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A Study of roluperidone coadministered with olanzapine in patients with negative symptoms (NS) of schizophrenia

An open-label safety trial

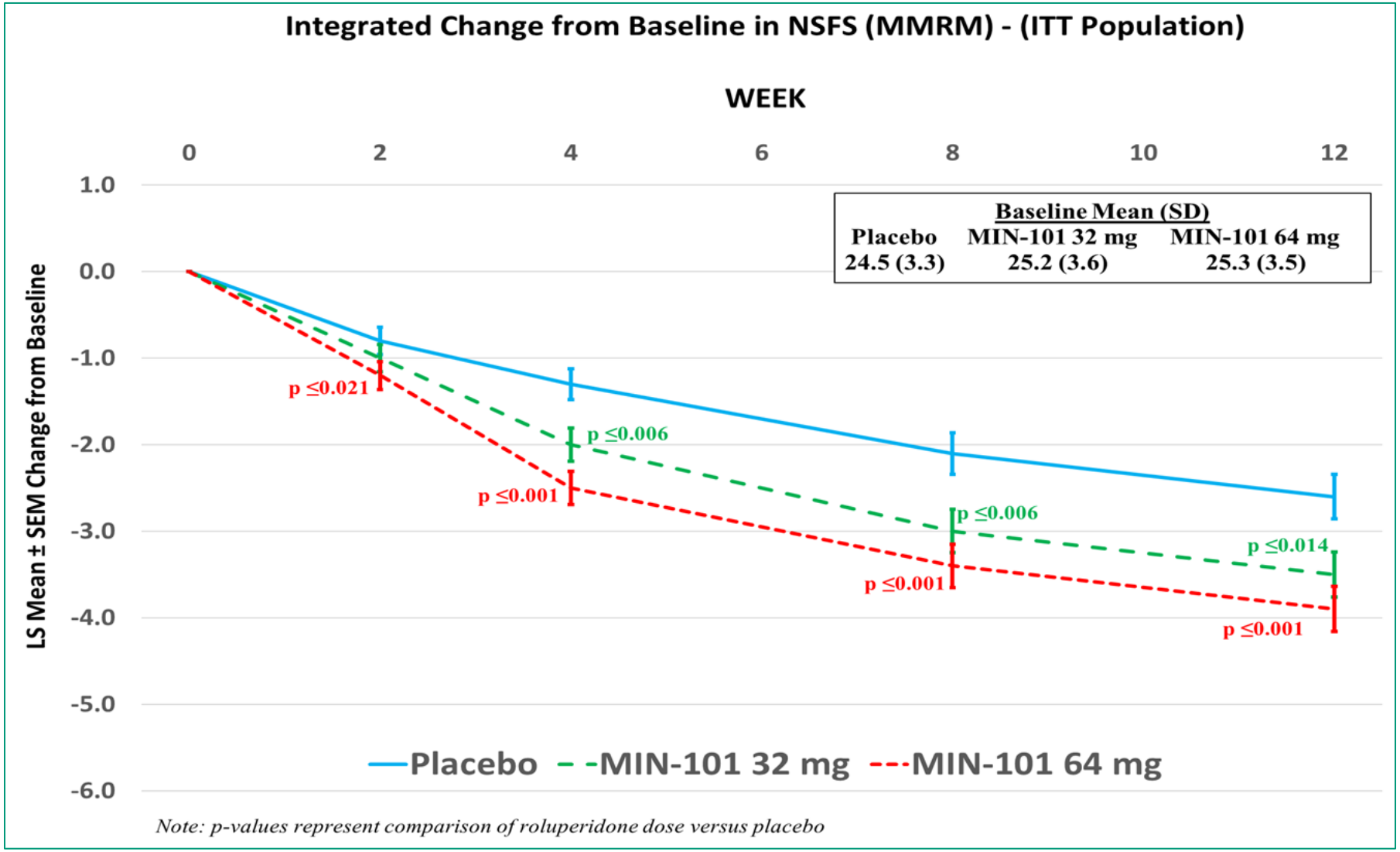
Michael Davidson MD
CMO Minerva Neurosciences

