Roluperidone Update

Webcast: Wednesday, April 13, 2022, at 11:00 ET

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Participants

Remy Luthringer, PhD	**Executive Chairman & CEO**
Geoff Race	**President**

Philip D. Harvey, PhD

Dr Harvey is Leonard M. Miller Professor of Psychiatry and director of the Division of Psychology at the University of Miami Miller School of Medicine, as well as a senior Research health Scientist at the Department of Veterans Affairs. He is the author of over 1,000 scientific papers and abstracts and he has written over 60 book chapters. He is a widely cited author who was repeatedly designated by Thompson-Reuters as the being in the top 1% of all researchers in mental health in citations each year since 2010. He has received continuous funding from the US National Institute of Health since 1984. He is the Principal Investigator of the largest in-person study to date of cognition and functioning in severe mental illness, with a focus on the genomics of cognition and disability, which was funded by a $35 million dollar grant from the Department of Veterans Affairs.

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The proposed indication

Minerva is developing roluperidone as a monotherapy for patients diagnosed with schizophrenia with moderate to severe negative symptoms and stable positive symptoms

Why?

- There are no approved treatments for negative symptoms in the US

We are not developing

- another antipsychotic
- an add-on to antipsychotics treatment

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Summary of outcomes from Type C meeting held March 2nd 2022

- **Topics discussed during the meeting:**
  - Can Minerva reliably identify patients who may benefit from roluperidone as monotherapy?
  - Does roluperidone interfere with the safety and efficacy of antipsychotics when used to treat recurrence of positive symptoms?

- **Topics discussed which Minerva believes are matters of review following NDA submission:**
  - Applicability of the results of the Phase 2b (conducted in Europe) to the US population
  - Analyses of the primary endpoint results of the Phase 3 study

- **Topics agreed without further discussion:**
  - Pivotal Bioequivalence study adequate but remains a matter of review
  - Agreed Initial Pediatric Plan (iPSP) dated November 28th 2017 remains in force

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Identification of patients with negative symptoms who may benefit from roluperidone in monotherapy

Schizophrenia is a heterogeneous condition: “One size therapy does not fit all”

- **Schizophrenia is a heterogeneous syndrome in which some patients manifest:**
  - A single episode of psychosis
  - Infrequent, intermittent and self-limiting episodes of psychosis while on or off antipsychotic medication
  - Continuous but residual or low-level symptoms of psychosis
  - No or limited psychosis in older patient groups in whom positive symptoms have ‘burnt out’
  - Each of these courses are commonly accompanied by social disability mostly caused by negative symptoms

- **Patients consequently have diverse treatment needs**

- **Antipsychotics are not for every patient**
  - Around 40% of patients with schizophrenia are unable to tolerate antipsychotics (Perkins 2008; Czobar 2015) or discontinue treatment on their own
  - Occasionally, antipsychotics may improve negative symptoms indirectly but often have a deleterious impact on negative symptoms (Carpenter 2017)
  - Antipsychotic discontinuation studies have suggested that a substantial proportion of patients do not relapse after discontinuation of treatment (e.g. HAMLETT Study, Begemann 2020)

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Can Minerva reliably identify patients who do not need antipsychotics?

- **In the Phase 2b and Phase 3 studies Minerva enrolled participants from a subgroup of patients with moderate to severe negative symptoms of schizophrenia who:**
  - Are readily identifiable by clinicians
  - Have been identified and enrolled by other sponsors and investigators in academia in their clinical trials (e.g. PDE10 inhibitors)
  - Have been studied in detail for 30 years and conceptualized as having primary negative symptoms (e.g. Kirkpatrick 2021)
  - Can be clearly characterized in a prescribing label

