

Supplementary Materials

Supplementary Table 1. Approving Institutional Review Boards or Independent Ethics Committees

Study Center	IRB/EC Name/Address	IRB/EC Chairperson
1000-1009 1011-1019	Copernicus Group IRB / 5000 Centregreen Way Suite 200, Cary, NC 27513, USA	Glenn Veit
2001, 2002 2005-2007 2009, 2011, 2012	Bulgarian Drug Agency / Ethics Committee for Multicenter Trials / 8 “Damyan Gruev” Str., fl. 1, room 104, Sofia 1303, Bulgaria	Dr. Todor Popov
4000	LEC at MSc Scientific Research Inst. of Psychiatry / Ethical Council at the MoH of RF / IEC of Federal State Budgetary Institution "Moscow Scientific and Research Institute of Psychiatry" of the Ministry of Healthcare of the Russian Federation, 3, building 10, Poteshnaya street, Moscow, 107076, Russia	Ya. Gurovich
4001	IEC "Tomsk Clinical Psychiatric Hospital" / Ethical Council at the MoH of RF / 5 Kooperativny Street, Tomsk, Russian Federation	Elena Vladimirovna Gutkevich
4002	LEC Mental Health Research Center / Ethical Council at the MoH of RF / 34, Kashirskoye shosse, 115522, Moscow, Russian Federation	Elena Vladimirovna Kolyutskaya
4003	LEC of SPBSHI "Psychiatric Hospital #1 n.a. P.P.Kaschenko" / Ethical Council at the MoH of RF / IEC of Saint Petersburg State	Natalia Vladimirovna Semenova

	Budgetary Institution of Healthcare "Psychiatric Hospital # 1 named after P.P. Kashchenko"; 10, Menkovskaya street, settlement Nikolskoe, Gatchinskiy district, Leningrad region, 188357, Russia	
4004-4007 4009, 4010	LEC at SPB SR Psychoneurological Inst. n.a.V.M.Bekhterev of MoH / Ethical Council at the MoH of RF / Bekhtereva Street 3, 192019 St. Petersburg, Russia	Aleksandra Alekseyevna Burma (16-Jul-2013) N. V. Semenova (21-Sep-2017)
4008	EC of the SBHI "Sverdlovsk Regional Clinical Psychiatric Hospital" / Ethical Council at the MoH of RF / Ulitsa Roshchinskaya, 72, Yekaterinburg, Sverdlovskaya oblast', 620023, Russia	E. Iu. Dunaeva
4011	LEC at Msc Scientific Research Inst. of Psychiatry / Ethical Council at the MoH of RF/ Bekhtereva Street 3, 192019 St. Petersburg, Russia	Aleksandra Alekseyevna Burma (16-Jul-2013) N. V. Semenova (21-Sep-2017)
4012	EC at SBHI "Samara Psychiatric Hospital" / Ethical Council at the MoH of RF / Ulitsa Nagornaya, 78, Samara, Samarskaya oblast, 443016, Russia	Vladimir Nikolayevich VOSTOKIN
4013	LEC at SHI "Psychiatric hospital #1 n. a. N.A. Alexeev" / Ethical Council at the MoH of RF/ Bekhtereva Street 3, 192019 St. Petersburg, Russia	Aleksandra Alekseyevna Burma (16-Jul-2013) N. V. Semenova (21-Sep-2017)
4014	IEC at "Arte Med Assistance" LLC / IEC at "Arte Med Assistance" LLC , 27, building C, office 44, prospect Engel'sa, St. Petersburg, 194156, Russia	Prof. B. V. Andreev

