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Supplementary Material

Article Title: Efficacy and Safety of HP-3070, an Asenapine Transdermal System, in Patients With Schizophrenia: A Phase 3, Randomized, Placebo-Controlled Study

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List of Supplementary Material for the article

1. Supplementary Methods

2. Table 1 — Baseline PANSS Total Score and Change from Baseline in PANSS Total Score Through Week 6 by Region in Patients with Schizophrenia Treated with HP-3070 or Placebo (Full Analysis Set)

3. Table 2 — Sensitivity Analyses of Placebo-Adjusted Change from Baseline in PANSS Total Score through Week 6 in Patients with Schizophrenia Treated With HP-3070 or Placebo (Full Analysis Set)

4. Table 3 — Other Secondary Endpoints in Patients with Schizophrenia Treated With HP-3070 or Placebo (Full Analysis Set)

5. Figure 1 — Patient Disposition for Placebo-Controlled Study of HP-3070 for Patients with Schizophrenia

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Supplementary Methods: The primary analysis method for the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression-Severity of Illness (CGI-S) endpoints was based on a mixed-model repeated-measures (MMRM) approach that utilized all available data (complete and partial) from subjects included in an analysis set. The MMRM-based approach assumed that data were missing at random (MAR). MAR refers to a missingness mechanism that was independent of missing responses, conditionally on observed response history and covariates. This assumption inherently implies that the treatment effect was similar for those who discontinued prematurely and for those who completed the study in their respective treatment arms. To assess the robustness of the MAR assumption, sensitivity analyses that utilized multiple imputations and a different assumption about unobserved outcomes was performed. Missing not at random (MNAR) mechanisms were assessed using pattern-mixture modeling (PMM) with placebo-based multiple imputation. Change from baseline (CFB) to each post-baseline time point was computed based on observed and imputed data. Each imputed complete dataset was analyzed with the MMRM as used for the primary analysis. Sensitivity analyses were performed and supported the robustness of the primary and key secondary efficacy endpoints.

Supplementary Table 1. Baseline PANSS Total Score and Change from Baseline in PANSS Total Score Through Week 6 by Region in Patients with Schizophrenia Treated with HP-3070 or Placebo (Full Analysis Set)

	HP-3070 7.6mg/24h (n=203)		HP-3070 3.8mg/24h (n=201)		Placebo (n=203)	
	PANSS Total Score, Mean (SD)	**CFB in PANSS Total Score, LSM estimate (95% CI)**	**PANSS Total Score, Mean (SD)**	**CFB in PANSS Total Score, LSM estimate (95% CI)**	**PANSS Total Score, Mean (SD)**	**CFB in PANSS Total Score, LSM estimate (95% CI)**
	Baseline	Week 6	Baseline	Week 6	Baseline	Week 6
North America	n=60	n=37	n=59	n=46	n=61	n=49
	94.4 (8.28)	-20.6 (-25.18 to -15.96)	94.2 (9.67)	-21.1 (-25.49 to -16.62)	95.6 (9.92)	-13.9 (-18.28 to -9.59)
Russia	n=60	n=49	n=59	n=48	n=59	n=44
	94.5 (7.64)	-23.1 (-27.21 to -18.92)	96.0 (8.49)	-22.8 (-27.04 to -18.61)	96.8 (8.46)	-10.8 (-15.08 to -6.44)
Eastern Europe[a]	n=83	n=78	n=83	n=74	n=83	n=72
	97.3 (9.44)	-18.4 (-21.58 to -15.28)	99.6 (10.15)	-22.7 (-25.87 to -19.55)	99.1 (11.04)	-20.7 (-23.94 to -17.51)

[a]Includes Bulgaria, Ukraine, and Serbia.

Abbreviations: CI = confidence interval, LSM = least-squares mean, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation.

Supplementary Table 2. Sensitivity Analyses of Placebo-Adjusted Change from Baseline in PANSS Total Score through Week 6 in Patients with Schizophrenia Treated With HP-3070 or Placebo (Full Analysis Set)

	HP-3070 7.6mg/24h (n=203)		HP-3070 3.8mg/24h (n=201)	
	PANSS Total Score	**CGI-S Score**	**PANSS Total Score**	**CGI-S Score**
Pattern-mixture model[a] for dropout pattern 1[b], LSM estimate (95% CI)	-4.3** (-7.44 to -1.09)	-0.3** (-0.52 to -0.13)	-5.9*** (-9.11 to -2.76)	-0.4*** (-0.60 to -0.21)
Pattern-mixture model for dropout pattern 2[c], LSM estimate (95% CI)	-4.2** (-7.36 to -1.06)	-0.3** (-0.52 to -0.13)	-6.0*** (-9.12 to -2.80)	-0.4*** (-0.60 to -0.21)
Pattern-mixture model for dropout pattern 3[d], LSM estimate (95% CI)	-4.3** (-7.46 to -1.14)	-0.3** (-0.52 to -0.13)	-6.0*** (-9.15 to -2.83)	-0.4*** (-0.60 to -0.21)