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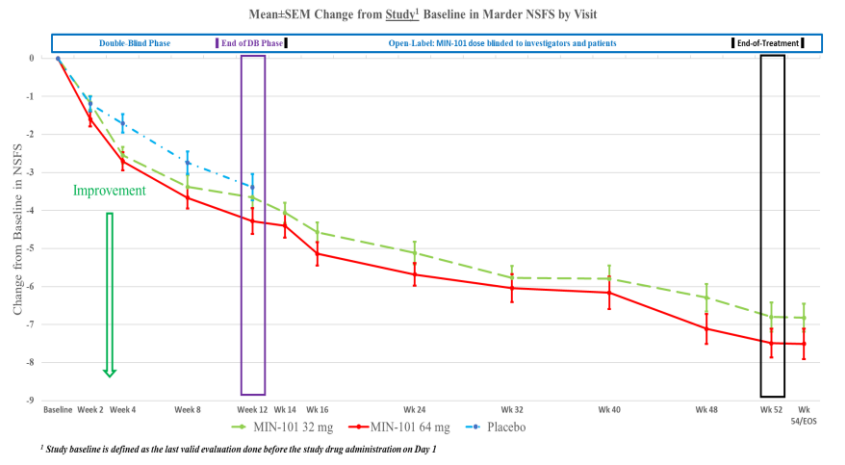
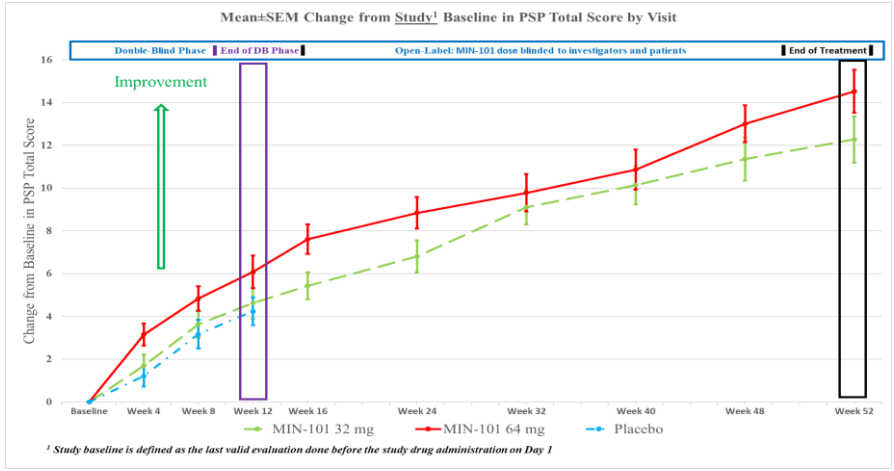
This patient sub group improved in all key efficacy parameters: Phase 3 Double-Blind & Open-Label Extension – Study Baseline

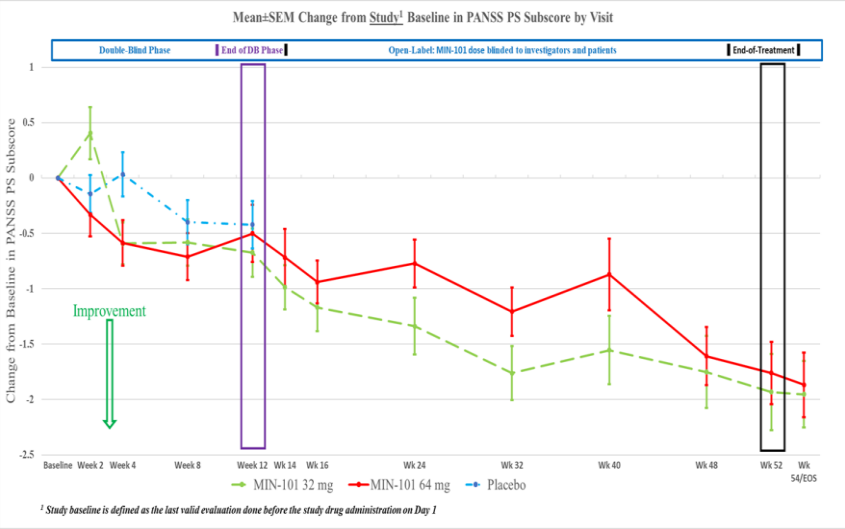
PANSS MARDER Negative Score (NSFS) (Primary Endpoint)



