



## Investor Presentation

March 2020

## Forward-Looking Statement Safe-Harbor

This presentation contains forward-looking statements about Minerva Neurosciences which are subject to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts, reflect management's expectations as of the date of this presentation, and involve certain risks and uncertainties. Forward-looking statements include, but are not limited to: the benefits, efficacy and safety of our new formulations; the potential of the diagnosis and treatment of negative symptoms of schizophrenia and other diseases; whether studies performed on analogs or backups of our compounds are a good predictor of the clinical efficacy of our compounds; statements with respect to the timing and results of future clinical milestones with roluperidone (MIN-101) and seltorexant (MIN-202), including the Phase 3 trial of roluperidone and the Phase 3 trials of seltorexant; statements regarding our ability to successfully develop and commercialize our therapeutic products; our expectations regarding approval for our products by the U.S. Food and Drug Administration or equivalent foreign regulatory agencies; estimates regarding the market potential for our products; and future performance. All of such statements are subject to certain risks and uncertainties, many of which are difficult to predict and generally beyond the control of the Company, that could cause actual results to differ materially from those expressed in, or implied or projected by, the forward-looking statements. These forward-looking statements are based on our current expectations and may differ materially from actual results due to a variety of factors including, without limitation, whether any of our therapeutic products

will advance further in the clinical trials process and whether and when, if at all, they will receive final approval from the U.S. Food and Drug Administration or equivalent foreign regulatory agencies and for which indications; whether the results of future clinical trials of roluperidone, seltorexant and MIN-301, if any, will be consistent with the results of past clinical trials; whether roluperidone, seltorexant and MIN-301 will be successfully marketed if approved; whether our therapeutic product discovery and development efforts will be successful; our ability to achieve the results contemplated by our co-development agreements; the strength and enforceability of our intellectual property rights; competition from pharmaceutical and biotechnology companies; the development of and our ability to take advantage of the market for our therapeutic products; our ability to raise additional capital to fund our operations on terms acceptable to us; and general economic conditions. These and other potential risks and uncertainties that could cause actual results to differ from the results predicted are more fully detailed under the caption "Risk Factors" in our filings with the Securities and Exchange Commission, including our Quarterly Report on Form 10-K for the year ended December 31, 2019, filed with the Securities and Exchange Commission on March 9, 2020. Copies of reports filed with the SEC are posted on our website at [www.minervaneurosciences.com](http://www.minervaneurosciences.com). Our audience is cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof, and we disclaim any obligation to update any forward-looking statements, except as required by law.

## Minerva Neurosciences (NASDAQ: NERV)

Founded in 2014

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Our goal is to transform the lives of patients suffering from CNS disease including schizophrenia, depression, insomnia and Parkinson's disease

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Our late stage clinical programs focus on the development of several proprietary compounds which have innovative mechanisms of actions which in turn we believe will lead to better treatments for patients



## Advancing a broad pipeline to address unmet needs in CNS healthcare

Program	Primary Indications	Mechanism of Action	Preclinical	Phase 1	Phase 2	Phase 3	
<b>Roluperidone MIN-101</b>	Negative symptoms in schizophrenia	<ul style="list-style-type: none"><li>• 5-HT<sub>2A</sub> antagonist</li><li>• Sigma<sub>2</sub> antagonist</li><li>• α<sub>1A</sub>-adrenergic antagonist</li><li>• α<sub>1B</sub>-adrenergic antagonist</li></ul>	<b>Pivotal Phase 3 (MIN-101C07) Screening Complete – TLR Q2 '20</b>				
<b>Seltorexant MIN-202</b>	Primary insomnia	<ul style="list-style-type: none"><li>• Selective orexin-2 antagonist (SORA)</li></ul>	<b>Phase 2b (MDD2001) Top Line Readout Q2 '19</b>				<b>completed</b>
	Major depressive disorder, as adjunctive therapy		<b>Phase 2b (ISM2005) Top Line Readout Q2 '19</b>				<b>completed</b>
			<b>Phase 2 (MDD2002) Top Line Readout Q3 '19</b>				<b>completed</b>
<b>MIN-301</b>	Parkinson's disease	<ul style="list-style-type: none"><li>• Neuregulin-1β1 activating ErbB4</li></ul>	<b>Pre-clinical</b>				

# Roluperidone (MIN-101)

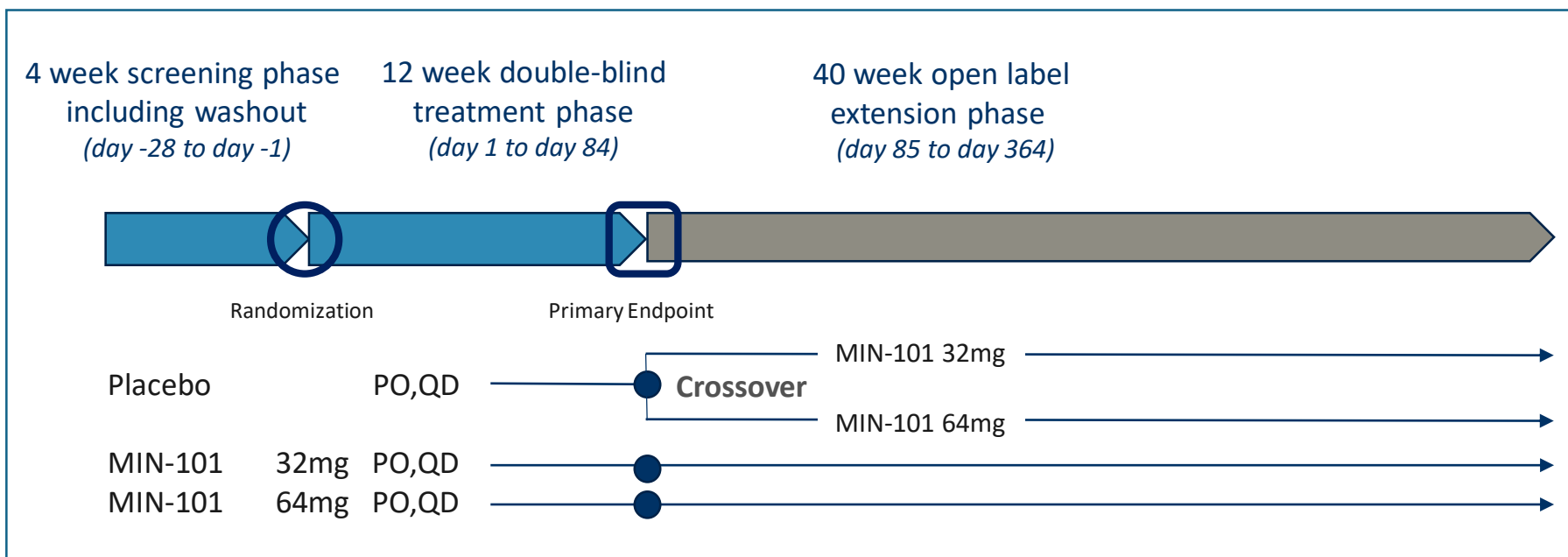
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## Phase 3

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Screening complete early January 2020  
Top line results Q2 2020