[a]Sensitivity analyses of primary and key efficacy variables were considered to separate informative (treatment failures) vs. non-informative cases based on the reasons of discontinuation when imputation of missing values was performed (see definitions in footnotes b, c, and d).
[b]Discontinuation for any of the reasons (an AE, death, noncompliance, lack of efficacy, requiring treatment with a prohibited medication, pregnancy, physician decision, study terminated by investigator/sponsor, withdrawal of consent, or other) was informative.
[c]Discontinuation due to lack of efficacy, AE, or death was informative, and discontinuations due to all other reasons were non-informative.
[d]Discontinuation due to lack of efficacy was informative, and discontinuations due to all other reasons were non-informative.
**P<.01; ***P<.001.
Abbreviations: CGI-S = Clinical Global Impression-Severity of Illness, CI = confidence interval, LSM = least-squares mean, PANSS = Positive and Negative Syndrome Scale, SE = standard error.

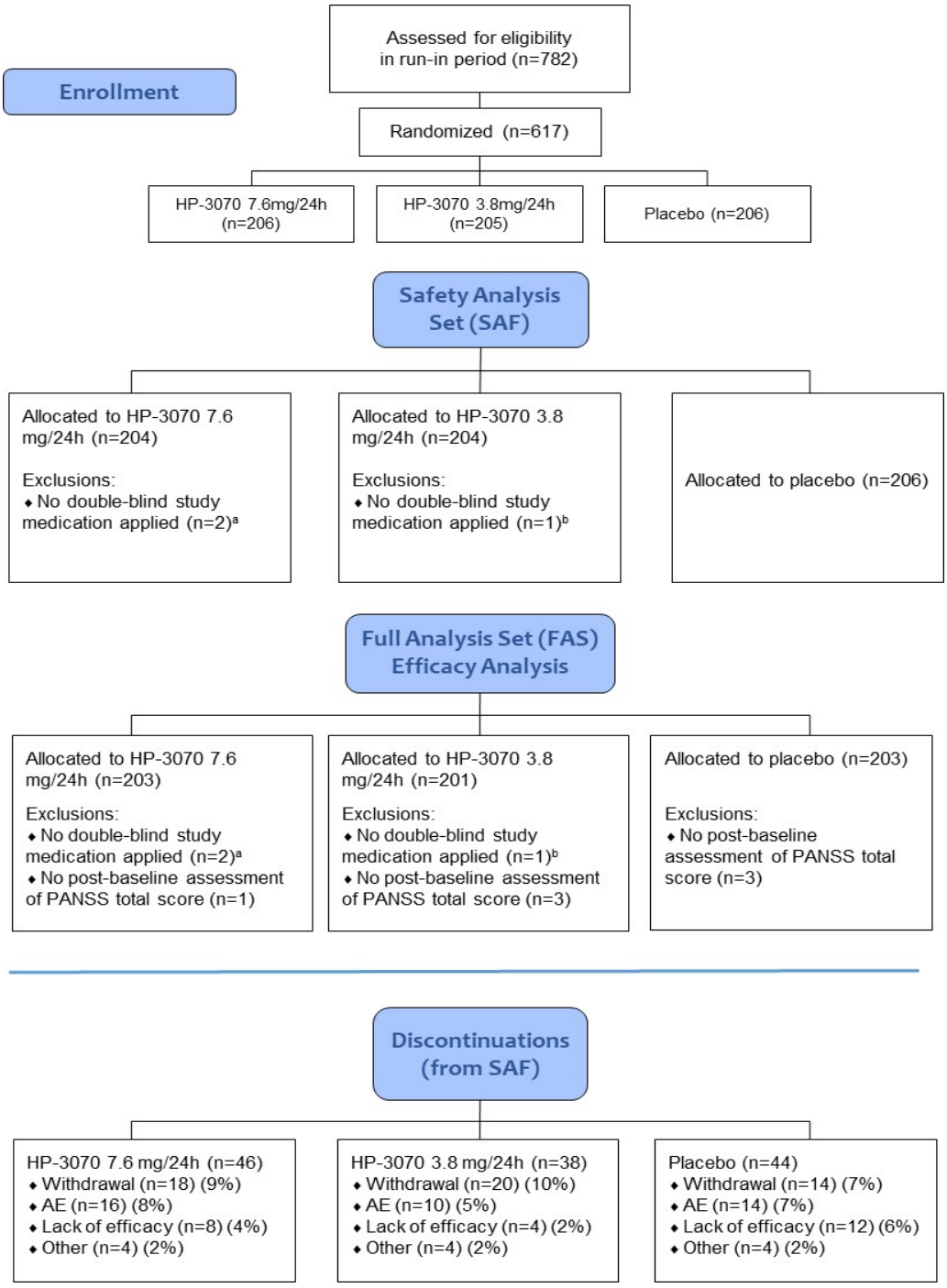
Supplementary Table 3. Other Secondary Endpoints in Patients with Schizophrenia Treated With HP-3070 or Placebo (Full Analysis Set)

