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Research Article

A Placebo Controlled Trial of PH10: Test of a New Rapidly Acting Intranasally Administered Antidepressant

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ABSTRACT

Background: More rapidly acting antidepressants are needed for individuals with major depressive disorder (MDD). A new class of neuroactive steroids called pherines have shown rapid and potent effects when administered intranasally. A study of pherine PH10 was conducted in subjects with MDD.

Methods: Thirty subjects with MDD were randomized to 8 weeks of self-administered intranasal PH10 low dose (3.2μg), PH10 high dose (6.4 μg), or placebo. Changes on the Hamilton 17-item depression rating scale (HAM-D-17) were compared.

Results: Overall comparison of HAM-D-17 endpoint scores for the three treatment groups showed a trend for difference ($p = 0.07$). Pairwise comparisons showed a greater reduction in HAM-D-17 scores for high dose PH10 ($p = 0.022$) and a trend for low dose PH10 ($p = 0.101$) compared to treatment with placebo. There were strong effect sizes for both active treatment groups versus placebo at study endpoint, as well as after one week of treatment. Treatments were well tolerated and there were no Serious Adverse Events.

Conclusions: Results from this small trial must be considered tentative. Findings suggest that PH10 could represent a useful treatment for MDD with a rapid onset of efficacy, and continue to validate the nasal chemosensory neural circuits as a novel mechanism of action of pherines.

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INTRODUCTION:

Adult depression is among the most common psychiatric conditions and poses a major health problem because of its high prevalence, negative effects on quality of life, and disability that results in enormous economic impact.

Worldwide, depression affects about 120 million people, and it is estimated that one in five adults will develop a depressive disorder during their lifetime. By 2020 depression is expected to become the second most common cause of disability after cardiovascular disease (Murray & Lopez, 1997).

There are a variety of antidepressants currently available, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and other products. Despite this therapeutic arsenal, on average 40 to 50% of patients do not respond to treatment with SSRIs or to newer antidepressants in 6-12 week trials, and more than 60% do not achieve remission. Furthermore, even when helpful, these treatments usually take at least 4-6 weeks to achieve clinically significant results, are of limited help for many affected individuals, and often have troubling side effects (Rush, 2009). Therefore, there is a clear need for antidepressants with new mechanisms of action, faster onset of therapeutic benefit, and minimal side effects.

Nasal chemosensory circuits

Transduction of chemical signals in olfactory chemosensory neurons triggers sensory inputs that reach the limbic amygdala and the hypothalamus through a rapid (oligosynaptic) neural path (Maclean, 1955). In mammals, including humans, neurons in the epithelial lining of the dorsal nasal recess and adjacent areas express functional chemosensory receptors (Buck & Axel, 1991). Primary odors produce olfactory awareness, but other odorless chemical signals can induce behavioral and physiological responses, without olfactory awareness (Grosser, Monti-Bloch, Jennings-White, & Berliner, 2000; Monti-Bloch & Grosser, 1991; Monti-Bloch, Jennings-White, Dolberg, & Berliner, 1994; Monti-Bloch, Jennings-White, & Berliner, 1998; Rodriguez, Greer, Mok, & Mombaerts, 2000; Savic, Berglund, Gulyas, & Roland, 2001). A new family of synthetic neuroactive steroids called pherines, which are odorless, have shown specific affinity to receptors in the human nasal chemosensory mucosa followed by rapid activation of neural circuits involving the limbic amygdala, hypothalamus, frontal gyrus, and prefrontal cortex, which is different from the brain areas activated by primary odors (Monti-Bloch & Grosser, 1991; Monti-Bloch, Jennings-White, Dolberg, & Berliner, 1994; Monti-Bloch, Jennings-White, & Berliner, 1998; Sobel et al., 1999). The rapid onset of brain activation by pherines does not induce olfactory awareness and can modulate behavioral and autonomic nervous system responses (Monti-Bloch, Jennings-White, & Berliner, 1998; Sobel et al., 1999).