Roluperidone

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

- Specific Affinity for 5-HT2A, σ 2, and σ 1-adrenergic receptors
- No affinity (>1000 nM) for other receptors including dopaminergic, muscarinic, cholinergic and histaminergic receptors
- **No direct Dopamine binding, unlike most (or all) available antipsychotics**
- The behavioural pharmacology package is consistent with an antagonistic effect for Sigma2 and 5-HT2A receptors
- Partial evidence of therapeutic contribution of alpha-1 activity in terms of efficacy and better safety profile

Roluperidone Monotherapy: NSFS Integrated Analysis from Studies C03 & C07



ES=0.26

ES=0.37

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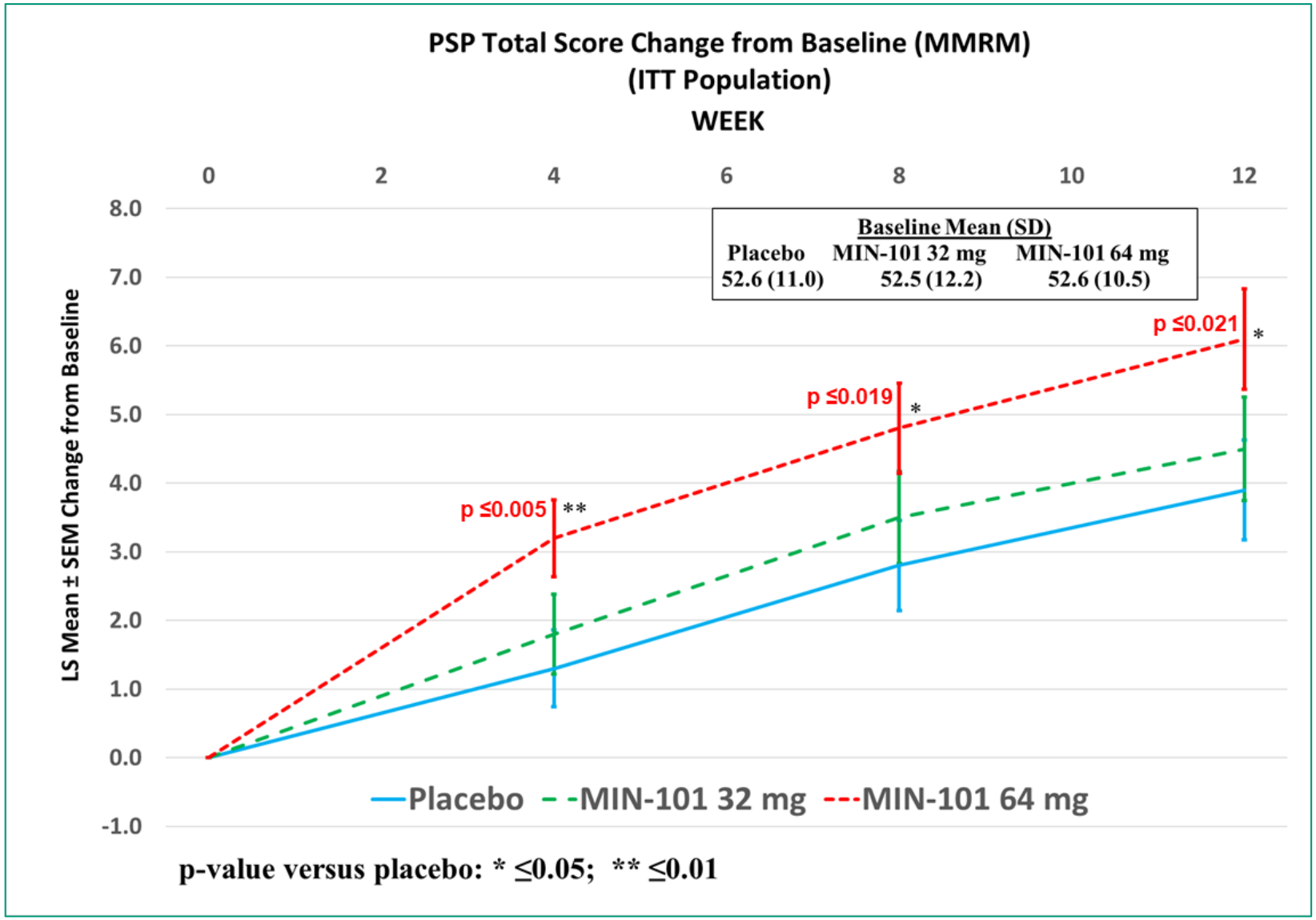
Roluperidone Monotherapy: Study C07: Significant Improvement in Functioning (PSP), the Sole Key Secondary Endpoint

