Innovation to change the way we treat CNS disease

May 2017

Nasdaq: NERV

Forward-Looking Statement Safe-Harbor

Investment highlights

- Late-stage pipeline targets schizophrenia, major depressive disorder (MDD), insomnia and Parkinson's

- Our product candidates represent true innovation in disease treatment and management by addressing significant unmet needs of large patient populations

- MIN-101 may change schizophrenia treatment paradigm
  - FDA end-of-Phase 2 meeting took place early Q2 2017
  - Initiation of Phase 3 expected in H2 2017

- ~$85.4 million in cash 31 Mar 2017

- Experienced clinical development team who have participated in more than 800 clinical studies

Our team

- *Remy Luthringer, Ph.D., President and Chief Executive Officer*
  - Deep clinical development experience with > 150 CNS molecules
  - Previous head of FORENAP Institute for Research in Neurosciences and Neuropsychiatry
  - Extensive practice in clinical psychiatry, with Ph.D. in neurosciences and clinical pharmacology

- *Geoff Race, Executive Vice President, Chief Financial Officer and Chief Business Officer*
  - Senior executive with multiple clinical and development-stage biopharmaceutical companies
  - Expertise in mergers, acquisitions and licensing
  - Track record in business development

- *Michael Davidson, M.D., Chief Medical Officer*
  - Consultant to the biopharmaceutical industry, with insights into development strategy and regulatory review of CNS compounds
  - Internationally recognized author, researcher, award recipient and thought leader
  - Professor of Psychiatry at Sackler School of Medicine, Tel Aviv University

True differentiation in our approach

- Extensive knowledge of the pathology, course and impact of CNS diseases

- Focus on outcomes that address unmet needs (no "me-too" products) and on patient populations who will benefit from treatment with our compounds

- Understanding of the impact of novel MOAs and the limitations of current treatments

- Expertise in CNS clinical trial design and conduct

Changing the way we treat CNS diseases

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Program	Origin	Primary Indications	Mechanisms of Action	Pre-clinical	Phase I	Phase II	Status	Next Steps
MIN-101	Mitsubishi Tanabe	Schizophrenia	● 5-HT2A antagonist ● Sigma2 antagonist	**Phase IIb completed** →			Results announced May & October 2016	• End of Phase II meeting with FDA held early in Q2 2017 • Initiation of pivotal Phase III trial expected in H2 2017
MIN-202	Janssen (under co-development)	Primary Insomnia Major Depressive Disorder	● Selective Orexin2 antagonist	**Phase IIa completed** → **Phase Ib completed** →			Results Announced January 2016 Results announced March 2016	• Phase II trial preparation underway • Next trials in insomnia disorder and MDD planned for second half of 2017
MIN-117	Mitsubishi Tanabe	Major Depressive Disorder	● 5-HT1A ● 5HT transporter ● Alpha-1a, b ● Dopamine transporter ● 5-HT2A antagonist	**Phase IIa completed** →			Results announced May 2016	• Planning underway for next phase of clinical trials expected to begin in late 2017
MIN-301	Mind-NRG	Parkinson's Disease	● Neuregulin 1β1 activating ErbB4	**Pre-clinical** →			Pre-clinical activities ongoing	• Filing of IND or IMPD, with Phase I expected to initiate thereafter

MIN-101

A new paradigm for the treatment of schizophrenia

Schizophrenia: a devastating chronic disease with a high burden for patients, families and society

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- **Affects ~30 million people worldwide[1]**

- **Often starts in late teens or early adulthood[2]**

- **75% patients are non-adherent to existing therapies within 2 years of being discharged from hospital[3]**

- **Medication non-adherence is the single largest factor in relapse[4]**

- **Schizophrenia: not a classic neurodegenerative disease yet associated with progressive atrophic changes**

What do we need?

Treatments that:

- Improve negative symptoms and cognition
- Free patients from debilitating side-effects
- Improve sleep

1. Global Prevalence of Schizophrenia PLOS Medicine, 2005
2. NIMH
3. Weiden PJ et al. Psychiatr Serv,1995; 46:1049-1054
4. Weiden PJ (2004), Kozma C, Grogg A et al. Psychiatr Serv, 2004, 55:886-891

Schizophrenia is a dynamic chronic disease - prevalence of symptoms changes over the lifetime of the patient
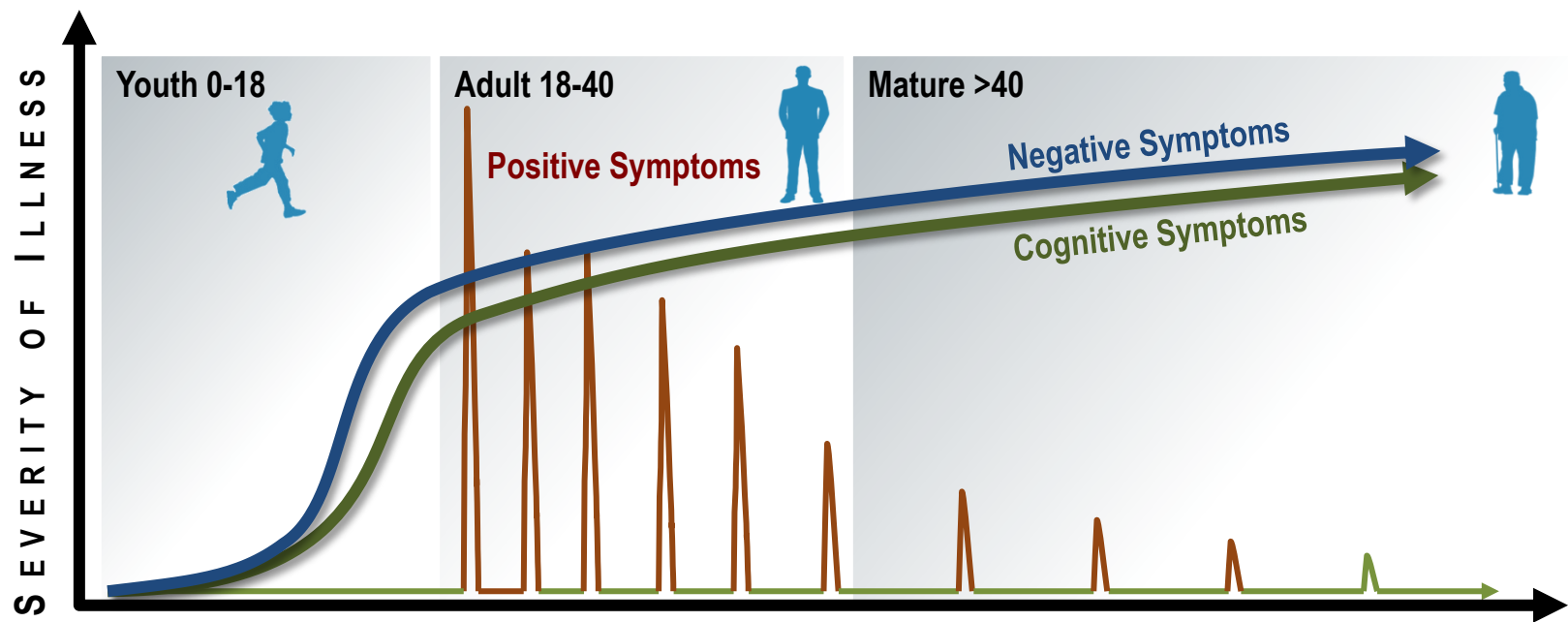
The unmet needs in schizophrenia

Tranquilizers and antipsychotics treat

1. Positive Symptoms

- *delusions and hallucinations*

but not
- **Cognition**
- **Negative Symptoms**

and have
- *debilitating side effects caused by blocking D2*

2. Impaired Cognition

3. Negative Symptoms

- *apathy*
- *restricted social interaction*
- *poor emotional feelings*
- *physical and mental slowness*
- *depressed mood*

Normal brain

Brain of a patient with long-standing schizophrenia

Rate of Grey Matter Loss:

🟥	High
🟨	Moderate / low
🟦	None
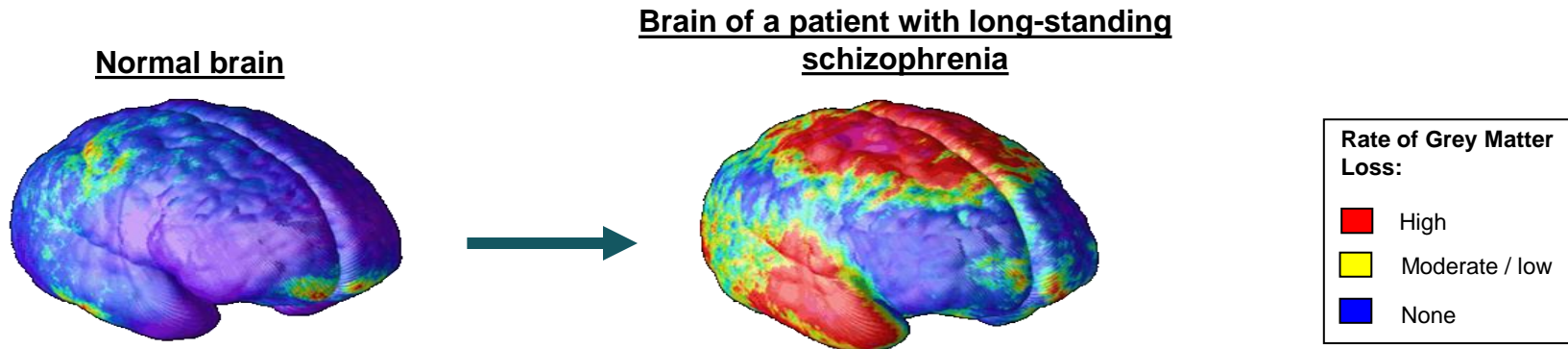
Responding to unmet needs in schizophrenia

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Unmet need

MIN-101 clinical benefits (Ph IIb)

Lack of efficacy of current Rx on negative symptoms

✓ A direct (not pseudo-effect) on <u>negative symptoms</u> and an improvement in <u>depression</u> in schizophrenia