PH10

PH10 (pregn-4-en-20-yne-3-one) is a synthetic, odorless neuroactive steroid from the family of pherines, discovered and developed at Pherin Pharmaceuticals and recently licensed to VistaGen Therapeutics. PH10, formulated for intranasal administration in microgram doses, engages nasal chemosensory receptors to rapidly modulate neural circuits in the limbic amygdala and other basal forebrain structures, inducing antidepressant-like effects (Liebowitz, Nicolini, Hanover, & Monti, 2013; Monti-Bloch, Jennings-White, Dolberg, & Berliner, 1994; Monti-Bloch, Jennings- White, & Berliner, 1998).

PH10 induced a concentration-dependent effect in isolated, living human nasal chemosensory neurons (ED50= 0.2 M) (Monti, Garity, & Murray, 2000). Intranasal administration to healthy human male and female volunteers (n=12) produced dose- dependent depolarization of the local electrogram recorded from the surface of the nasal chemosensory mucosa. This was followed by increased respiratory and cardiac rate within physiologic range, increased sympathetic nervous system tone (3%), and increased electrodermal activity (skin conductance). There was no significant effect on the corrected QT intervals of

the electrocardiogram (QTc) (Monti, Diaz-Sanchez, & Schapper, 2001).

The same subjects showed a significant increase in blood norepinephrine (NE) 60 minutes after intranasal administration of 1.6 µg PH10. Metabolites 3-methoxy-4- hydroxymandelic acid (VMA) and normetanephrine (NMT) showed an increased trend in urine drawn 24 hours after dosing with PH10. Blood dopamine and urine homovanillic acid did not change significantly. Serotonin and its main urine metabolite, 5-hydroxyindoleacetic acid, also showed an increased trend after dosing with PH10 (Monti et al., 2001).

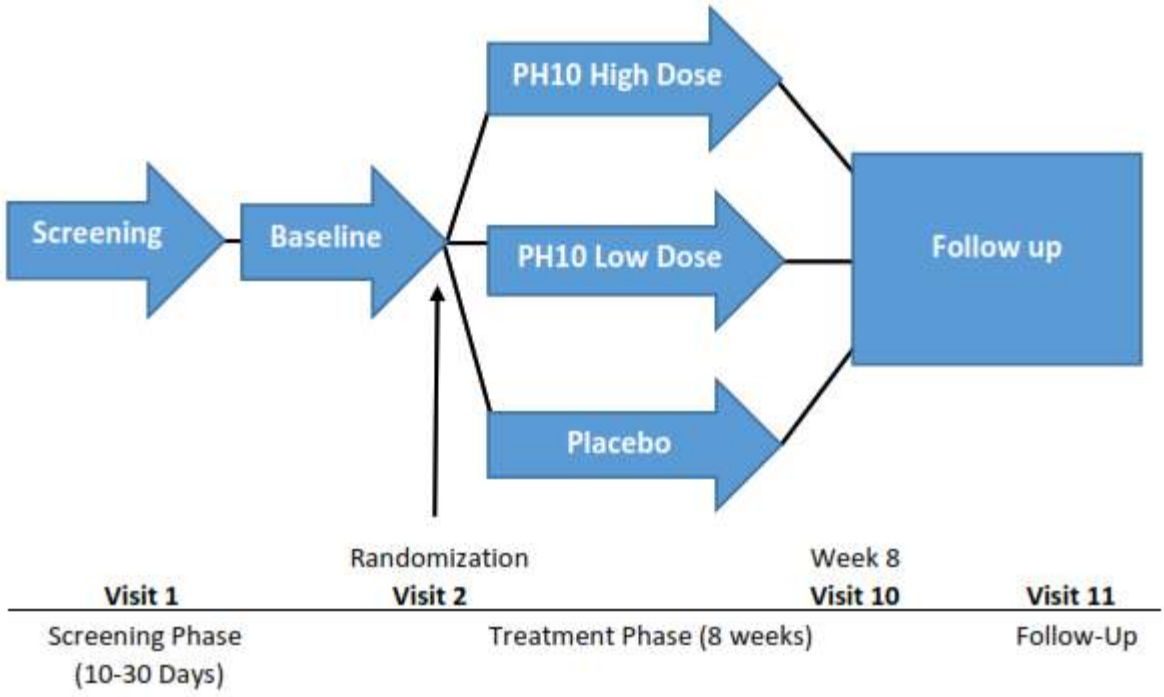
In a Phase 1, open label, flexible dose escalation clinical trial to study the safety and tolerability of intranasal PH10 (daily dose [g]: 0.8; 1.6; 2.4; 3.2; 4.8 and 6.4) in healthy volunteers (n=10), there were no statistically significant differences in any of the safety parameters evaluated for PH10 and placebo. There were no serious adverse events (SAEs), and the most frequent adverse events were increased appetite and dizziness. No statistically significant differences were found between different PH10 doses on clinical laboratory markers, vital signs, neuropsychological assessments, cognitive brain mapping, or evoked (cognitive) potentials (Nicolini, 2011).