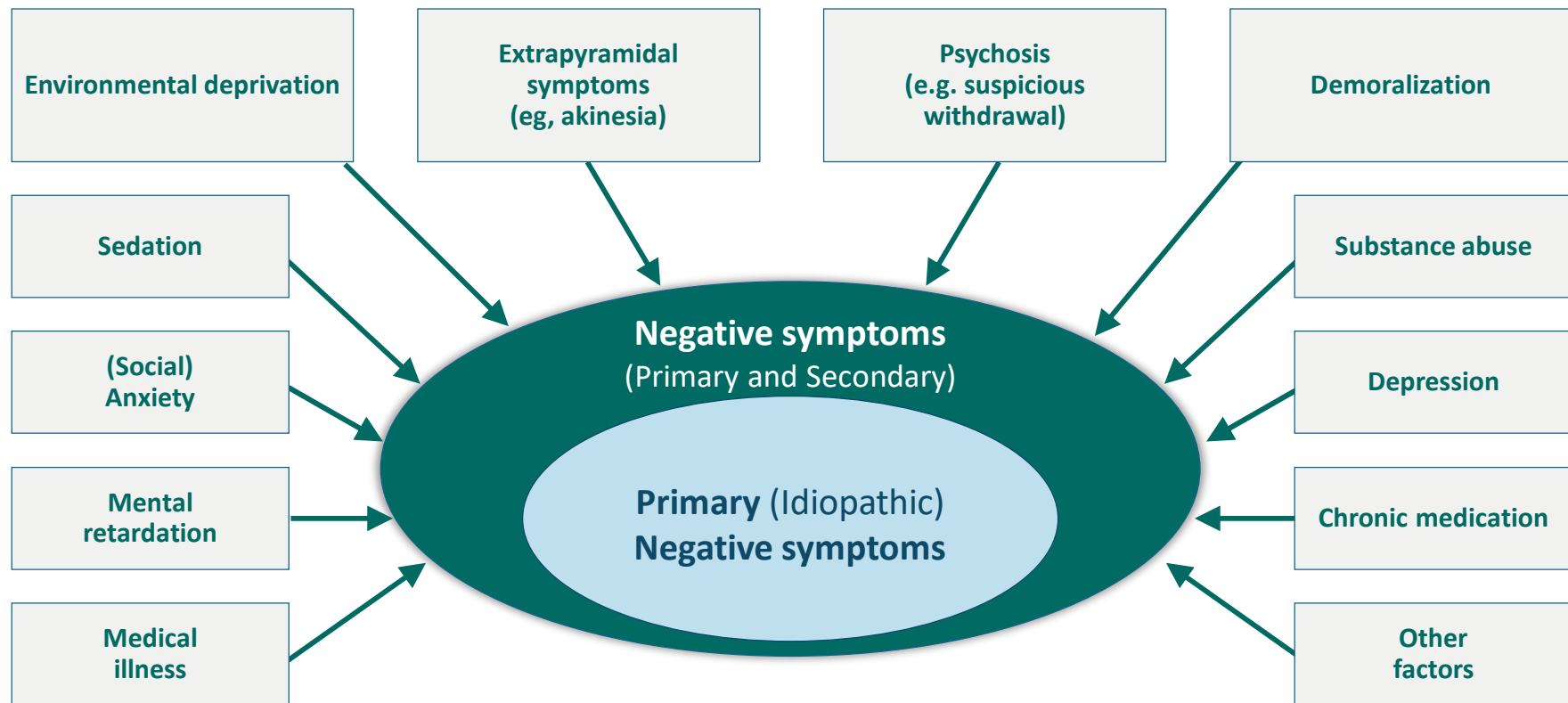
# Roluperidone (MIN-101 C07): Pivotal Phase 3 study to evaluate efficacy and safety in 501 schizophrenic patients with negative symptoms



- Primary endpoint:** Reduction in PANSS Negative Symptoms Factor Score (NSFS; Marder score) from baseline after 12 weeks administration
- Secondary endpoints:** Personal and Social Performance scale (PSP), Clinical Global Impression of Severity (CGI-S), 40 weeks (9 months) open-label extension
- Number of patients:** 501 patients randomized 1:1:1 (167 in each arm)
- Main inclusion criteria:** DSM-5 schizophrenia diagnosis, Baseline score  $\geq 20$  on the 7 items PANSS negative score, Symptomatically stable and manifesting negative symptoms for 6 months as judged by the PI, Age 18-55
- Powering Assumptions:** 90% powered and 40% drop-out rate

## Roluperidone (MIN-101 C07): Why monotherapy and placebo controlled?

- Demonstrate specific effect on negative symptoms
- No approved positive control
- Avoids unblinding of the study



Sources: Fervaha et al, European Psychiatry 2014; [Issues and Perspectives in Designing Clinical Trials for Negative Symptoms in Schizophrenia](#); SR Marder et al, *Schizophrenia Research Journal*/article/S0920-9964(13)00447-7

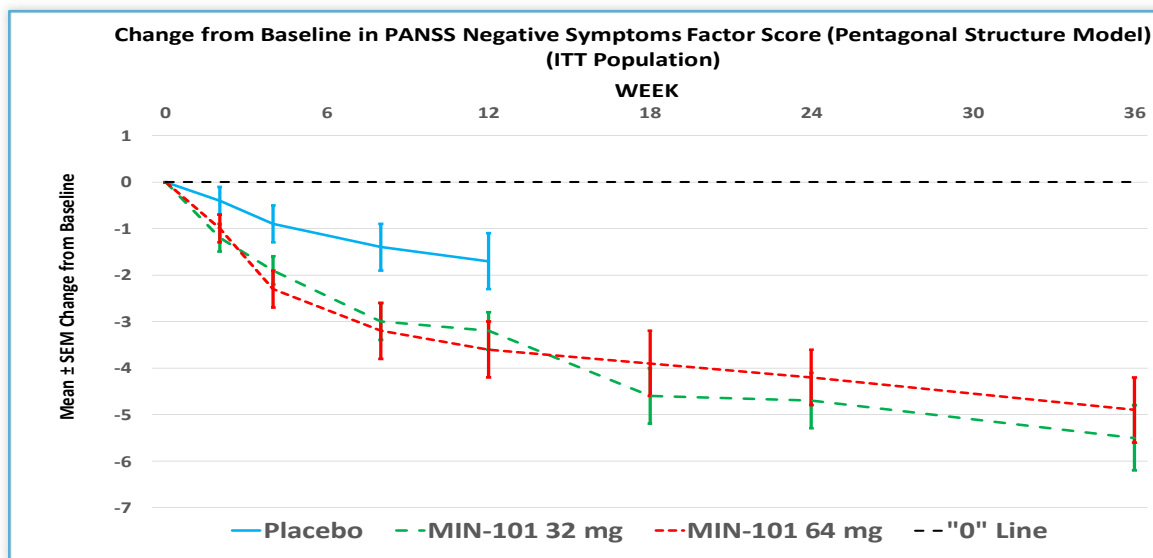
## Roluperidone (MIN-101 C07): Ongoing activities in parallel with Phase 3 trial

- DDI studies
- CMC work for commercialization
- NDA filing preparation
- Commercial launch plan
- KOL and prescribers meetings
- Evaluation of other therapeutic indications

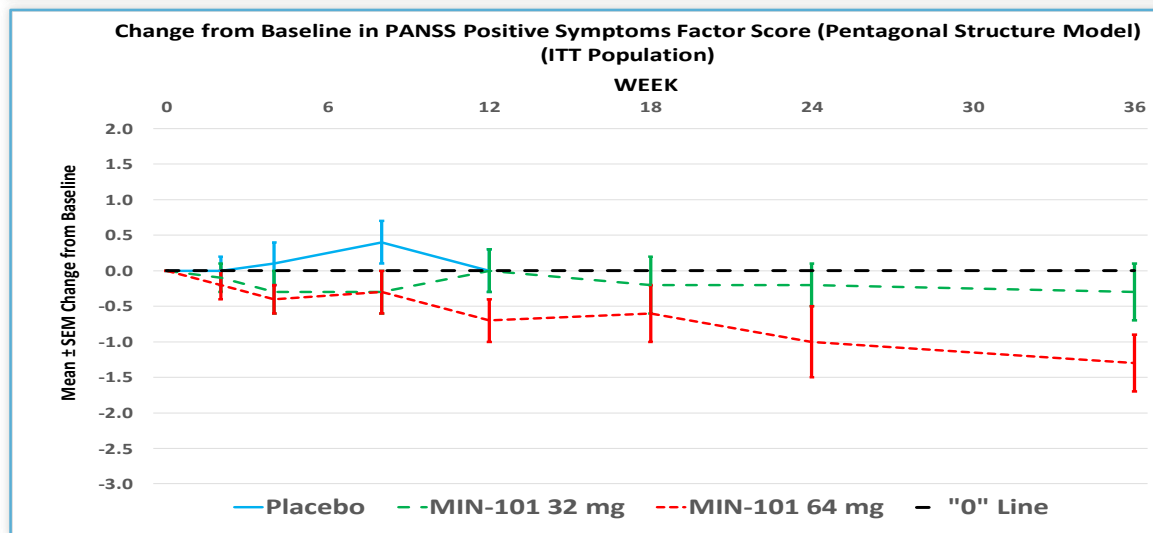


## Roluperidone: A reminder of the Phase 2b data - continuous improvement in negative symptoms over 36 weeks and control of positive symptoms

Negative symptoms



Positive symptoms



Source: Clinical Study Report, data on file.

