Effect of As-Needed Use of Intranasal PH94B on Social and Performance Anxiety in Individuals with Social Anxiety Disorder

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Abstract

Social Anxiety Disorder (SAD) is a common and sometimes disabling condition. A Phase 2 trial was conducted with laboratory social interaction and performance challenges in which subjects receiving PH94B had a significantly greater decrease in mean SUDS scores compared to placebo. A subsequent Phase 3 pilot 4 week crossover trial then compared treatment with intranasal PH94B or placebo, and there were significantly greater decreases in average peak SUDS scores when subjects received PH94B. There was also a significantly greater decrease in LSAS avoidance scores for subjects who received PH94B first. Here we present additional data from the Phase 3 pilot trial and their implications for Phase 3 trial design.

Introduction

Social Anxiety Disorder (SAD) is a common and sometimes disabling condition involving excessive fear and avoidance of situations in which individuals feel scrutinized or evaluated by others. SAD affects as many as 15 million Americans. What was called generalized social anxiety disorder in DSM IV, and is called social anxiety disorder in DSM 5, can lead to compromised academic, social, and vocational functioning and often predisposes individuals to depression and substance abuse. Several treatments have emerged for this condition, such as selective serotonin reuptake inhibitors, a serotonin norepinephrine reuptake inhibitor, certain monoamine oxidase inhibitors and benzodiazepines. Cognitive behavior therapy (CBT) has also shown effectiveness for SAD, but many individuals do not pursue CBT. The present FDA-approved drug treatments of SAD are often of limited help to individuals, can have troubling side effects, and are not indicated for as-needed (PRN) treatment, such as just before a feared social or performance event. Because many individuals with social anxiety experience distress in events that occur infrequently and can be anticipated, a rapidly acting treatment that can be used on an as-needed basis could be highly useful.

PH94B is a synthetic molecule developed by Pherin Pharmaceuticals and licensed to VistaGen Therapeutics that is administered intranasally in microdoses and acts via nasal chemosensory receptors to rapidly affect brain structures including the amygdala, hypothalamus, hippocampus and prefrontal cortex[1]. There are previously presented data to show that PH94B rapidly and transiently relieved symptoms of Generalized Anxiety Disorder (GAD)[2]. PH94B was also shown in a double-blind placebo-controlled trial to be significantly more effective than placebo in reducing public speaking and social interaction anxiety in laboratory challenges of individuals with SAD[3].

Due to these promising results, the next step was to determine if PH94B would be effective in reducing public speaking and social anxiety in people with SAD using the medication in their daily lives as needed. Previous nonclinical and clinical studies revealed a 30–50% lower threshold to PH94B in women than in men. Therefore, the single dose for females in this study was 1.6 micrograms (the same as in Phase 2 studies) while the single dose for males was 3.2 micrograms[4] .

Methods

- Study subjects between 18 and 65 years of age were randomized on a 1:1 basis to PH94B or placebo for two weeks, and then crossed over to the opposite treatment for an additional two weeks (see Figure 1).
- The primary outcome measure was the average peak anxiety level measured via the subject-rated Subjective Units of Distress Scale (SUDS), where anxiety scores ranged from 0 (no anxiety) to 100 (maximum anxiety ever experienced). Within each 2-week treatment phase, all subjective peak anxiety ratings were summed and divided by the number of events recorded.
- Secondary and exploratory outcome measures included Liebowitz Social Anxiety Scale (LSAS) total scores at week 4 and LSAS (total and subscale) and SUDS scores at weeks 1 and 2.