The primary objective of the present study was to ascertain whether PH10 would be effective in subjects diagnosed with major depressive disorder. The secondary objectives were to assess the safety and tolerability of PH10 administered intranasally.

METHODS

This study was IRB-approved and all subjects signed informed consent before study procedures were initiated. The study was a double blind, randomized, placebo controlled, 9 week parallel group trial, conducted at a single clinical site (Figure 1).

Figure 1. Schematic diagram of the study design
PH10 Low Dose: 3.2 µg daily; PH10 High Dose: 6.4 µg daily



Inclusion criteria required that subjects were males or females age 18 to 60 years, meeting DSM-IV-TR criteria for major depressive disorder (MDD), with a Hamilton Depression-17 (HAM-D-17) score of at

least 17, a Clinical Global Impression of Severity (CGI-S) score of at least 4, and a Mini-Mental State Examination (MMSE) score of at least 25 at both screening and baseline.

Exclusion criteria included any imminent suicide risk or history of a prior suicide attempt, female subjects of reproductive age not using a safe and effective method of contraception, use of central nervous system (CNS) medications during the two weeks prior to screening, any previous exposure to PH10, presence of any uncontrolled medical illness, history of bipolar depression or schizophrenia, lifetime history of resistance to antidepressant treatment (defined as failure to respond to two or more adequate trials of antidepressant treatments), presence of other axis I DSM-IV diagnoses (subjects were excluded from participating in the study if these were the primary disorder or the major reason for seeking treatment), and any other medical condition that in the judgment of the Principal Investigator (PI) could put the subject at risk or could affect the outcome of the study.

Weekly evaluations at the study site included scales for the assessment of psychiatric symptoms and quality of life, including the HAM-D-17, the CGI-S, CGI-I, and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

PH10 and placebo (vehicle) were provided by Pherin Pharmaceuticals in 5 mL amber glass metered dose spray vials. Activation of the spray pump delivered a single dose of PH10 in 50 L of aqueous excipient.

Subjects were recruited through the clinical trial site's database, as well as through advertisements placed in newspapers and on the public transportation system. A pre- screening psychiatric interview was performed to verify the existence of major depressive disorder. Upon selection, the subject then signed the IRB-approved informed consent, with a description of the procedures to be undertaken according to the research protocol and in accordance with good clinical practice.

At the screening visit (Visit 1), the clinical investigator performed a semi-structured clinical interview to gather information including demographics, medical history (including family history), and history of medications, to verify the inclusion and exclusion criteria. If the subject met the study eligibility requirements, the remaining screening visit evaluations were performed, including physical examination and Mini International Neuropsychiatric Interview (MINI).

Study subjects also received a screening clinical examination of the nasal passages, electrocardiogram (ECG), and the following clinical laboratory tests: blood count, blood chemistry, urinalysis, urine drug screen, and immunological pregnancy test.

At the baseline visit (Visit 2), subjects meeting all inclusion criteria and no exclusion criteria were randomly assigned to receive double-blind PH10 High Dose, PH10 Low Dose, or placebo treatment for the next 8 weeks. Randomized subjects were also instructed, and started, to self-administer the study medication twice daily. The daily dose of PH10 administered to the Low Dose group was 1.6 μg twice daily (total daily dose 3.2 μg PH10); that of the High Dose group was 3.2 μg twice daily (total daily dose 6.4 μg PH10).

Visits 3 to 10 were treatment visits. Subjects were instructed to return to the clinic at the end of each week of double-blind treatment (weeks 1-8) for clinical evaluation (Figure 1). At each treatment visit, they returned the used spray vials for evaluation of study medication compliance, and were dispensed a new vial of study medication. No new study medication was dispensed at Visit 10. Upon completion of the treatment period (Visit 10 or Early Termination visit), all subjects were seen at the clinic one week later for a final follow-up evaluation (Visit 11).