5001	State Expert Center of the Ministry of Health of Ukraine / LEC CI Kherson Regional Psychiatric Hospital / Off . 601, 40, K. Ushinsky Str., Kyiv, 03151, Ukraine	S. A. Yerokhin
5002, 5009	State Expert Center of the Ministry of Health of Ukraine / LEC State Institution Institute of Neurology, Psychiatry and Narcology of NAMSU / Off . 601, 40, K. Ushinsky Str., Kyiv, 03151, Ukraine	Liudmyla Mykolayivna Tantsura
5003	State Expert Center of the Ministry of Health of Ukraine / LEC Odesa Regional Psych. Dispensary / Off . 601, 40, K. Ushinsky Str., Kyiv, 03151, Ukraine	N.B. Verevka
5004, 5010	State Expert Center of the Ministry of Health of Ukraine / LEC CI" Lviv Regional Clinical Psychiatric Hospital" / Off . 601, 40, K. Ushinsky Str., Kyiv, 03151, Ukraine	O. R. Lemishko
5005	State Expert Center of the Ministry of Health of Ukraine / LEC CI Vinnytsya Regional Psychoneurological Hospital named after O.Yuschenko / Off . 601, 40, K. Ushinsky Str., Kyiv, 03151, Ukraine	Yu.P. Lytvynenko
5006	State Expert Center of the Ministry of Health of Ukraine / LEC CI Cherkasy Reg.Psych.Hospital / Off . 601, 40, K. Ushinsky Str., Kyiv, 03151, Ukraine	V.I. Shevchuk
5007	State Expert Center of the Ministry of Health of Ukraine / LEC Kharkiv Reg.Clin.Psych.Hosp.#3 / Off . 601, 40, K. Ushinsky Str., Kyiv, 03151, Ukraine	Kostiantyn Valeriyovych Kosterev

5008	State Expert Center of the Ministry of Health of Ukraine / LEC City Clinical Psychoneurological Hospital #1 / Off . 601, 40, K. Ushinsky Str., Kyiv, 03151, Ukraine	M. Yu. Ignatov
5011	State Expert Center of the Ministry of Health of Ukraine / LEC Ternopil Reg.Com. Clinical Psychoneurological Hospital / Off . 601, 40, K. Ushinsky Str., Kyiv, 03151, Ukraine	O.M. Bondarenko
5012	State Expert Center of the Ministry of Health of Ukraine / LEC State Institution Institute of Neurology, Psychiatry and Narcology of NAMSU / Off . 601, 40, K. Ushinsky Str., Kyiv, 03151, Ukraine	Kostiantyn Valeriyovych Kosterev
6000	Ethics Committee of Institute of Mental Health/ Palmotićeva 37, 11000 Belgrade, Serbia	Dr. Nenad Rudic
6001	Ethics Committee of Clinical Center Dragisa Misovic/Heroja Milana Tepica 1 11000 Belgrade, Serbia	Dr. Biljana Pencic Popovic
6002	Ethics Committee of Clinical Center Serbia / Pasterova 2 11000 Belgrade, Serbia	Dr. Branislav Stefanovic
6003, 6007	Ethics Committee of Clinical Center Kragujevac / Zmaj Jovina 30, 34000 Kragujevac, Serbia	Dr. Dejana Ruzic Zecevic
6005	Ethics Committee of Clinical Center of Vojvodina / Hajduk Veljka 1, 21137 Novi Sad, Vojvodina	Dr. Edita Stokic

Supplementary Table 2. Clinician-Rated Clinical Global Impression-Severity and CGI-Improvement scales

CGI-S	CGI-I
1="Normal, not at all ill"	1="Very much improved"
2="Borderline mentally ill"	2="Much improved"
3="Mildly ill"	3="Minimally improved"
4="Moderately ill"	4="No change"
5="Markedly ill"	5="Minimally worse"
6="Severely ill"	6="Much worse"
7="The most extremely ill"	7="Very much worse"

CGI-I, Clinician-Rated Clinical Global Impression-Improvement; CGI-S, Clinician-Rated Clinical Global Impression-Severity; PANSS, Positive and Negative Syndrome Scale.

Supplementary Table 3. Correlation Between PANSS Total Score and CGI Scores

PANSS Score	N	Pearson Correlation Coefficient	Spearman Correlation Coefficient
Total score	615	CGI-S: 0.53	CGI-S: 0.50
Change from baseline	497	CGI-S: 0.72	CGI-S: 0.73
		CGI-I: 0.81	CGI-I: 0.80
Percentage change in unadjusted PANSS Score from baseline	497	CGI-S: 0.78	CGI-S: 0.79
		CGI-I: 0.82	CGI-I: 0.82

All *P*-values are <.0001. CGI-I, Clinician-Rated Clinical Global Impression-Improvement; CGI-S, Clinician-Rated Clinical Global Impression-Severity; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Supplementary Table 4. MSD and MSRs for Change From Baseline to Week 6 in PANSS

Total Score by CGI-S at Baseline for Responders

CGI-S at baseline	n	Mean (SD)	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile
All Responders ^a	393	-26.23 (11.17)	-41	-33	-26	-18	-12
4="Moderately ill"	85	-25.6 (10.43)	-39	-32	-24	-19	-12
5="Markedly ill"	261	-25.74 (10.94)	-41	-33	-26	-18	-11
6="Severely ill"	47	-30.04 (13.10)	-51	-41	-30	-20	-14

Shading indicates the MSRs.