The Personal Social Performance (PSP) scale assesses functioning across four dimensions:
(socially useful activities, personal and social relationships, self-care, disturbing and aggressive behaviors)



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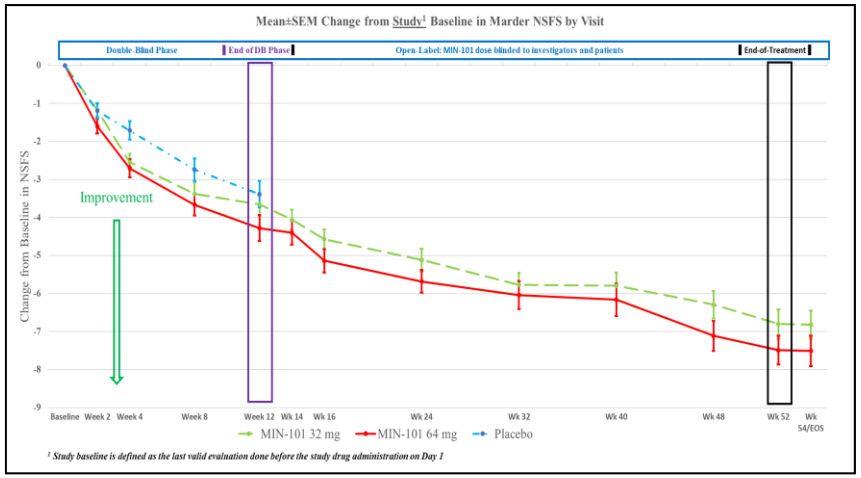
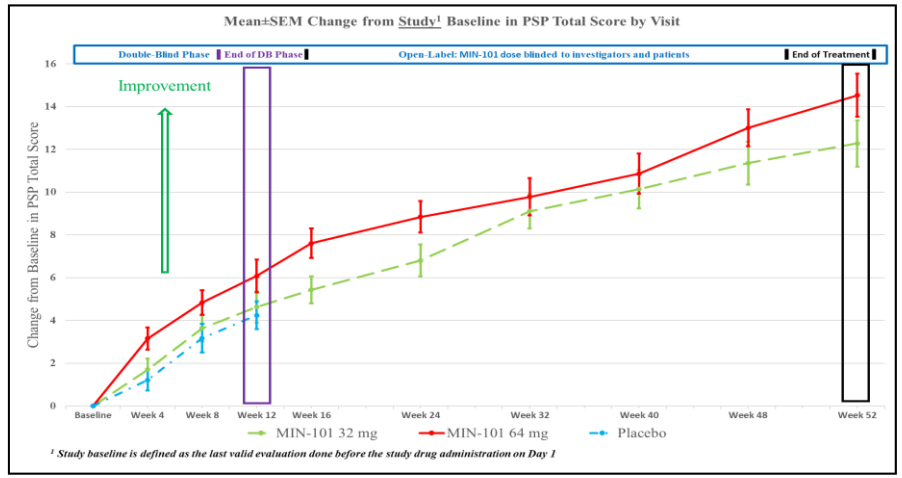
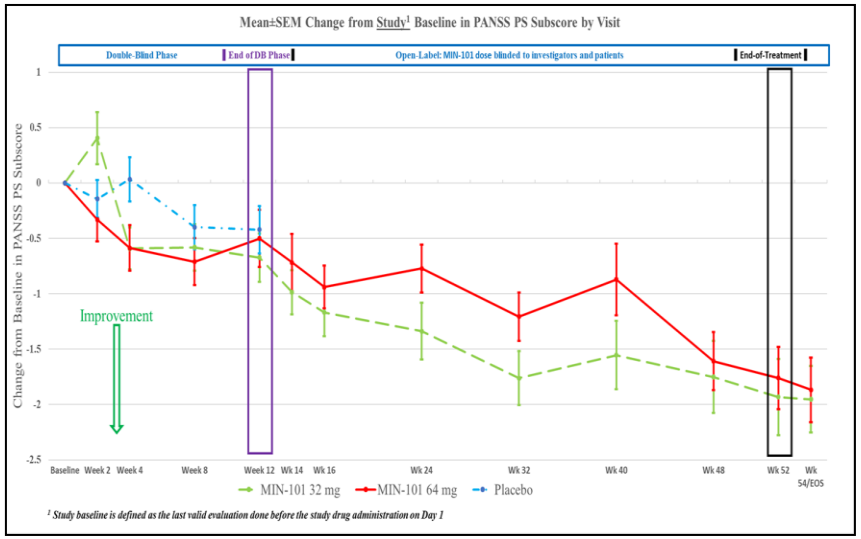
Roluperidone Monotherapy: Study C07 with 9-month Extension
Improvement in All Key Efficacy Parameters

