4)
Olanzapine	70 (31.5)	61 (27.2)
Risperidone[c]	60 (27.0)	60 (26.8)
Duration of background antipsychotic (months)	30.5 (2.6)	25.2 (2.6)
NSA-16 total score	60.9 (0.53)	61.3 (0.54)
CGI-SCH-S of negative symptom score	4.8 (0.04)	4.8 (0.04)
PSP score	44.9 (0.70)	44.8 (0.72)

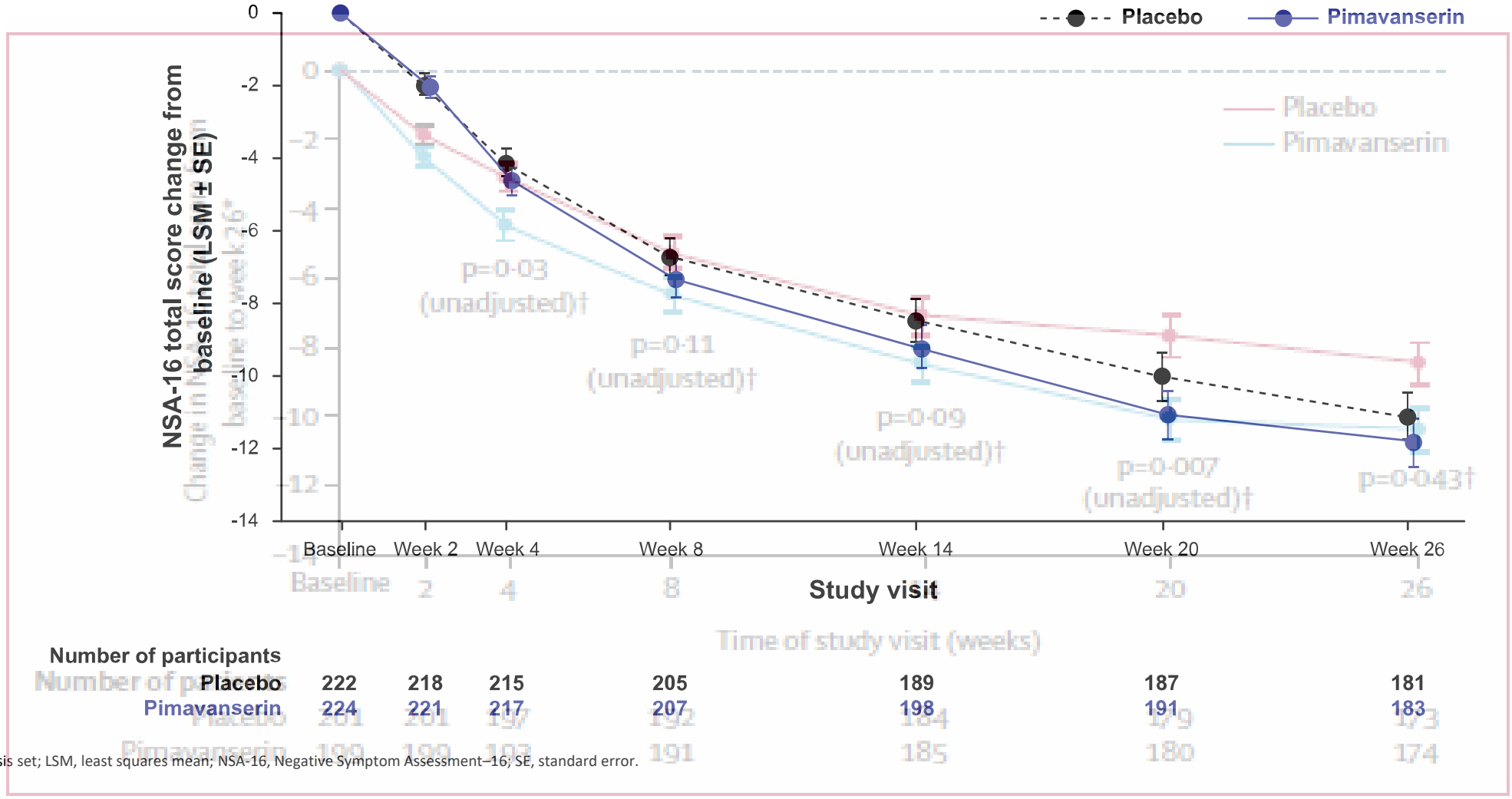
Primary endpoint: LS mean change in the NSA-16 total score from baseline to Week 26 (FAS)



