# MIN-101: A sigma2 and 5HT2 antagonist drug in development for the treatment of symptomatically stable schizophrenia patients with negative symptoms

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The trial was sponsored by Minerva Neurosciences, Inc. USA and managed by PPRS, France. MD, JR, RL are employees of Minerva Neurosciences, Inc. JS, CS, NN, EL, SW, JYS are employees of PPRS. JR and MW are paid consultants to Minerva Neurosciences, Inc.

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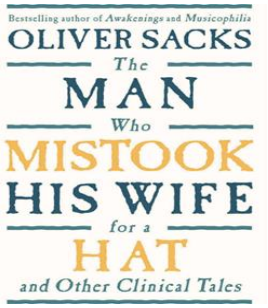
**We tend to be impressed by the unusual and the outlier, and less by the mundane and the ordinary, regardless of their impact and consequences**

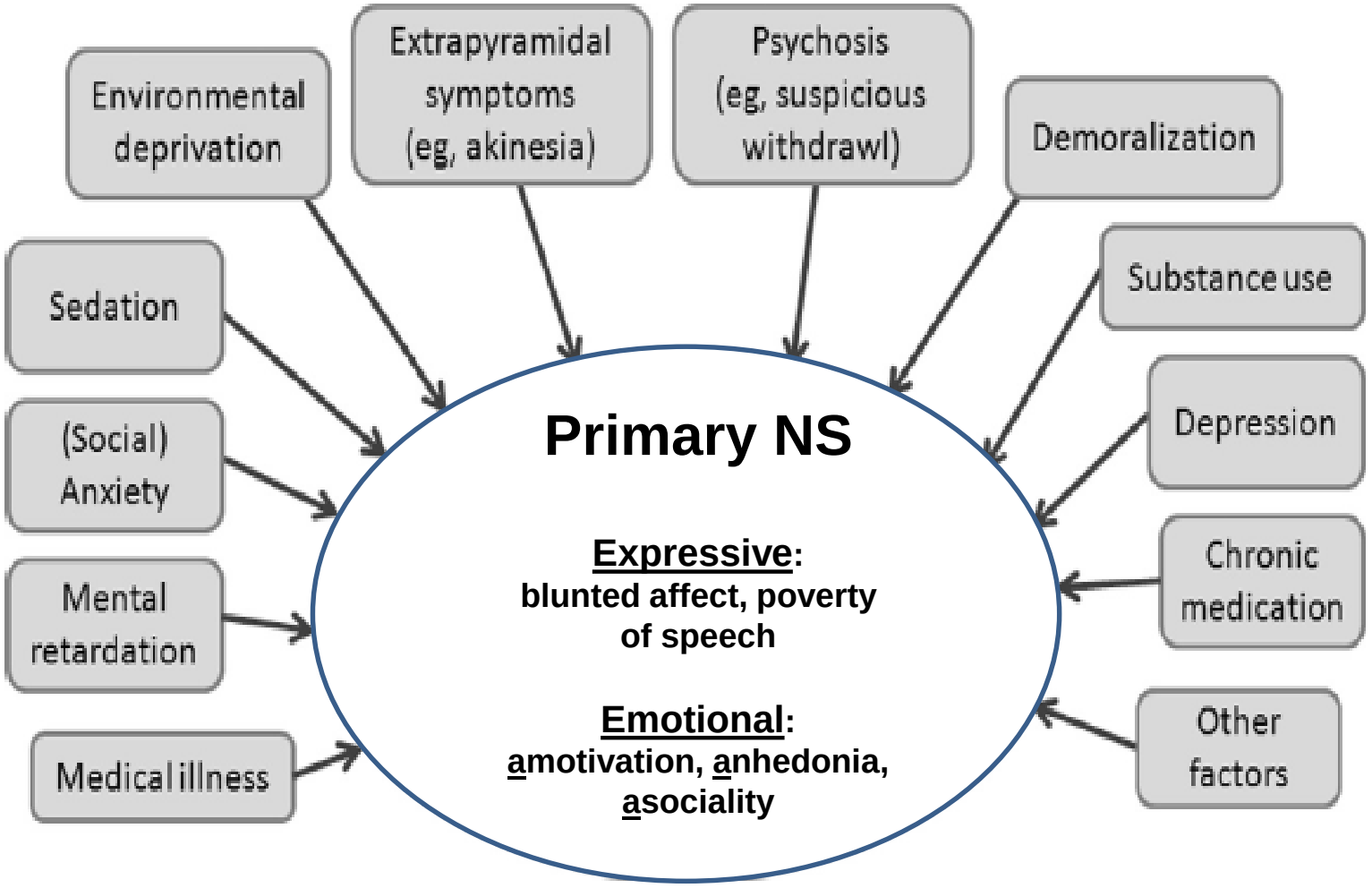



## Positive symptoms

- Present only intermittently in most patients
- Over-diagnosed due to miscommunications between interviewer and interviewee
- Not always affecting social and vocational functioning
- Ameliorate with Rx and often remit spontaneously

## Negative symptoms

- Present in the majority of patients and persistent
- Easy to recognize and diagnose (difficult to classify)
- Affect social and vocational functioning
- Rarely ameliorate spontaneously and no effective Rx exists




- **Negative symptoms improve secondary to:**
  - **Amelioration of psychosis (spontaneous or induced by antipsychotic drugs)**
  - **Environmental effects (nursing care, participation in research)**

- **Antipsychotic drugs might worsen apathy and amotivation**
  - **Differences in degree of worsening between antipsychotics (clozapine worsens NS less than haloperidol) ?**
  - **Dose dependent worsening?**

# MIN-101: a 5HT2 and Sigma 2 antagonist

| Receptor subtypes | Materials | Ki values, nmol/L |
|---|---|---|
| Serotonin 5-$HT_{2a}$ | Rat, cerebral cortex<br>Human recombinant | 7.5<br>5.2 |
| $Sigma_2$ | Guinea pig, brain | 8.2 |
| $Sigma_1$ | Guinea pig, brain | 253.8 |
| $A_1$ adrenergic | Rat, brain | 14.4 |

- No affinity (>1000 nM) for other receptors including dopaminergic, muscarinic, cholinergic and histaminergic receptors
- No direct DA binding
- However, $sigma_2$ receptors might be implicated in the modulation of DA (Katz et al 2012; Lever et al 2014) and glutamatergic pathways (Skuza 2012) as well as calcium neuronal modulation (Vilner et al 2000)
- Inhibition of apomorphine induced hyper-locomotion
- Amelioration of PCP-induced social interaction deficits