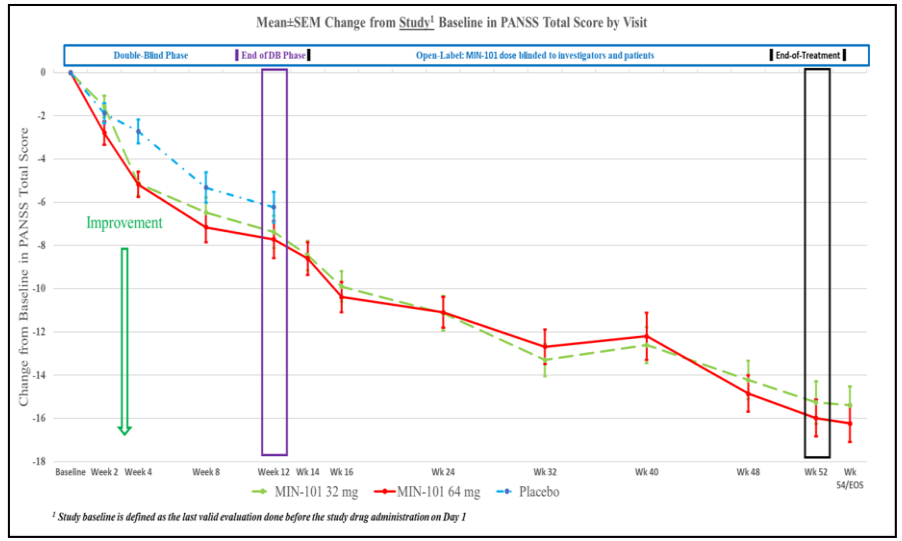
PANSS MARDER Negative Score (NSFS) (Primary Endpoint)



PSP Total Score (Key secondary endpoint)