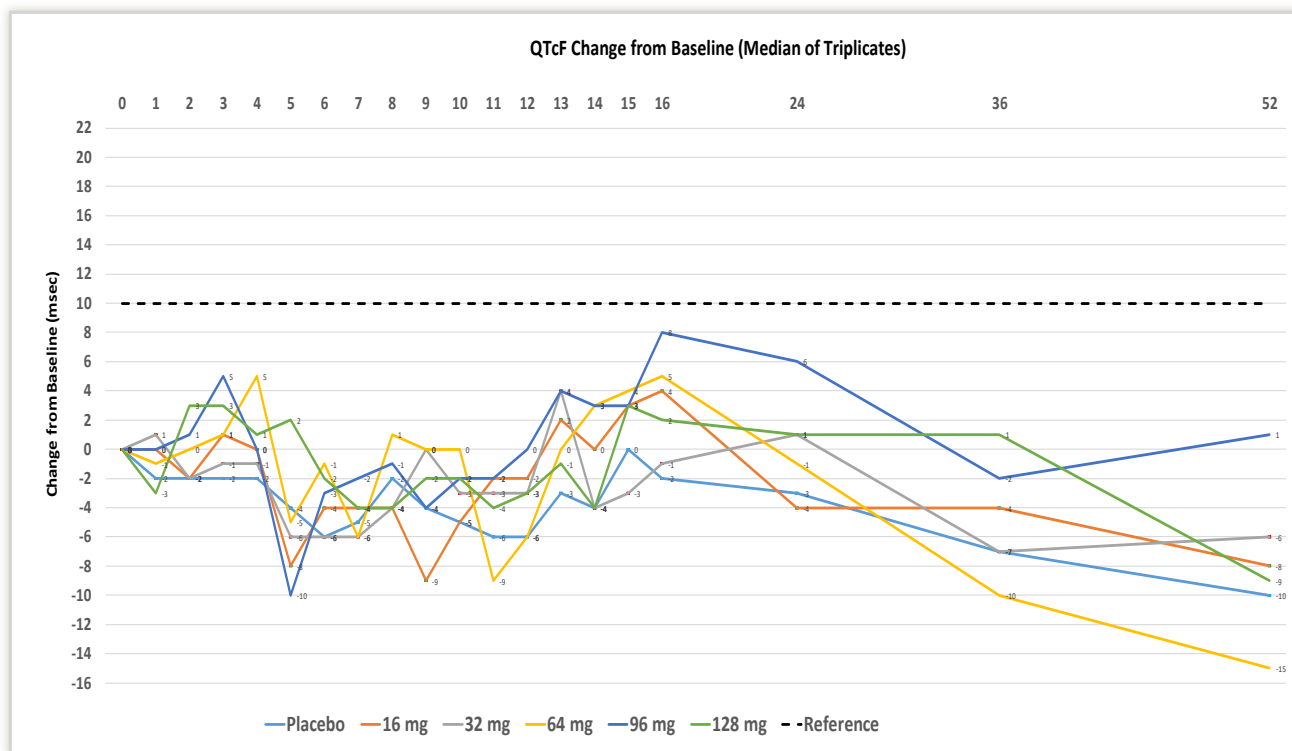
## Roluperidone: A reminder of the Phase 2b data – statistically significant on multiple primary and secondary endpoints

Endpoint	P-Value		Effect Size	
	MIN-101 versus Placebo		MIN-101 versus Placebo	
	32 mg	64 mg	32 mg	64 mg
<b>Primary Objective</b>				
PANSS Negative Subscale Score (Pentagonal Structure Model)	0.0213	0.0030	0.45	0.58
<b>Secondary Objectives</b>				
PANSS Total Score	0.0714	0.0027	0.35	0.59
PANSS Positive Subscale Score (Pentagonal Structure Model)	0.5933	0.1926	-0.10	0.25
Dysphoric Mood Subscale Score (Pentagonal Structure Model)	0.5156	0.0238	0.12	0.43
Activation Subscale Score (Pentagonal Structure Model)	0.0213	0.0111	0.45	0.49
Autistic Preoccupation Subscale Score (Pentagonal Structure Model)	0.7004	0.2586	0.08	0.22
PANSS Negative Subscale Score	0.0058	0.0004	0.55	0.70
PANSS Positive Subscale Score	0.3388	0.2832	0.18	0.21
PANSS General Psychopathology Subscale Score	0.2270	0.0032	0.23	0.57
Brief Negative Symptoms Scale	0.0934	0.0044	0.33	0.56
Clinical Global Impression of Severity	0.0964	0.0266	0.28	0.28
Clinical Global Impression of Improvement	0.2345	0.0042	0.41	0.69
Brief Assessment of Cognition in Schizophrenia	0.0388	0.5947	0.40	0.10
<b>Exploratory Objectives</b>				
Calgary Depression Scale for Schizophrenia	0.2315	0.0090	0.23	0.50
Personal and Social Performance	0.2193	0.0021	0.24	0.59

Green text indicates statistical significance and moderate or large ES

## Roluperidone's safety profile differs from atypical antipsychotics

- No weight gain
- No sedation
- No prolactin increase
- No EPS (Extra Pyramidal Symptoms)
- No significant QtcF increase at 2x high dose (128mg)

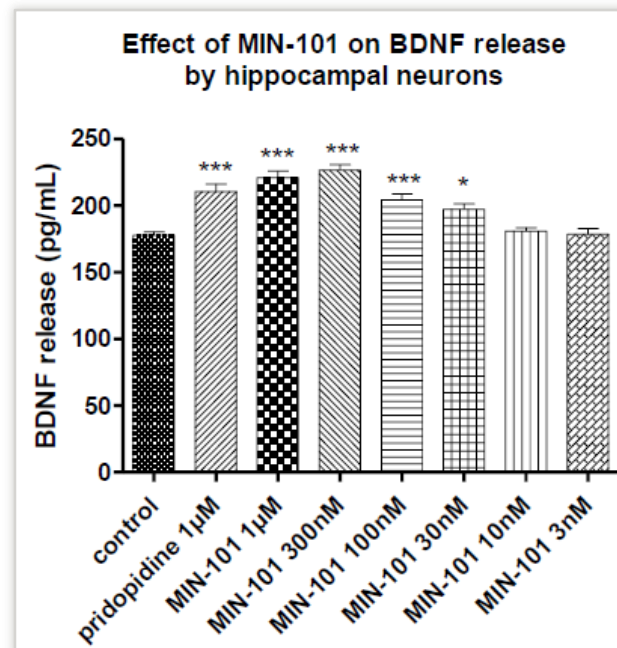
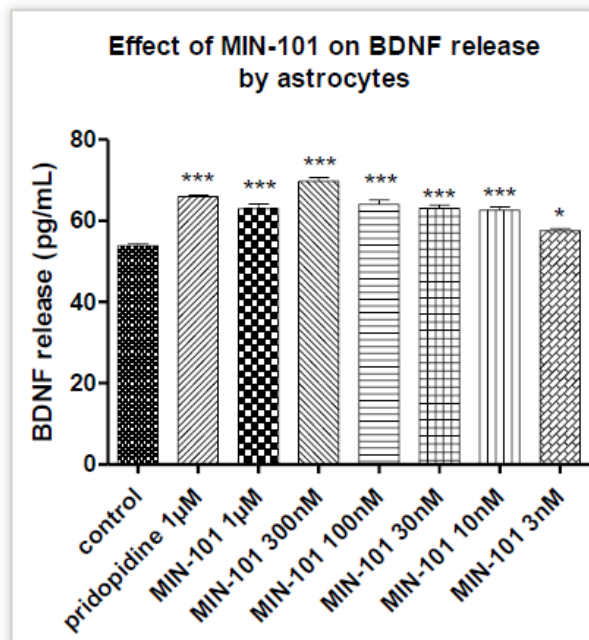


Source: Clinical Study Report, data on file. A Phase I Randomized, Double-Blind, Placebo-Controlled, Single-Dose Escalation Study to Evaluate the Pharmacokinetics, ECG Pharmacodynamics, Safety, and Tolerability of MIN-101 Gastro-Resistant Modified Release Formulation in Healthy Male and Female Subjects