Substantial side effect burden

✓ Absence of typical side effects associated with D2 blockers

Lack of efficacy of current Rx on cognitive decline

✓ MIN-101 showed cognitive improvement

In addition, positive symptom scores remained stable over ~9 months when patients were taking MIN-101

MIN-101: a new approach and MOA

- A unique dual MOA; 5-HT$_{2A}$ antagonist + Sigma$_2$ antagonist

- No direct dopamine blocking, unlike most (or all) available antipsychotics

- Specific affinity for σ_2, 5-HT$_{2A}$ and α_1-adrenergic receptors

- No affinity (>1000 nM) for other receptors including dopaminergic, muscarinic, cholinergic and histaminergic receptors

- Behavioral pharmacology is consistent with an antagonistic effect for σ_2 and 5-HT$_{2A}$ receptors

MIN-101 Phase IIb study: monotherapy, double-blind, placebo-controlled in schizophrenic patients with negative symptoms

≤ 4 weeks Screening

12 week double-blind phase 'core study'

24 week open-label 'extension' phase

R

MIN-101 64mg (n = 83)

MIN-101 32mg (n = 78)

Placebo (n = 83)

Crossover

MIN-101 64mg

MIN-101 32mg

Screening

Treatment & Assessments
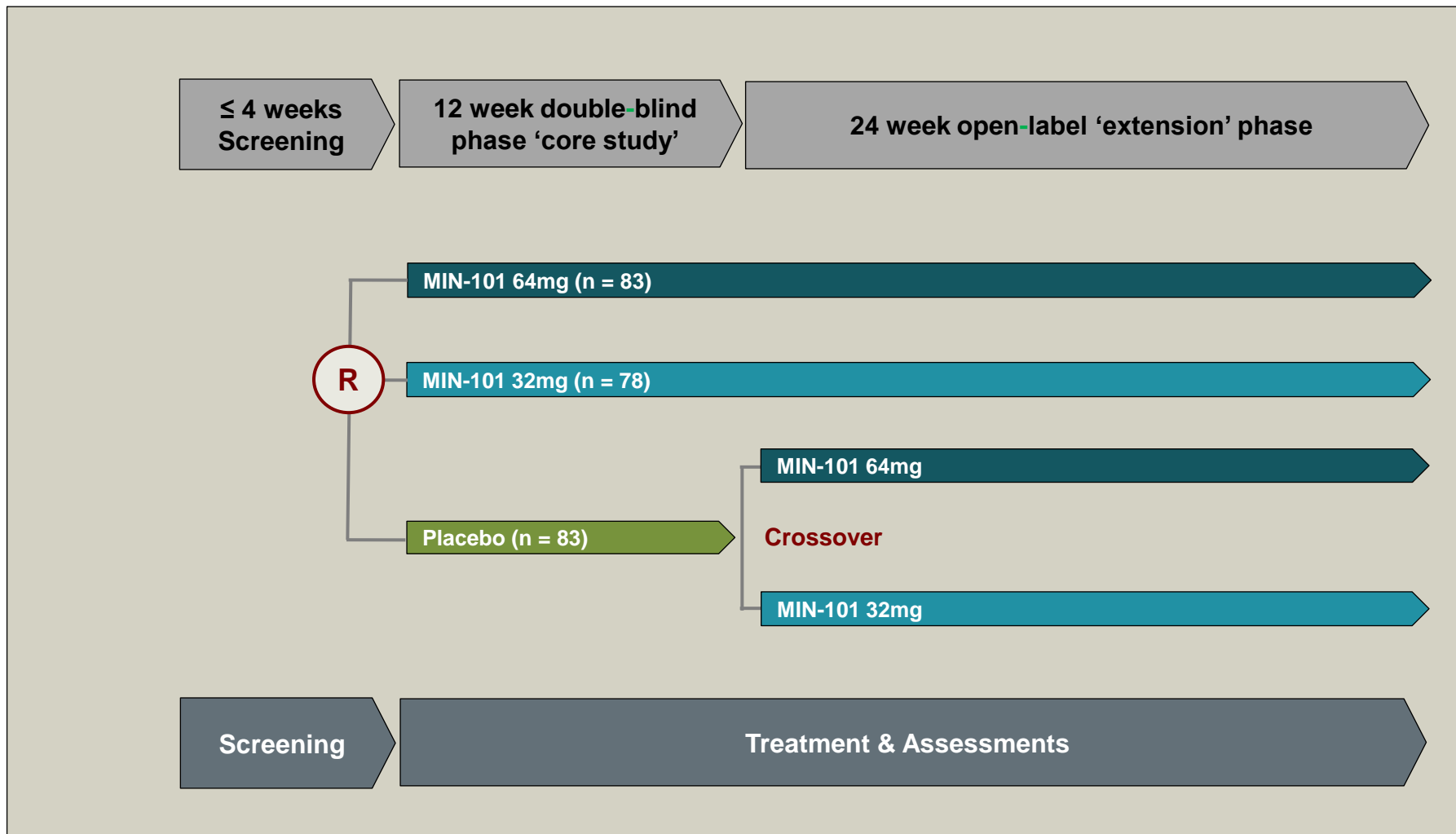
R = Randomization

MIN-101 Phase IIb data – *setting a new standard*

- Treatment resulted in **statistically significant improvement in PANSS negative symptoms** and total PANSS scores

- Statistically **superior to placebo on multiple key secondary endpoints**

- Positive **effects were specific for negative symptoms** and not secondary to improvement in other symptoms or side effects

- MIN-101 **well tolerated**, with incidence and types of side effects not differing significantly from placebo; no "atypical side-effects" observed

  (two patients (2/162) receiving highest dose of MIN-101 discontinued based on QT prolongation)

Final results of MIN-101 Phase IIb efficacy analyses (12 weeks)

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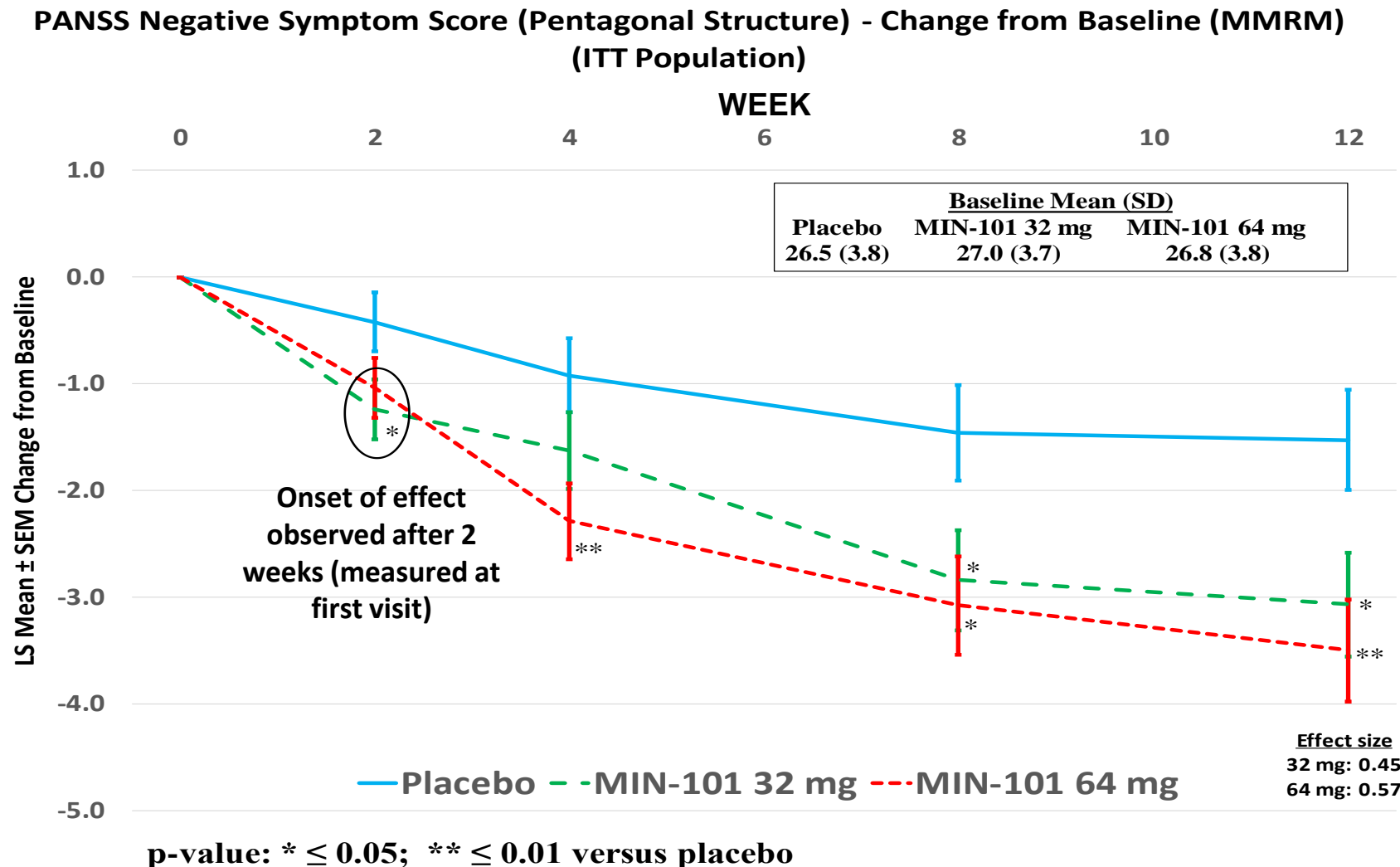|	Endpoint at 12 weeks	p-value (MIN-101 vs placebo)		Effect size (MIN-101 vs placebo)	
		32mg	64mg	32mg	64mg
Primary objective	5-Factor Negative Score (i.e., Negative Symptoms, Pentagonal Structure):	**0.0240**	**0.0036**	**0.45**	**0.57**
Secondary objectives	PANSS total score	0.0819	**0.0031**	**0.34**	**0.57**
	3-Factor Negative Score	**0.0064**	**0.0004**	**0.54**	**0.70**
	3-Factor Positive Score	0.4018	0.3067	0.16	0.20
	3-Factor General Psychopathology Score	0.2359	**0.0034**	0.23	**0.56**
	5-Factor Positive Score	0.5045	0.2146	-0.13	0.24
	5-Factor Dysphoric Mood Score	0.5644	**0.0266**	0.11	**0.43**
	5-Factor Activation Score	**0.0240**	**0.0118**	**0.44**	**0.49**
	5-Factor Autistic Preoccupation Score	0.6700	0.2408	0.08	**0.22**
	CGI-S* (severity)	0.0982	**0.0234**	**0.35**	**0.43**
	CGI-I** (improvement)	0.2378	**0.0032**	**0.33**	**0.57**
	BNSS (Brief Negative Symptom Scale)	0.0869	**0.0040**	**0.33**	**0.56**
	BACS cognition assessment (Composite T-Score)	0.0595	0.6967	**0.30**	0.06
	- Executive Function: Tower of London	0.3937	0.5995	**0.16**	**-0.10**
	- Motor Function: Token Motor Test	**0.0306**	**0.0493**	**0.42**	**0.38**
	- Motor Function: Symbol Coding Task	0.6310	0.0781	**-0.09**	**-0.33**
	- Total Verbal Fluency	**0.0076**	0.0554	**0.51**	**0.36**
	- Verbal Memory & Learning: Verbal Memory	0.1544	0.3158	0.27	0.19
	- Working Memory: Digit Sequence Task	0.0664	0.8826	**0.36**	0.03
Exploratory objectives	CDSS depression scale	0.1756	**0.0091**	**0.25**	**0.46**
	PSP personal and social performance				
	- Socially Useful Activities	0.4775	0.0601	0.14	**0.38**
	- Personal & Social Relationships	0.9174	**0.0129**	0.02	**0.53**
	- Self-care	0.1736	**0.0210**	0.27	**0.46**
	- Disturbing & Aggressive Behavior	0.0532	**0.0057**	**0.36**	**0.51**