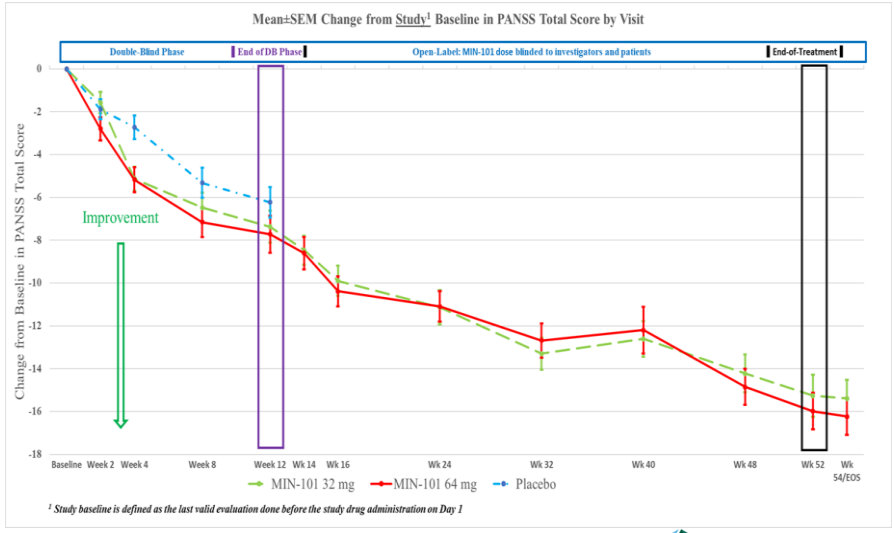
PSP Total Score (Key secondary endpoint)



PANSS Positive Symptoms Score



PANSS Total Score



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Does roluperidone improve negative symptoms at the expense of increased relapse?

Relapse* rate in the Phase 3 Double-Blind Phase and Open-Label Extension

Study Phase		Placebo (N=172)		MIN-101 32 mg (N=170)	MIN-101 64 mg (N=171)
Double-Blind	# of Patients	8 (4.7%)		18 (10.6%)	9 (5.3%)
	Mean±SEM Days to Relapse	79.8±0.91		68.5±1.35	80.2±1.13
Open-Label	Treatment	MIN-101 32 mg (N=59)	MIN-101 64 mg (N=63)	MIN-101 32 mg (N=107)	MIN-101 64 mg (N=104)
	# of Patients	6 (10.2%)	0 (0%)	9 (8.4%)	10 (9.6%)
	Mean±SEM Days to Relapse	253.6±6.98	-	232.4±4.86	186.7±3.67

Over the total study period (one year duration) the overall relapse rate was 11.7% which is lower than the approx. 25%[1] relapse rate in trials randomized to antipsychotics for the same period of time

** Relapse is defined as worsening of schizophrenia symptoms that lead to permanent discontinuation from the study*

Reference 1. Arato et al, 2002; Leucht et al 2012; Durgan et al 2016.

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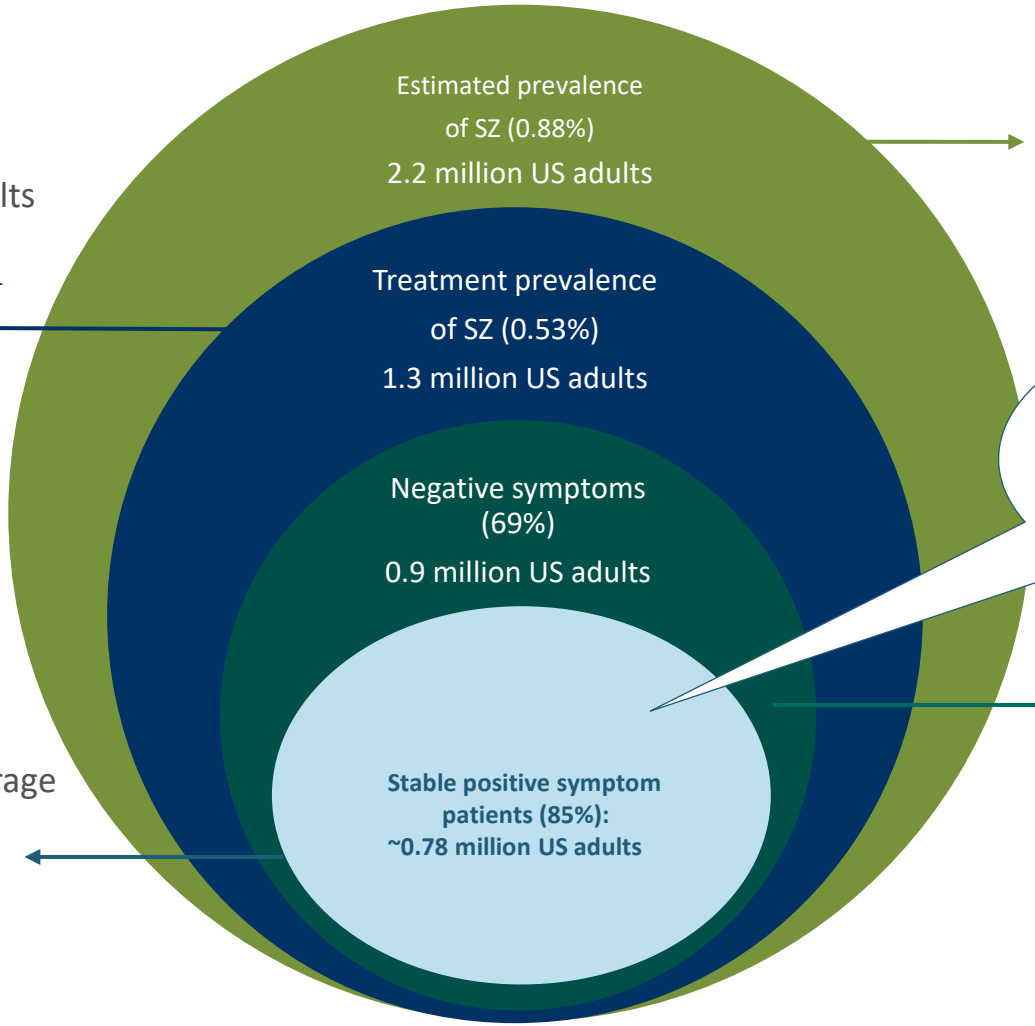
Significant unmet medical need: large patient group and currently no approved treatments