Number of participants							
Placebo	222	218	215	205	189	187	181
Pimavanserin	224	221	217	207	198	191	183

FAS, full analysis set; LSM, least squares mean; NSA-16, Negative Symptom Assessment–16; SE, standard error.

Primary endpoint: LS mean change in the NSA-16 total score from baseline to Week 26 (FAS)



FAS, full analysis set; LSM, least squares mean; NSA-16, Negative Symptom Assessment–16; SE, standard error.

SIRS
Schizophrenia International Research Society

Key and other secondary outcomes (FAS)

	Placebo (n = 222)		Pimavanserin (n = 224)				
	Mean (SE) Baseline	LS Mean (SE) Change	Mean (SE) Baseline	LS Mean (SE) Change	LS Mean (SE) Difference [95% CI]	p value	Cohen's d Effect Size
CGI-SCH-S negative symptom score[a,b,c]	4.85 (0.04)	-0.86 (0.06)	4.83 (0.04)	-0.87 (0.06)	-0.01 (0.09) [-0.19, 0.17]	0.89	0.014
CGI-SCH-I negative symptom score[a,b,c]	-	2.94 (0.06)	-	2.81 (0.06)	-0.13 (0.09) [-0.31, 0.04]	0.14	0.151
PSP[a,b,c]	44.85 (0.70)	11.18 (0.78)	44.77 (0.72)	12.03 (0.78)	0.85 (1.10) [-1.32, 3.02]	0.44	0.078
PANSS total score[a,b,c]	72.56 (0.61)	-9.41 (0.68)	72.71 (0.64)	-10.66 (0.67)	-1.24 (0.95) [-3.11, 0.62]	0.19	0.134
PANSS negative symptoms subscales[a,b,c]	27.59 (0.24)	-5.02 (0.32)	27.71 (0.25)	-5.29 (0.32)	-0.27 (0.45) [-1.16, 0.63]	0.56	0.060
PANSS Marder factor (negative symptoms) score[a,b,c]	26.85 (0.21)	-5.72 (0.32)	26.79 (0.22)	-6.06 (0.31)	-0.34 (0.45) [-1.22, 0.54]	0.45	0.077

Data are mean (SE) unless otherwise stated.
[a]LS mean from MMRM with effects of treatment (pimavanserin or placebo added to ongoing antipsychotic treatment), study visit (weeks 2, 4, 8, 14, 20, 26), region (Europe and Rest of world), Baseline score, treatment-by-visit interaction, and the baseline-by-visit interaction. An unstructured covariance matrix is used to model the within-subject errors.
[b]Difference between LS mean changes for pimavanserin and placebo (pimavanserin – placebo) at the specified visit from MMRM analysis.
[c]Two-sided p-value for treatment difference at specified visit from MMRM analysis.
CGI-SCH-I, Clinical Global Impression of Schizophrenia Scale-Improvement; CGI-SCH-S, Clinical Global Impression of Schizophrenia Scale-Severity; FAS, full analysis set; LS, least squares; MMRM, mixed model for repeated measures; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance; SE, standard error.