Safety Evaluations

Subject safety was monitored and evaluated through weekly clinical interviews including open-ended assessment of adverse events, measurement of vital signs, and clinical laboratory tests (blood count, blood chemistry, and urinalysis) performed during the follow-up visit.

Statistical analysis

Differences in baseline to study endpoint changes in HAM-D-17 and Q-LES-Q scores for the high and low dose PH10 and placebo groups were evaluated using fixed-effects analysis of covariance (ANCOVA) (baseline HAM-D-17 as covariate) with the last observation carried forward (LOCF) for the intent-

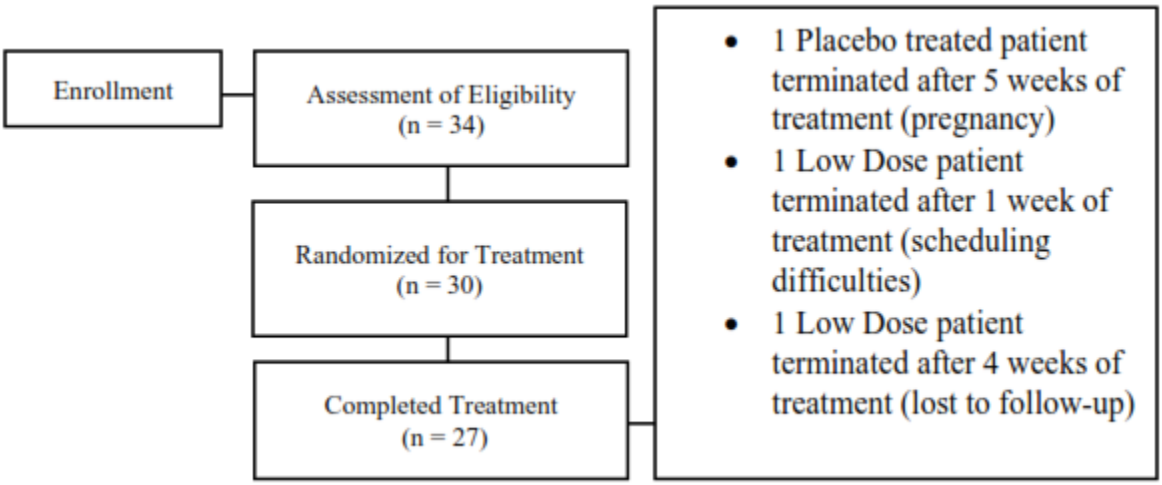
to-treat (ITT) analysis group. Planned pair-wise independent t-test comparisons between each of the PH10 dose groups and placebo mean changes from baseline were also conducted.

HAM-D-17 responders (defined as >50% reduction from baseline HAM-D-17 score), HAM-D-17 remissions (defined as a final HAM-D score < 7), and CGI-I responders (defined as a final CGI-I score of 1, very much improved, or 2, much improved) were compared across groups using Fisher's Exact test for binomial proportions.

RESULTS

Of 34 subjects screened and accepted for the study, 4 decided not to participate and 30 were randomized to double-blind treatment and completed at least one post-randomization visit. From the 30 subjects randomized for treatment, twenty-seven subjects (n= 27) completed the study (Figure 2). Three of the randomized subjects did not complete the full 8 week treatment period but had at least one post- treatment assessment; for these subjects, the last observation carried forward (LOCF) was used for endpoint responses. Of these three subjects, one subject (in the placebo group) completed 5 weeks of treatment and then was terminated from the study because of pregnancy, and two subjects (in the PH10 Low Dose group) left the study after 1 week (due to study visit scheduling conflicts with work) and 4 weeks (lost to follow-up) of treatment (Figure 2).

Figure 2. Consort diagram



At baseline, the treatment groups did not differ significantly in the proportion of males to females but did differ in age; subjects assigned to high dose treatment were older than those assigned to low dose ($p = 0.013$). The treatment groups did not differ significantly in baseline HAM-D-17 scores or Q-LES-Q scores (Table 1).

