Subjective Units of Distress Scale (SUDS) is a psychometrically valid and reliable outcome measure for the assessment of anxiety in social anxiety disorder (SAD) clinical trials

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INTRODUCTION

- Social Anxiety Disorder (SAD) is a chronic, serious and prevalent neuropsychiatric condition characterized by feelings of intense and persistent fear and avoidance of social or performance-related situations.
- BNC210 is a novel, negative allosteric modulator (NAM) of the α7 nicotinic acetylcholine receptor (α7nAChR) that has shown anxiolytic activity comparable to benzodiazepines without severe side effects in Phase 1 and 2 clinical studies.
- PREVAIL study was conducted to evaluate acute anxiolytic efficacy induced by a public speaking challenge and safety of BNC210 in patients with moderate to severe SAD.
- In the PREVAIL study BNC210 demonstrated reduction of anxiety provoked by a public speaking challenge compared to placebo and good tolerability.
- Subjective Units of Distress Scale (SUDS) is a self-reported Visual Analog Scale (VAS) which measures the subjective intensity of disturbance or distress and is a standard instrument for rating social, anticipatory, and performance anxiety in patients with SAD during role-playing situations (Wolpe, 1969).
- SUDS (or similar VAS scales) has been used in industry-sponsored and academic studies to evaluate potential treatment effect of both psychotherapy and pharmacotherapy interventions for SAD.

METHODS

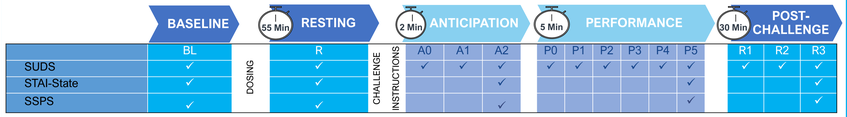
PREVAIL was a multicenter, double-blind, placebo-controlled, single-dose, Phase 2 study (NCT05193409).

Key Inclusion Criteria: 18-65 years of age; a current diagnosis of SAD, as defined by the DSM-5; a Liebowitz Social Anxiety Scale (LSAS) total score ≥ 70 at Screening.

Key Exclusion Criteria: history of schizophrenia, bipolar disorder, or psychotic disorders; a current clinically predominant diagnosis of any other Axis I disorder, other than SAD; HAM-D score ≥18; use of psychotropic medications within 30 days of screening.

Study Design and Efficacy Assessments: Eligible participants were randomized 1:1:1 to receive a single dose of 225 mg BNC210, 675 mg BNC210 or placebo. Approximately 60 minutes following treatment administration they took part in a public speaking challenge which involved 2-minutes for speech preparation (anticipation phase) and a 5-minute speech in front of a small audience (performance phase). Three efficacy measures were taken pre-dose, pre-challenge, at the anticipation and performance phases of the challenge (at 1-minute intervals for SUDS), and post-challenge, as illustrated in Figure 1.

Figure 1: PREVAIL Schedule of Key Efficacy Assessments



Subjective Units of Distress Scale (SUDS; primary and secondary measure): VAS from 0-100 that measures self-reported intensity of anxiety and/or distress.

State-Trait Anxiety Inventory (STAI-State subscale; secondary measure): self-reported questionnaire with 20 anxiety-related questions marked on a 4-point scale (Spielberger, 1983).

Self-Statements During Public Speaking scale (SSPS-N negative self-statements; secondary measure): self-reported 5-item questionnaire capturing negative cognitions during a public speaking situation.

SUDS Psychometric Analysis Methods:

The psychometric properties of the SUDS were evaluated to assess the SUDS's fit for measuring the reduction in self-reported anxiety severity provoked by a public speaking challenge in patients with SAD. The following parameters were evaluated:

- **Reliability:** Pearson's correlations, concordance correlation coefficient, intraclass correlation coefficient, and Bland-Altman limits of agreement using the SUDS at 20- and 30-minutes post-challenge (public speaking challenge)
- **Validity:** Pearson's correlations between the SUDS at baseline and STAI-State at baseline, and the results of a Kruskal-Wallis test that the means of the SUDS are the same across groups defined by tertiles of the STAI-State.

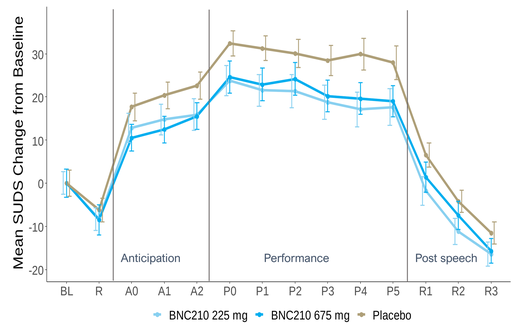
PREVAIL RESULTS

Table 1: PREVAIL Patient Demographics and Baseline Characteristics

	BNC210 225 mg	BNC210 675 mg	Placebo	Overall
Full Analysis Set	50	51	50	151
Mean Age in Years (Min, Max)	35.5 (18,65)	37.7 (19,65)	34.5 (21,58)	35.9 (18,65)
Male/Female (%Female)	17/33 (66.0)	16/35 (68.6)	23/27 (54.0)	56/95 (62.9)
Mean Screening LSAS Score (SD)	98.7 (15.75)	98.3 (16.98)	95.3 (16.34)	97.4 (16.33)
Mean Baseline SUDS (SD)	40.3 (18.53)	37.9 (22.98)	32.9 (21.26)	37.0 (21.10)
Mean Baseline STAI-State (SD)	54.3 (9.94)	49.7 (11.63)	49.2 (12.20)	51.1 (11.45)

LSAS = Liebowitz Social Anxiety Scale at screening; SUDS = Subjective Units of Distress score at baseline (pre-dose); SD = standard deviation