## Elucidating MoA further: Risperidone increases BDNF release

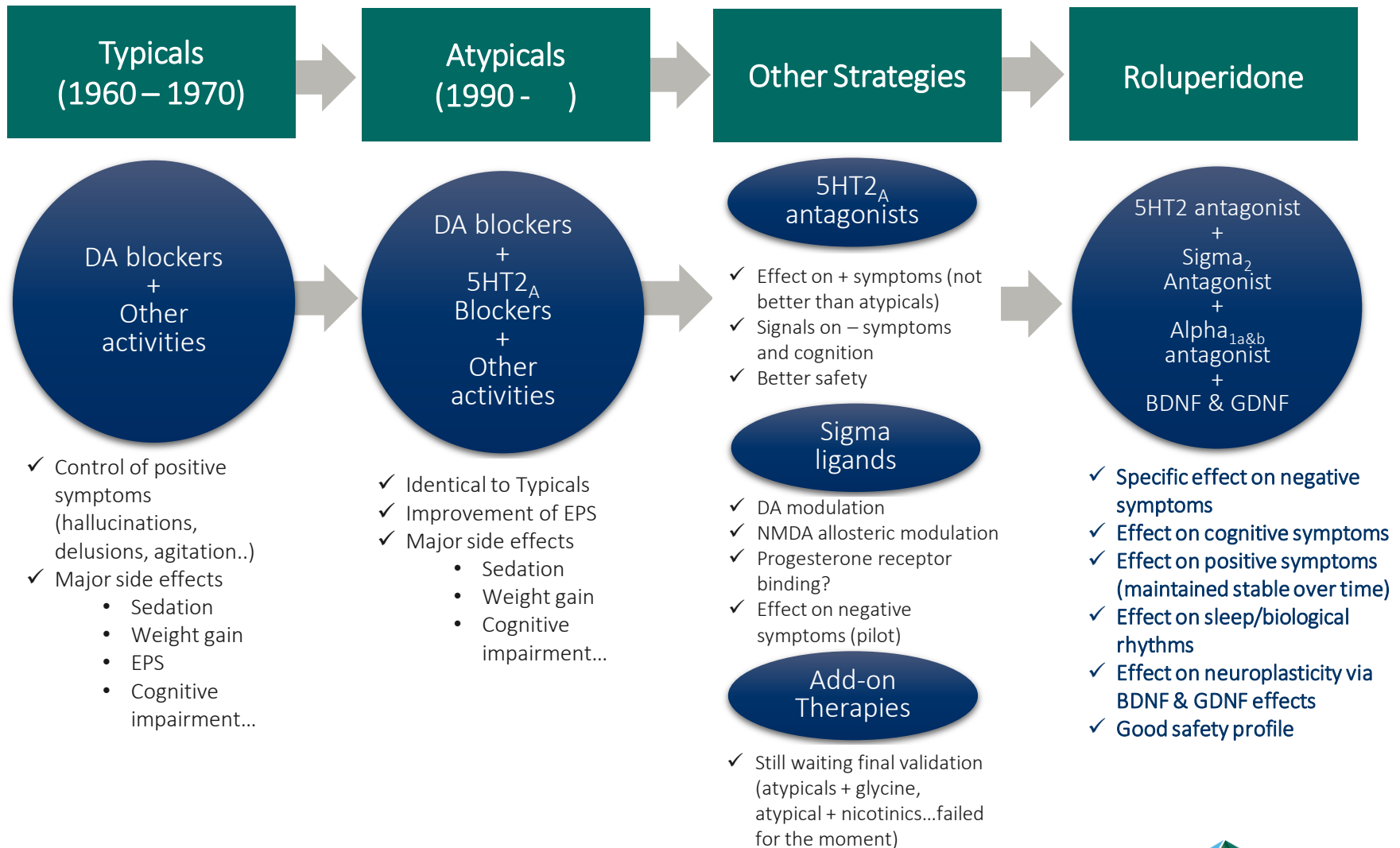
### Evaluation of MIN-101 effect (6 concentrations)

- *In-situ* ELISA for BDNF detection
- Rat primary astrocytes (5 days of incubation)
- Rat primary hippocampal neurons (3 days of incubation)



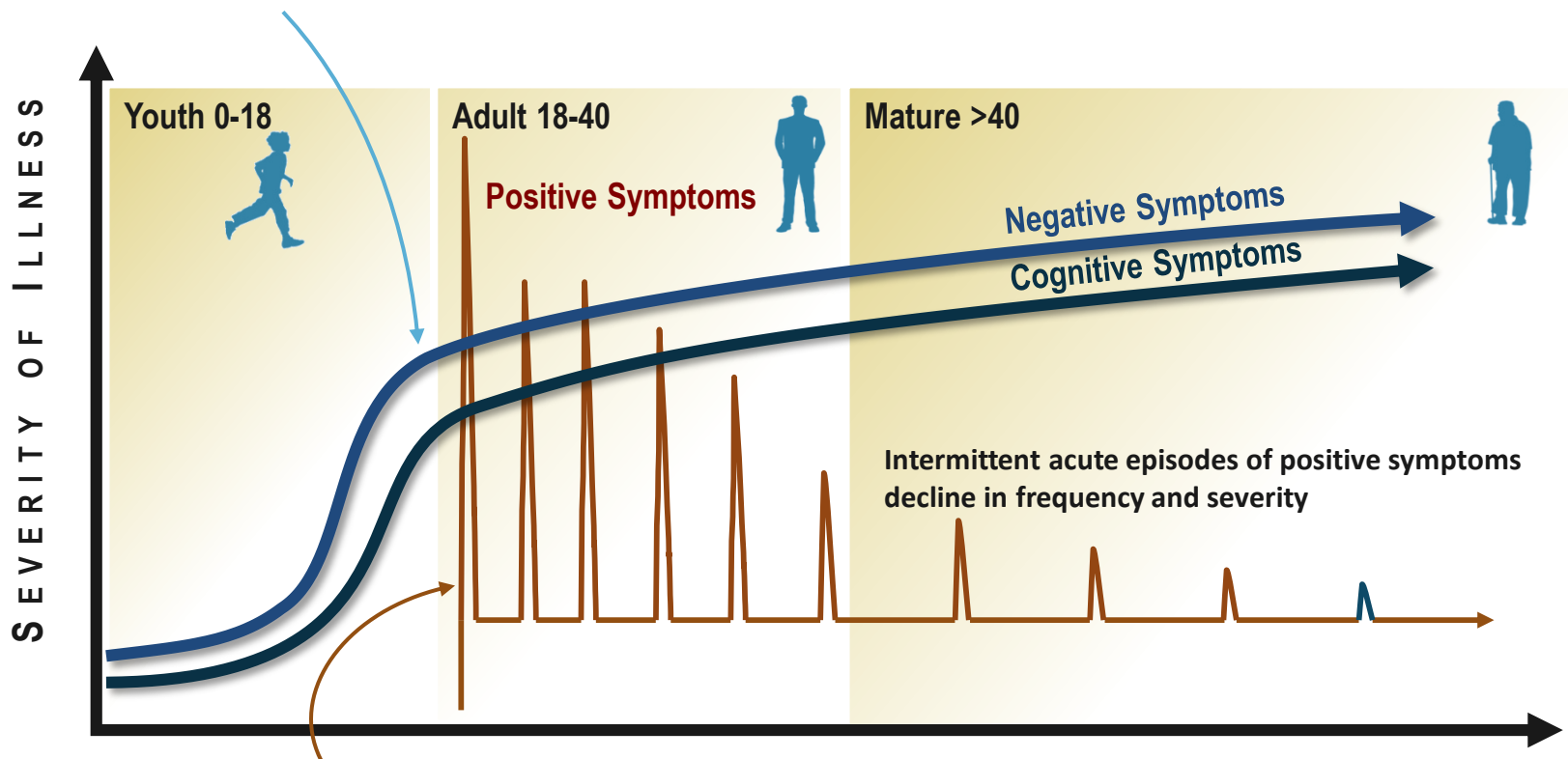
Source: Noel et al., Risperidone increases *in-vitro* Brain-Derived Neurotrophic Factor(BDNF) release: a possible mechanistic role in negative symptoms? Data presented at the 2019 Congress of the Schizophrenia International Research Society

# MoA : Right pharmacology to address unmet medical needs combined with good safety profile



## Paradigm shift underway?

Negative symptoms and cognitive impairment are evident at onset of illness and are lifelong debilitating symptoms



All antipsychotics directly target dopamine (DA) receptors and have only shown efficacy against positive symptoms; none are indicated for negative symptoms or cognitive impairment

## Roluperidone commercial opportunity summary

**Negative symptoms are an ever-worsening aspect of schizophrenia for majority of patients and there is currently no approved treatment to address**

- Around 70% of treated patients have predominant/persistent negative symptoms
- 

**Physicians cite negative symptoms as one of the key unmet needs in the treatment of schizophrenia**

- Anti-depressants commonly used off-label despite being viewed as ineffective by most physicians
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**Recent quantitative market research suggests psychiatrists intend to prescribe roluperidone to approximately 25% of their patients with negative symptoms**

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**Negative symptoms are significant driver of total cost burden in schizophrenia**