Table 2 shows the raw data for the ANCOVA. PH10 induced trend improvement for adjusted group differences at study endpoint [$F(2,26) = 2.95$; $p = 0.070$]. Mean HAM- D-17 reductions at endpoint were 17.8 for the high dose group, 16.3 for the low dose group, and 10.9 for the placebo group (high dose versus placebo, $p = 0.022$; low dose versus placebo, $p = 0.101$). Further analysis showed an effect size (Cohen's d) of 0.74 for HAM-D-17 reductions in the low dose group and 0.95 for the high dose group when compared to the placebo group after 8 weeks of treatment.

Figure 3 shows the group means for the total HAM-D-17 scores across all ten study visits (S = screening, B = baseline, and weeks 1-8 of treatment). The change in mean HAM-D-17 scores from baseline for each week of treatment is shown in Table 3 and Figure 4.

Table 1. Demographic characteristics of the subjects that completed treatment in the study (n = 27)

	PH10 High Dose	PH10 Low Dose	Placebo
Age	46.6 (7.5)	33.2 (12.9)	36.6 (7.9)
Sex	40% male	40% male	50% male
Baseline HAM-D-17	24.7 (7.1)	22.4 (8.7)	21.0 (4.9)
Baseline Q-LES-Q	36.9 (10.7)	40.7 (13.6)	44.9 (13.8)

Table 2. HAM-D-17 scores and change from baseline for groups by Treatment Week: Pairwise Comparisons (n = 30)

Treatment Week	High Dose M (SD)	High Dose versus Placebo			Low Dose M (SD)	Low Dose versus Placebo			Placebo M (SD)	High Dose versus Low Dose		
		Mean Diff.	t	p		Mean Diff.	t	p		Mean Diff.	t	p
Baseline	24.7 (7.1)	3.7	0.65	0.53	22.4 (8.7)	1.4	0.44	0.66	21.0 (4.9)	2.3	1.36	0.19
1	14.6 (5.2)	5.9	2.35	0.03	14.0 (6.7)	4.2	1.69	0.11	16.8 (4.8)	1.7	0.59	0.56
2	16.8 (7.8)	1.2	0.49	0.63	11.7 (4.8)	4.0	1.22	0.24	14.3 (4.7)	2.8	0.91	0.38
3	12.9 (6.6)	1.9	0.75	0.46	10.4 (4.4)	2.1	0.68	0.51	11.1 (5.2)	0.2	0.07	0.94
4	12.0 (6.5)	4.0	1.64	0.12	10.6 (4.2)	3.1	1.03	0.32	12.3 (5.60)	0.9	0.25	0.80
5	9.5 (6.1)	5.5	1.90	0.07	7.9 (4.5)	4.8	1.57	0.13	11.3 (4.1)	0.7	0.19	0.85
6	9.4 (5.8)	5.3	1.65	0.12	7.3 (3.9)	5.1	1.67	0.11	11.0 (5.2)	0.2	0.05	0.96
7	8.1 (6.5)	4.5	1.43	0.17	5.8 (3.9)	4.5	1.31	0.21	8.94.7)	0.0	0.00	1.00
8†	6.9 (5.2)	6.9	2.51	0.02	6.1 (3.5)	5.4	1.73	0.10	10.1 (3.9)	1.5	0.39	0.69

†*Change from Baseline at Week 8:*
High Dose versus placebo, p = 0.022; Low Dose versus placebo, p = 0.101