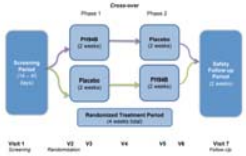


Figure 1

Results

Subject Sample

- In this Phase 3 pilot study, 31 subjects were recruited, eight of whom did not meet eligibility, while the remaining 23 were randomized.
- Twenty-two subjects were included in the final data set for analysis: 21 completed the whole trial, while one other completed 2 weeks of one treatment and 1 week of the other before being terminated due to an adverse event. One other subject withdrew consent before receiving the second treatment (placebo) and was not included in the data analyses.
- The final study sample had 11 males and 11 females, with an average age of 40.2 (11.6) years, and 15.3 (2.9) years of education. The sample was 18% Caucasian, 9% Asian, 27% Hispanic, 36% African American, and 9% other.
- The mean age of SAD onset was 10.3 (5.6) years. The mean baseline LSAS score was 97.9 (20.2), with a CGI-S of 5.1 (0.6).

SUDS Outcomes

- For the primary outcome measure, the average change from baseline SUDS for all subjects while on PH94B was a 15.6 point decrease, and while on placebo, a 8.3 point decrease (paired t = 3.09; p = .006; effect size, .658).
- Early suggestions of drug/placebo differences were seen in Week 1 and 2 SUDS scores: the average change in SUDS at week 1 was 16.1 for PH94B versus 3.4 for placebo (t=1.86, p=.078, ES .79), and at week 2, the average change was 15.9 for PH94B and 6.9 for placebo (t= 1.35, p=0.192, ES .576) (see Figure 2).
- The peak SUDS score for the PH94B group increased when crossed over to placebo, though not back to the baseline level (see Figure 2).

LSAS Outcomes

- In the sample as a whole, the drop in LSAS scores after treatment did not differ between groups, because subjects receiving PH94B first continued to improve when crossed over to placebo (see Figure 3).
- After the first 2 weeks of treatment, subjects who received PH94B dropped an average of 23.2 points on the LSAS, while those who received placebo dropped only 8.2 points, showing a trend difference (t=1.9, p=.07) with a large effect size of .812 (Fig 3).
- This was mostly attributable to changes in the LSAS avoidance subscale: after 2 weeks of treatment, subjects who received PH94B first had a significantly greater decrease than did those who received placebo first (14.3 versus 3.27) (t=2.53, p = .02, ES 1.078) (see Figure 4).
- Decreases for the PH94B (8.91) and placebo (4.91) groups were not significantly different on the LSAS anxiety subscale at Week 2 (t=1.03, p=0.314, ES .438) (see Figure 5).
- Looking at the LSAS performance and social subscales at Week 2, the PH94B groups showed a significantly greater decrease than placebo on the social subscale (12.3 versus 2.00, t=2.59, p=0.018, ES 1.19) but not on the performance subscale (11.8 versus 5.27, t=1.64, p=0.117, ES .699).
- Similar trend differences on total LSAS scores were seen after 1 week of treatment, where the PH94B group showed a 17.8 point drop compared to a 3.5 point drop with placebo (t=2.02, p=.057, ES .86) (Fig 3).
- Subjects who received PH94B first had a significantly greater decrease in their LSAS avoidance score after 1 week of treatment than did those who received placebo first (11.2 versus 0.82, t=2.54, p=.002, ES 1.08) (Fig 4) but not on the anxiety subscale (6.6 versus 2.64, t=1.16, p=0.258, ES .49) (see Figure 5). At this timepoint, PH94B trend superiority over placebo was similar for the LSAS performance subscale (8.9 versus 1.18, t=2.01, p=.059, ES .87) and LSAS social subscale (8.7 versus 1.36, t2.00, p=.059, ES .856).
- Changes in total LSAS scores were closely associated with change in SUDS peak anxiety scores at Week 1 (R-sq (adj) 45.2%) (see Figure 6) and at Week 2 (R-sq (adj) 34.95%). Looking at LSAS subscales, the strongest associations for SUDS peak anxiety scores were with the LSAS avoidance subscale at Week 1 (R-sq (adj) 58.78%) and Week 2 (R-sq (adj) 42.74%), and LSAS performance at Week 1 (R-sq (adj) 50.33%).

Subject Safety

There were no reports of SAEs, and the adverse effects were minimal, with headache being the most commonly reported (3 on PH94B, 1 on placebo).