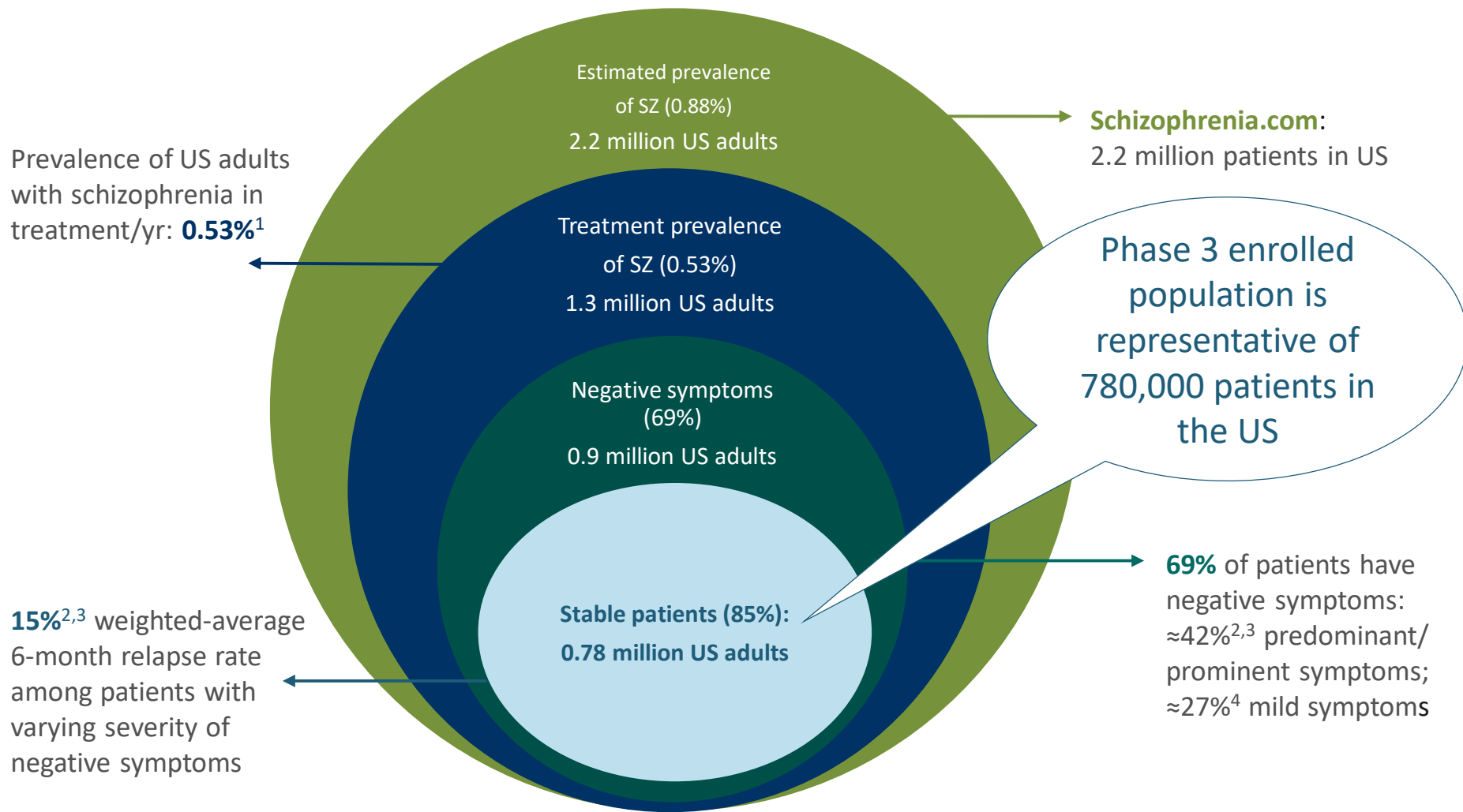
- Direct costs: utilization of in-patient and out-patient services
  - Indirect costs: lack of productivity
- 

**Payers anticipate roluperidone will be covered comparably to existing brand treatments at parity pricing with opportunity for premium pricing based on the outcome of ongoing clinical study**

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**Negative symptoms exist beyond schizophrenia and are poorly addressed in a broad range of indications (e.g. Alzheimer's disease, Parkinson's disease, depression, etc.)**

## Around 70% of patients diagnosed with schizophrenia and treated have negative symptoms



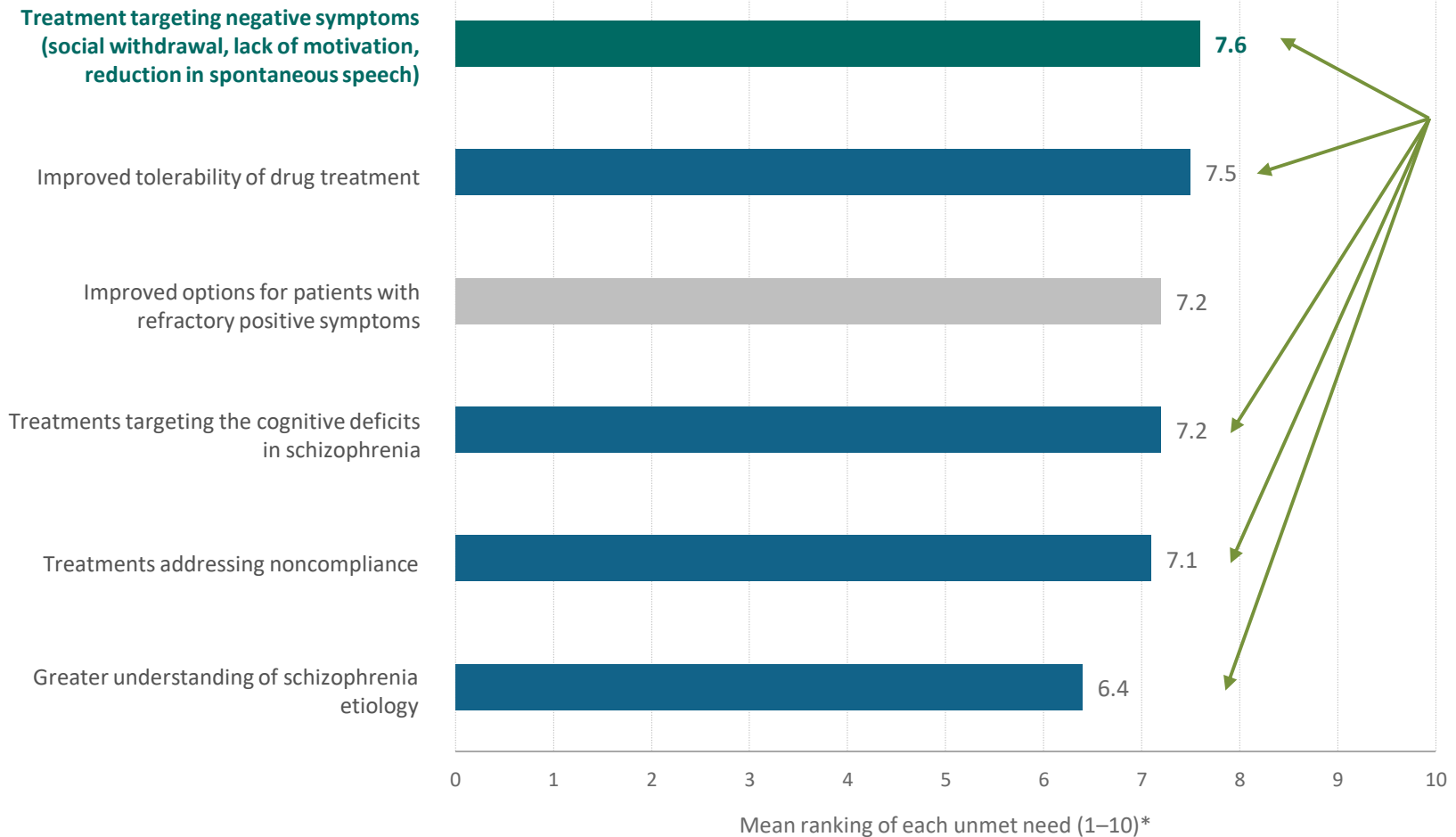
SZ=schizophrenia.

1.Wu et al. *Psychol Medicine*. 2006; 2. Millier et al. *J Market Acc Health Policy*. 2017;  
3.Haro et al. *Schizophr Research*. 2015; 4. Nordstroem et al. *J Social Psychiatry*. 2017.