# Phase 2B Study Design

- Withdrawn from depot antipsychotics for ≥ 1 month and from all psychotropics for ≥ 3 days prior to randomization
- Randomized to **MONOTHERAPY** with MIN-101 32 mg/day, 64 mg/day or, placebo 1:1:1 ratio for 12 weeks
- Hospitalized for at least 3 days before and 2 days after randomization
- No psychotropic medications except rescue medications given for insomnia or agitation (oral lorazepam, zolpidem, or injectable sodium amytal)
- Assessments for efficacy and safety at baseline and at weeks 2, 4, 8 and 12 or upon premature termination
- After the 12 week-RCT, patients could continue on the same dose of MIN-101 or be switched from placebo to MIN-101 for 24 additional weeks

# Patients

Inclusion:

- DSM-5 schizophrenia
- Symptomatically stable and manifesting negative symptoms for 3 months as judged the PI
- **Baseline score ≥ 20 on the 7 PANSS item "classic" negative symptoms scale (N1-N7)**
- <4 on the PANSS: excitement, hyperactivity, hostility, suspiciousness, uncooperativeness, and poor impulse control

Exclusion:

- Personal or familial history of long QT syndrome, a QTc
- Poor or intermediate metabolizers for P450 CYP2D6, as determined by genotyping

# Outcomes

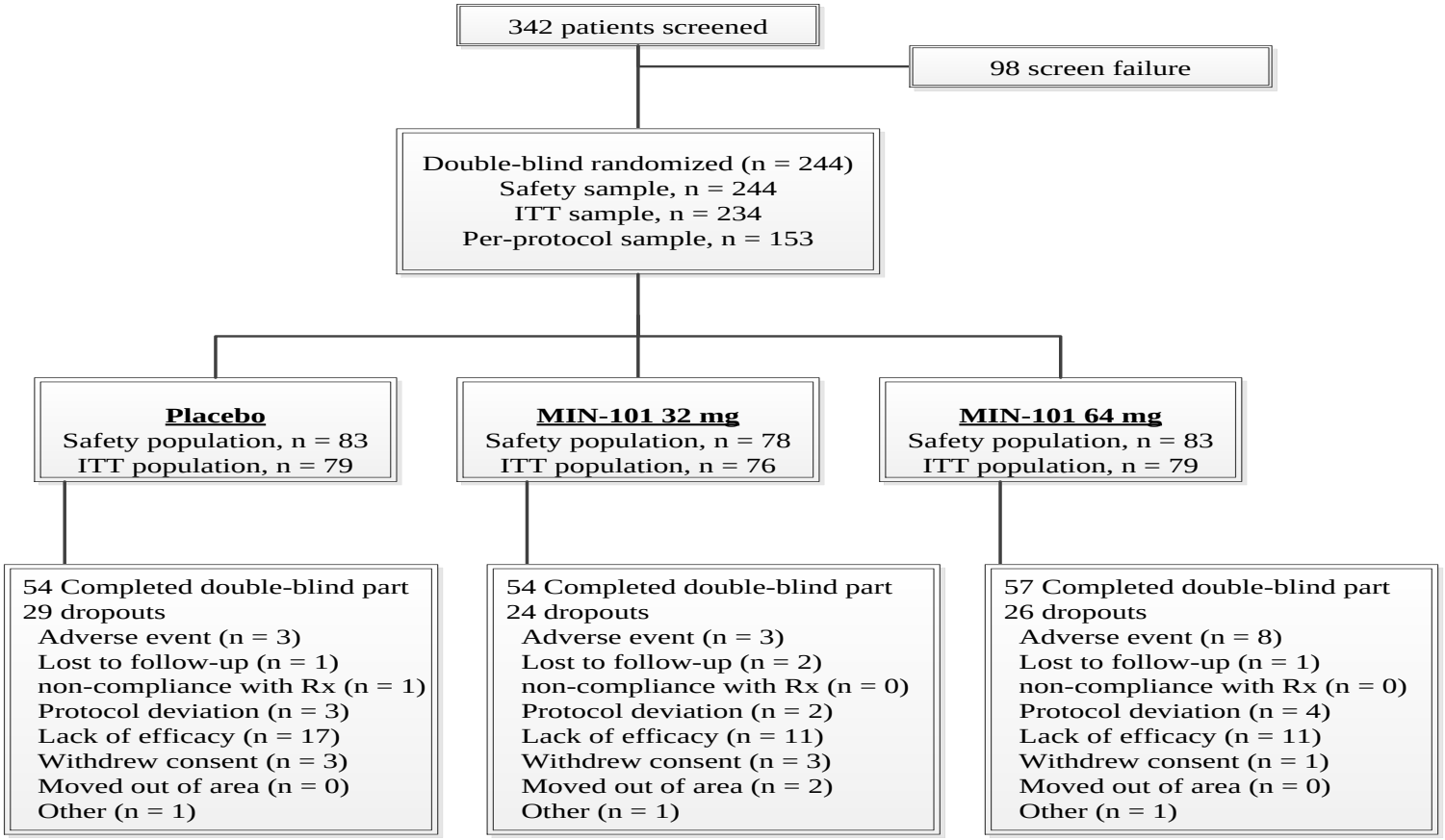
Primary

- Negative factor score of the PANSS from the pentagonal structure model (N1-4, 6; G7,8,13,14) (White et al 1997)

Secondary

- PANSS total, positive, negative and general subscale score, CGI-S, CGI-
- The Brief Negative symptoms Scale (BNSS)
- Brief Assessment of Cognition in Schizophrenia (BACS)
- Calgary Depression Scale for Schizophrenia (CDSS)
- Personal and Social Performance (PSP)
- Safety
  - Lab, VS, ECG
  - Sheehan-suicidality tracking scale (S-STS)
  - Abnormal Involuntary Movement Scale (AIMS)