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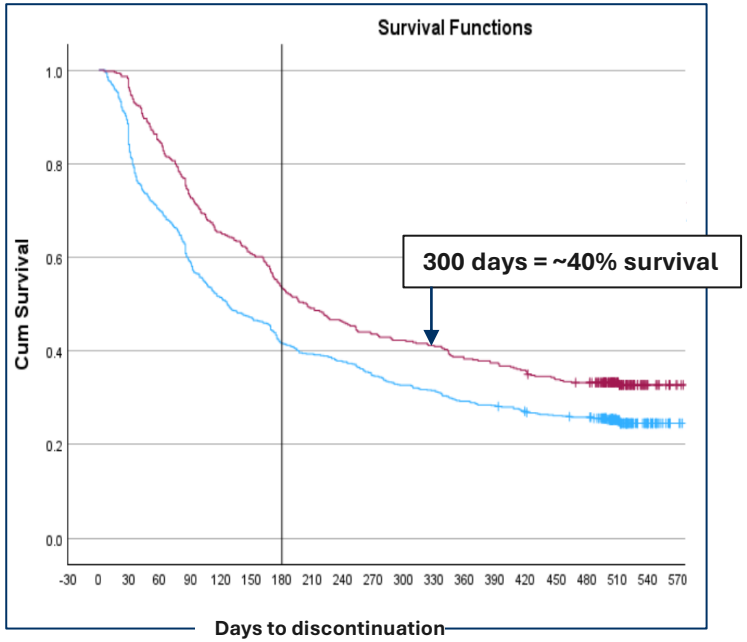
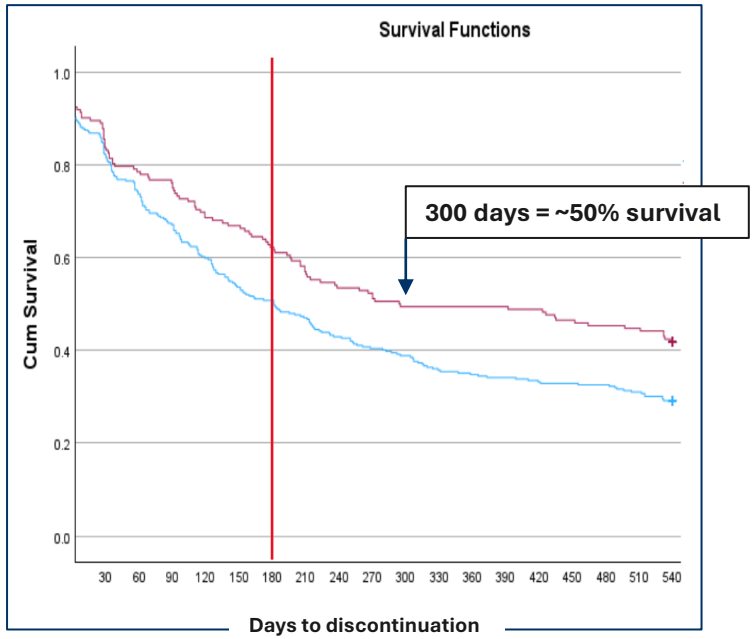
Independent Confirmation that Patients with Moderate to Severe NS (Similar to Patients Included in the Roluperidone Trials) Can Maintain Remission in Absence of Rx with Antipsychotics

