Glycine transporter type 1 (GlyT1) inhibitor RG1678: results of the proof-of-concept study for the treatment of negative symptoms in schizophrenia

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Abstract

Negative symptoms of schizophrenia are a key factor determining long-term disability associated with this disorder. Effective treatments for these symptoms are lacking. Deficient signaling through the N-methyl-D-aspartate (NMDA) receptor may underlie many signs and symptoms of schizophrenia, in particular negative symptoms. Targeting the modulatory glycine site of the NMDA receptor by reuptake inhibition of glycine offers a safe approach to enhance deficient NMDA receptor functioning.

RG1678 is a potent and noncompetitive inhibitor of glycine transporter type 1 (GlyT1), with >1000-fold selectivity for human GlyT1 versus GlyT2 and at least 300-fold greater selectivity over other targets. Preclinically, RG1678 shows efficacy in assays of NMDA receptor functioning and schizophrenia models, and increases cerebrospinal fluid glycine levels in a dose-dependent fashion.

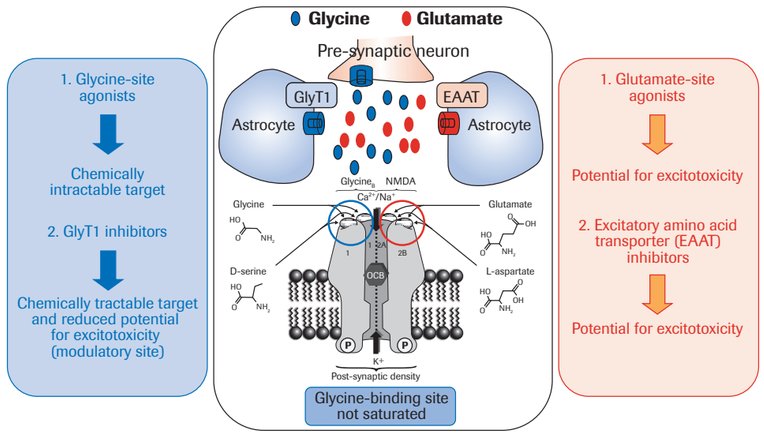
The effects of three doses (10, 30, and 60 mg) of RG1678 on negative symptoms of schizophrenia were investigated in an 8-week Phase IIb proof-of-concept study in 323 patients. Concurrently a positron emission tomography (PET) occupancy study was conducted with a novel PET ligand for GlyT1 in healthy volunteers.

Eight weeks of treatment with 10 mg/day of the glycine reuptake inhibitor (**GRI**) RG1678 resulted in a significant reduction of negative symptoms and improved functioning in schizophrenic patients with predominant negative symptoms, whereas higher doses were less effective or ineffective. RG1678 was well tolerated.

Modeling the occupancy at the glycine transporter in patients using data from a PET study in healthy volunteers indicates that occupancy <60% is sufficient for optimal efficacy consistent with results in preclinical assays.

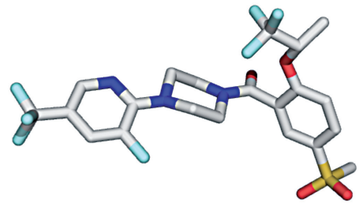
This proof-of-concept study provides clinical support for glycine reuptake inhibition and enhancement of NMDA signaling as a therapeutic approach for negative symptoms in patients with schizophrenia. To our knowledge, RG1678 is the first compound in clinical development to demonstrate convincing efficacy against negative symptoms. If these findings are confirmed in Phase III trials, this agent has the potential to expand the therapeutic options for patients with schizophrenia.

