What is the minimally clinically important change in negative symptoms of schizophrenia? PANSS based post hoc analyses of a phase III clinical trial

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INTRODUCTION

The Positive and Negative Syndrome Scale (PANSS) is the most widely-used standardized instrument for assessing symptom severity in clinical trials of schizophrenia.

Research established the minimally clinically important difference (MCID) with different methods for the total score of this scale.

As reported by an analysis from Leucht et al. a reduction of 19-28% in the PANSS total score corresponds to a minimal improvement on the Clinical Global Impression Improvement (CGI-I=3) scale [1].

According to Hermes et al. a 14.7 point change from baseline is considered clinically minimally important, using a 1 point decrease in the Clinical Global Impression Severity Scale (CGI-S) as anchor [2].

To date, no data exists addressing the MCID in predominantly negative symptom (PNS) patients on negative symptom scales.

STUDY OBJECTIVE

The aim of the present study was to establish the MCID on the PANSS-factor score for negative symptoms (PANSS-FSNS) [3] in schizophrenia patients with predominantly negative symptoms (PNS).

METHODS

Both, anchor-based and distribution-based methods were applied to analyze the data from a Phase 3 study with PNS (PANSS-FSNS ≥24 and no pseudospecific factors, e.g. high positive symptoms, extrapyramidal symptoms, depression) patients with schizophrenia. Study medication included 4.5 mg cariprazine (CAR) or 4 mg risperidone (RISP) for 26 weeks [4].

The presented methods use the Clinical Global Impression-Improvement (CGI-I) score and the Clinical Global Impression-Severity (CGI-S) score to quantify minimally clinically important differences (CGI-I=3 and CGI-S change=-1) or no change in the clinical status (CGI-I=4 and CGI-S change=0) on the measure of interest (PANSS-FSNS).

In the present paper the minimally clinically important difference is given in the pooled CAR-RISP population (N=454) at the earliest time of its occurrence.

RESULTS

Baseline characteristics
PANSS FSNSN baseline: 27.6

Anchor based methods for MCID *(Table 1)*
Anchor-based analyses show that using the CGI-I as anchor, the MCID was defined between a 2.2 and 3.8 points decrease of PANSS-FSNS, corresponding to a percentage change of 8%-14%. Using the CGI-S as anchor, the minimally clinically important difference falls into a range of -4.0 and -6.7 point change, corresponding to 18%-24% improvement from baseline.

Within patients score change refers to a subgroup of events when patients were considered minimally improved, and gives the corresponding mean change from PANSS FSNS baseline.

Between patients score change is the difference between mean changes of improved and non- improved events.

The PANSS FSNS change which most effectively (maximal Youden's J index) differentiates between patients with true positive (CGI-I=3; CGI-S change=-1) and false positive (CGI-I=4; CGI-S change=0) classification was defined by the receiver operating characteristic (ROC) curve as the optimal cut-off.

Table 1   Anchor based analyses for Minimally Clinically Important Difference on PANSS-FSNS in patients with negative symptoms of schizophrenia [5,6]

Anchor	Change from baseline in PANSS-FSNS (percentage change)	
	CGI-I = 3	CGI-S change = -1
Within patients score change approach Mean change from baseline	-3.8 (14%)	-6.7 (24%)
Between patients score change approach Difference between mean change of first improvement and mean change of non-improved cases	-2.2 (8.%)	-4.0 (15%)
ROC curve approach Optimal cut-off for improvement	-3.0 (12%)	-5.0 (18%)

CONCLUSIONS

- Depending on the underlying concept, different methods lead to different results for the MCID in patients with PNS.
- The Leucht analyses conclude that while a 50% PANSS total score reduction is relevant for acutely ill patients, in treatment refractory patients a smaller, 20%-25% reduction might be clinically important. Our CGI-I based results show that in the predominantly negative symptom population an even smaller (8%-14%) change from baseline is already considered clinically important difference.
- Further, this smaller degree of change to be sufficient was reflected in our CGI-S based results as well, where a 15-24% improvement of negative symptoms was considered clinically important, in contrast to the conclusion of 32% by Hermes et al.

Distribution based methods for MCID *(Table 3)*
Distribution based methods generally use statistical characteristics of the sample. The effect size (ES) based and Standardized Response Mean analyses are similar, using only different (baseline and change from baseline) standard deviations to estimate the effect sizes.

Standard error of measurement (SEM) separates noise from signal by giving the variability of PANSS-FSNS score change of non-improved patients (CGI-I=4 or no change on CGI-S).

According to the limits of agreement (LoA) analysis, to be scored with a probability of 95% as minimally clinically improved on the CGI-I, or one category less severe on the CGI-S, PANSS-FSNS decrease shall exceed -5.1 or -7.2.

Table 3   Distribution based analyses of PANSS-FSNS, CGI-S and CGI-I in patients with negative symptoms of schizophrenia [5,6]

	Change from baseline in PANSS FSNS	
Anchor:	CGI-I = 3	CGI-S change = -1
Effect size approach (ES=Cfb/SD_{bl}) Cohen's definition ES=0.5	-1.2	-1.2
Observed ES=1.5 (CGI-I); 2.7 (CGI-S)	-3.8	-6.7
SRM approach (ES=Cfb/SD_{cfbl}) Cohen's definition ES=0.5	-1.2	-1.6
Observed ES=1.5 (CGI-I); 2.1(CGI-S)	-3.8	-6.7
Anchor:	CGI-I = 4	CGI-S change = 0
SEM approach (SEM=SD*sqrt(1-ICC))	0.9	1.0
LoA approach: (Lower 95% Confidenc Interval=Mean-(1.96*SD))	-5.1	-7.2

BI: baseline
Cfb: Change from baseline
SD: Standard deviation
ICC: Intraclass correlation coefficient

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