Bold red text indicates p-value ≤ 0.05

Green text indicates moderate or large ES

* Analyzed using ranked data: change from Baseline and ES are based on observed change from baseline data

** Analyzed using ranked data; ES is based on observed data

Efficacy: Primary endpoint – clinically meaningful effect on negative symptoms with rapid onset of effect and continuous improvement throughout the study at both doses

PANSS Negative Symptom Score (Pentagonal Structure) - Change from Baseline (MMRM) (ITT Population)

	Baseline Mean (SD)		
	Placebo	MIN-101 32 mg	MIN-101 64 mg
	26.5 (3.8)	27.0 (3.7)	26.8 (3.8)

Onset of effect observed after 2 weeks (measured at first visit)

Effect size
32 mg: 0.45
64 mg: 0.57

— Placebo – – MIN-101 32 mg – – – MIN-101 64 mg

p-value: * ≤ 0.05; ** ≤ 0.01 versus placebo

Efficacy: Secondary endpoint (1)
Improvement in negative symptoms also observed with
additional measurement scale

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PANSS Negative Symptom Score (3 Factors) - Change from Baseline (MMRM)
(ITT Population)
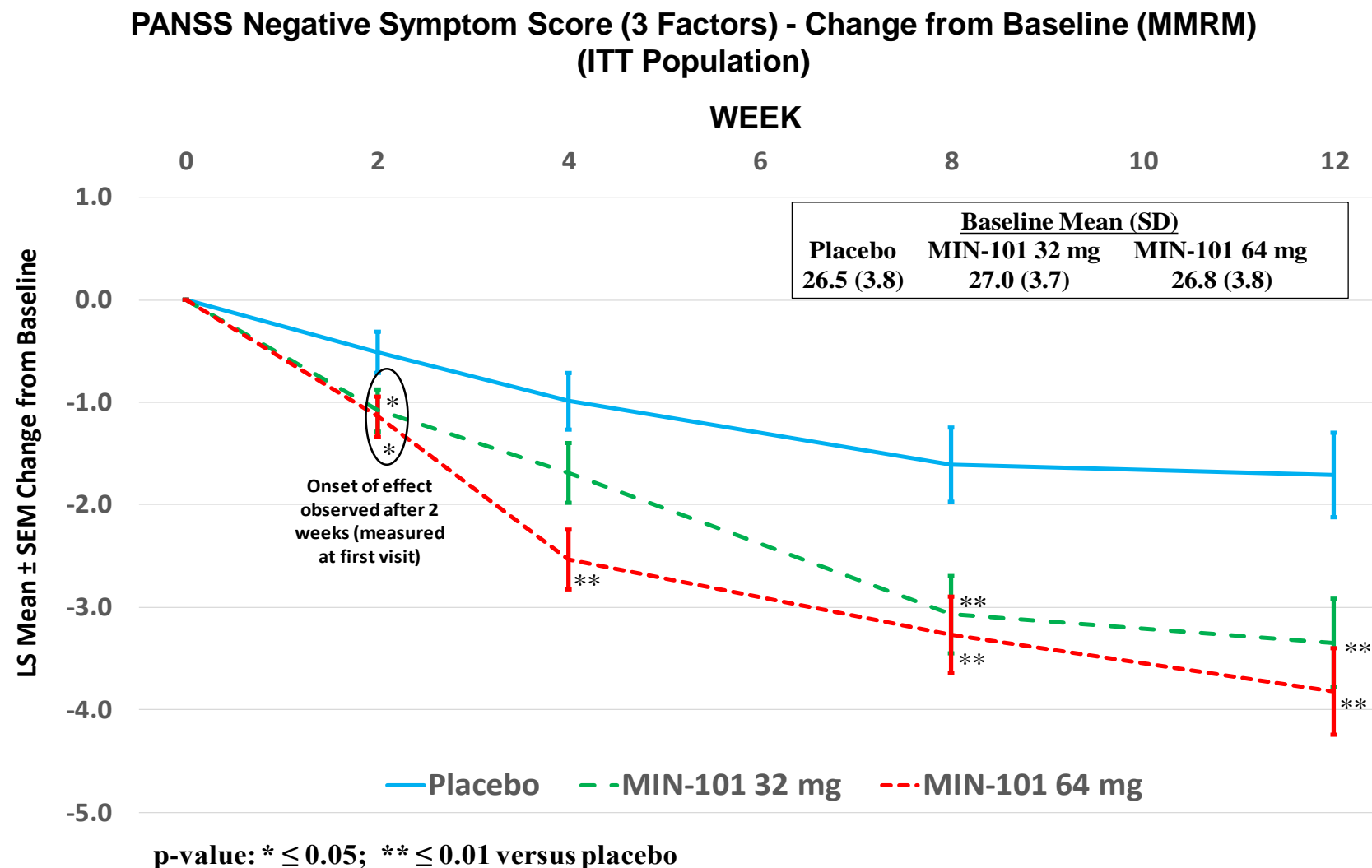
Efficacy: Secondary endpoint (2)
Demonstrated improvement in Total PANSS driven by
improvement in negative symptoms

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PANSS Total Score - Change from Baseline (MMRM)
(ITT Population)

Baseline Mean (SD)		
Placebo	**MIN-101 32 mg**	**MIN-101 64 mg**
80.2 (10.7)	81.2 (9.8)	79.7 (11.1)

