

Workshop on Negative Symptoms
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Presentation 1

Daniel Umbricht, F. Hoffman La Roche (same presentation as given at ECNP in Paris last year)

Analysis of common beliefs in the field and how this have resulted in their project.

1) *Level of Positive Symptoms.*

Change in Negative Symptoms measured as Marder factor (0-6) NSFS tends to be greater when Positive Symptoms are lower at baseline, regardless of Negative Symptom severity (higher positive symptoms being indicative of TRS).

They have observed that to restrict Positive Sx does not bring big benefits, limits the number of eligible patients.

2) *Level of Negative Symptoms.*

(A. Kahn, Neurocog trials).

They conducted an IRT analysis of NSA in Bitopetine Phase 3 and concluded that there is no need to go with strict threshold. PANSS scores of 50 to 80 with stratification according to severity of negative symptoms was suggested. However, also noted that key avolition scores of PANSS NFSF perform better around or below mean, i.e. patients with less severe symptoms may still be enrolled. Ability to measure change NSA is better than NSFS.

3) *Restricting the number of sites and study arms.* (Agid, et al 2013)

Placebo response not surprisingly increased with increasing number of sites and study arms. From a meta-analysis on placebo response and study sites, involving 17 studies, it was concluded that placebo response was higher at those sites where patients presented higher symptoms at baseline evaluation.

In Phase 2 bitopertin studies had a lower placebo effect. In Phase 3 they saw an increase in placebo response. The weak effects of bitopertin were obscured by variability in Phase 3. In conclusion, number of sites should be maintained low, e.g. around 30 sites per study.

4) *Background of antipsychotic treatment (PoM).*

Under the method of monetary incentive delay (MID) Task Reward as fMRI task, contradictory results were obtained with the PDE10 inhibitor RG7203. A reduction of striatal activation was observed when an increased activation was expected. Activation usually follows the performance of the MID task. Actually, they recognize not to know very much about what the tasks measures.

Risperidone shown to blunt the overall response to MID task. Thus, may not be favorable to combine new therapies with DA antagonists => argument for monotherapy (Möller et al, Psychopharmacology 1994).

Conclusions

— Patient Selection:

- Drop restrictions on the level of Positive Symptom severity as long as not disruptive.
- Consider enrolling patients with moderate severity of Negative Symptoms Score 14 and up on NSFS 0-6).
- Consider stratification into dominant vs predominantly negative symptoms

— Study Design:

- Keep number of sites and study arms low – Plan phase 3 for safety study separately.
- Monotherapy.

Other remarks:

Daniel suggested an observational study to better understand the behavior of all the items using IRT method on PANSS, NFS and other subscales.

The difference between NSFS and NSA is probably related to the fact that the evaluation of PANSS negative symptoms relies on informant report.

Results of IRT analysis item by item have been presented.

Presentation 2

Remy Luthringer, Minerva Neurosciences

A first question is whether it is possible to modify Negative Symptoms without acting on dopaminergic receptors. The pathology is diverse but there may be a patient subtype that can benefit from an agent that has no direct affinities for dopaminergic receptors. The issue is to see how this subtype of patients can be selected for an RCT.

Another question is to know which effect we look for Positive Symptoms (to calm down?) and if there is a ceiling effect over the total effect over Positive Symptoms. (A strong rebuttal from Steve Marder was heard: The notion of calming effect of antipsychotics is false, the evidence base for their efficacy on positive symptoms is strong).

Another question is to see if it is essential to have a minimal level of Negative Symptoms.

Minerva study inclusion criteria:

- DSM-5 SCZ patients scoring ≥ 20 on 7 PANSS Negative Scale.
- Age 18-60
- Stable and manifest negative symptoms over past 3 months, score < 4 on PANSS (P4, P6, P7, G8, G14), i.e. low levels of positive symptoms. These symptoms are responsive to DA blocking drugs, and to MIN-101.

Study design:

Three-armed study: MIN-101 32 mg vs. MIN-101 64 mg vs placebo. Study duration: 6 months + extension phase up to 36 weeks in total.

Patient population enrolled:

- Baseline age: mean of 40 years

- Total PANSS score ~80
- Neg. score: ~27
- Pos. score: ~14
- General psychopathology: ~39

Study was conducted in Europe exclusively, mainly Eastern European sites. A total of 240 pts were enrolled at 34 sites over a period of 9 months. The 'all-reason screen failure rate' was 35%.

Minerva included a functional outcome scale (not disclosed) as key secondary (not as co-primary) endpoint, as agreed with FDA.

The effect of on negative symptoms was maintained after controlling for depression using the Calgary Depression Scale. Results (reduction from baseline) on five factor PANSS neg. Subscale score (in 8-12 weeks):

- Placebo: -1,5
- MIN-101 32 mg: -3
- MIN-101 64 mg: -3,5

BNSS showed identical results than the NSA-16 although the conclusion is not valid since both scales were administered by the same rater in the study.

Significant effect seen on N2-N6, G6, G7, G10, G16, also in patients with mild severity of symptoms; No effects on N5 and N7; N4 was very low, which is unusual and G18 "Active social avoidance" scored very high, and improvement was attributed to the low positive symptoms.

They conducted an analysis item by item to assess if the study drug had an effect on the core items for negative symptoms. It looks like the drug act over core negative symptoms.

Effect size was greater in younger patients (<33 y/o) compared to older.

Negative symptoms continued to improve (up to 6 points in total) for both doses investigated over the extension phase of 36 weeks.

No big improvements were observed on Positive Symptoms. This was expected since MIN-101 has no effect on DA receptors.

Patients on placebo remained for the duration of the study (PB = 21% dropout rate vs MIN101 = 13%) also during the extension study. The low threshold on P6 Suspiciousness meant lower delusions and was consider to play a role in the stability of patients in the placebo arm. In addition to the low PANSS positive symptoms score of 14 points and the long-term stability inclusion criteria of the study.

The study screen failures were 35%; 240 patients were recruited in 9 months by 34 sites (all in Eastern Europe)

It is possible to identify a patient population in whom psychotic symptoms appear stable for extended periods in the absence of DA-blocking agents. Placebo arms in maintenance trials may be a suitable way to identify such patients.

Minerva program has been discussed with FDA and the company is currently doing a 'copy-paste' phase 3 trial; however, with a one year extension period. A relapse-prevention trial is in planning.

Drug profile include action over different types of receptors (5HT2A, Sigma 1, Sigma 2, Alpha 1, but none to DA receptors. Abolition has been typically associated to DA receptor blockade.

One of the critics that can be mentioned is the duration of the trials, i.e. 6 months being too short.

Also, was criticism in the academic community (comment from clinicians) that this type of patients (without many positive symptoms) do not exist. This has been proven wrong by the relatively quick enrollment in the MIN trial.

Minerva Neuroscience would allow others to look at Placebo data at maintenance period if someone wants to see specific questions related to scales.

FINAL GLOBAL DISCUSSION

- Comments on Antipsychotic withdrawal – each antipsychotic has its own washout and clearance period. Some drugs may induce biochemical changes persisting up to 3 months after the patient has been withdrawn from antipsychotic drugs (criticism trying to explain the relative stability of patients in the placebo arm).
- It was suggested to use a study design with 3 arms – Original drug vs Placebo vs study drug (monotherapy).
- Comments on Inclusion Criteria – It was mentioned that is worth limiting the severity of Positive Symptoms. This is the opposite view from the conclusions from Roche.
- The Minerva study was shown to be more sensitive to drug effects than the study from Roche that applied restrictions on positive symptoms (PANSS-14).