# Physicians cite negative symptoms as one of the key unmet needs in the treatment of schizophrenia

## Key unmet needs for schizophrenia, 2017

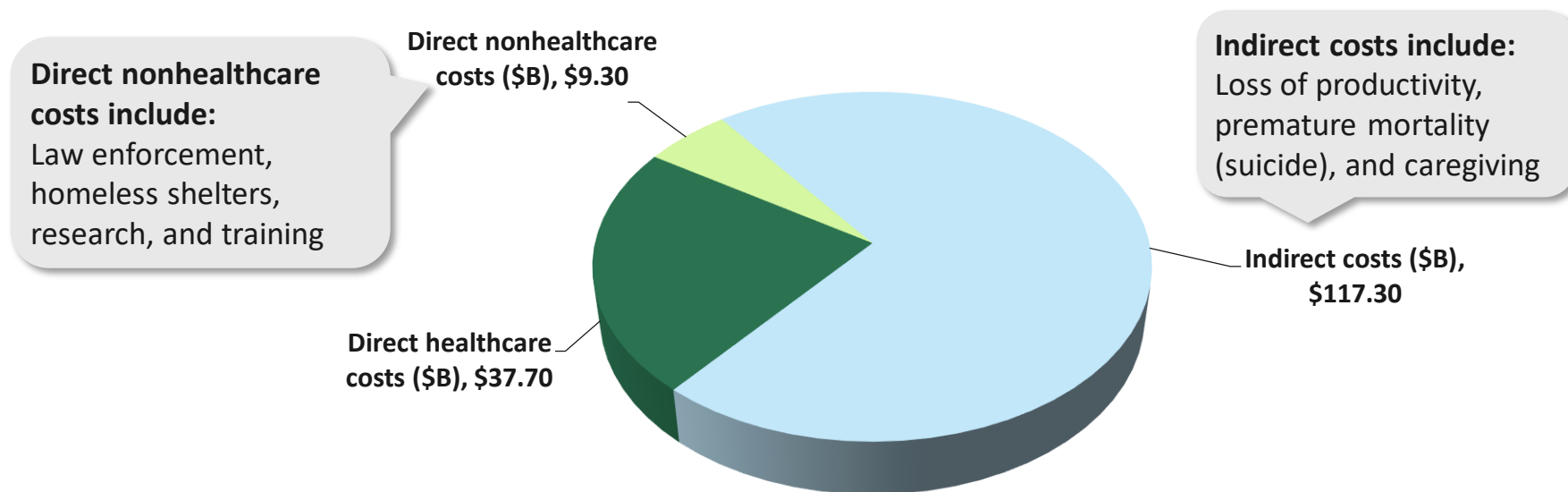


\*Higher scores denote greater importance assigned to the unmet need.

Source: Datamonitor Healthcare's proprietary schizophrenia survey, September 2017

## Economic burden of schizophrenia in the US is high; direct healthcare cost is \$37.7 B annually; total burden is \$155.7 B

The economic burden of schizophrenia includes<sup>1</sup>:



Negative symptoms are significant driver of total cost burden in schizophrenia<sup>2</sup>

There is also a great burden to caregivers including loss of productivity and emotional stress<sup>3</sup>

WHO estimates that the direct costs of schizophrenia range from 1.6% to 2.6% of total healthcare expenditures in developed countries<sup>4</sup>

WHO indicates World Health Organization. 1. Cloutier M, et al. The economic burden of schizophrenia in the United States in 2013. *J Clin Psychiatry*. 2016 Jun;77(6):764-71. <https://www.ncbi.nlm.nih.gov/pubmed/27135986>. Accessed December 29, 2017. 2. Lalonde et al. Real-World Evidence Investigation of Healthcare Utilization and Cost Among Negative Symptom Patients and Non-Negative Symptom Patients with Schizophrenia in the US, ISPOR 2019. 3. Nicholl D, Akhras KS, Diels J, Schadrack J. Burden of schizophrenia in recently diagnosed patients: Healthcare utilization and cost perspective. *Curr Med Res Opin* 2010;26:943-955. <https://www.ncbi.nlm.nih.gov/pubmed/20163295>. Accessed December 29, 2017. 4. WHO. Nations for Mental Health. Schizophrenia and public health. [http://www.who.int/mental\\_health/media/en/55.pdf?ua=1](http://www.who.int/mental_health/media/en/55.pdf?ua=1). Accessed December 29, 2017.

Landscape & Forecast

# Schizophrenia

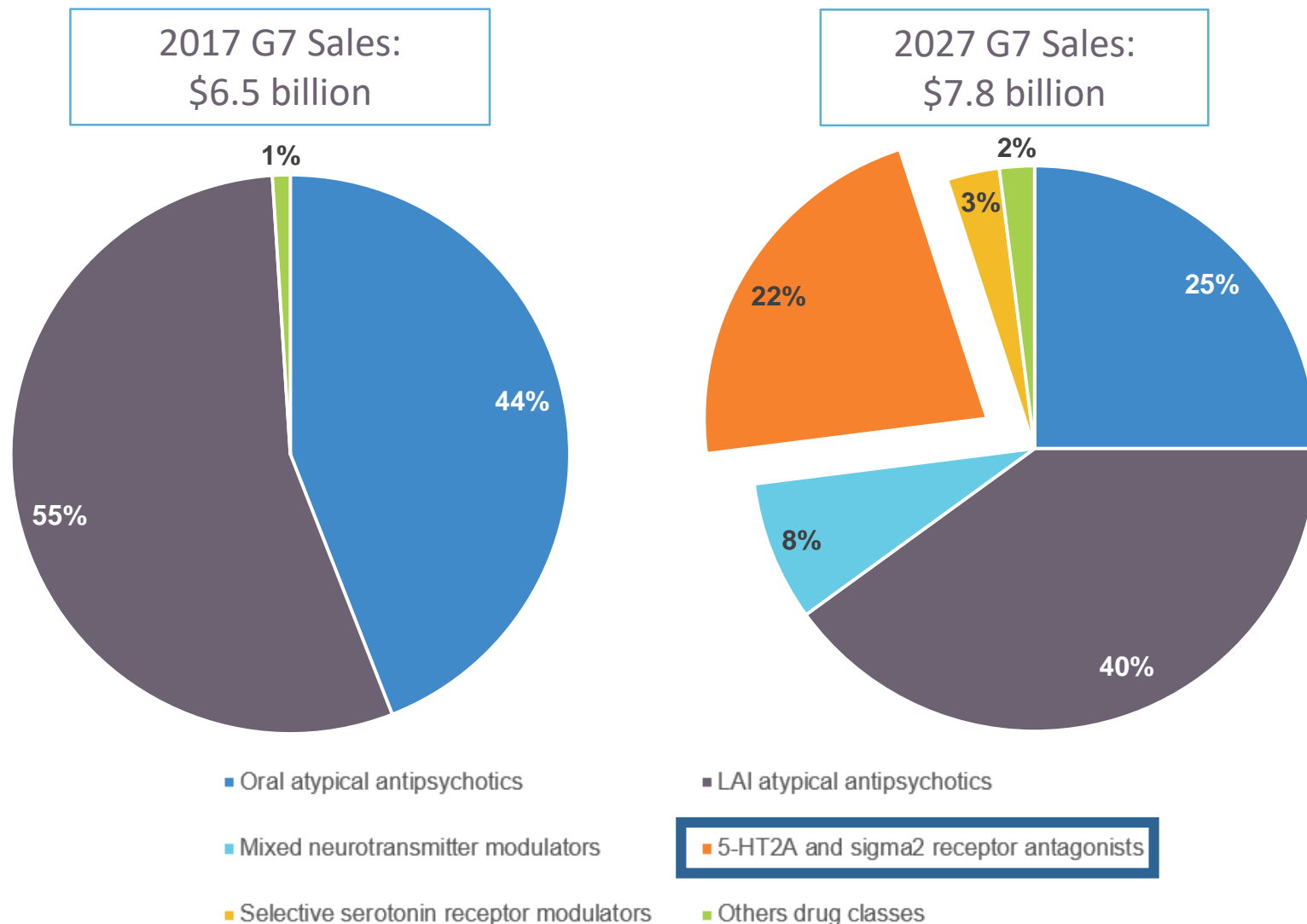
Disease Landscape & Forecast

If roluperidone is “approved for the treatment of negative symptoms—an indication of high unmet need and commercial potential— it will achieve blockbuster sales in this market (approximately \$1,740 million in 2027) **and will be the main driver for the schizophrenia market during the forecast period.**”

**“The most notable impact on the schizophrenia market will be from the availability of roluperidone, a 5-HT<sub>2A</sub> and sigma<sub>2</sub> receptor antagonist, for patients with the negative symptoms of schizophrenia—an area of high unmet need—in the United States and Europe.”** DRG anticipates that “Roluperidone will launch in these markets nearly halfway through the forecast period and will achieve blockbuster sales during this period.”