Legend: Placebo — MIN-101 32 mg — MIN-101 64 mg

p-value: * ≤ 0.05; ** ≤ 0.01 versus placebo
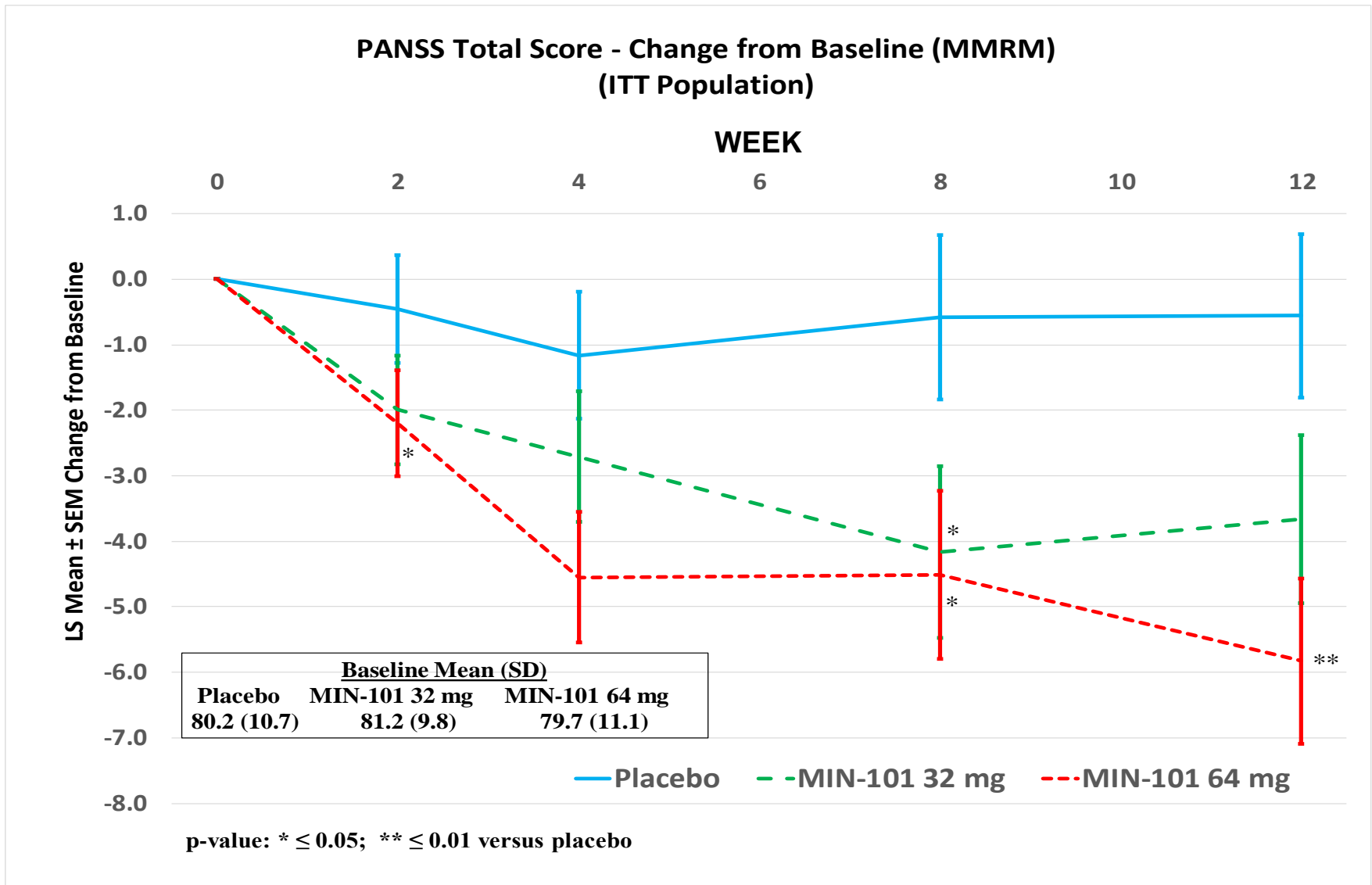
**Efficacy: Secondary endpoint (4)
PANSS positive symptoms score (3 Factors) indicates MIN-101
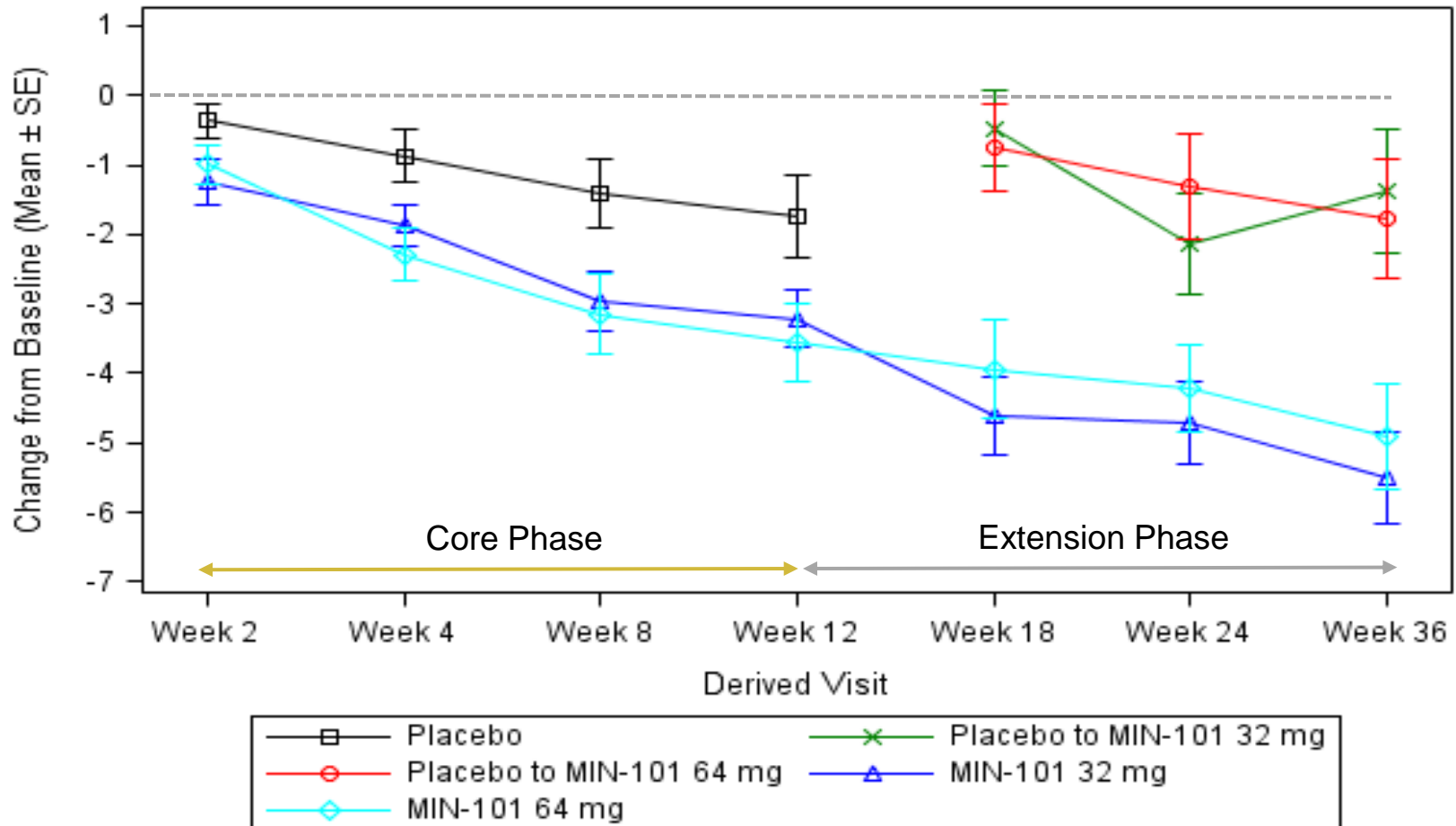maintains stability in positive symptoms**

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**PANSS Positive Symptom Score (3 Factors) - Change from Baseline (MMRM)
(ITT Population)**

	Baseline Mean (SD)	
Placebo	MIN-101 32 mg	MIN-101 64 mg
14.2 (3.0)	14.6 (3.3)	13.9 (3.3)
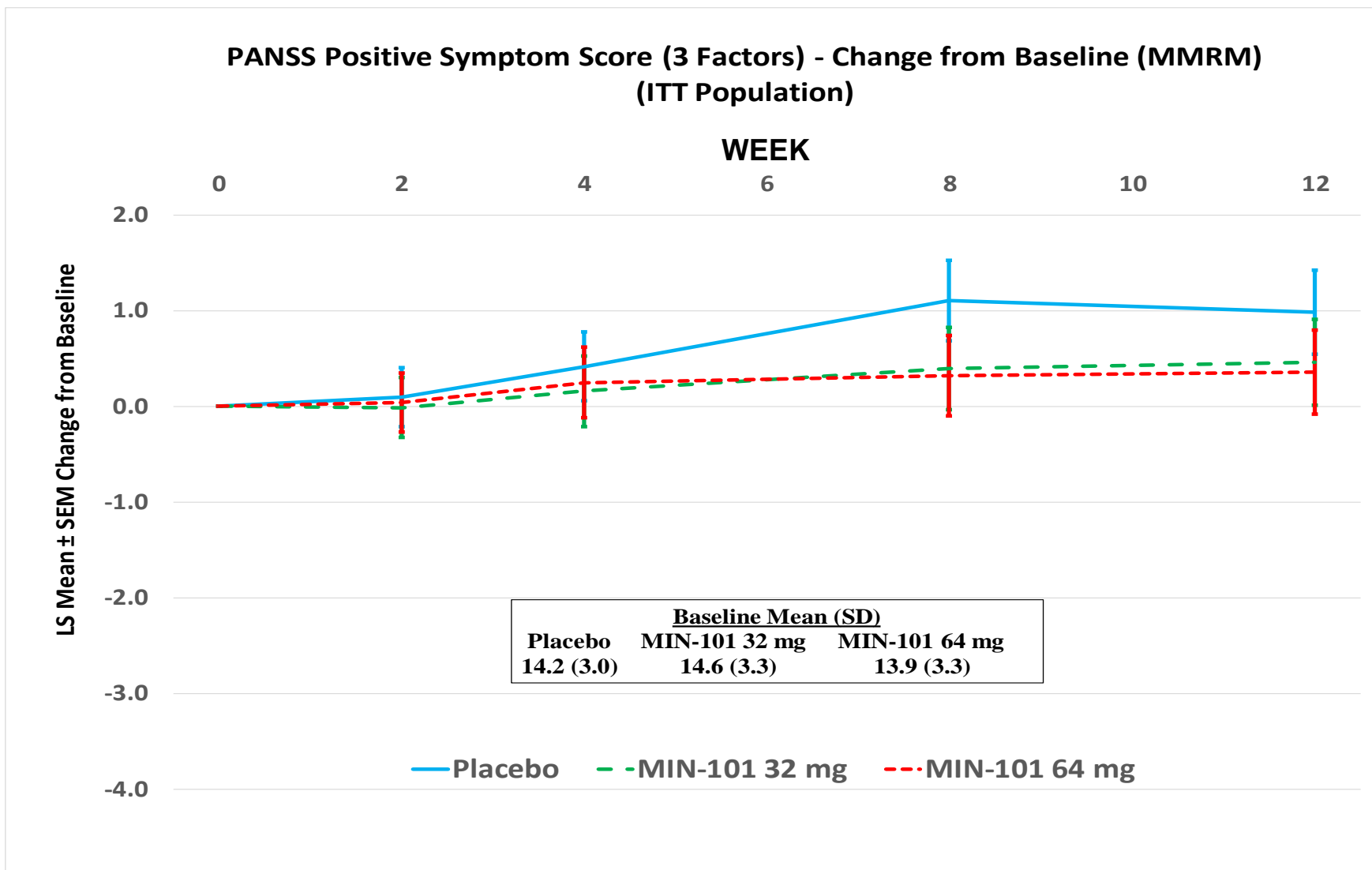
Extension Phase

Baseline for patients who crossed from placebo to MIN-101 is start of open label (Week 12)