		HP-3070 7.6mg/24h (N=203)	HP-3070 3.8mg/24h (N=201)	Placebo (N=203)
CGI-I Score				
Placebo-adjusted CFB by week LSM estimate (95% CI)[a]	Week 1	-0.1 (-0.26 to 0.09)	-0.1 (-0.27 to 0.09)	--
	Week 2	-0.2 (-0.36 to 0.00)	-0.2* (-0.40 to -0.03)	--
	Week 3	-0.2* (-0.38 to -0.01)	-0.1 (-0.32 to 0.05)	--
	Week 4	-0.3** (-0.44 to -0.07)	-0.4*** (-0.60 to -0.23)	--
	Week 5	-0.3*** (-0.53 to -0.15)	-0.4*** (-0.55 to -0.18)	--
	Week 6	-0.3** (-0.46 to -0.08)	-0.4*** (-0.58 to -0.20)	--
Percentage of responders[b], n (%)	Week 1	9 (4.4)	8 (4.0)	7 (3.4)
	Week 2	36 (17.7)	25 (12.4)	25 (12.3)
	Week 3	55 (27.1)	41 (20.4)	43 (21.2)
	Week 4	73 (36.0)*	78 (38.8)**	52 (25.6)
	Week 5	87 (42.9)**	93 (46.3)***	59 (29.1)
	Week 6	88 (43.3)*	100 (49.8)**	69 (34.0)

PANSS Total Score				
Percentage of responders[c], n (%)	Week 1	5 (2.5)	3 (1.5)	5 (2.5)
	Week 2	10 (4.9)	10 (5.0)	9 (4.4)
	Week 3	21 (10.3)	21 (10.4)	16 (9.7)
	Week 4	32 (15.8)	31 (15.4)	27 (13.3)
	Week 5	45 (22.2)	51 (25.4)	35 (17.2)
	Week 6	60 (29.6)**	62 (30.8)**	38 (18.7)

[a]MMRM included CGI-I score as the repeated dependent variable, with country, treatment, visit (Weeks 1-6), treatment by visit interaction, and baseline value of CGI-S score as covariates, and subject as random effect. *P* values refer to treatment comparison (Active-Placebo).
[b]Patients with a CGI-I score of 1 (very much improved) or 2 (much improved). Proportion of responders was tested using the CMH method stratified by country, with the hypothesis test based on the general association statistic. *P* values refer to treatment comparison (Active-Placebo).
[c]Patients demonstrating ≥30% improvement from baseline PANSS total score. Proportion of responders was tested using the CMH method stratified by country, with the hypothesis test based on the general association statistic. *P* values refer to treatment comparison (Active-Placebo).
*$P<.05$; **$P<.01$; ***$P<.001$.
Abbreviations: CFB = change from baseline, CGI-I = Clinical Global Impression-Improvement, CGI-S = Clinical Global Impression-Severity of Illness, CMH = Cochran-Mantel-Haenszel, MMRM = mixed-model repeated-measures, PANSS = Positive and Negative Syndrome Scale.

Supplementary Figure 1. Patient Disposition for Placebo-Controlled Study of HP-3070 for Patients with Schizophrenia



[a]One patient met exclusion criteria and was not dosed, and the other patient withdrew consent before the first dose. Both patients were randomized to HP 3070 7.6mg/24h and were not included in Safety or Efficacy Analysis Set.
[b]One patient was incorrectly assigned to HP 3070 3.8mg/24h. This patient met exclusion criteria for the study and was removed.
Abbreviations: AE = adverse event, PANSS = Positive and Negative Syndrome Scale.