[www.DecisionResourcesGroup.com](http://www.DecisionResourcesGroup.com)

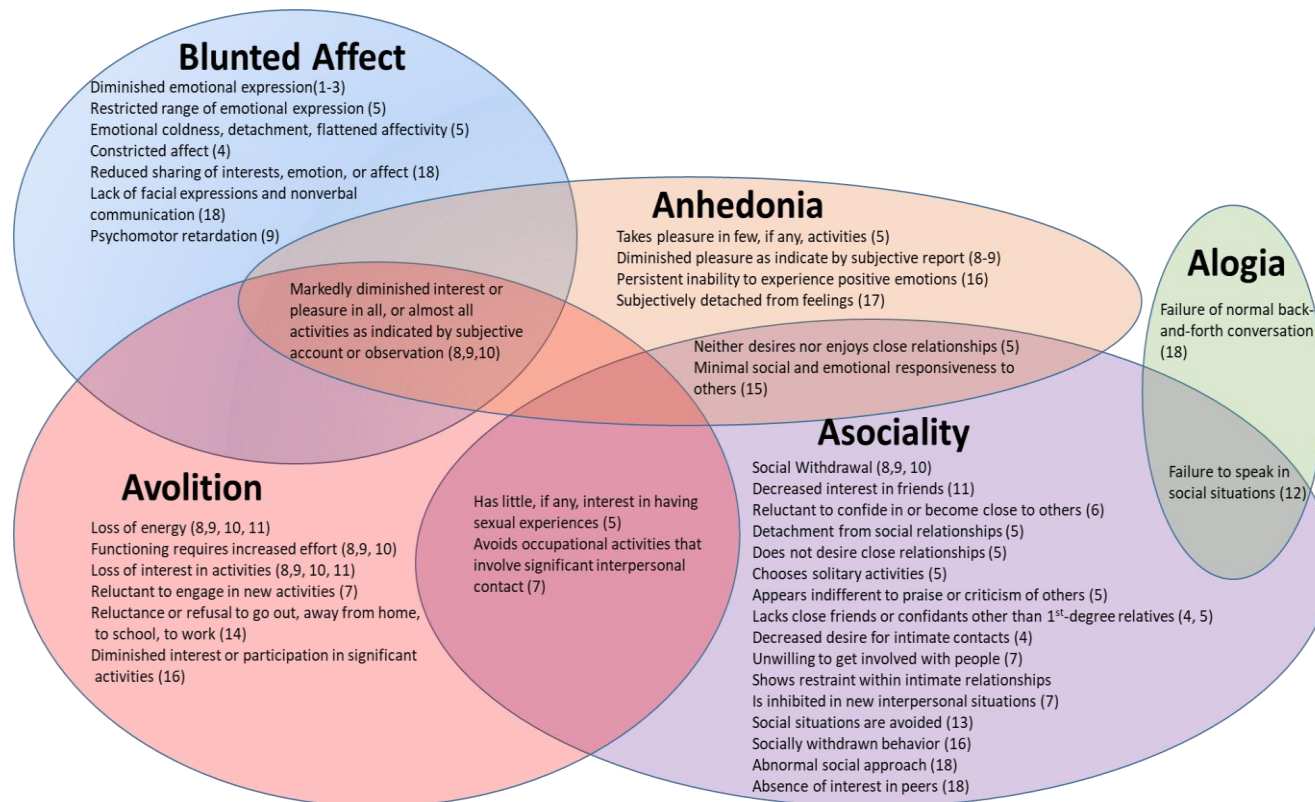
## Decision Resources Group estimates 5-HT2A and Sigma2 receptor antagonists will account for 22% of schizophrenia market by 2027



LAI – long-acting injectable. Other drug classes include oral, LAI, short-acting IM injections, and other formulations of typical antipsychotics; short-acting IM injections and other formulations of atypical antipsychotics,

Source: DRG's Schizophrenia | Disease Landscape & Forecast, 2018. Last updated December 2018.

# Negative symptoms occur outside of schizophrenia – we just don't call them that



1. Schizophrenia
2. Schizoaffective Disorder
3. Schizophreniform Disorder
4. Schizotypal Personality Disorder
5. Schizoid Personality Disorder
6. Paranoid Personality Disorder
7. Avoidant Personality Disorder
8. Bipolar Disorder (I and II)
9. Major Depressive Disorder
10. Persistent Depressive Disorder (Dysthymia)
11. Premenstrual Dysphoric Disorder
12. Selective Mutism
13. Social Anxiety Disorder
14. Separation Anxiety Disorder
15. Reactive Attachment Disorder
16. Posttraumatic Stress Disorder
17. Depersonalization/Derealization Disorder
18. Autism Spectrum Disorder
19. Neurocognitive Disorders

# Seltorexant (MIN-202)

A first-in-class selective Orexin-<sub>2</sub> antagonist for MDD and insomnia

MDD2001 positive TLR  
MDD2002 positive TLR  
ISM2005 positive TLR  
MDD1009 positive TLR  
Phase 3 programs in planning

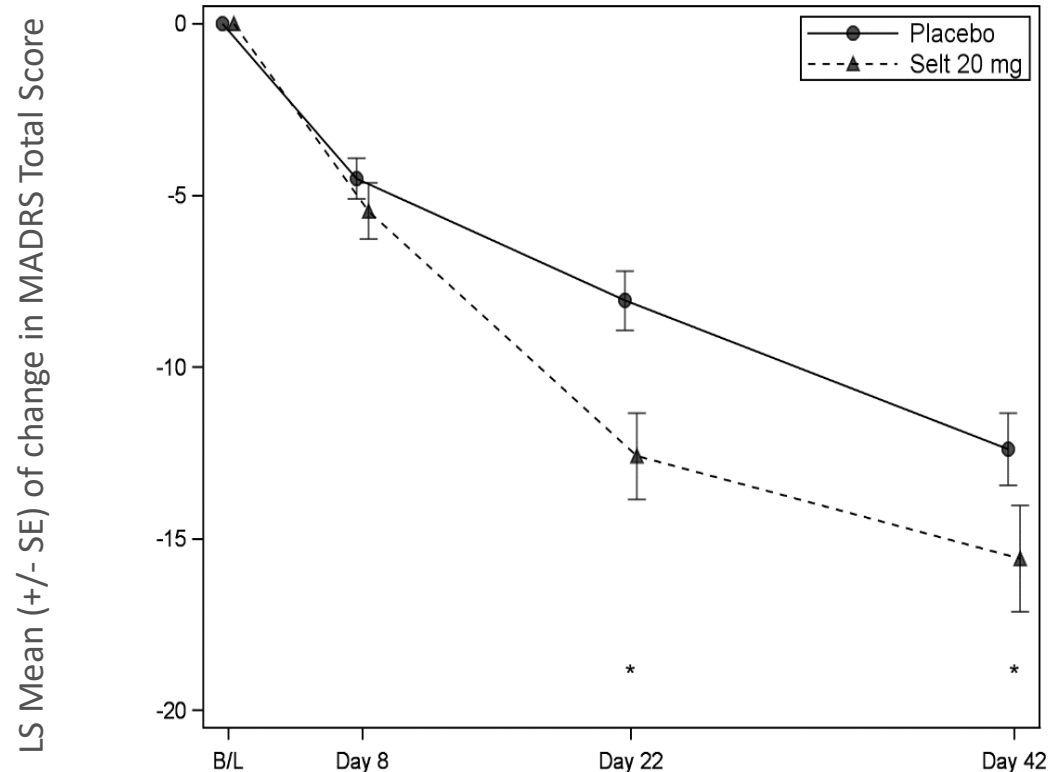
A co-development/co-commercialization program with



# Seltorexant (MIN-202): Phase 2b MDD2001 trial design and key results

## First MDD trial initiated Sep 2017 (clinicaltrials.gov: NCT03227224)

- Double-blind, randomized, parallel-group, placebo-controlled adaptive dose-finding study
- 4-week screening, 6-week double-blind treatment, and 2-week follow-up
- 287 MDD patients, not responding adequately to SSRIs and SNRIs, enrolled at 84 clinical sites in the US, Europe, Russia, and Japan
  - Safety and tolerability and dose-response and efficacy for up to 3 doses of seltorexant (10mg, 20mg & 40mg)