^aResponders are defined as CGI-I scores of 1, 2, or 3.

MSD is defined as change in PANSS total score from baseline to endpoint for at least 50% of responders (CGI-I=1, 2, 3).

CGI-I, Clinician-Rated Clinical Global Impression-Improvement; CGI-S, Clinician-Rated Clinical Global Impression-Severity; MSD, meaningful score difference; MSRs, meaningful score regions; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Supplementary Table 5. MSD and MSRs for Percentage Change From Baseline to Week 6 in PANSS Total Score (Unadjusted) by CGI-S at Baseline for Responders

CGI-S at baseline	n	Mean (SD)	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile
All responders ^a	393	-27.26 (11.50)	-42.4	-34.7	-26.4	-18.6	-12.8
4=“Moderately ill”	85	-28.57 (11.29)	-43.6	-34.4	-27.8	-21.4	-14.0
5=“Markedly ill”	261	-26.94 (11.64)	-42.2	-34.7	-26.0	-18.0	-12.2
6=“Severely ill”	47	-26.66 (11.15)	-42.1	-36.4	-25.7	-18.9	-11.9

Shading indicates the MSRs.

^aResponders are defined as CGI-I scores of 1, 2, or 3.

MSD defined as the percentage change in PANSS total score from baseline to endpoint for at least 50% of responders (CGI-I=1, 2, 3).

CGI-I, Clinician-Rated Clinical Global Impression-Improvement; CGI-S, Clinician-Rated Clinical Global Impression-Severity; MSD, meaningful score difference; MSRs, meaningful score regions; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Supplementary Table 6. MSD and MSRs for Percentage Change From Baseline to Week 6 in PANSS Total Score (Adjusted) by CGI-S at Baseline for Responders (CGI-I=1, 2)

CGI-S at baseline	n	Mean (SD)	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile
All responders ^a	257	-47.35 (14.75)	-66.1	-56.5	-46.5	-37.0	-29.0
4=“Moderately ill”	60	-49.39 (15.10)	-71.7	-57.7	-46.5	-38.8	-34.2
5=“Markedly ill”	171	-47.16 (14.93)	-65.5	-56.5	-46.6	-37.0	-28.4
6=“Severely ill”	26	-43.85 (12.30)	-59.1	-54.8	-40.6	-34.2	-28.3

^aResponders are defined as CGI-I scores of 1 or 2.

MSD is defined as percentage change in PANSS total score from baseline to endpoint for at least 50% of responders (CGI-I=1, 2).

CGI-I, Clinician-Rated Clinical Global Impression-Improvement; CGI-S, Clinician-Rated Clinical Global Impression-Severity; MSD, meaningful score difference; MSRs, meaningful score regions; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Supplementary Table 7. MSD and MSRs for Percentage Change From Baseline to Week 6 in PANSS Total Score (Adjusted) by CGI-S at Baseline for Responders (CGI-I=1, 2, 3)

CGI-S at baseline	n	Mean (SD)	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile
All responders ^a	393	-39.88 (17.13)	-62.3	-51.0	-38.6	-27.1	-18.2
4="Moderately ill"	85	-43.08 (16.92)	-65.5	-51.7	-43.1	-32.3	-21.2
5="Markedly ill"	261	-39.45 (17.42)	-62.3	-51.0	-38.4	-26.0	-17.5
6="Severely ill"	47	-36.47 (15.19)	-58.7	-50.0	-35.6	-26.3	-15.9

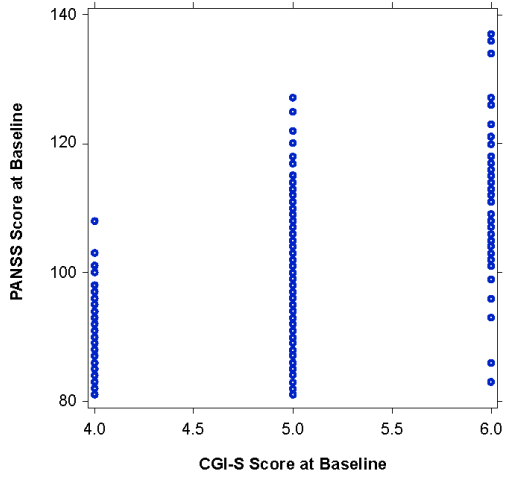
^aResponders are defined as CGI-I scores of 1, 2, or 3.