Figure 2: Mean observed SUDS scores plotted as change from baseline demonstrating reduced anxiety of BNC210 treatment compared to placebo



- Participants in both BNC210 dose groups (225 mg and 675 mg) showed reduced increases in anxiety in the public speaking challenge compared to participants on placebo.
- The planned primary and secondary analyses for average, peak, and area-under-the-curve (AUC) SUDS endpoints demonstrated consistent improvements in the anticipation and performance phases of the challenge.
- Trends for improvement ($p<0.1$) were observed when the BNC210 dose groups were combined for increased powering in post-hoc analyses.
- Combining the anticipation and performance phases of the speaking challenge, BNC210 demonstrated significant improvement in SUDS scores in an AUC analysis ($p=0.044$; post-hoc).
- STAI-State revealed converging results, with reduced increases in anxiety throughout the public speaking challenge.

CONCLUSIONS

- BNC210 225 mg and 675 mg demonstrated reduced anxiety in patients with moderate to severe SAD in a public speaking challenge compared to placebo and was well tolerated.
- The PREVAIL Study revealed BNC210's potential as a non-sedating anxiolytic for the acute treatment of SAD and a Phase 3 trial is planned for Q1 2024.
- A psychometric analysis concluded that SUDS is a psychometrically valid, sensitive, and reliable tool for evaluation of social anxiety.
- Additional data on psychometric characteristics of the SUDS will be collected during the Phase 3 studies with BNC210 in SAD. A nested validation study will compare SUDS to the standard assessments of Clinical Global Impression scale (CGI) capturing clinician-rated and Patient Global Impression scale (PGI) capturing self-rated severity of anxiety during the public speaking paradigm.

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SUDS PSYCHOMETRIC ANALYSIS RESULTS

Sensitivity

No floor or ceiling effects were observed in the use of the SUDS in the PREVAIL study. At all measured time points, the full 100-point range of the scale was used. The absence of appreciable floor or ceiling effects indicate that the SUDS is highly sensitive to change over the entirety of its range.

Reliability

The reliability of the SUDS at 20- and 30-minutes post-challenge was very high with a Pearson's correlation coefficient of 0.91 in both the placebo and full populations, respectively. The concordance and intraclass correlation coefficients were also high with values of 0.84 and 0.86 in the placebo and full populations, respectively. The Bland-Altman plots also demonstrated strong agreement between the 2 time points. The reliability results were similar in the placebo and total population (Table 2).

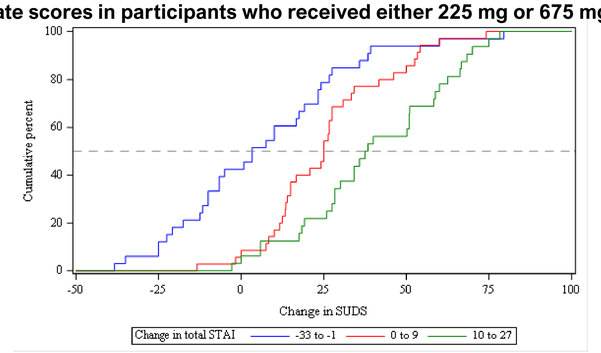
Table 2: SUDS Test-retest Reliability at 20 and at 30 Minutes Post-challenge

	Placebo	Total Population
SUDS at 20 min and 30 min	50	150
Pearson's correlation coefficient	0.91	0.91
Concordance correlation coefficient	0.84	0.86
Intraclass correlation coefficient	0.84	0.86
Bland-Altman:		
Mean difference	7.36	6.97
Lower limit of agreement	-7.91	-9.88
Upper limit of agreement	22.63	23.82

Validity

Baseline SUDS scores demonstrated good convergent validity when compared with STAI-State scores (Figure 3).

Figure 3: Change from baseline SUDS scores by tertiles of change from baseline STAI-State scores in participants who received either 225 mg or 675 mg BNC210



The empirical cumulative distribution function curve of the change from baseline in SUDS is plotted for all participants with a change from baseline in STAI between -33 and -1 (blue), a change from baseline in STAI between 0 to 9 (red), and a change from baseline in STAI between 10 and 27 (green). The dashed line represents the median of the group.

The Pearson's correlation coefficients between the SUDS and STAI at baseline showed the strongest correlations for the STAI total score and the 5 questions listed in Table 3:

Table 3: Pearson's Correlation Coefficients for STAI-State

Total score r = 0.627	Q13 – I am jittery r = 0.493
Q12 – I feel nervous r = 0.550	Q9 – I feel frightened r = 0.488
Q5 – I feel at ease r = -0.537	Q15 – I am relaxed r = -0.487

The STAI-State also demonstrated strong known-groups validity with the mean value of the SUDS within each tertile of the STAI-State total score tracking with the SUDS, and statistically significant discrimination between groups (baseline SUDS and STAI, Table 4):

Table 4: Known-group Validity – STAI-State Tertiles

SUDS at baseline	Lower (N=52)	Middle (N=47)	Upper (N=51)
Mean	24.08	34.47	52.88
Standard deviation	15.13	15.79	20.83
p-value (calculated using the Kruskal-Wallis test)		<0.05	

References: Spielberger CD, et.al., Manual for the State-Trait Anxiety Inventory: STAI (form Y). Palo Alto (CA): Consulting Psychological Press; 1983; Wolpe J. The Practice of Behavior Therapy. New York (NY): New York: Pergamon Press; 1969.

Disclosures: Spyros Papapetropoulos, Elizabeth Doolin, Dharam Paul are employed by Bionomics Limited; Lisa Weissfeld and Mark Opler are employed by WCG Clinical