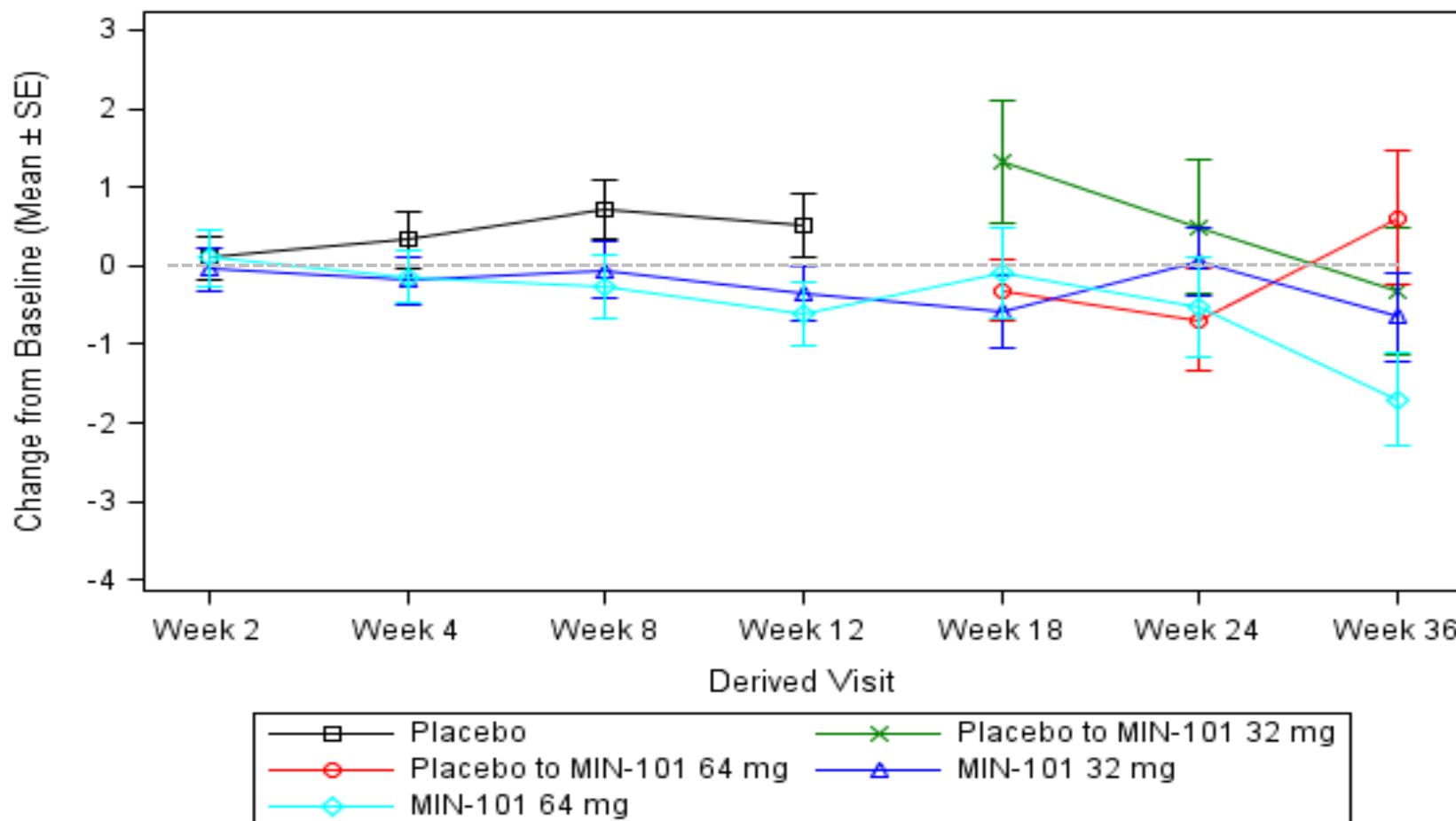Baseline for Placebo-to-MIN-101 is From Start of Open Label (Week 12)

Baseline for Placebo-to-MIN-101 is From Start of Open Label

MIN-202

(JNJ42847922)

A drug to treat insomnia & depressive disorders by restoring physiological sleep

A co-development/co-commercialisation program with;

- ~85% of patients with major depressive disorder have symptoms of insomnia, which often persists despite treatment with currently available sleep medications
  - ~13.6 million Americans have major depression and insomnia

- Most existing treatments "force" sleep, rather than physiologically attenuating the "wake drive"

- The Orexin system regulates the wake drive
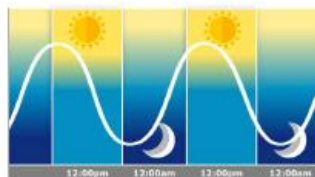
CNS *Spectr*. 2010 Jun;15(6):394-404.
Insomnia in patients with depression: a STAR*D report.
NIMH

Circadian Rhythm

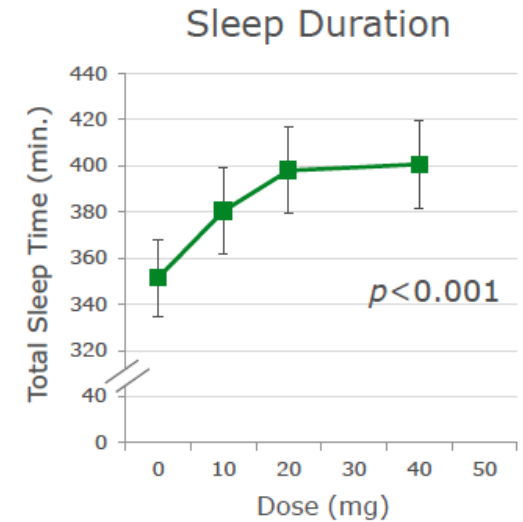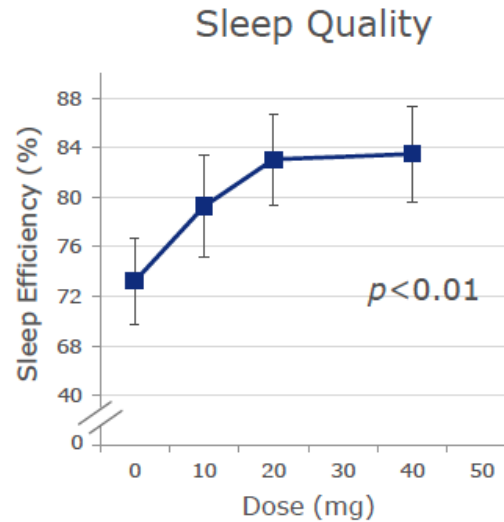## What Do We Need?

Therapies that provide:
- A more physiological approach to treat insomnia
- Rapid onset of action
- Preservation of deep, restful sleep
- Minimal residual daytime sleepiness or cognitive impairment

MIN-202: Exploratory study in patients with MDD and comorbid insomnia (n=20) indicate significant improvements in key sleep metrics

Time to Sleep Onset — Latency to Persistent Sleep (min.) vs. Dose (mg); p<0.001

Sleep Quality — Sleep Efficiency (%) vs. Dose (mg); p<0.01

Sleep Duration — Total Sleep Time (min.) vs. Dose (mg); p<0.001
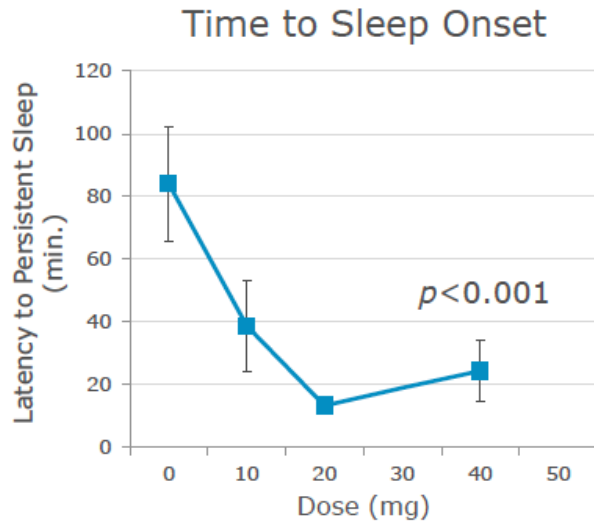
Reference: Internal data, study 42847922ED1002, disclosed by Minerva Neurosciences, Q1 2015.

Phase IIa in primary insomnia: achievement of primary endpoint of improvement in sleep efficiency complemented by increase in total sleep time

42847922ISM2002
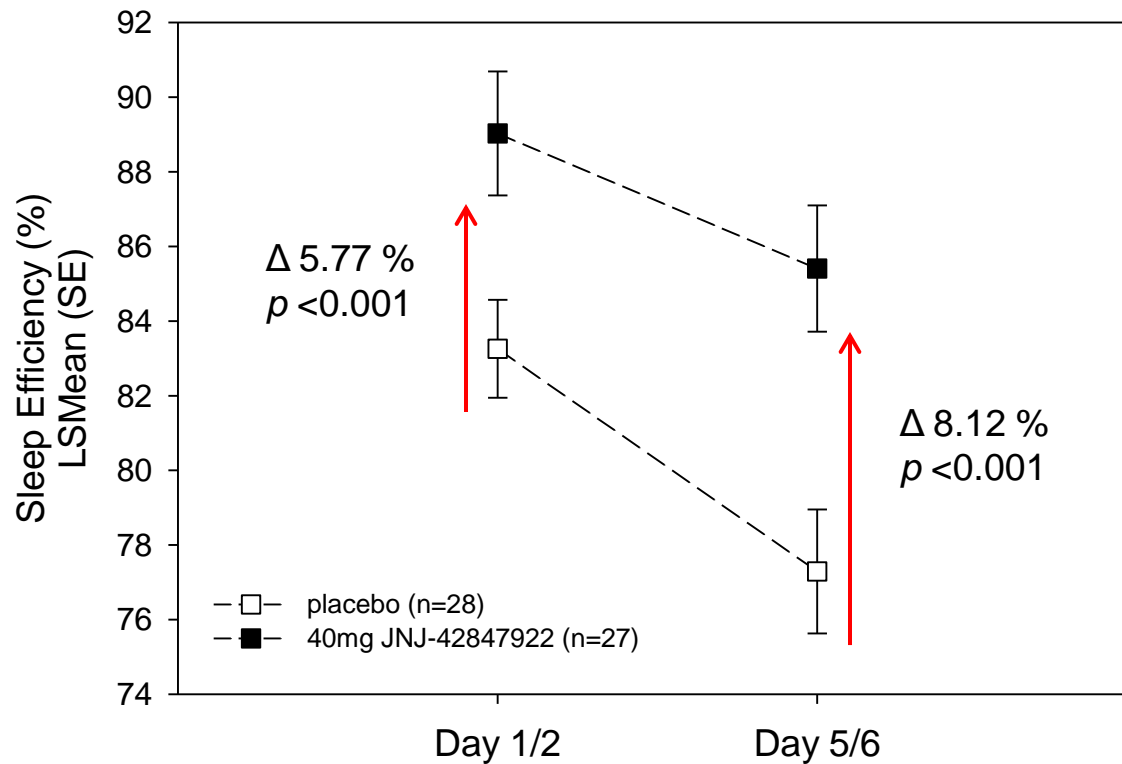
Sleep Efficiency = (Total Sleep Time/480) * 100%