MSD is defined as percentage change in PANSS total score from baseline to endpoint for at least 50% of responders (CGI-I=1, 2, 3).

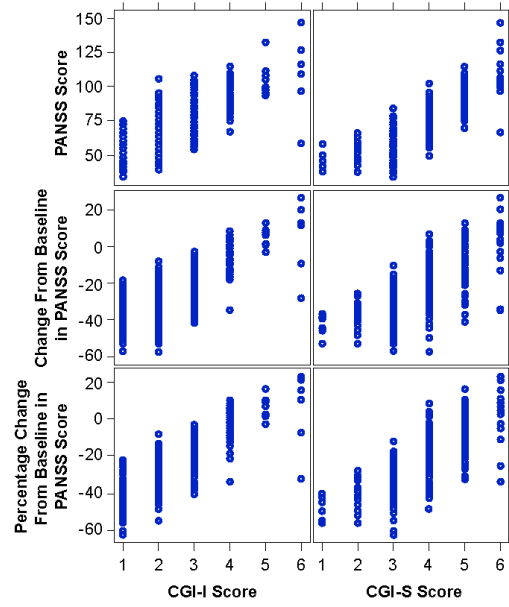
CGI-I, Clinician-Rated Clinical Global Impression-Improvement; CGI-S, Clinician-Rated Clinical Global Impression-Severity; MSD, meaningful score difference; MSRs, meaningful score regions; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Supplementary Figure 1. Relationship between PANSS total score (unadjusted) and CGI at baseline (A) and Week 6 (B)

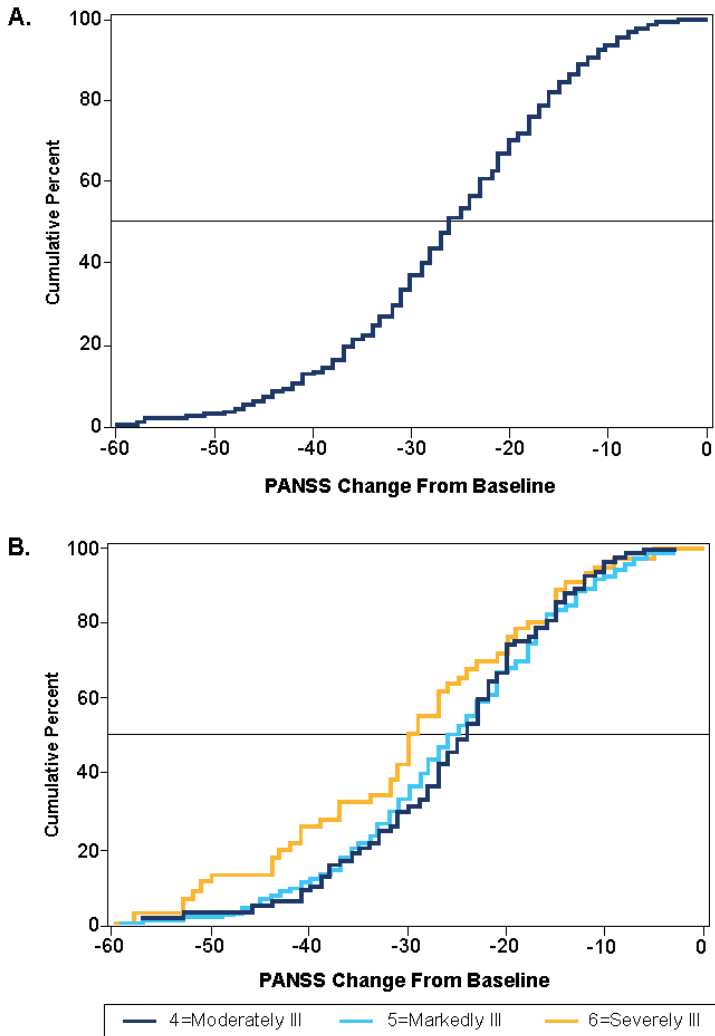
A.



B.