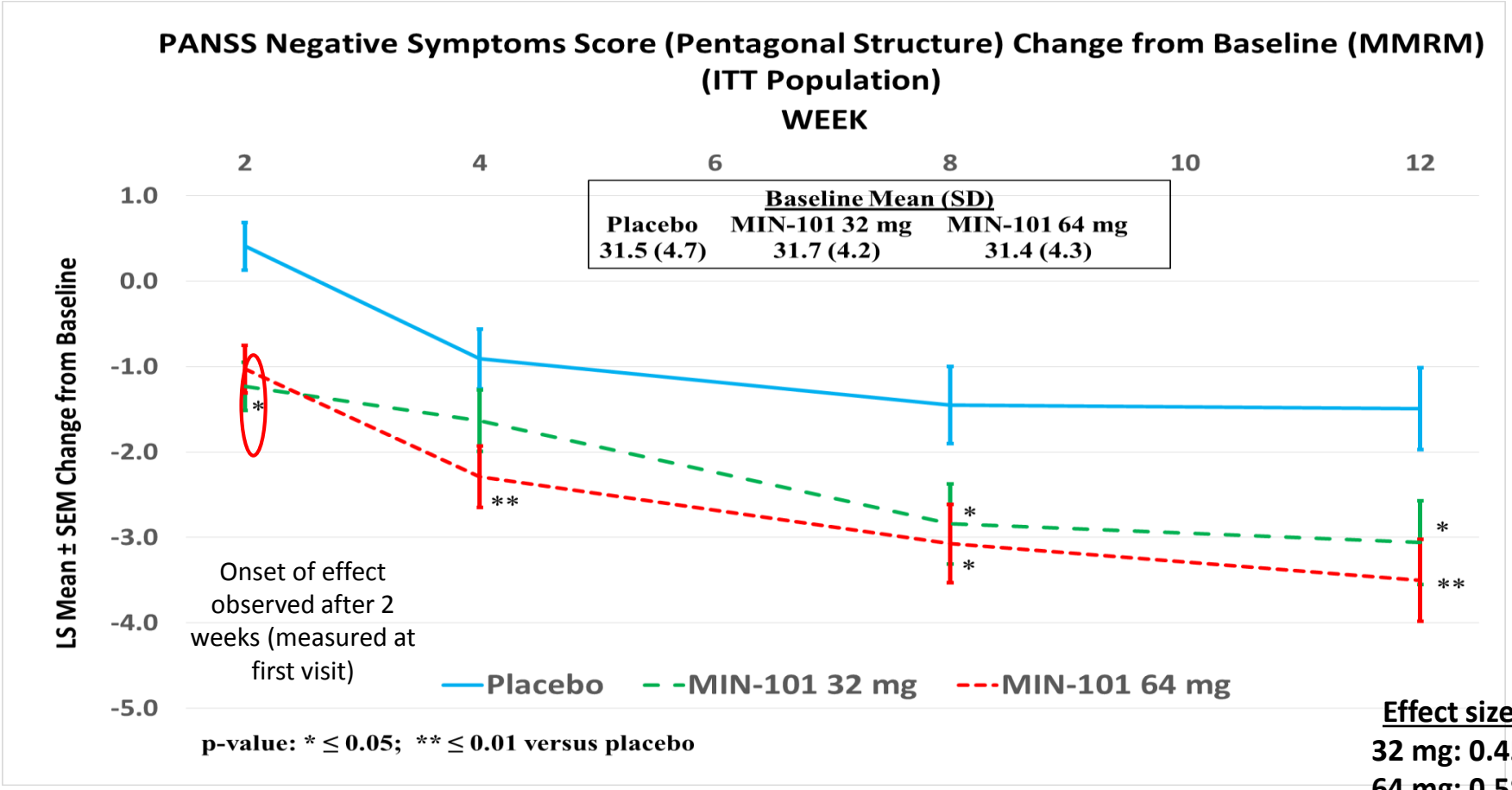
# Flow Chart




**N=234 balanced in terms of demographics and baseline severity**

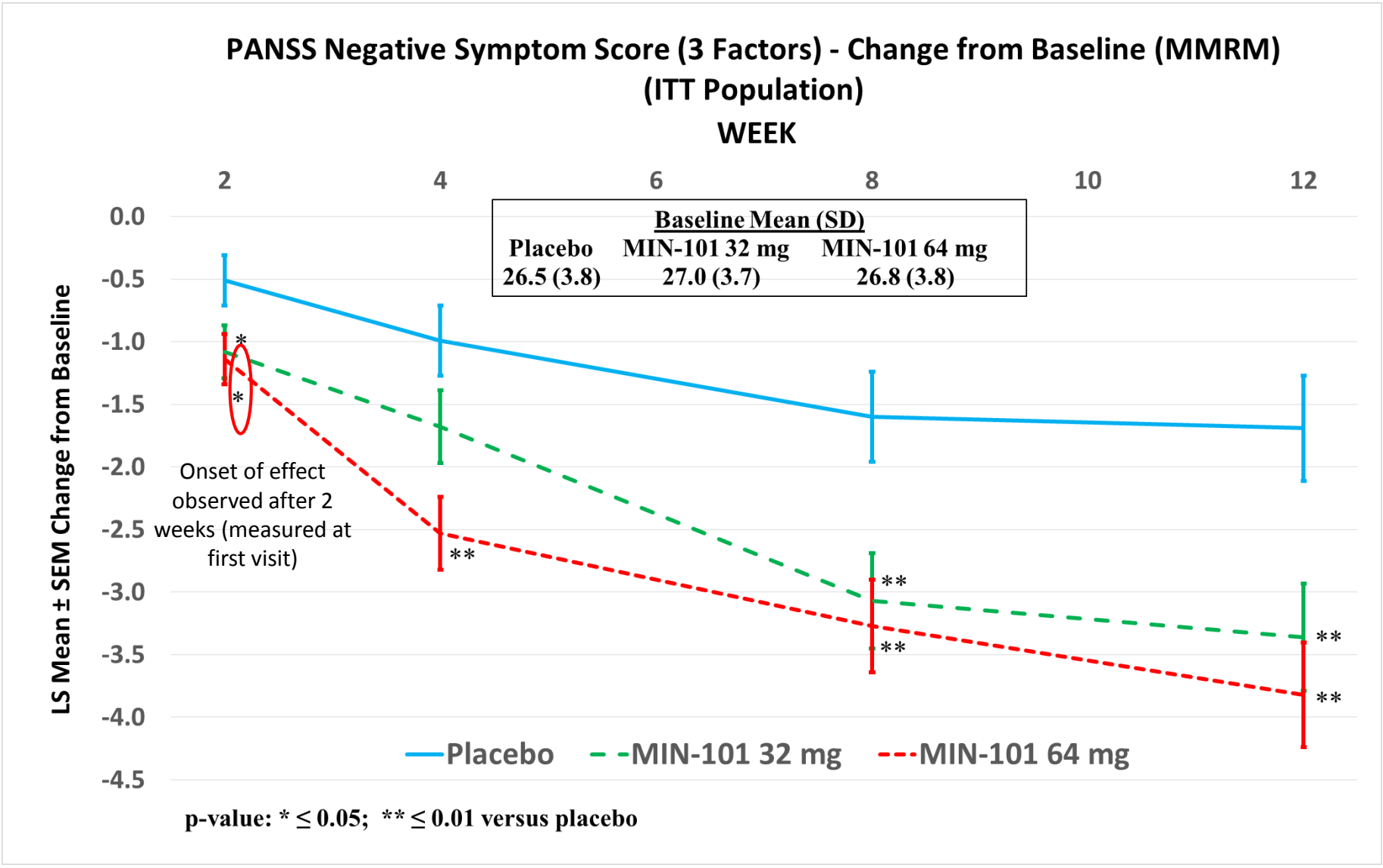
- Age 40y/o (21-60); Male 57%; BMI 25
- PANSS Total **81** (57-103)
- NS **27** (21-38)
- PS **14** (7-22)
- GS **40** (25-54)