PSG recording = 480 min

MIN-202: observed efficacy on depressive symptoms is independent of effects on sleep

DAY 11, N=47

Mean Change HDRS$_{17}$
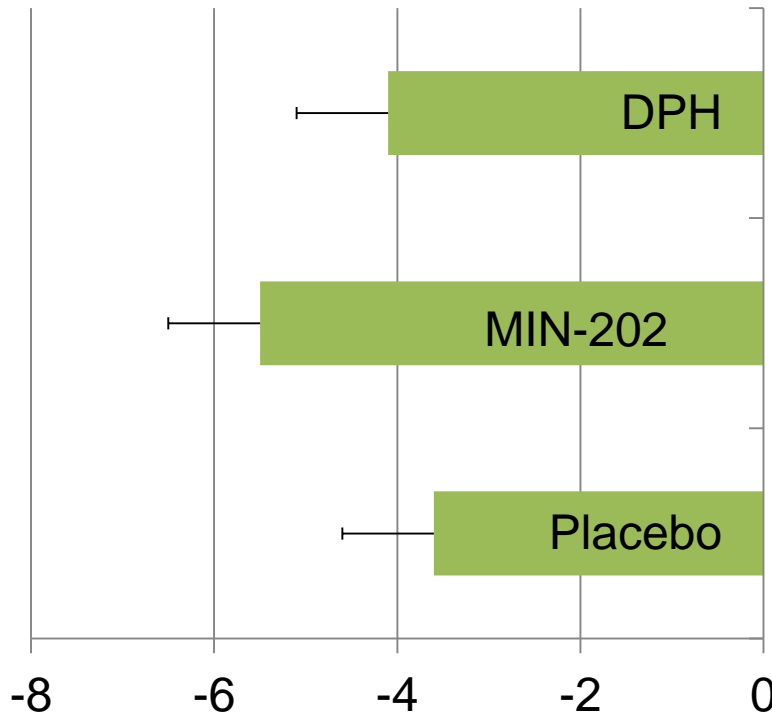
Mean Change *Adjusted* HDRS$_{17}$
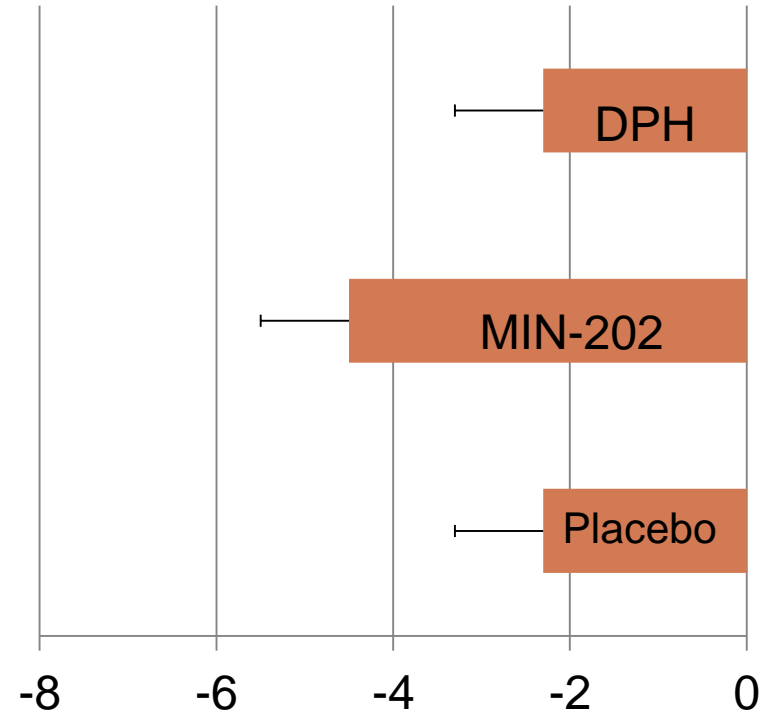
HDRS$_{17}$ = Hamilton Depression Rating Scale
Adjusted HDRS$_{17}$ = Hamilton Depression Rating Scale with 3 sleep items removed

MIN-117

Potential for a more effective and safer treatment to address the unmet medical needs of Major Depressive Disorder patients

Unmet need in Major Depressive Disorder: treatments with faster onset and better response, without side effects
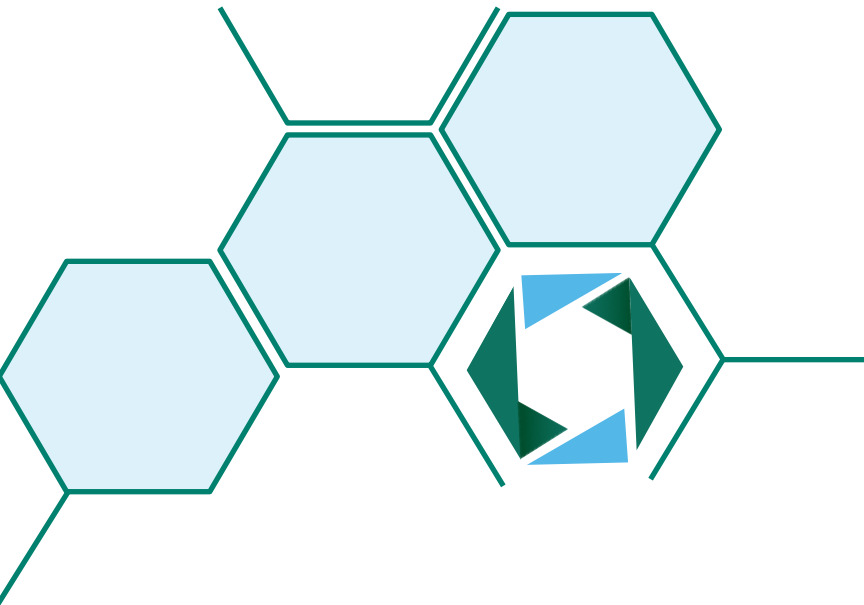
- Major depression: primary cause of disability worldwide by 2030[1]

- ~6 million patients in US with treatment- resistant depression[2]

- Only ~30% of patients achieve remission using current treatments[3]

- Current therapies have slow onset of effect; typically 4 – 8 weeks

What do we need?

Treatments that:
- Act rapidly
- Are effective in patients who do not respond to or receive only partial benefit from existing medicines
- Do not impair cognition or sexual function
- Free patients from debilitating side-effects
- Improve sleep

1. *World Health Organization, "Global Burden of Mental Disorders," 2011*
2. *IMS and Truven Health*
3. *Cleveland Clinic Journal of Medicine Volume 75. Number 1 January 2008*

MIN-117C01: Phase IIa study design

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> **4 weeks Screening Day -28 to -1***