- Seltorexant 20mg showed a statistically significant improvement in the MADRS score compared to placebo
- Improvement is more significant in patients with insomnia as compared to patients without insomnia
- Seltorexant was well tolerated with an adverse events rate similar to that of placebo

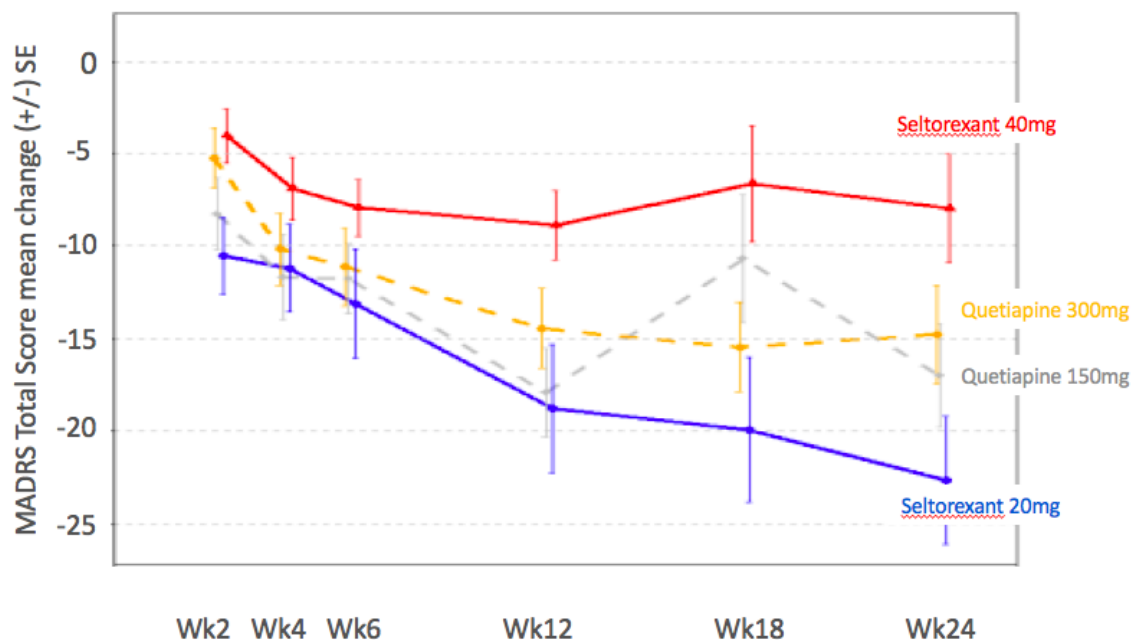
Source: Clinical Study Report, data on file.

# Seltorexant (MIN-202): Phase 2 MDD2002 trial design and key results

## Second MDD trial initiated Dec 2017 (clinicaltrials.gov: NCT03321526)

- Double-blind, randomized, randomized, flexible-dose parallel-group study
- 4-week screening, 6-month double-blind treatment, and 2-week follow-up
- 102 MDD patients, not responding adequately to SSRIs and SNRIs, enrolled at clinical sites in the US, Europe, Russia, and Japan
  - Assess the efficacy of flexibly dosed seltorexant compared with flexibly dosed quetiapine as adjunctive therapy to baseline antidepressant therapy (either an SSRI or SNRI) in delaying time to all-cause discontinuation of study drug over a 6-month treatment period

MADRS Total Score change over time by modal dose



- **20 mg dose** of seltorexant demonstrated a larger improvement at week 24 in the MADRS (-22.7 points) than patients in other groups
- As seen in the previous MDD trial (MDD2001), subjects with **insomnia** (Severity Index  $\geq 15$ ) who received the 20 mg dose of seltorexant showed greatest improvement

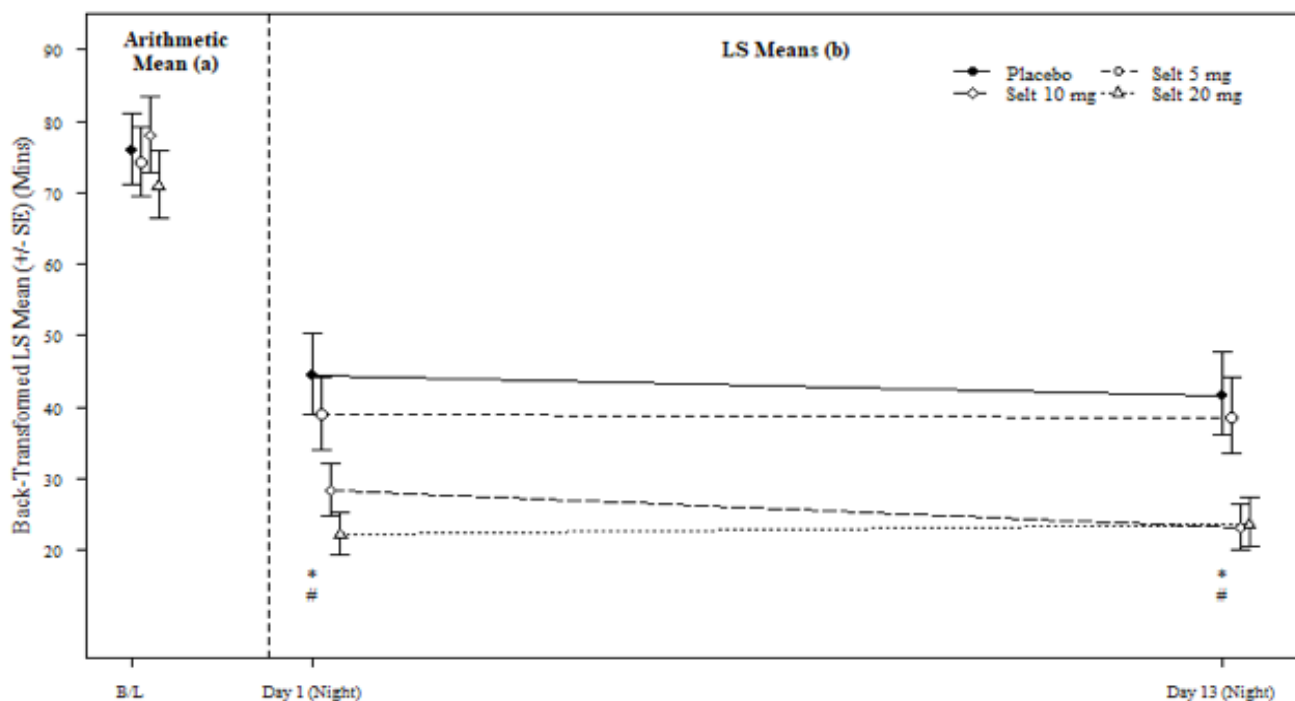
Source: Clinical Study Report, data on file.



# Seltorexant (MIN-202): Phase 2b ISM2005 trial design and key results

## Insomnia trial initiated Dec 2017 (clinicaltrials.gov: NCT03375203)

- Double-blind, randomized, parallel-group, active- and placebo-controlled adaptive dose-finding study
- Up to 61-day duration, including screening and follow-up
- 365 patients with a diagnosis of insomnia enrolled at 56 clinical sites in the US, Europe and Japan (~70 in each group)
- Efficacy and safety analyzed in both adults and elderly subjects randomized to receive placebo, seltorexant (5 mg, 10 mg and 20 mg), and zolpidem (available under Ambien brand name)



- **Primary Endpoint LPS (latency to persistent sleep) at night 1**, with adjusted 1-sided p-values <0.001
- **Mean decreases** from baseline at Night 1 in LPS were 15 minutes for placebo, 30 minutes for seltorexant 5 mg, 43 minutes for seltorexant 10 mg, and 45 minutes for seltorexant 20 mg
- Seltorexant showed superior and more sustained efficacy compared to zolpidem
- Seltorexant showed a good safety and tolerability profile in both adult and elderly patients

Source: Clinical Study Report, data on file.

## Summary

### Roluperidone in Phase 3

- Roluperidone study screening complete January 2020; TLR expected Q2 2020
- Potential for multiple indications where negative symptoms are part of the disease

### Three Phase 2b TLR readouts in 2019 support Phase 3 design

- Seltorexant MDD (two trials)
- Seltorexant insomnia
- Phase 3 development plan under discussion

### Well capitalized through multiple data read-outs in 2019/H1 2020

- \$46.0 m cash balance on December 31, 2019