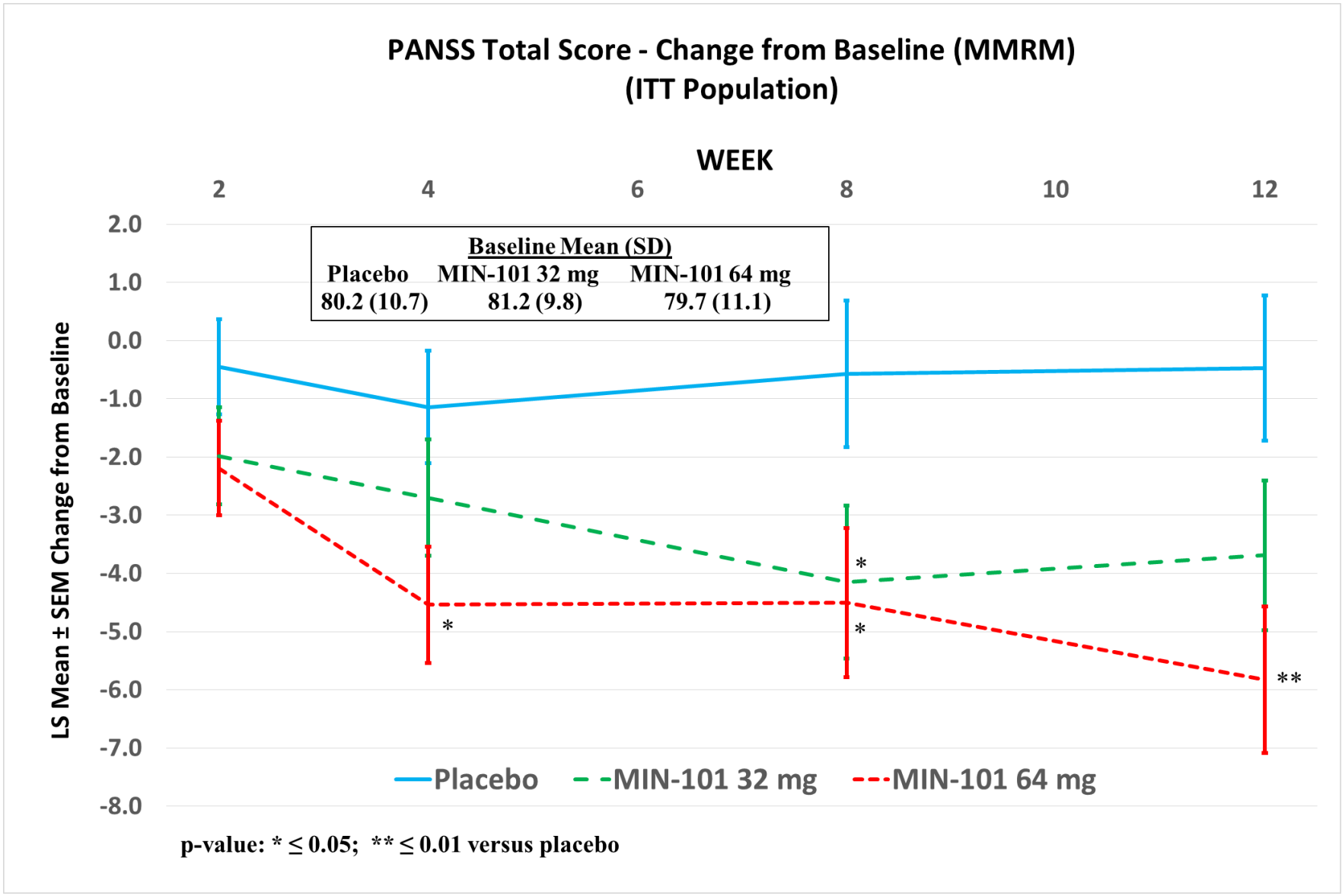
# Efficacy: Primary Outcome
# PANSS negative subscale (pentagonal structure)




**Effect size**
**32 mg: 0.45**
**64 mg: 0.58**

**The largest effect occurred in the younger patients < 33y/o**
**ES= 1.19, p=.005 for the 32 mg dose; ES= 1.30, p=.001 for the 64 mg/dose.**


PANSS Negative Symptom Score (3 Factors) - Change from Baseline (MMRM)
(ITT Population)
WEEK
2
4
6
8
10
12
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
LS Mean ± SEM Change from Baseline
Baseline Mean (SD)
Placebo
26.5 (3.8)
MIN-101 32 mg
27.0 (3.7)
MIN-101 64 mg
26.8 (3.8)
Onset of effect observed after 2 weeks (measured at first visit)
*
*
**
**
**
**
**
Placebo
MIN-101 32 mg
MIN-101 64 mg
p-value: * ≤ 0.05; ** ≤ 0.01 versus placebo


PANSS Total Score - Change from Baseline (MMRM)
(ITT Population)
WEEK
2
4
6
8
10
12
2.0
1.0
0.0
-1.0
-2.0
-3.0
-4.0
-5.0
-6.0
-7.0
-8.0
LS Mean ± SEM Change from Baseline
Baseline Mean (SD)
Placebo
MIN-101 32 mg
MIN-101 64 mg
80.2 (10.7)
81.2 (9.8)
79.7 (11.1)
*
*
*
**
Placebo
MIN-101 32 mg
MIN-101 64 mg
p-value: * ≤ 0.05; ** ≤ 0.01 versus placebo

# Safety (1)

- No clinically relevant changes from baseline to end of study in
  - PRL
  - AIMS
  - Glucose
  - Weight
  - BP
  - Sheehan-suicidality tracking scale (S-STS)
- Increase in QT/QTc between 30 and 60 ms.
  - Placebo = 3.6 %
  - 32 mg = 9.8%
  - 64 mg 14.7%
- Increase in QT/QTc ≥ 60 ms. 5% on 64 mg/day (2 out of 6 had QTcF > 500ms , 1 patient had bradycardia and syncope)