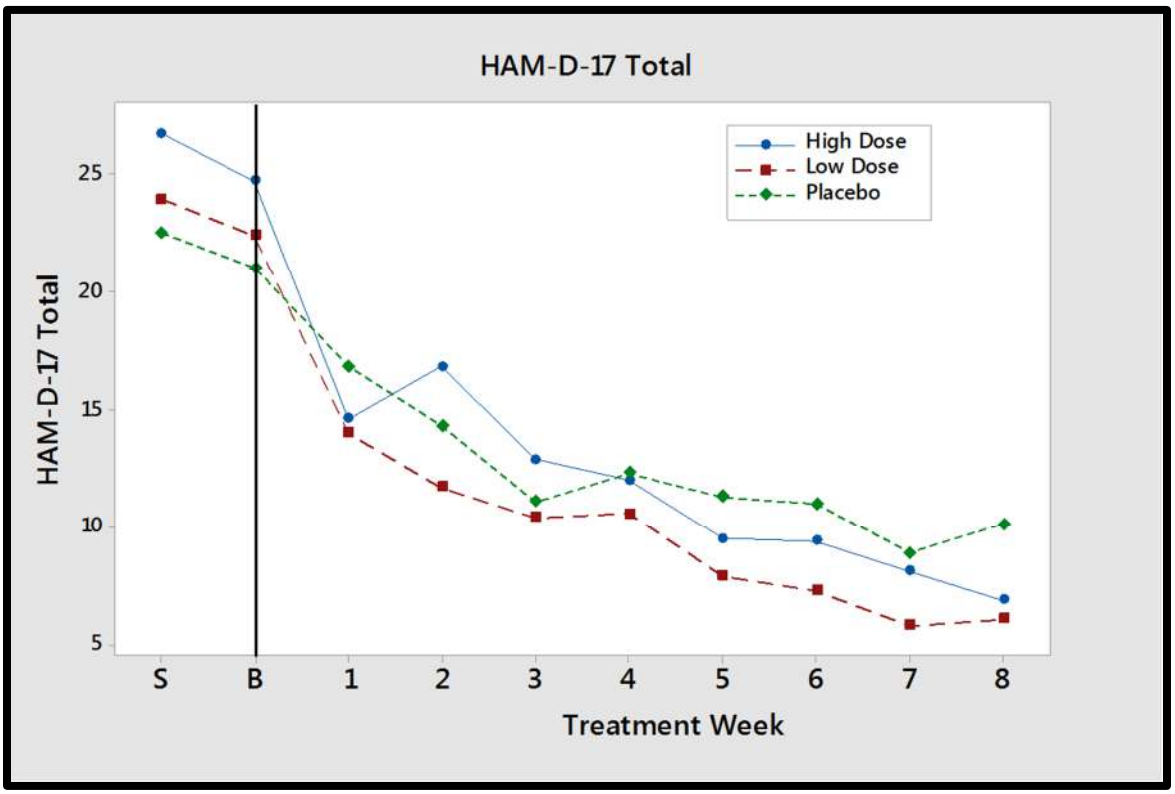
Table 3. Adverse events reported after treatment with PH10 and placebo

Adverse Event	PH10 High Dose	PH10 Low Dose	Placebo
Dry nose / local irritation in the nose	4	2	3
Runny nose	1	2	1
Increased appetite	5	1	3
Daytime sleepiness	4	0	0
Headache	3	5	1
Cold or flu	1	1	0
Dizziness	1	1	0
Rash / itchy feeling / pruritus	1	1	0
Constipation	1	0	0
Sedation	1	0	0
Irritability	1	0	0
Abdominal distension	1	1	0
Diarrhea	0	0	2
Paresthesia	0	0	1
Abdominal Pain	0	0	1

Bitter taste	0	4	0
High blood pressure	0	1	0
Joint pain	0	1	0
Anxiety	0	1	0
Colored urine (red colored)	0	1	0
Dry mouth	0	1	0

At the end of the last treatment week (Week 8), the PH10 High Dose group showed a mean HAM-D-17 score reduction of 17.8, which was statistically greater than treatment with placebo (t= 2.51, p= 0.02; Table 2). HAM-D-17 scores also improved from baseline during weeks 2, 3, 4, 5 and 7, but these effects did not reach statistical significance. There was also a small dose-dependent effect between the High Dose and Low Dose treatment groups, but this did not reach statistical significance (Table 2 and Figure 4).

Figure:3 Total HAM-D-17 scores during screening (S), at baseline (B) and during each of the 8 weeks of treatment with intranasal PH10 Low Dose (3.2 μg), PH10 High Dose (6.4 μg) and placebo.

