MIN-101: A Drug in Development for the Treatment of Negative Symptoms in Schizophrenia

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Background: MIN-101 is a novel cyclic amido derivative, with high affinities for sigma$_2$ and 5-HT$_{2A}$ receptors. Although MIN-101 has no affinities for DA receptors it is very probable that sigma$_2$ receptors are implicated in the modulation of DA and glutamatergic pathways.
Methods: This multi-national Phase 2b trial enrolled 244 patients diagnosed with schizophrenia who were symptomatically stable for ≥ 3 months prior to entering the trial and had scores ≥ 20 on the negative scale of the PANSS. Patients were randomized to monotherapy with MIN-101 32 mg/day, MIN-101 64 mg/day, or placebo for 12 weeks, after which all patients received active drug for 24 additional weeks. Primary endpoint was the PANSS negative symptoms 5 factor sub-score.
Results: Statistically significant reduction in the primary endpoint score was demonstrated for MIN-101 32 mg and 64 mg compared to placebo (p ≤ 0.022, ES=0.45 and p≤ 0.003, ES=0.58, respectively). Similar effects were demonstrated on most of the secondary outcomes reflecting general psychopathology, personal and social performance, and mood. Patients continued to improve during the 24-week open label phase of the trial. The significant effects on negative symptoms were maintained after controlling for baseline depression. There were no statistically significant differences in PANSS positive subscale scores between MIN-101 and placebo and no change in EPS or metabolic parameters.
Conclusions: MIN-101 demonstrated statistically significant efficacy in reducing negative symptoms and good tolerability in stable schizophrenia patients with negative symptoms. The effect was not secondary to improvement in other symptoms.
Study registration: EudraCT Number: 2014-004878-42

Background:

- MIN-101 is a novel cyclic amido derivative, which has high affinities for sigma$_2$ and 5-HT$_{2A}$ receptors. Although MIN-101 has no affinities for DA receptors it is very probable that sigma$_2$ receptors are implicated in the modulation of DA and glutamatergic pathways.

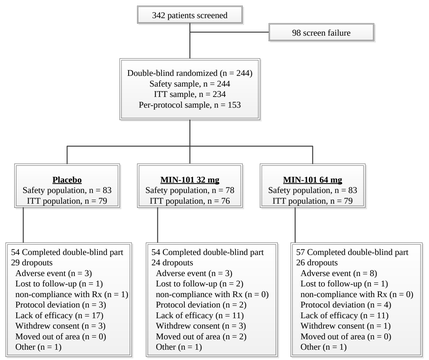
Objectives:

- Compare the efficacy, safety, and tolerability of MIN-101 to placebo in treating negative symptoms in stable patients with schizophrenia.

Methods:

- Inclusion criteria: DSM-5 schizophrenia confirmed by MINI, symptomatically stable, manifesting negative symptoms over the 3 months prior, baseline score ≥ 20 on the 7 item negative symptoms scale of the PANSS and scores < 4 on the PANSS: excitement, hyperactivity, hostility, suspiciousness, uncooperativeness, and poor impulse control.
- Exclusion criteria: Personal or familial history of long QT syndrome, a QTc (Fridericia-corrected) > 430 msec. for males and > 450 msec. for females or if they were poor or intermediate metabolizers for P450 CYP2D6, as determined by genotyping.
- **Study design**
  - Patients were withdrawn from depot antipsychotics for ≥ 1 month and from all psychotropic drugs for ≥ 3 days prior to randomization.
  - Patients were randomized to oral MIN-101 32 mg/day, 64 mg/day or placebo in a 1:1:1 ratio.
  - Patients were hospitalized for at least 3 days prior to randomization. Two days after randomization patients could be discharged or continue as inpatients at discretion of investigator.
  - No psychotropic medications were allowed during the 12-week trial duration except for rescue medications given for insomnia or agitation (oral lorazepam, zolpidem, or injectable sodium amytal).
  - After the 12 week double blind trial patients could continue to receive the same dose of MIN-101 or be switched from placebo to MIN-101 for 24 additional weeks.
  - Assessments for efficacy and safety were conducted at baseline before the first dose of medication and at weeks 2, 4, 8 and 12 or upon premature termination.
- **Outcome measures**
  - Primary outcome was the negative factor score of the PANSS from the pentagonal structure model (White et al 1997).
  - Secondary outcomes: PANSS total and positive, negative and general psychopathology scales, BNSS scores, CGI-S CGI-I, CDSS and PSP.
  - Safety was evaluated by monitoring the frequency, severity and timing of adverse events, clinical laboratory test results, 12-lead EKG, vital signs body weight, S-STS and AIMS.