# Safety (2)

The Incidence of Common Treatment Emergent Adverse Events by System Organ Class and Preferred Term

| System Organ Class<br>Preferred Term | Placebo<br>(N = 83) | MIN-101<br>32 mg<br>(N = 78) | MIN-101<br>64 mg<br>(N = 83) | MIN-101<br>Total<br>(N = 161) | Overall<br>(N = 244) |
|---|---|---|---|---|---|
| Subjects with Any Common TEAE | 21 ( 25.3%) | 20 ( 25.6%) | 22 ( 26.5%) | 42 ( 26.1%) | 63 ( 25.8%) |
| General disorders and administration site conditions | 2 ( 2.4%) | 5 ( 6.4%) | 4 ( 4.8%) | 9 ( 5.6%) | 11 ( 4.5%) |
| Asthenia | 2 ( 2.4%) | 5 ( 6.4%) | 4 ( 4.8%) | 9 ( 5.6%) | 11 ( 4.5%) |
| Nervous system disorders | 3 ( 3.6%) | 7 ( 9.0%) | 5 ( 6.0%) | 12 ( 7.5%) | 15 ( 6.1%) |
| Headache | 3 ( 3.6%) | 7 ( 9.0%) | 5 ( 6.0%) | 12 ( 7.5%) | 15 ( 6.1%) |
| Psychiatric disorders | 18 ( 21.7%) | 13 ( 16.7%) | 15 ( 18.1%) | 28 ( 17.4%) | 46 ( 18.9%) |
| Schizophrenia | 9 ( 10.8%) | 5 ( 6.4%) | 8 ( 9.6%) | 13 ( 8.1%) | 22 ( 9.0%) |
| Anxiety | 5 ( 6.0%) | 5 ( 6.4%) | 6 ( 7.2%) | 11 ( 6.8%) | 16 ( 6.6%) |
| Insomnia | 8 ( 9.6%) | 4 ( 5.1%) | 5 ( 6.0%) | 9 ( 5.6%) | 17 ( 7.0%) |

Note: Common TEAEs are TEAEs that occurred = 5% of subjects in any treatment group

# What supports the validity of the results?

- **Secondary outcomes point to the same direction as the primary outcome**
- Results of the continuation open-label phase do not diverge from the RCT phase
- There are no AE which could un-blind  investigators or patients

# Secondary efficacy outcomes

| | Change from Baseline (Least Square Means) | | | p-value | | Effect Size | |
|---|---|---|---|---|---|---|---|
| | | MIN-101 | | MIN-101 versus Placebo | | MIN-101 versus Placebo | |
| | Placebo | 32 mg | 64 mg | 32 mg | 64 mg | 32 mg | 64 mg |
| **Primary Objective** | | | | | | | |
| **5-Factor Negative Score** | **-1.49** | **-3.06** | **-3.50** | **0.021** | **0.003** | **0.45** | **0.58** |
| **Secondary Objectives** | | | | | | | |
| PANSS Total Score | -0.47 | -3.69 | -5.83 | **0.0714** | **0.0027** | 0.35 | 0.59 |
| 3-Factor Negative Score | -1.69 | -3.36 | -3.82 | **0.0058** | **0.0004** | 0.55 | 0.70 |
| 3-Factor General Psychopathology Score | 0.00 | -1.05 | -2.56 | 0.2270 | **0.0032** | 0.23 | 0.57 |
| 5-Factor Dysphoric Mood Score | -0.04 | -0.33 | -1.04 | 0.5156 | **0.0238** | 0.12 | 0.43 |
| 5-Factor Activation Score | 1.10 | -0.07 | -0.18 | **0.0213** | **0.0111** | 0.45 | 0.49 |
| Clinical Global Impression of Severity* | | N/A | | 0.0964 | **0.0266** | 0.28 | 0.28 |
| Clinical Global Impression of Improvement* | | N/A | | 0.2345 | **0.0042** | 0.41 | 0.69 |
| **Brief Negative Symptoms Scale Total Score** | **-3.25** | **-5.42** | **-6.94** | **0.0934** | **0.0044** | **0.33** | **0.56** |
| Calgary Depression Scale for Schizophrenia | 0.07 | -0.30 | -0.81 | 0.2315 | **0.0090** | 0.23 | 0.50 |
| Personal and Social Performance Total Score | -0.69 | -1.17 | -1.89 | 0.2193 | **0.0021** | 0.24 | 0.59 |

* Analyzed using ranked data

# Effect of MIN-101 On BNSS Items

BNSS ANCOVA LOCF change to endpoint vs. placebo controlling for baseline and site

| | 32 mg | | 64 mg | |
|---|---|---|---|---|
| | Mean diff | P= | Mean diff | P= |
| BNSS Total Score | 1.69 | 0.143 | 3.376* | **0.003** |
| Alogia Total Score | 0.329 | 0.182 | .731* | **0.003** |
| Anhedonia Total Score | 0.253 | 0.478 | .781* | **0.028** |
| Asociality Total Score | 0.428 | 0.091 | .615* | **0.015** |
| Avolition Total Score | 0.131 | 0.583 | 0.422 | **0.075** |
| Blunted Affect Total Score | 0.267 | 0.414 | 0.543 | **0.093** |
| Items | | | | |
| Asociality - Behaviour | .306* | 0.019 | .337* | **0.009** |
| Asociality - Internal Experience | 0.14 | 0.353 | 0.275 | 0.066 |
| Avolition – Behaviour | 0.024 | 0.85 | 0.161 | 0.201 |
| Avolition - Internal Experience | 0.097 | 0.467 | 0.259 | 0.051 |
| Distress | 0.166 | 0.252 | 0.207 | 0.148 |
| Expressive Gestures | 0.091 | 0.48 | .305* | **0.018** |
| Facial Expression | 0.063 | 0.6 | 0.131 | 0.273 |
| Frequency of Pleasure During Activities | 0.026 | 0.852 | 0.194 | 0.156 |
| Intensity of Exp Pleasure in Future Act | 0.105 | 0.444 | .284* | **0.037** |
| Intensity of Pleasure During Activities | 0.07 | 0.586 | .256* | **0.044** |
| Quantity of Speech | 0.205 | 0.14 | .416* | **0.003** |
| Spontaneous Elaboration | 0.126 | 0.348 | .300* | **0.024** |
| Vocal Expression | 0.079 | 0.575 | 0.119 | 0.395 |

*p<0.05

# PANSS Item level MIN-101 treatment effects Negative and General Psychopathology

ANCOVA LOCF change to endpoint vs. placebo controlling for baseline and site

| | 32 mg | | 64 mg | |
|---|---|---|---|---|
| Item | Mean diff | p= | Mean diff | p= |
| N1 Blunted Affect | 0.121 | 0.25 | 0.14 | 0.17 |
| N2 Emotional Withdrawal | .273* | 0.01 | .248* | 0.02 |
| N3 Poor Rapport | .401* | 0.00 | .533* | 0.00 |
| N4 Passive/Apathetic Social Withdrawal | 0.125 | 0.29 | .290* | 0.01 |
| N6 Lack of Spontaneity/Flow of Conversation | 0.224 | 0.07 | .314* | 0.01 |
| G5 Mannerisms and Posturing | -0.119 | 0.33 | 0.02 | 0.89 |
| G7 Motor Retardation | 0.050 | 0.68 | .248* | 0.04 |
| G8 Uncooperativeness | 0.110 | 0.41 | -0.02 | 0.86 |
| G13 Disturbance of Volition | -0.137 | 0.25 | -0.02 | 0.88 |
| G14 Poor Impulse Control | 0.016 | 0.89 | 0.07 | 0.56 |
| G16 Active Social Avoidance | .299* | 0.01 | .397* | 0.00 |
| G1 Somatic Concern | -0.141 | 0.33 | 0.05 | 0.73 |
| G10 Disorientation | .252* | 0.04 | 0.07 | 0.58 |
| G11 Poor Attention | 0.038 | 0.74 | 0.04 | 0.74 |
| G12 Lack of Judgment and Insight | -0.026 | 0.82 | 0.19 | 0.10 |
| G15 Preoccupation | -0.012 | 0.91 | 0.20 | 0.08 |
| G2 Anxiety | -0.003 | 0.99 | 0.25 | 0.16 |
| G3 Guilt Feelings | 0.094 | 0.39 | 0.10 | 0.36 |
| G4 Tension | 0.057 | 0.69 | 0.18 | 0.21 |
| G6 Depression | 0.173 | 0.19 | .324* | 0.01 |
| G9 Unusual Thought Content | 0.122 | 0.30 | .318* | 0.01 |
| N5 Difficulty in Abstract Thinking | -0.027 | 0.80 | 0.08 | 0.45 |
| N7 Stereotyped Thinking | 0.085 | 0.49 | 0.16 | 0.19 |