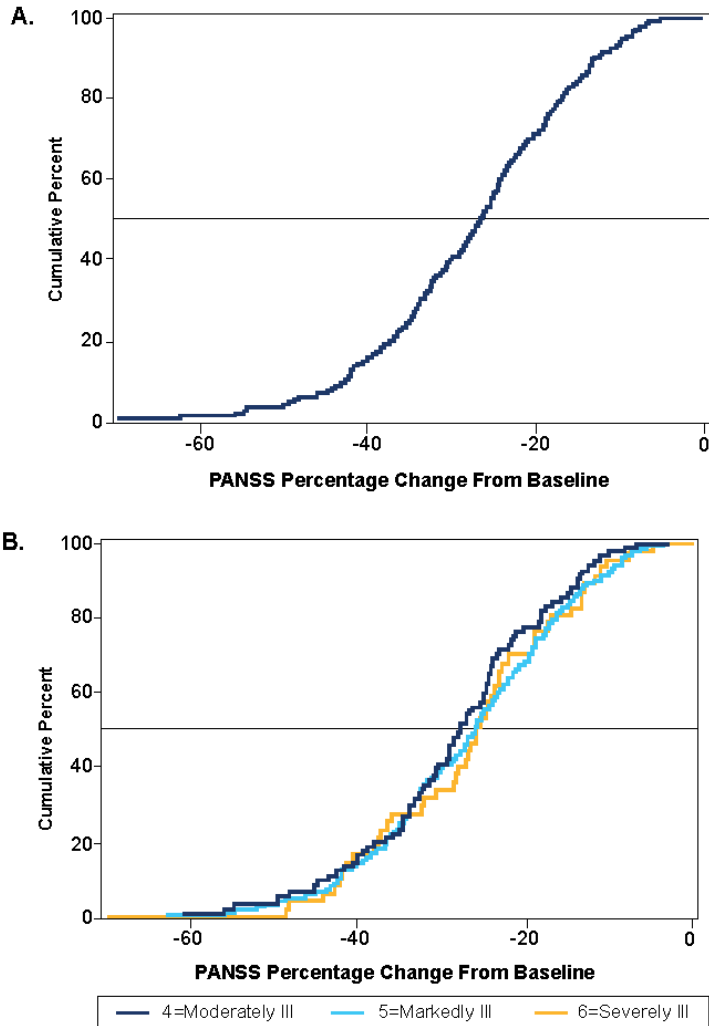
Supplementary Figure 2. Change in PANSS total score from baseline to Week 6 for responders^a (A) overall and (B) by baseline CGI-S



^aResponders are defined as CGI-I scores of 1, 2, or 3.

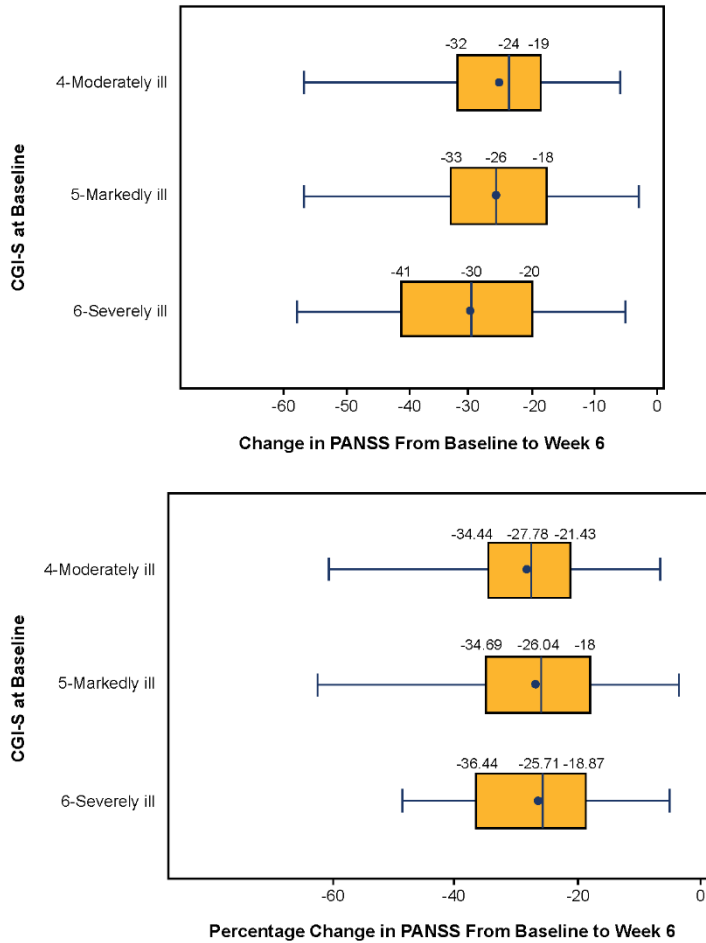
CGI-I, Clinician-Rated Clinical Global Impression-Improvement; CGI-S, Clinician-Rated Clinical Global Impression-Severity; PANSS, Positive and Negative Syndrome Scale.