CATIE



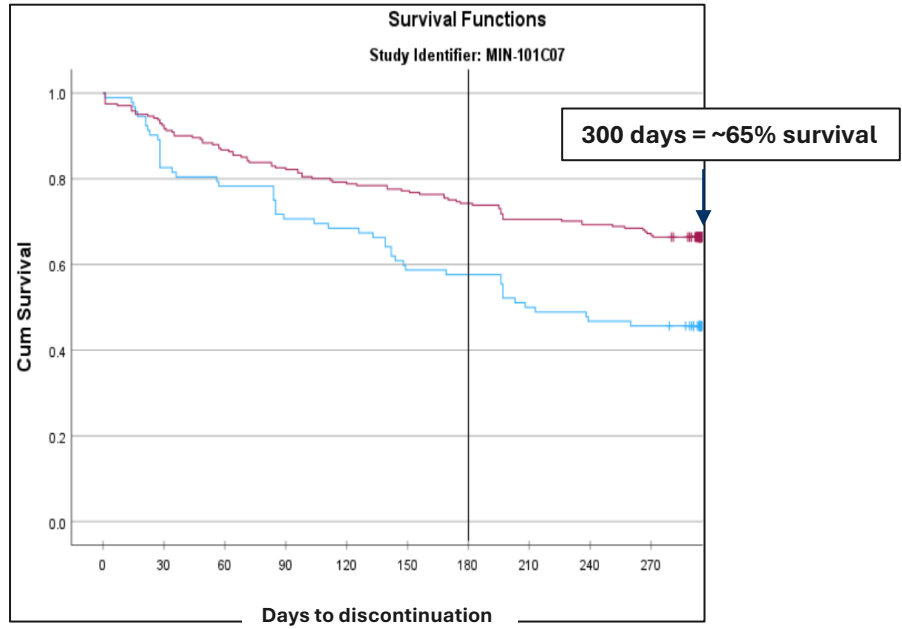
PANSS negative >20 and low agitation at baseline = red line (n=454) and the remainder of patients = blue line (n=880)

EULAST



PANSS negative >20 and low agitation at baseline = red line (n=172) and the remainder of patients = blue line (n=319)

MINERVA TRIALS



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Roluperidone is being developed for monotherapy treatment of NS

- Roluperidone is being developed as a monotherapy - and not as an add-on to an antipsychotic drug - because we believe the sub-population identified may be able to maintain long periods of psychosis remission without antipsychotic maintenance treatment

    - roluperidone has $5HT_2$ blocking properties which may prevent psychotic exacerbation
    - some antipsychotics may increase negative symptoms (secondary negative symptoms) and therefore concomitant treatment may block the benefits of roluperidone (treatment of primary negative symptoms)

- This clinical trial was designed to investigate the pharmacodynamic, pharmacokinetic effects and safety of concomitant therapy of roluperidone with an established and widely used antipsychotic

Roluperidone + Olanzapine inclusion/exclusion criteria

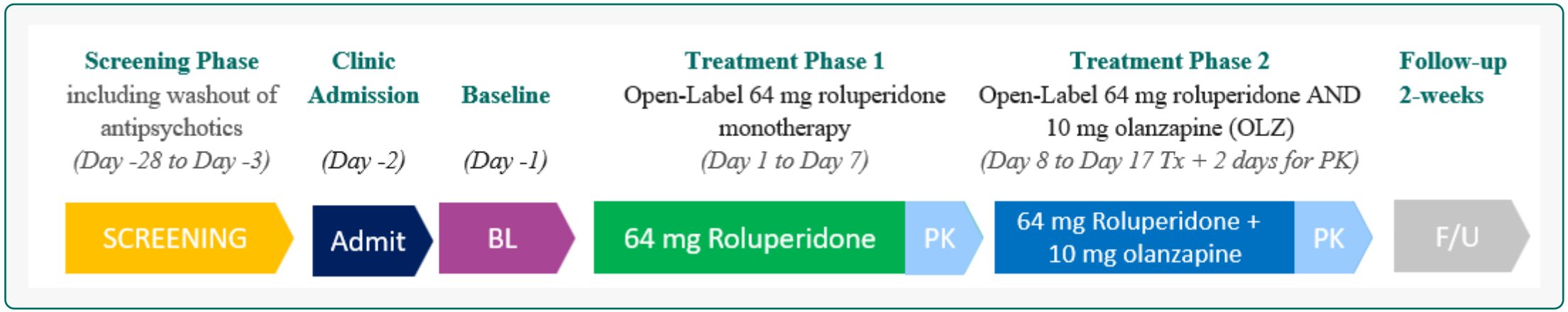
Inclusion

- Outpatients DSM schizophrenia by MINI for at least 1 year
- Aged 18-55, and symptomatically stable > 3 months
- PANSS > 20 on the original NS subscale (Sum of N1+N2+N3+N4+N5+N6+N7)
- Normal metabolizer for CYP2D6, defined as a subject that had at least 1 functional allele