Note: Positive differences favor treatment, negative favor placebo

*p<0.05

# Effect of MIN-101 On Cognition – BACS composite score

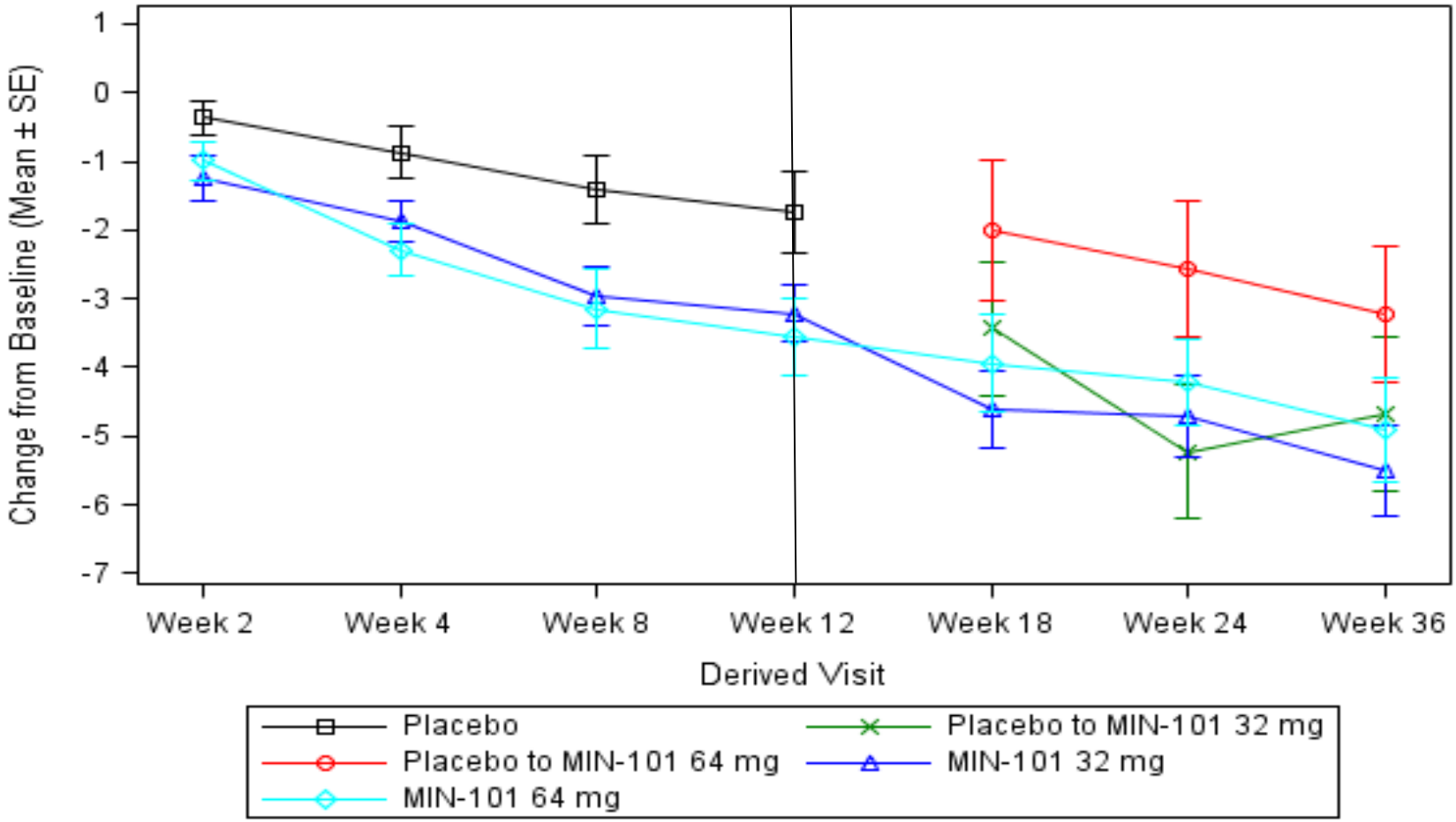
| | | Mean Difference | Std. Error | Sig. |
|---|---|---|---|---|
| Placebo | MIN-101 32 mg | -.286* | .102 | .017 |
| Placebo | MIN-101 64 mg | -.101 | .100 | .938 |

# What supports the validity of the results?

- Secondary outcomes point to the same direction as the primary outcome
- **Results of the continuation open-label phase do not diverge from the RCT phase**
- There are no AEs which could un-blind investigators or patients