> **6 week double blind treatment phase**

> **2 wk post treatment follow-up phase**

*****Includes overlapping washout period of up to 4 weeks**

Study drug is double-blind and double-dummy

R

> **MIN-117 2.5mg (n = 21)**

> **MIN-117 0.5mg (n = 21)**

> **Paroxetine 20mg (n = 21)**

> **Placebo (n = 21)**

> **Screening**

> **Treatment & Assessments**
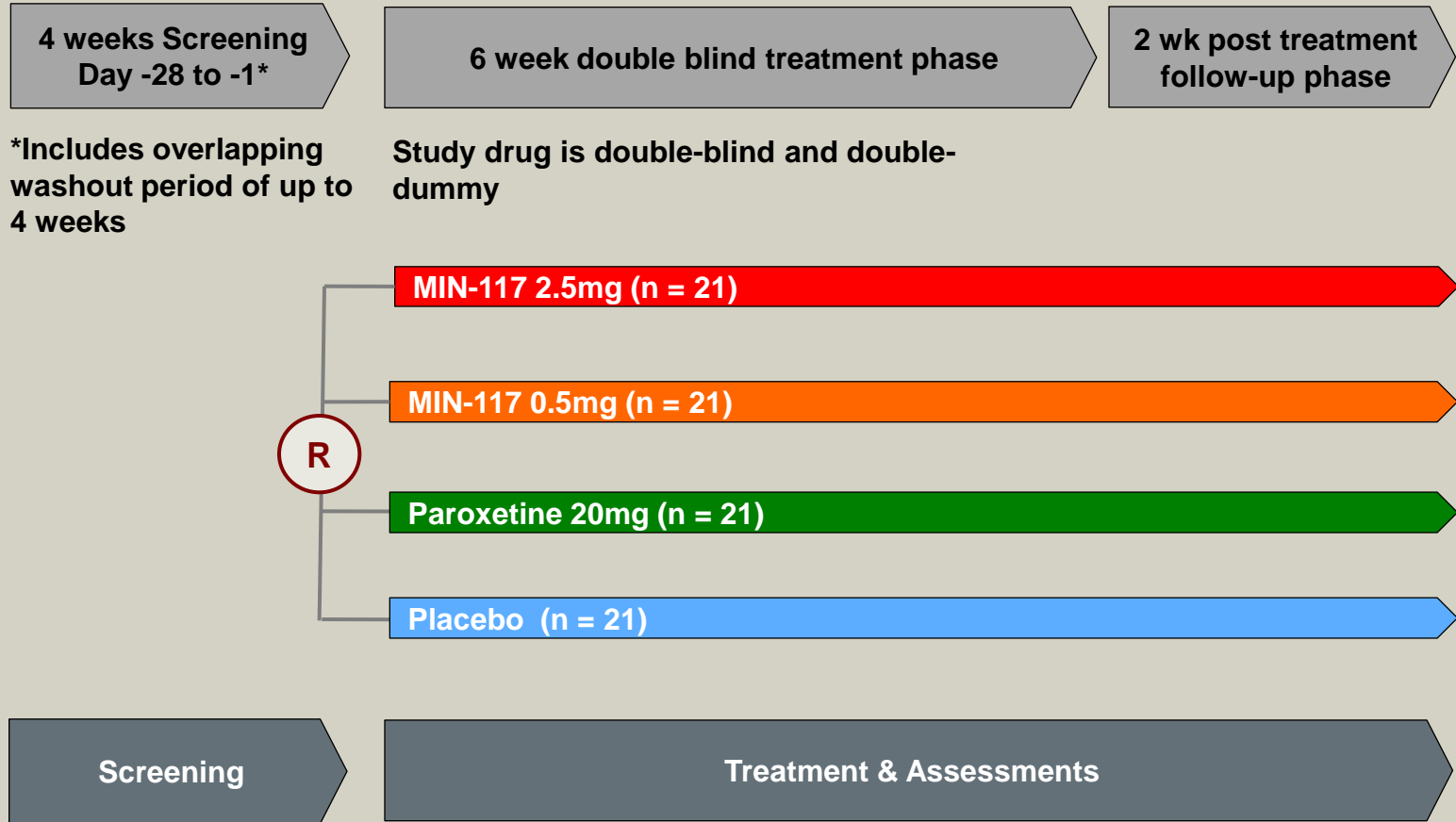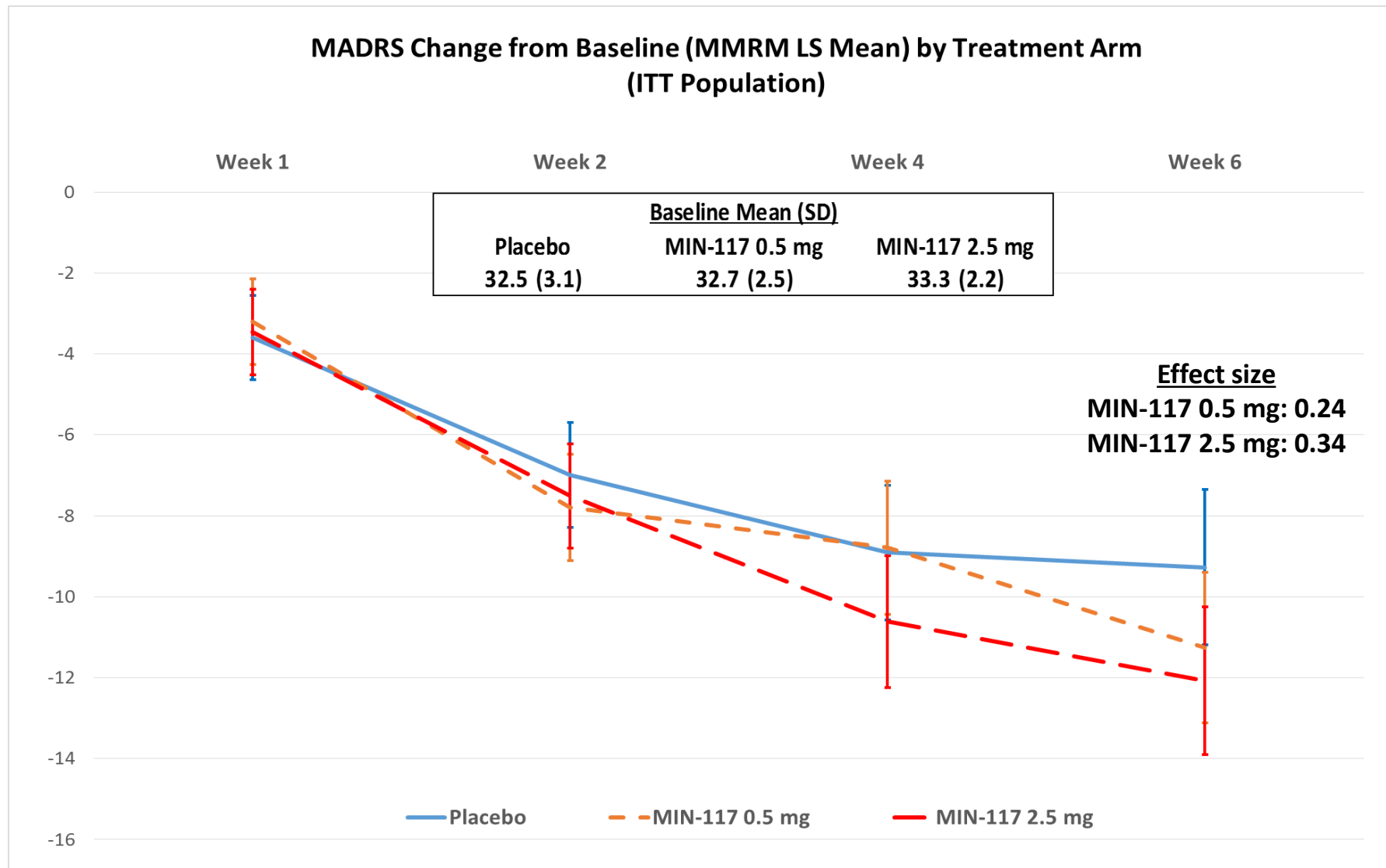
Phase IIa efficacy: MADRS primary endpoint
Clinically meaningful effect in a depressed patient population at both doses

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MADRS Change from Baseline (MMRM LS Mean) by Treatment Arm
(ITT Population)

	Baseline Mean (SD)		
	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg
	32.5 (3.1)	32.7 (2.5)	33.3 (2.2)

Effect size
MIN-117 0.5 mg: 0.24
MIN-117 2.5 mg: 0.34

Placebo — MIN-117 0.5 mg — MIN-117 2.5 mg

Phase IIa efficacy: HAM-A secondary endpoint Unexpected effect on anxiety

HAM-A Change from Baseline (Observed Data) by Treatment Arm (ITT Population)

	Baseline Mean (SD)	
Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg
24.0 (6.4)	27.1 (4.9)	24.5 (6.4)