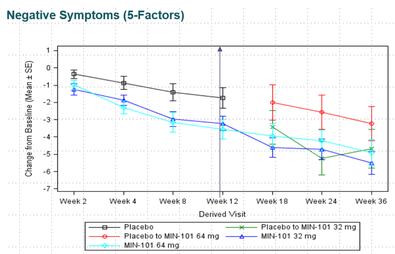
Flow Chart 1: Patient Disposition

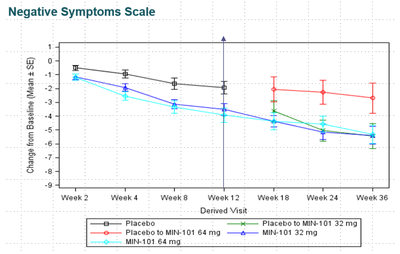


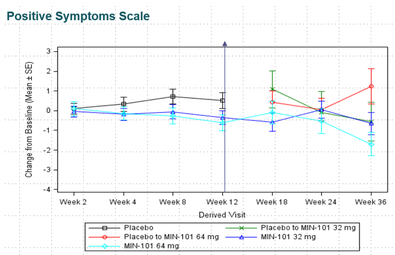
Summary of Efficacy Endpoints, MIN-101 Compared to Placebo

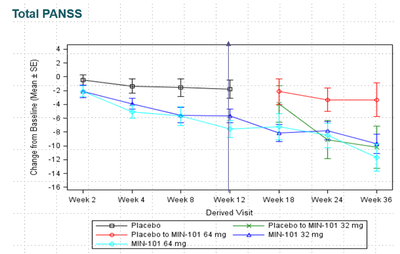
	Change from Baseline (Least Square Means)			p-value		Effect Size	
		MIN-101		MIN-101 versus Placebo		MIN-101 versus Placebo	
	Placebo	32 mg	64 mg	32 mg	64 mg	32 mg	64 mg
Primary Objective							
5-Factor Negative Score	-1.49	-3.06	-3.50	0.0213	0.0030	0.45	0.58
Secondary Objectives							
PANSS Total 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 Positive Score	1.00	0.41	0.34	0.3388	0.2832	0.18	0.21
3-Factor General Psychopathology Score	0.00	-1.05	-2.56	0.2270	**0.0032**	0.23	0.57
5-Factor Positive Score	0.31	0.55	-0.25	0.5933	0.1926	-0.10	0.25
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
5-Factor Autistic Preoccupation Score	-0.66	-0.85	-1.20	0.7004	0.2586	0.08	0.22
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
Brief Assessment of Cognition in Schizophrenia	11.94	23.69	14.90	**0.0388**	0.5947	0.40	0.10
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









Results:

- **Primary endpoint: statistically significant reduction on PANSS negative factor (pentagonal) for both MIN-101 32 mg and 64 mg compared to placebo (p ≤ 0.022, ES=0.45 and p≤ 0.003, ES=0.58, respectively).**
- Statistically significant superiority of MIN-101 over placebo on most secondary outcomes such as the "classic" PANSS negative and total scores, CGI, CGI-S, BNSS, PSP, and CDSS.
- No statistically significant differences between the 3 treatment groups on PANSS positive symptoms scores at week 12 and no significant worsening in these symptoms compared to baseline.
- Effects remained after controlling for improvement on depression.
- Change from baseline to endpoint on negative factor and negative scale and CDSS showed low correlations (r=.26 and r=.22) supporting the conclusion that improvement in negative symptoms in this study was not synonymous with improvement on mood.
- ANCOVA analysis showed that even after controlling for changes on the CDSS significant differences on changes in negative symptoms remained (negative factor 32 mg p=.12, 64 mg p=.02; negative subscale 32 mg p=.01, 64 mg; p=.002).
- Improvement on negative symptoms was greatest among younger patients reaching an ES=1.3 in patients younger than 33 years of age.

Safety and tolerability. No weight gain or clinically significant changes from baseline in vital signs, prolactin, routine laboratory values, and EPS ratings expressed by AIMS scores. Two patients on 64 mg were discontinued prematurely due to cardiac related AE, one for T waves inversion and a second for sinus bradycardia and QTcF interval prolongation beyond a-priori established criteria.

Discussion:

- This is the first report of a drug with specific therapeutic effects on negative symptoms in schizophrenia.
- The improvement was not secondary to improvement in others symptoms or EPS.
- ES of the improvement of negative symptoms on MIN-101 compared to placebo was similar to improvement of currently marketed drugs to treat psychotic symptoms and/or many drugs utilized to treat chronic diseases in general medicine (Leucht et 2012).
- Since phenomena similar to negative symptoms often described as apathy or depression are manifest in many psychiatric disorders and in brain degenerative disorders such as Alzheimer's disease and Parkinson's disease, future trials should investigate the drug's effects in these patient populations.

References
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Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. British Journal of Psychiatry. 2012;200(2):97-106.

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