# 24 weeks open label continuation

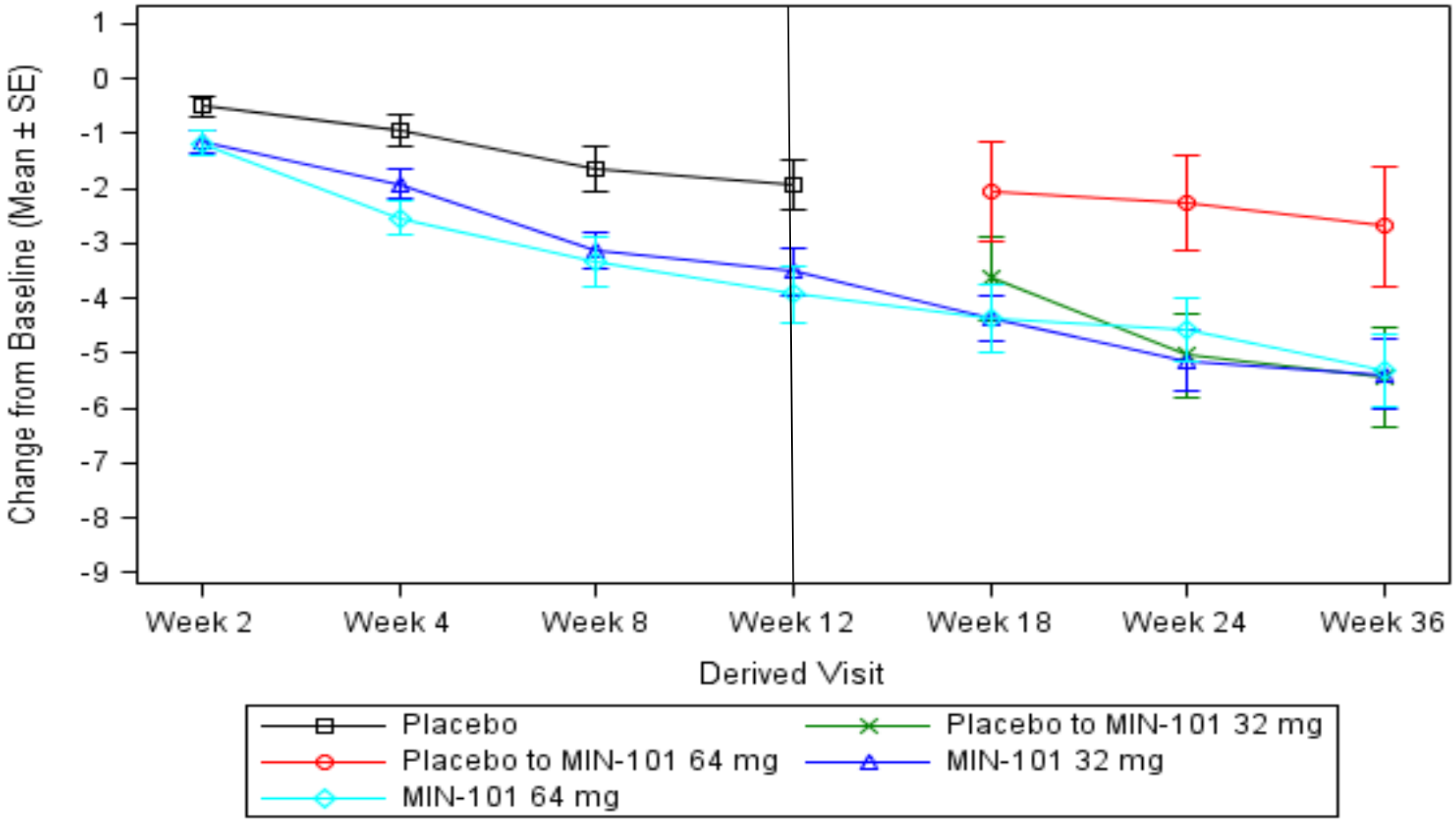
## Negative Symptoms (5-Factors)




Baseline for Placebo-to-MIN-101 is DB Baseline at start of trial

# 24 weeks open label continuation

## Negative Symptoms (3-Factors)




Baseline for Placebo-to-MIN-101 is DB Baseline at start of trial

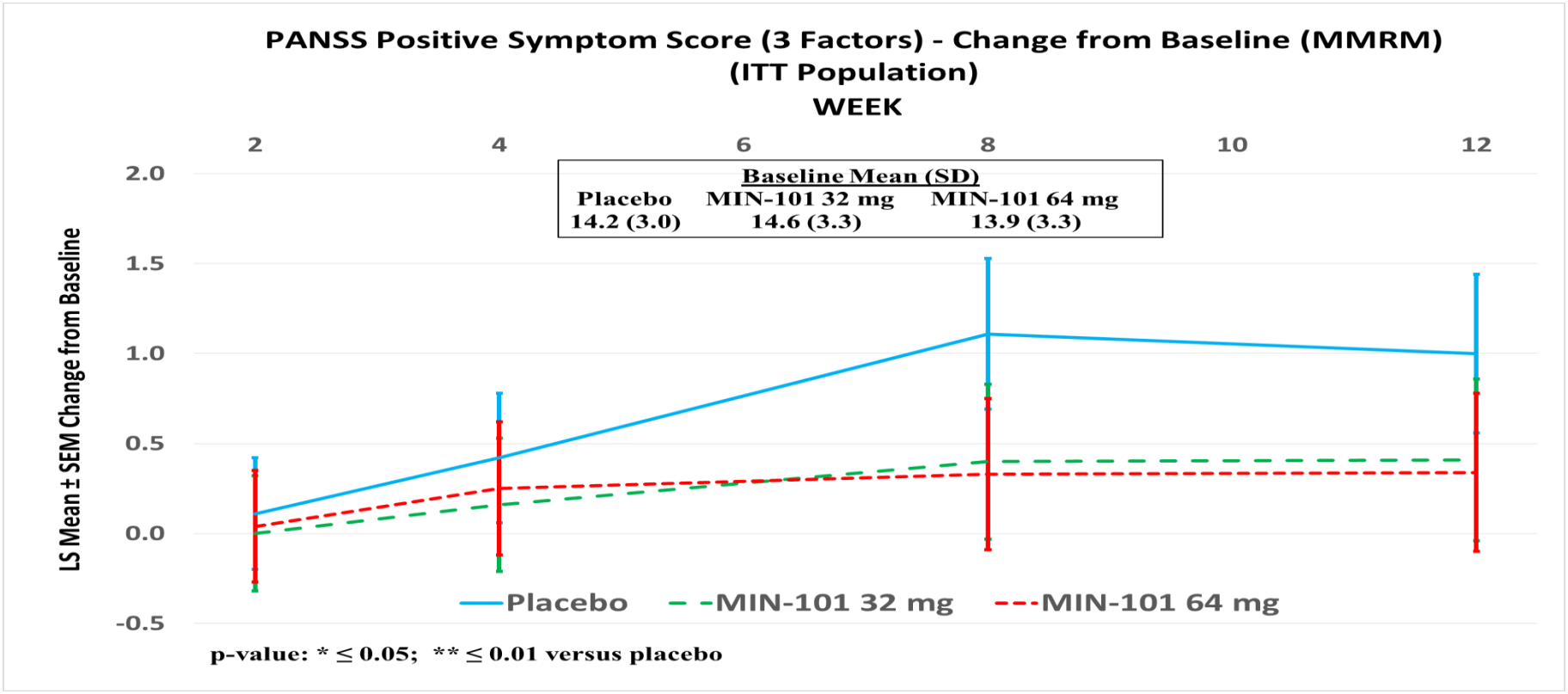
# What supports the validity of the results?