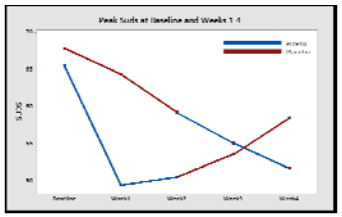
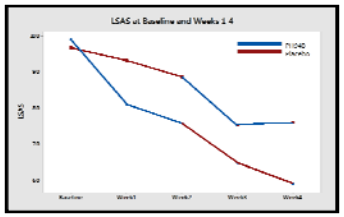


Figure 2



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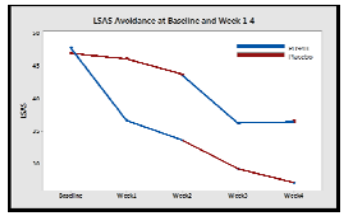

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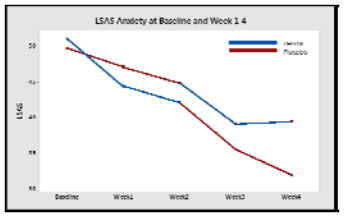

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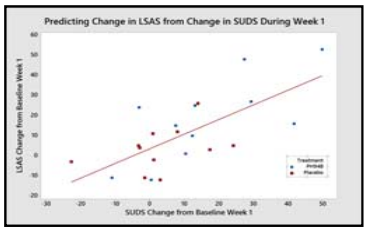

Figure 6

Methods (continued)

Main Inclusion Criteria:

- Clinician-rated LSAS total score ≥60 at both Screening and Baseline visits
- CGI-Severity score ≥4 at both Screening and Baseline visits
- Subject must have:
  - experienced and documented a minimum total of six social interaction or performance events during the two week Screening Period prior to the Baseline Visit, and
  - for at least three of these events, must have achieved a peak score of ≥60 on the Subjective Units of Distress Scales (SUDS), as rated in the Patient Diary

Main Exclusion Criteria:

- Two or more documented failed treatment trials with a registered medication approved for SAD during the previous six months
- Use of any psychotropic medication within 30 days prior to study entry (other than eszopiclone, ramelteon, zaleplon, or zolpidem for insomnia)
- Concomitant use of non-study anxiolytics, such as benzodiazepines or beta blockers, or any over-the-counter, prescription product, or herbal preparation for treatment of the symptoms of social anxiety during the study or within 30 days prior to study entry
- History of bipolar disorder (I or II), schizophrenia, schizoaffective disorder, psychosis, eating disorders, or obsessive-compulsive disorder

Statistical Analysis:

Subjects served as their own control, and comparisons for SUDS and total LSAS scores were made using a within-subjects model and paired t-test statistic. Findings were also analyzed using an independent sample t-test of the differences between the outcomes in the two periods within the individual. It was prospectively planned that if carryover effects of improvement were seen for subjects receiving PH94B first followed by placebo, then between groups comparisons would also be evaluated for the first two weeks of treatment. These comparisons would use a between groups model and independent t-test statistic on change from baseline data. Effects sizes were calculated using Cohen's *d*. Regression analyses were used to compare changes on SUDS versus LSAS.

Conclusion

In sum, in both the Phase 2 and Phase 3 pilot study, PH94B proved to be more effective than placebo in the whole sample on the primary outcome measure (SUDS). Between group comparisons showed that in the first two weeks of the phase 3 pilot study both the LSAS and SUDS seemed able to discriminate drug from placebo. In addition, change as measured by the SUDS and the LSAS appear highly correlated. We therefore believe that a 4 week parallel group comparison of PH94B versus placebo used on an as-needed basis rather than a crossover design would be a strong study design going forward (see Figure 7). Furthermore, the LSAS appears to be a suitable primary outcome measure for future trials of PH94B in SAD, with the SUDS as a secondary measure.

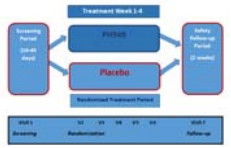

Figure 7

References

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