Around 69% of patients diagnosed with schizophrenia and treated have negative symptoms



Prevalence of US adults with schizophrenia in treatment/yr: **0.53%**[1]

Schizophrenia.com: 2.2 million patients in US

Phase 3 enrolled population is representative of ~780,000 patients in the US

69% of patients have negative symptoms: ≈42%[2,3] predominant/ prominent symptoms; ≈27%[4] mild symptoms

15%[2,3] weighted-average 6-month relapse rate among patients with varying severity of 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

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Does treatment with roluperidone interfere with the safety and efficacy of antipsychotics?

Prospective labeling is intended to specifically exclude adjunctive treatment with antipsychotics

- **Roluperidone is anticipated to be prescribed only for patients who:**
  - Manifest significant negative symptoms (anhedonia, amotivation, or asociality)
  - Absent or minimal agitation
  - No substance use disorder
  - Stable positive symptoms
- **Concurrent use of roluperidone and an antipsychotic has not been evaluated. It is anticipated that if a patient using roluperidone has a clinically significant exacerbation of positive psychotic symptoms, or symptoms suspected to predict impending relapse, the prescriber should:**
  - Stop roluperidone
  - Prescribe antipsychotic treatment
  - Continue antipsychotic treatment until remission or amelioration of positive symptoms
- **Resumption of treatment with roluperidone should be considered upon symptoms stabilization**

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Did roluperidone interfere with the efficacy of antipsychotics in Minerva's studies?

Table 1:
Median Time (Days) to Symptom Resolution by Treatment Group (Phase 2b and Phase 3) after Study Drug is Withdrawn and Patients are Treated with Antipsychotics

	Double-Blind Phase		
Parameter	Placebo	Roluperidone 32 mg	Roluperidone 64 mg
No. of patients reporting SAEs	**6**	**13**	**5**
Median Days to Resolution	**23**	**16**	**18**

Table 1 (additional data submitted to the FDA post Type C meeting):
Number of patients reporting schizophrenia symptoms worsening and the median time (in days) to recovery/resolution. During the double-blind phase of the combined 2 trials, the median times to recovery in subjects on placebo, roluperidone 32 mg, and roluperidone 64 mg were 23 days, 16 days, and 18 days, respectively.

Conclusion:
In summary, the median time to resolution of symptom worsening was comparable irrespective of the treatment received during the double-blind phase of the 2 studies. The time range of symptoms improvement by antipsychotics reported above is consistent with the range reported in the literature (Agid et al 2004). These data demonstrate that the efficacy of antipsychotics was not diminished or impacted by exposure to roluperidone.

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Potential Route to NDA

- **Finalization of the roluperidone NDA package is estimated to be complete summer 2022, including further analyses to support topics discussed with FDA;**

1. **Demonstrate that patients who would benefit from roluperidone can be reliably identified and described**
2. **Discuss a clear label to assist prescribers to define the patient sub-group**
3. **Discuss a treatment regimen in order to identify and manage recurrence of positive symptoms**
4. **Provide data showing roluperidone does not interfere with the safety and efficacy of antipsychotics in a rescue setting**

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Q&A