NMDA receptor: modulatory strategies

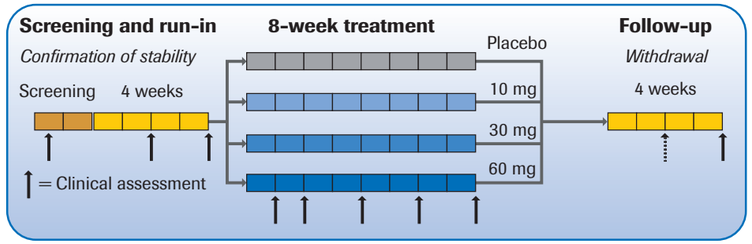


RG1678: preclinical characteristics

- [4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-((S)-2,2,2 trifluoro-1-methyl-ethoxy)-phenyl]-methanone OR RG1678
- Non-sarcosine derivative
- Potent, noncompetitive, and selective GlyT1 inhibitor (IC_{50} GlyT1=25 nM)
- More than 1000-fold selectivity for human GlyT1 versus GlyT2
- More than 700-fold selectivity versus 86 other binding sites
- At least 300-fold selectivity for GlyT1 versus 16 other enzymes/transporters



Study design: placebo-controlled, double-blind study of RG1678 as adjunct to antipsychotic treatment in patients with predominant negative symptoms



Inclusion criteria

- Total score ⩾40 for the sum of the 14 negative and disorganized thought factor score items on the Positive and Negative Syndrome Scale (PANSS)[1]
  - Patients with high negative symptoms tend to score high on disorganized thought factor
  - To mitigate against baseline inflation
- Total score <28 on the PANSS positive symptom factor score[1]
  - The scores for items P1, P3, P6, and G9 had to meet the following requirements:
    - No more than two items with a score of 4 ('moderate')
    - All of the above items with a score <5 ('moderately severe')

Efficacy measures for negative symptoms

- PANSS negative symptom factor score (NSFS)[1]
- Clinical Global Impression-Improvement (CGI-I) in Negative Symptoms[2]
- Negative symptom response rate (⩾20% change)

Additional efficacy measures

- PANSS total and other symptom factor scores[1]
- Functioning (Personal and Social Performance [PSP] scale)

1. Marder SR et al. J Clin Psychiatry 1997; 58: 538-546
2. Haro JM et al. Acta Psychiatr Scand Suppl 2003; 416: 16-23

Populations analyzed

- **Intent-to-treat (ITT):** all randomized patients who received one dose of double-blind study medication and had one post-baseline assessment
- **Modified ITT (mITT):** ITT population, excluding patients whose centre or rater failed an audit or was decertified
- **Per protocol (PP):** all randomized patients who completed 8 weeks of double-blind treatment without any major protocol violations
- **Safety:** all randomized patients who received at least one dose of double-blind study medication

		RG1678				
	Placebo	10 mg/day	30 mg/day	60 mg/day	Total	%
All randomized	81	82	81	79	323	100
ITT	77	81	77	77	312	97
mITT	74	76	73	73	296	92
PP	61	60	57	53	231	72
Safety	80	82	81	78	321	–

Demographics, ITT

		RG1678		
	Placebo (n=77)	10 mg/day (n=81)	30 mg/day (n=77)	60 mg/day (n=77)
Male, n (%)	47 (61)	57 (70)	44 (57)	52 (68)
Race, n (%)				
White	45 (58)	54 (67)	56 (73)	51 (66)
Black	17 (22)	13 (16)	9 (12)	11 (14)
Asian	11 (14)	11 (14)	9 (12)	11 (14)
Other	4 (5)	3 (3)	3 (4)	4 (5)
Age (years)[a]	39.3 (10.5)	40.5 (10.5)	40.3 (10.0)	39.5 (9.8)
Age, first symptoms (years)[a]	26.3 (9.7)	26.3 (9.0)	26.9 (9.8)	26.3 (9.5)
Paliperidone, risperidone, risperidone long-acting, n (%)	37 (48)	35 (51)	33 (43)	35 (45)
Olanzapine, n (%)	21 (28)	23 (29)	21 (28)	22 (29)
Study completion (⩾49 days) n, %	69 (85)	71 (87)	66 (82)	66 (84)

[a]Mean ± standard deviation (SD)