Effect size
MIN-117 0.5 mg: 0.49
MIN-117 2.5 mg: 0.45

Placebo   — MIN-117 0.5 mg   — MIN-117 2.5 mg
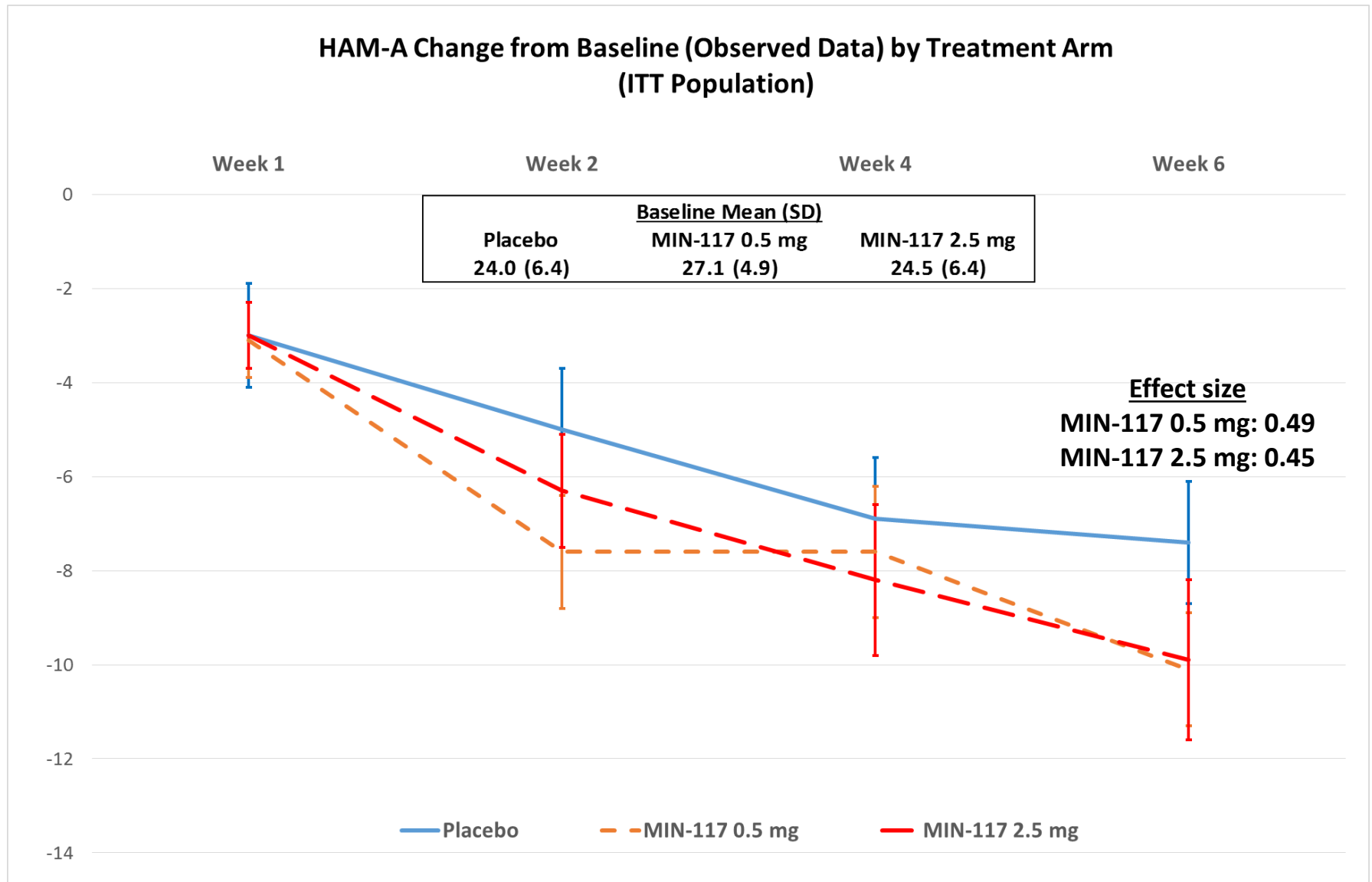
PSG REM Latency Change from Baseline (Observed Data) by Treatment Arm (ITT Population)
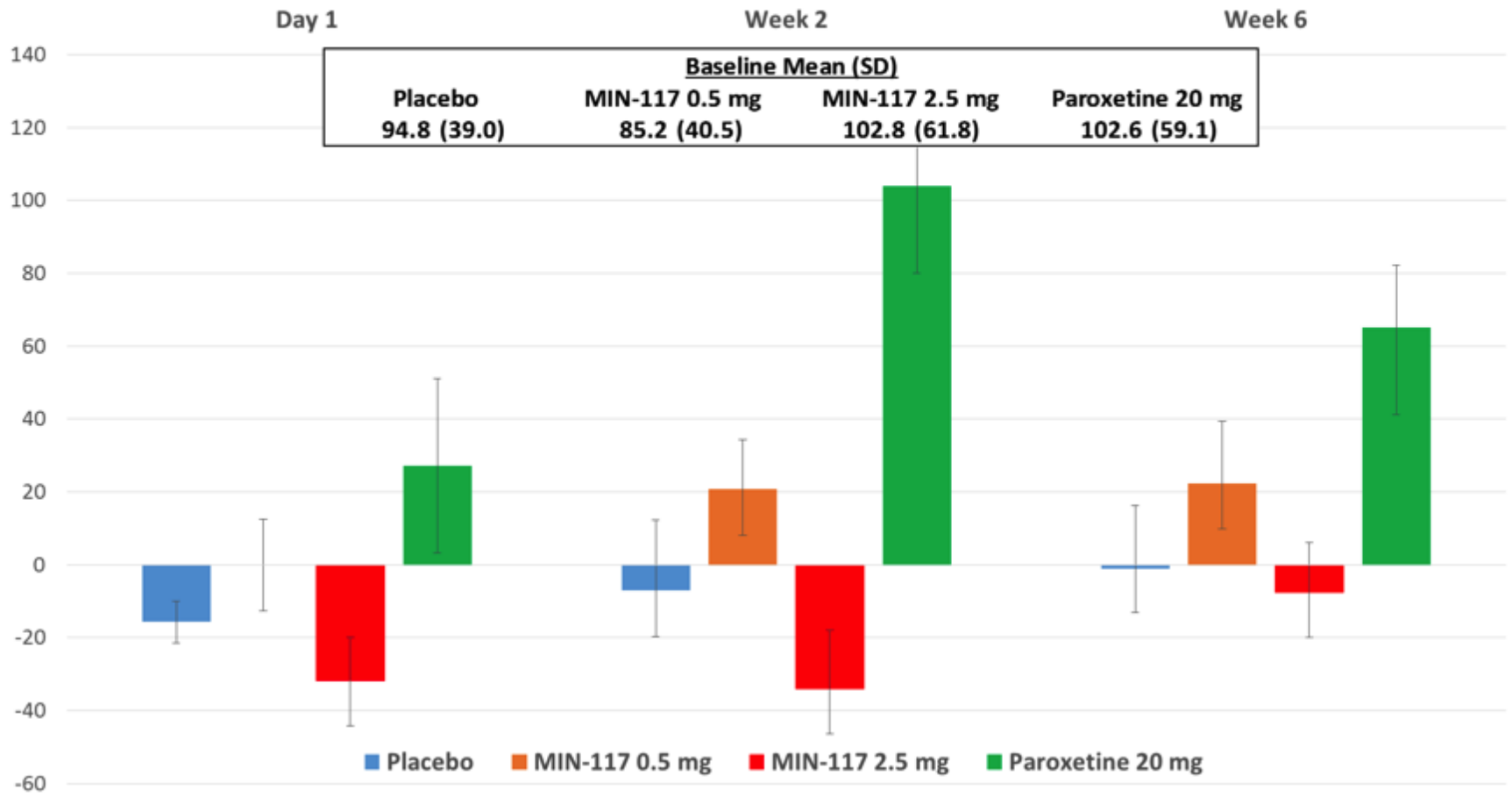
MIN-301

A protein drug with disease modifying potential for the treatment of unmet medical needs in major CNS indications

Caused by a cascade of events leading to the death of dopamine-generating cells

- Progressive and incurable
- Leads to lower quality of life, disability
- Loss of speech, mobility, cognitive abilities
- Lower life expectancy

- Parkinson's disease is a chronic, degenerative neurological disorder that affects one in 100 people over age 60.

- The average age at onset is 60

- There is no objective test, or biomarker

- Estimates of the number of people living with the disease vary but recent research indicates that at least one million people in the US and more than 5 million worldwide have the disease
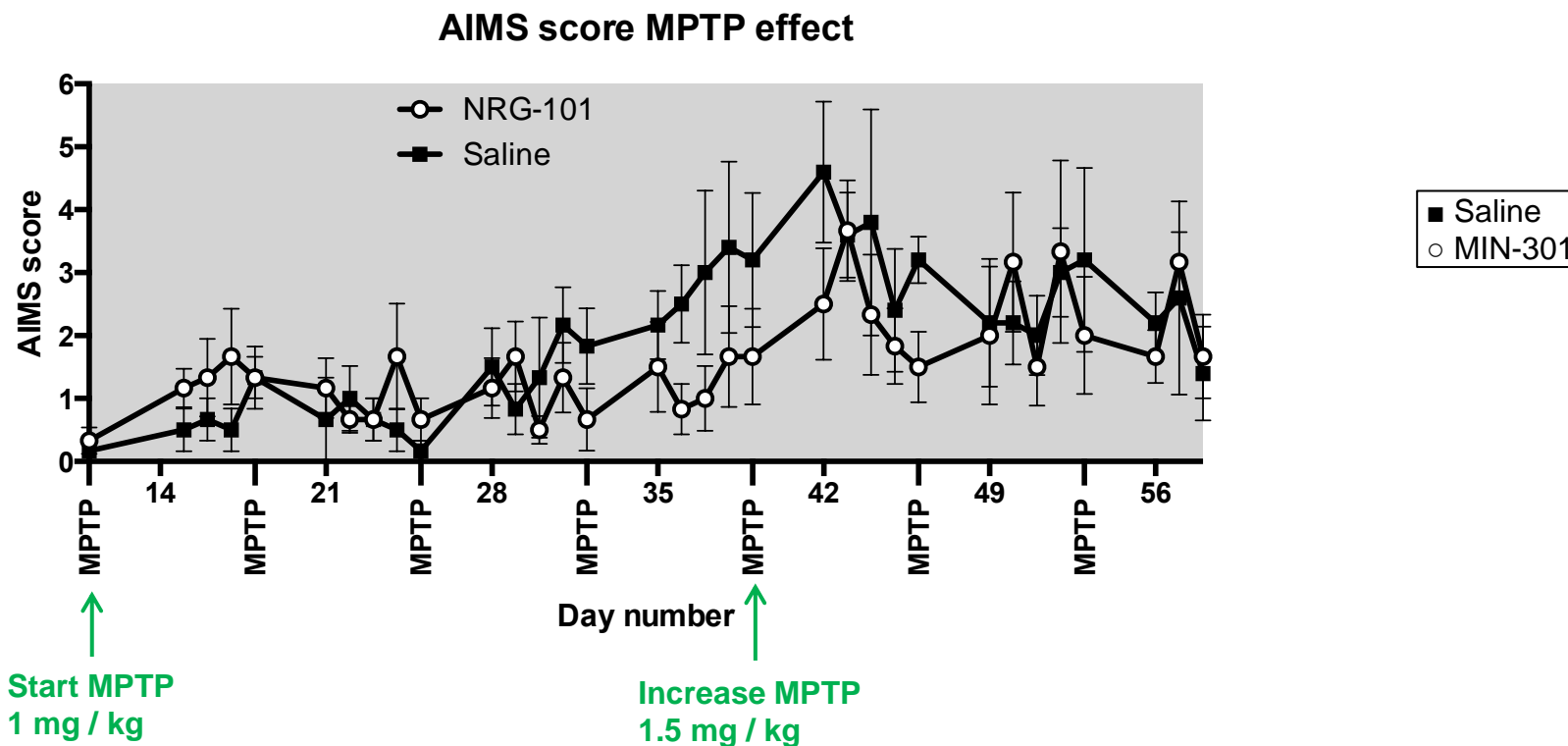
What do we need?

Treatments that;

- **Are disease modifying**

- **Have less side effects**

- **Treat all symptoms particularly cognitive decline and not just the motor impairment**

AIMS score MPTP effect

- **Clear MPTP-induced increase in AIMS scores**
- **Scores in MIN-301-treated animals lower during low MPTP (< 1 mg/kg) induction as compared to placebo**

Upcoming milestones and value drivers

Program	Primary Indication	Status
MIN-101	Schizophrenia	• End of Phase II meeting with FDA held in early Q2 2017 • Initiation of pivotal Phase III trial planned in H2 2017
MIN-202	Primary Insomnia and Major Depressive Disorder	• Phase II trial preparation underway • Next trials in insomnia disorder and MDD planned in 2017
MIN-117	Major Depressive Disorder	• Planning underway for next phase of clinical trials expected to begin in 2017
MIN-301	Parkinson's Disease	• IND or IMPD, with Phase I expected to initiate thereafter

Financial position

- ~$85.4 million cash balance (cash and cash equivalents) at March 31, 2016

  – sufficient to fund operations for at least 12 months from May 4, 2017 (date of Q1 2017 10-Q filing)

- Shares outstanding at May 1, 2017: ~36.7 million (~41.0 million fully diluted at May 4, 2016)