Exclusion

- Subject with PANSS item score of > 4 on:
  - P4 Excitement/Hyperactivity
  - P6 Suspiciousness/persecution
  - P7 Hostility
  - G8 Uncooperativeness
  - G14 Poor impulse control
- Subject with a clinically significant ECG abnormality, including QT interval > 430 msec for males and > 450 msec for females or with any risk factors for Torsades de Pointes

Roluperidone + Olanzapine trial design



- Discontinuation of psychotropics at least 2 days prior to the start of Rx (Day 1)
- Inpatient on Day -2 for Baseline visit on Day -1
- Discharged from the clinic at least 48 hours after the last administration of the study drugs
- Rescue medication for agitation (lorazepam) and sleep (zolpidem) is allowed
- PK and EEG daily
- PANSS, CGI-S, BARS, AIMS, CDSS at baseline, day 7, and day 17

Subject Disposition

Table 4-1: Subject Disposition, Full Set

	Overall (N=43) n (%)	Treatment Phase 1 (Roluperidone 64 mg) (N=17) n (%)	Treatment Phase 2 (Roluperidone 64 mg + Olanzapine 10 mg) (N=15) n (%)
Number of subjects screened	43 (100.0)		
Number of subjects who met all eligibility criteria	23 (53.5)		
Number of subjects who completed study	13 (30.2)		
Number of subjects who discontinued study	30 (69.8)	2 (11.8)	2 (13.3)
Primary reasons for study discontinuation			
Adverse event	1 (2.3)	1 (5.9)	0
Protocol deviation	1 (2.3)	0	1 (6.7)
Stopping criterion	0	0	0
Screen failure	22 (51.2)	0	0
Withdrew consent	3 (7.0)	1 (5.9)	1 (6.7)
Other	3 (7.0)	0	0
Full Set[a]	43 (100.0)	17 (100.0)	15 (100.0)
Safety Set[a]	17 (39.5)	17 (100.0)	15 (100.0)
PK Set[a]	12 (27.9)	12 (70.6)	12 (80.0)
PK Completer Set[a]	11 (25.6)	11 (64.7)	11 (73.3)

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Pharmacokinetics Data

- The PK parameters on day 7 of Roluperidone administered alone, were consistent with those reported in previous clinical studies and the accumulation observed for Cmax and AUC 0-24 were consistent with those observed in a multi-dosing study in healthy subjects.

- The PK profile of olanzapine when added to Roluperidone was consistent with that reported in the olanzapine (Zyprexa®) label and previous studies of olanzapine PK.

- The coadministration of olanzapine with roluperidone at steady state resulted in statistically significant, but not clinically relevant increases in roluperidone exposure.

