Application of A Novel Analytic Methodology to Improve PANSS Data Quality and Signal Detection in a Global Clinical Trial of Schizophrenia

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SUBMISSION DETAILS

What is the Methodological Question Being Addressed? Can data quality flags and risk signals be applied to manage site and rater performance to improve data quality and efficacy signal detection?

Introduction The objective was to evaluate the impact of data monitoring procedures following methods described by past ISCTM-driven publications on regional and site performance evaluated by active drug-placebo separation on rating scale outcomes.

Methods 614 in patients with acute exacerbation of schizophrenia participated in a Phase III randomized, double-blind placebo-controlled study to evaluate the efficacy and safety of asenapine transdermal system (HP-3070) (ClinicalTrials.gov identifier: NCT02876900). The study included 59 sites in the USA, Bulgaria, Russia, Ukraine, and Serbia (Citrome et al. 2021). Eligible patients were randomized (1:1:1) and received 3.8 mg/24h HP-3070 (n=204), 7.6 mg/24h HP-3070 (n=204) or placebo (n=206) transdermal patches.

Algorithms for PANSS and CGI monitoring during the study included flags developed by the ISCTM Algorithms/Flags workgroup, along with other in-study performance indicators, such as numbers of raters per patient and PANSS-CGI correlations. Discrepancies were reviewed and a series of interventions was implemented to improve data quality.

Results 45% of all visits had ≥1 PANSS or PANSS/CGI flag, 8% had ≥2 flags. Some PANSS/CGI flags showed significant group differences between placebo and drug conditions, where the placebo arm triggered differentially higher flag rates.

Among regions with higher placebo response and lower drug-placebo difference (Bulgaria, Serbia, Ukraine), higher rates of differentially distributed high-risk ISCTM flags were detected for all three treatment arms (placebo: $t=4.41$, $df=1137.6$, $p<0.0001$; 7.6 mg/24h; $t=6.78$, $df=1078.9$, p-value<0.0001; 3.8 mg/24h: $t=5.59$, $df=1095.8$, $p<0.0001$).

Suboptimal performing sites, defined as those with with higher differential flag rates in regions that did not separate showed significantly larger change from baseline in the placebo arm compared to optimally performing sites ($t=2.19$, $df=51.45$, $p=0.0328$). When suboptimal sites were removed from the analysis, effect sizes increased for both doses (Cohen’s d=0.38-> d=0.54, for 3.8 mg/24h; Cohen’s d=0.26->d=0.44, for 7.6 mg/24h). This suggests that suboptimally performing sites, identified by a specific pattern of data quality flags, reduce signal detection.

Additional complimentary risk factors were analyzed. PANSS/CGI-S correlations by site ranged from 0.35-0.98. 41 sites showed high correlations (r≥ .80), while 18 were moderate-low (r<.80). When moderate-low sites were removed, effect sizes increased for both 3.8 mg/24h (Cohen's d=0.48) and 7.6 mg/24h (Cohen's d=0.32). Additionally, sites were classified using three metrics: no assessments >2 ISCTM-predictor flags, PANSS/CGI correlations ≥0.8, and ≤2 raters/subject (high rater consistency). Sites with all three conditions were classified as Excellent (n=19), those with two of three were classified as Good (n=25), and 1 of these conditions were classified as Poor (n=15). Excellent sites showed larger placebo-drug difference scores (Placebo - 9mg = 11.9, Placebo - 18mg = 8.78), while poor sites had lower difference scores (Placebo - 9mg = 3.81, Placebo - 18mg = -.30). When Poor sites were removed, effect sizes increased for both 9mg (d=0.43) and 18mg (d=0.35) conditions.

Conclusion The results show that the methodology described by the ISCTM Flags/Algorithms workgroup has the potential to improve signal detection, while also demonstrating that the effect size of some treatments may be higher than reported due to measurement error and noise in clinical trials. These results suggest that certain ISCTM flags, PANSS-CGI-S correlation, and rater consistency may be used as actionable indicators of data quality. Further work is required to better understand and refine the use of this methodology.

Co-Authors

* Presenting Author

First Name	Last Name	Affiliation
Mark *	Opler *	WCG MedAvante-ProPhase
Selam	Negash	WCG MedAvante-ProPhase
Kazunori	Tatsumi	WCG MedAvante-ProPhase
Cong	Liu	WCG MedAvante-ProPhase
Brittney	Starling	Noven Pharmaceuticals, Inc.
Komaroff	Marina	Noven Pharmaceuticals, Inc.
Gianna	Capodilupo	WCG MedAvante-ProPhase
Masami	Hasebe	Hisamitsu Pharmaceutical Co., Inc.
Barbara	Echevarria	WCG MedAvante-ProPhase
Raymond	Blattner	WCG MedAvante-ProPhase
Leslie	Citrome	New York Medical College, WCG MedAvante-ProPhase

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Guidelines I have read and understand the Poster Guidelines

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