NEWMEDS: Challenges, Issues and Perspectives in Designing and Conducting Studies of Negative Symptoms in Schizophrenia

Florence, Italy 19 April 2012

Current recruiting trails

- 2 TMS trials
- TC-5619 – Targacept – α 7 nicotinic
- LY2140023 – Lilly -- mGlu2/3
- Rasagiline -- U Md -- irreversible inhibitor of monoamine oxidase
- oxytocin, galantamine – U Md
- RO4917838 -- Roche, Genentech -- GlyT1
- AMG 747 – Amgen Gly1

Trail Duration (weeks)

Drug	Duration
TC-5619	24
Lisdexamfetamine (completed)	>10
Rasagiline	12
Oxytocin, Galantamine	6
Pregnenolone	8
LY2140023	17
RO4917838	>24
Org 25935	12
D-serine	12
AMG 747	12

Age

Drug	Age
TC-5619	18-60
Lisdexamfetamine (completed)	18-55
Rasagiline	18-64
Oxytocin, Galantamine	18-64
Pregnenolone	21-65
LY2140023	18-65
RO4917838	>18
Org 25935	18-55
D-serine	18-65
AMG 747	18-60

Negative Symptom Instrument

Drug	Scale
TC-5619	SANS
Lisdexamfetamine (completed)	SANS
Rasagiline	SANS
Oxytocin, Galantamine	SANS
Pregnenolone	SANS
LY2140023	NSA-16
RO4917838	PANSS –neg
Org 25935	SANS
D-serine	PANSS --neg
AMG 747	NSA-16

Positive Symptom criteria

Drug	Scale
TC-5619	Yes
Lisdexamfetamine (completed)	Yes
Rasagiline	Yes
Oxytocin, Galantamine	Yes
Pregnenolone	No
LY2140023	?
RO4917838	Yes
Org 25935	Yes
D-serine	no
AMG 747	yes

Issues agreed on prior to the meeting NewMeds – April, 2012

- Subjects entered into negative symptom trials should have no fewer than two negative symptoms and at least one should be rated as moderate or greater.
- Subjects with notable extrapyramidal side effects from antipsychotic medications should be excluded.
- Scales measuring the extrapyramidal syndromes should be included in negative symptom trials.

Issues agreed on prior to the meeting (cont)

- Subjects prescribed first and/or second-generation antipsychotics should be included in negative symptom trials of co-prescribed medication (that is, medication that is added to an antipsychotic) for negative symptoms.
- Negative symptom trials should include an assessment battery to measure cognition.
- Ratings for negative symptoms should include a single global score.

Issues agreed on prior to the meeting (cont)

- Ratings for negative symptoms should include global scores for major domains such as expressiveness and apathy/asociality.
- Subjects currently treated with clozapine should not be excluded in negative symptom trials of co-medication.

Issues agreed on at the meeting

- Patients in Phase 2 proof-of-concept studies should be under the age of 65. The inclusion of substantial numbers of subjects early in their illness may be helpful in clarifying if there are age effects.
- Patients should not be excluded from negative symptom trials on the basis of a cut-off score on the Hamilton Depression Rating Scale (HDRS) or similar scales. They should be excluded for the presence of a selection of depressive symptoms that do not overlap with negative symptoms. Patients with the co-diagnosis of a Major Depressive Episode should be excluded.

Issues agreed on at the meeting

- Since negative symptoms have face validity, a functional measure should not be required as a co-primary. Functional measures, including functional capacity measures or real world functioning measures, should be included in negative symptom trials as key secondary measures.
- While subjective reports from informants should not be an essential requirement for negative symptom trials, if possible, information from informants should be included in ratings.
- A duration of at least 12 weeks is recommended for Phase 2 negative symptom trials. A duration of 6 months is preferred for Phase 3 studies.

Issues agreed on at the meeting

- Prior to entry into a negative symptoms study, subjects should demonstrate clinical stability for a period of 4 to 6 months by collection of retrospective information.
- Prior to entry, the stability of negative and positive symptoms should be confirmed prospectively for four weeks or longer.