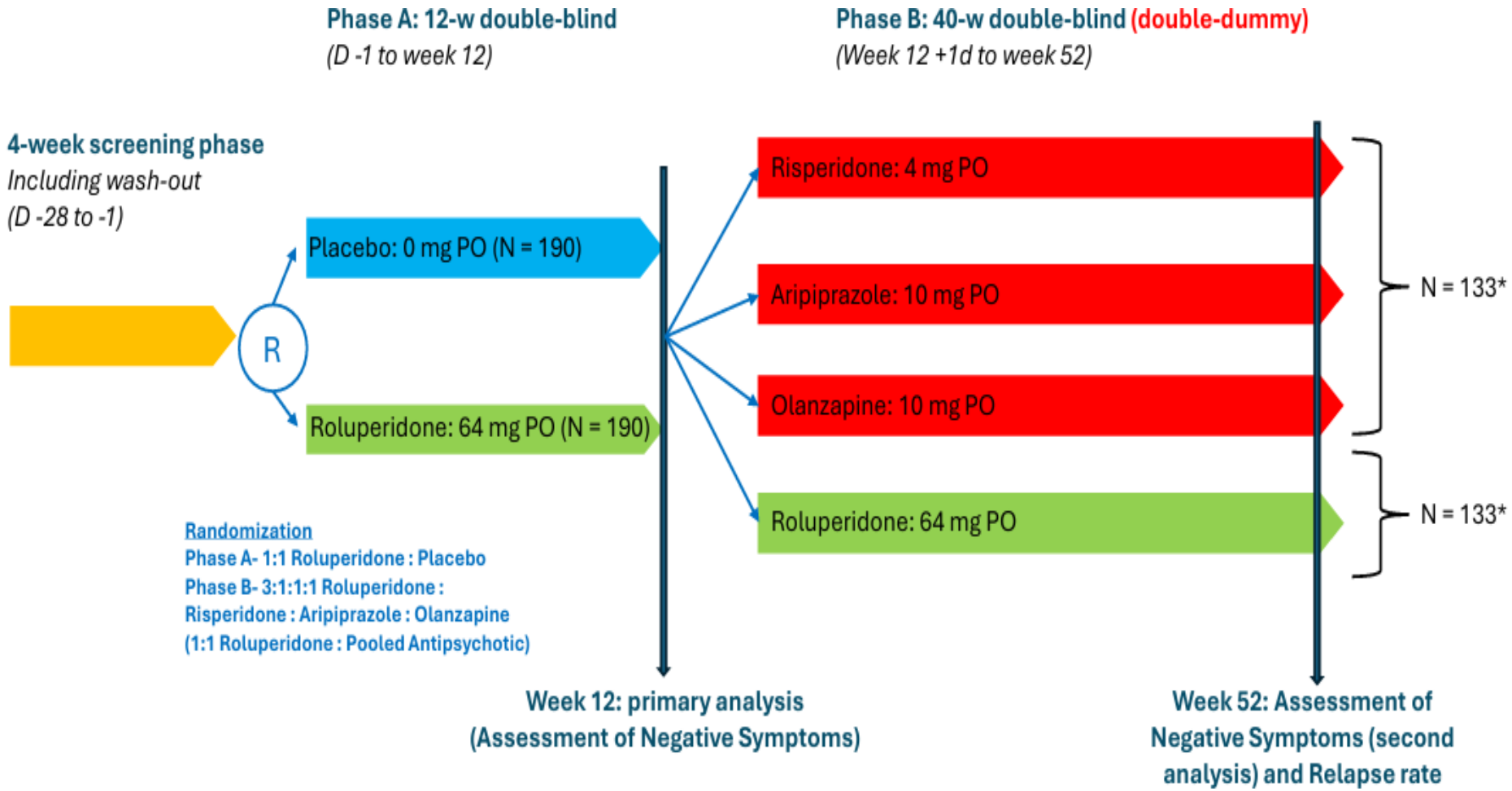
Conclusions

- No clinically significant adverse effects, no change in either drug tolerability
- No clinically significant changes in EKG
- No meaningful pharmacodynamic changes
- No clinically relevant increases in exposure to roluperidone
- Due to the short study duration, no changes in the disease state were expected

Confirmatory Study (C19) Planned Initiation in Q2 2026

Phase A: 12-Week, Primary efficacy of roluperidone compared to placebo in improving NS measured by the Marder Negative Symptoms Factor Scores (NSFS) and main secondary Personal and Social Performance (PSP) Treatment Satisfaction Scale (TSS-3) completed the by the subject and by the caregiver

Phase B: 40-Week, Double-Dummy, Antipsychotic-Controlled Treatment Phase evaluating the safety and tolerability of roluperidone and antipsychotics and assess the number of subjects who relapse in the roluperidone group versus the antipsychotics



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Thank you!