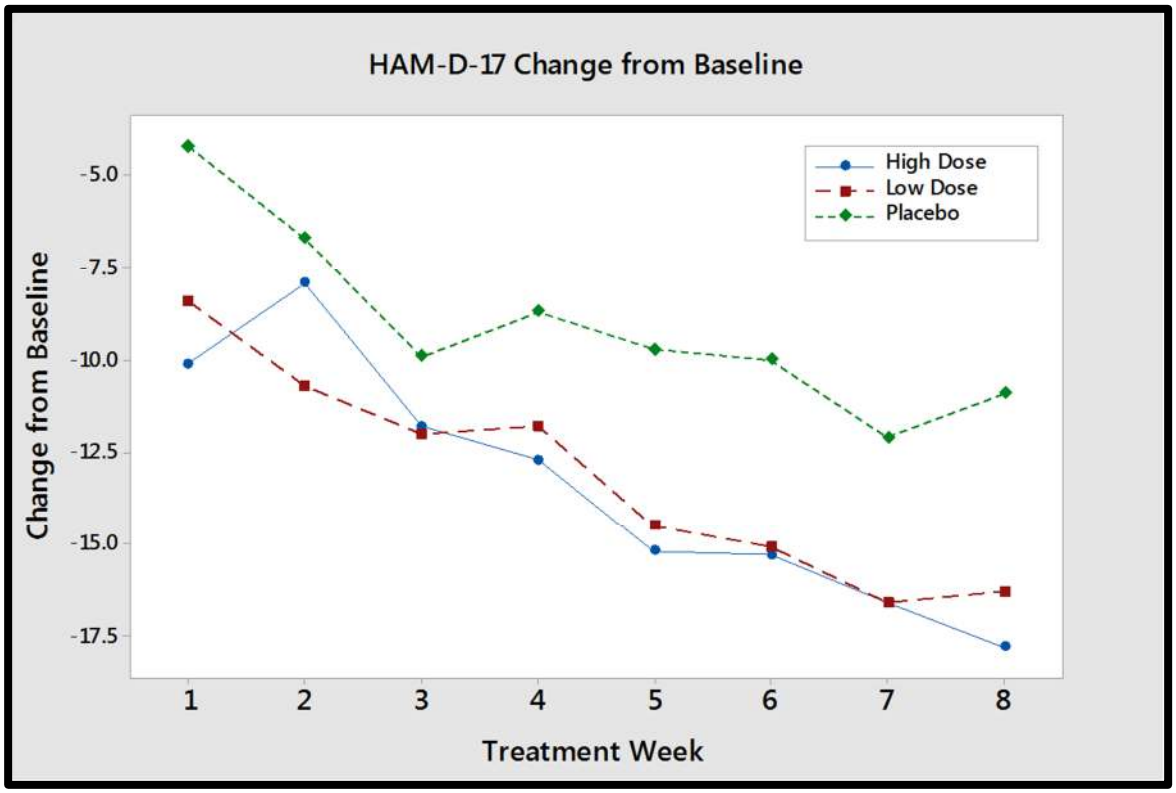


A rapid antidepressant benefit was evidenced by changes in HAM-D-17 scores at the end of the first week of treatment. Although the ANCOVA was not statistically significant [F(2,26) = 2.10; p = 0.142], the mean reduction in HAM-D-17 scores after one week of treatment was 8.4 for the Low Dose group, 10.1 for the High Dose group, and 4.2 for the placebo-treated group. The difference in lowering HAM-D-17 scores was significant for High Dose versus placebo (t = 2.35, p = 0.03; Table 2). The effect size for treatment with PH10 in comparison to placebo was 0.72 for the Low Dose group and 1.01 for the High Dose group.

At study endpoint, HAM-D-17 responder rates did not differ significantly between treatment groups: in the PH10 Low Dose group, 90% of subjects met responder criteria; in the PH10 High Dose group, 80%; and in the placebo group, 60% (all p values > 0.05). HAM-D-17 remission rates were 80% for the Low Dose group, 60% for the High Dose group, and 20% for the placebo group. The comparison between Low Dose and placebo group remission rates

was statistically significant, p = 0.023; but not for High Dose and placebo (p= 0.17). CGI-I responder rates did not show significant differences between the Low Dose (40%), High Dose (50%), and placebo (30%) groups. Similarly, for the Q-LES-Q the differences between the treatment groups were not statistically significant, but the effect size for treatment with PH10 High Dose was moderately large (Cohen's d= 89%).

Figure :4 Change from baseline in HAM-D-17 scores during each week of treatment with intranasal PH10 Low Dose (3.2 μg daily), PH10 High Dose (6.4 μg daily), and placebo.



Adverse Events

There were no reports of serious adverse events. The following mild to moderate adverse events were numerically more common during administration of PH10 and less frequent with placebo (Table 3): increased appetite, daytime sleepiness, nasal dryness, headache, and bitter taste. Weight gain did not differ between groups. All adverse events resolved spontaneously without the need of therapeutic intervention.