Incidence of treatment-emergent adverse events

Characteristic, n (%)	Placebo (n = 226)	Pimavanserin (n = 227)
Any TEAE	91 (40.3)	69 (30.4)
Drug-related TEAE	26 (11.5)	22 (9.7)
Serious TEAE	7 (3.1)	2 (0.9)
TEAE leading to death	0	0
Discontinuation due to TEAE	14 (6.2)	6 (2.6)
TEAEs occurring in ≥ 2% of either treatment group		
Headache	16 (7.1)	9 (4.0)
Insomnia	7 (3.1)	4 (1.8)
Schizophrenia	7 (3.1)	1 (0.4)
Somnolence	7 (3.1)	5 (2.2)
COVID-19	6 (2.7)	2 (0.9)
Diarrhea	1 (0.4)	5 (2.2)
Dizziness	1 (0.4)	5 (2.2)

Data are from the safety analysis set.
TEAE, treatment-emergent adverse event.

Summary and conclusions

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- In ADVANCE-2, the pimavanserin and placebo groups did not differ significantly on the primary efficacy endpoint of the change in the NSA-16 total score from baseline to Week 26
- The treatment groups did not differ significantly on the key secondary efficacy endpoint of the change in the CGI-SCH-S score from baseline to Week 26 or the other secondary endpoints
- Safety findings were largely similar between the two groups
- There were no new safety signals with pimavanserin
- This study did replicate the magnitude of the pimavanserin effect from the prior Phase 2 ADVANCE study; unfortunately, the placebo effect in this study was greater than in the prior[1]
- There were many challenges during this program with some of the more prominent challenges including carry-over effects of the COVID-19 pandemic and the ongoing conflict in Ukraine

1. Bugarski-Kirola, D, et al. Lancet Psychiatry. 2022;9:46–58.
This study was funded by Acadia. Medical writing support was provided by Nathan Hutcheson, PhD, from Citrus Scientific, a Citrus Health Group, Inc. company (Chicago, IL), in accordance with Good Publication Practices (GPP) 2022.
CGI-SCH-I, Clinical Global Impression of Schizophrenia Scale-Improvement; CGI-SCH-S, Clinical Global Impression of Schizophrenia Scale-Severity; NSA-16, Negative Symptom Assessment–16; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance.

Baseline characteristics (continued)

Characteristic[a]	Placebo (n = 222)	Pimavanserin (n = 224)
Region, n (%)		
Europe	183 (82.4)	185 (82.6)
Rest of world	39 (17.6)	39 (17.4)
Race[b], n (%)		
White	220 (99.1)	222 (99.1)
American Indian or Alaska Native	1 (0.5)	0
Other	1 (0.5)	2 (0.9)
Body mass index (kg/m^2)	26.6 (0.3)	26.3 (0.3)
Diagnosed with schizophrenia >5 years, n (%)	170 (76.6)	148 (66.1)
Employment status		
Full time	18 (8.1)	14 (6.3)
Part time	22 (9.9)	21 (9.4)
Unemployed	137 (61.7)	142 (63.4)
Retired	45 (20.3)	47 (21.0)
Time since first antipsychotic (years)	11.5 (0.5)	10.3 (0.5)

[a]Data are presented as mean (SE) unless indicated as otherwise. [b]Percentages not shown for Asian, American Indian/Alaska Native, Native Hawaiian/other Pacific Islander, or Other.

Baseline characteristics (continued)

Characteristic, mean (SE)	Placebo (n = 222)	Pimavanserin (n = 224)
Schizophrenia negative symptoms		
NSA-16 ≤ 55	58 (26.1)	59 (26.3)
NSA-16 > 55	164 (73.9)	165 (73.7)
PANSS total score	72.6 (0.6)	72.7 (0.6)
PANSS positive symptoms subscore	11.6 (0.2)	11.8 (0.2)
PANSS negative symptoms subscore	27.6 (0.2)	27.7 (0.3)
WoRQ total score	15.7 (0.2)	15.9 (0.2)
CDSS total score	0.8 (0.1)	0.8 (0.1)

CDSS, Calgary Depression Scale for Schizophrenia; PANSS, Positive and Negative Syndrome Scale; NSA-16, Negative Symptom Assessment–16; SE, standard error; WoRQ, Work Rehabilitation Questionnaire.