Supplementary Figure 3. Percentage change in PANSS total score (unadjusted) from baseline to Week 6 for responders^a (A) overall and (B) by baseline CGI-S



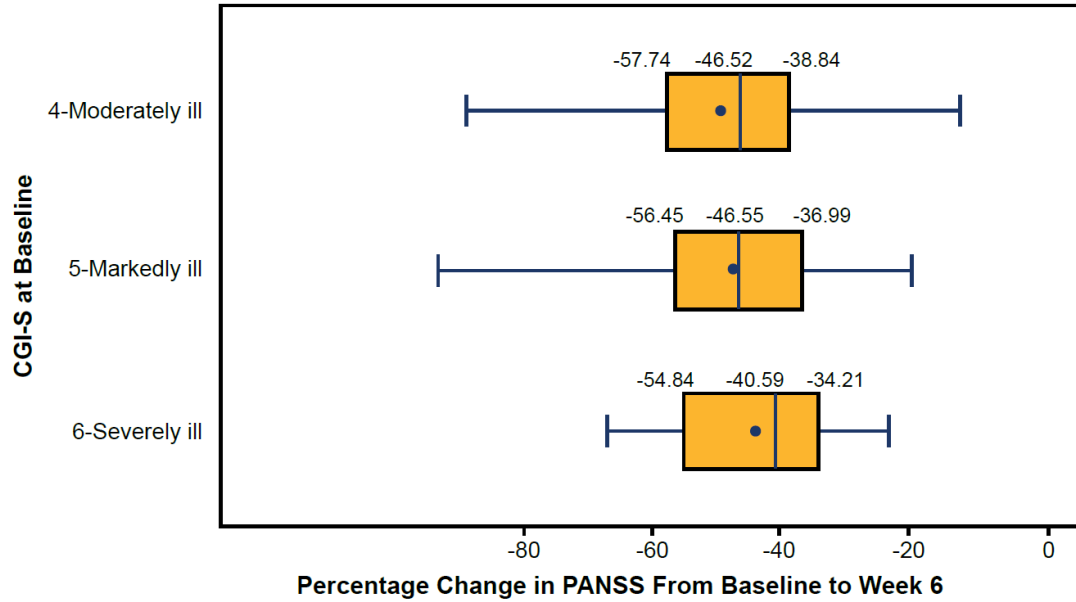
^aResponders are defined as CGI-I scores of 1, 2, or 3.
CGI-I, Clinician-Rated Clinical Global Impression-Improvement; CGI-S, Clinician-Rated Clinical Global Impression-Severity; PANSS, Positive and Negative Syndrome Scale.

Supplementary Figure 4. Meaningful regions of change and percentage change (unadjusted) in PANSS total score corresponding to severity at baseline for responders (CGI-I=1, 2, 3)



Box and whisker plots display the 25th (left edge of box), 50th (line inside box), and 75th (right edge of box) percentiles of the PANSS score distributions corresponding to each CGI-S level. Whiskers indicate scores $\pm 1.5 \times$ interquartile range. Means are represented by dots. CGI-I, Clinician-Rated Clinical Global Impression-Improvement; CGI-S, Clinician-Rated Clinical Global Impression-Severity; PANSS, Positive and Negative Syndrome Scale.

Supplementary Figure 5. Meaningful regions of percentage change in PANSS total score (adjusted) corresponding to severity at baseline for responders (CGI-I=1, 2)



Box and whisker plots display the 25th (left edge of box), 50th (line inside box), and 75th (right edge of box) percentiles of the PANSS score distributions corresponding to each CGI-S level. Whiskers indicate scores $\pm 1.5 \times$ interquartile range. Means are represented by dots.

CGI-I, Clinician-Rated Clinical Global Impression-Improvement; CGI-S, Clinician-Rated Clinical Global Impression-Severity; PANSS, Positive and Negative Syndrome Scale.