- Secondary outcomes point to the same direction as the primary outcome
- Results of the continuation open-label phase do not diverge from the RCT phase
- **There are no AEs which could un-blind investigators or patients (EPS, PRL, sedation)**

# What supports the specificity of the effect?

## Not a pseudo-effect

- No improvement in PANSS positive scores
- The statistically significant superiority of MIN-101 is maintained after controlling for baseline depression and change in depression.
  - ANCOVA analysis for the primary outcome after controlling for changes on the Calgary Depression Schizophrenia Scale 32 mg p=.01; 64 mg; p=.002.
- No improvement in EPS


PANSS Positive Symptom Score (3 Factors) - Change from Baseline (MMRM)
(ITT Population)
WEEK
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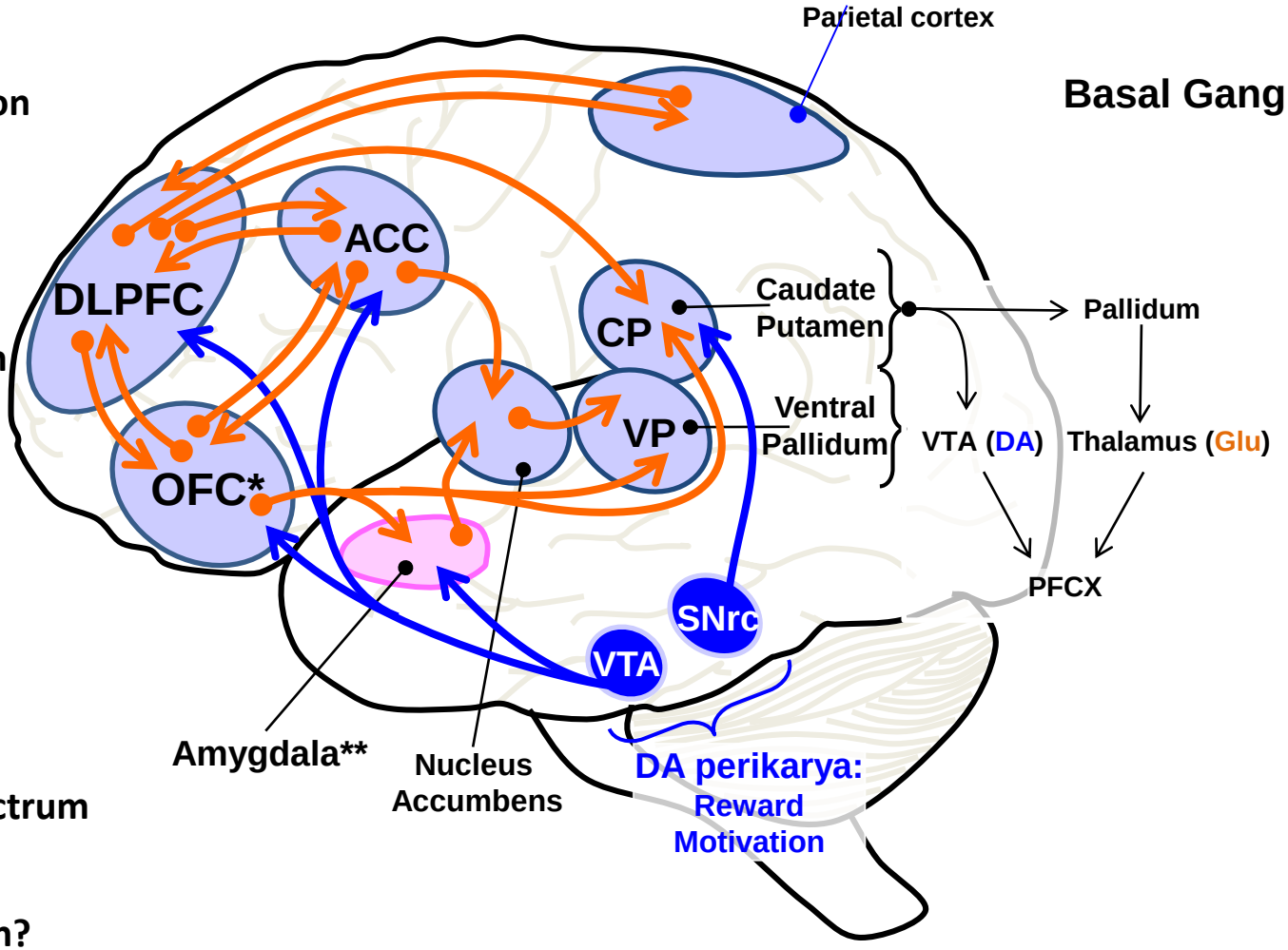
4
6
8
10
12
Baseline Mean (SD)
Placebo
14.2 (3.0)
MIN-101 32 mg
14.6 (3.3)
MIN-101 64 mg
13.9 (3.3)
LS Mean ± SEM Change from Baseline
2.0
1.5
1.0
0.5
0.0
-0.5
Placebo
MIN-101 32 mg
MIN-101 64 mg
p-value: * ≤ 0.05; ** ≤ 0.01 versus placebo

**ANCOVA analysis for the primary outcome after controlling for changes on the Calgary Depression Schizophrenia Scale 32 mg p=.01; 64 mg; p=.002.**

# Are negative symptoms a non-specific reaction to a brain insult?

- Idiopathic Parkinson
- Major depression
- Alzheimer Disease
- Frontal dementia
- Mental retardation
- Viral encephalitis
- Epilepsy
- Post CVA
- Post brain trauma
- Autism spectrum
- Schizophrenia
- Schizophrenia spectrum
- Drug abuse
- General population?




PFC/PRC: working memory/attention-top down control of striatum
DLPFC-Dorsal striatum: goal-directed/flexible planning, reward obtention
OBPFC-Ventral striatum: value of reward, prediction, generation of dating
ACC-Nucleus accumbens: cost of obtaining reward

# Can an individual who meets diagnostic criteria for schizophrenia at a particular time be maintained on a drug which has no D2 blocking proprieties?

- Who can be maintained without D2 drugs?
- When to discontinue and when to renew D2 blocker drugs?
- Do patients who discontinue D2 blocking drugs lack insight, or are they intuitively making a choice between the certainty of AE and the increased risk of exacerbation?
- Is exacerbation worse than the certainty of AE?

JAMA Psychiatry 2013

Original Investigation

# Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy

## Long-term Follow-up of a 2-Year Randomized Clinical Trial

Lex Wunderink, MD, PhD; Roeline M. Nieboer, MA; Durk Wiersma, PhD; Sjoerd Sytema, PhD; Fokko J. Nienhuis, MA

PLOS Medicine 2015

ESSAY

# Antipsychotic Maintenance Treatment: Time to Rethink?

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*Psychological Medicine* (2012), **42**, 2145–2155. © Cambridge University Press 2012
doi:10.1017/S0033291712000220

ORIGINAL ARTICLE

# Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study

M. Harrow*, T. H. Jobe and R. N. Faull

*Department of Psychiatry, University of Illinois College of Medicine, Chicago, IL, USA*

Presynaptic Dopamine Capacity in Patients with Treatment Resistant Schizophrenia Taking Clozapine: An [18F]DOPA PET Study. Kim et al Neuropsychopharmacology. 2016