At the end of the treatment period all subjects reported to have tolerated the daily intranasal spray administration of 3.2 g, PH10, 6.4 g PH10, or placebo. There were no reports of abnormal values of clinical laboratory tests (hemo-analysis and urinalysis) performed at the end of the treatment period (Follow-up visit). Also, there were no reports of abnormal changes in the EGGs recorded at the end of the treatment period.

DISCUSSION

While significant further study is needed, the findings to date for PH10 suggest that it may be an effective, rapidly acting, and well-tolerated antidepressant. In the single- site study reported here, both doses of PH10 showed strong effect sizes after one week of treatment, as well as at the 8-week study endpoint. Given this, the fact that some of the statistical comparisons showed only trend significance was most likely due to the small sample size, which limited the statistical power of the study.

Subjects on PH10 showed only minor adverse events, suggesting that it may prove to be a safe and well-tolerated medication. If PH10 proves to be an effective antidepressant, it will also support the nasal chemosensory system as a novel way of delivering CNS active medications.

The relevance of the short (oligosynaptic) neural connections between nasal chemosensory cells and the limbic system in humans and their contribution to the emotional and visceral function of the limbic system have been reported several decades ago (Bard, 1928; Hess, 1949; Klüver, 1939; Maclean, 1955; Nauta, 1993; Papez, 1937). This was supported by later studies showing that bilateral resection of the olfactory bulbs in laboratory animals induced neuronal degeneration in the amygdala, hippocampus, locus ceruleus, raphe nucleus and prefrontal cortex, and impairment in the release of neurotransmitters NE, DA, serotonin and glutamate leading to depression that reversed with administration of antidepressants (Brück & Zeisberger, 1987; Connor, Song, Leonard, Anisman, & Merali, 1999; Dimitrov, Yanagawa, & Usdin, 2013; Frasnelli & Hummel, 2004; Pause, Miranda, Göder, Aldenhoff, & Ferstl, 2001; Reyes, Carvalho, Vakharia, & Bockstaele, 2011; Samuels & Szabadi, 2008; Song & Leonard, 1995). Furthermore, human subjects born with isolated congenital anosmia and atrophic olfactory bulbs develop depressive symptoms in early life that improve with antidepressant treatment (Croy, Nordin, & Hummel, 2014; Frasnelli & Hummel, 2004).

In earlier studies we reported that PH10 acting on nasal chemosensory cells triggers behavioral changes and activation of the autonomic sympathetic nervous system followed by increased ACTH, NE and serotonin and their urine metabolites (Liebowitz, Nicolini, Hanover, & Monti, 2013; Monti-Bloch, Jennings-White, Dolberg, & Berliner, 1994; Monti-Bloch, Jennings-White, & Berliner, 1998). This new mechanism of action of PH10 is in agreement with the reported activation of CRF neurons in the centromedial amygdala by glutamatergic afferents from the OB with a relay in the basolateral amygdala (Gauthier & Nuss, 2015; Hagino-Yamagishi, 2008; Kim, Farchione, Potter, Chen, & Temple, 2019; Jüngling et al., 2015; Pape, Jüngling, Seidenbecher, Lesting, & Reinscheid, 2010; Tovote, Fadok, & Lüthi, 2015).

Our research group has previously reported efficacy in social anxiety disorder for another intranasally administered pherine, PH94B (Liebowitz et al., 2014; Liebowitz et al., 2016) that also is active via the nasal chemosensory system. Noteworthy about both PH94B and PH10 is that they are administered in microgram dosages.

The major limitation to this trial is its small sample size, which limits the generalizability of the findings. The study population was selected to not be treatment resistant, so it is not clear how PH10 would perform with subjects having treatment resistant depression (TRD). Also, there was no outcome measurement point before one week of treatment, so it cannot be determined from this study if PH10 has efficacy before 7 days of treatment. It should be noted that at the end of the first week of treatment with High Dose PH10 (Treatment Week 1) there was a significant reduction of the HAM-D-17 scores as compared with the effect of placebo ($t = 2.35$, $p = 0.03$; Table 2). This finding, the progressive improvement of HAM-D-17 scores along the treatment period with PH10 (figure 4), and a previous study in healthy volunteers showing a rapid onset of effect of PH10 on autonomic nervous system parameters (Monti et al., 2001) suggest that the antidepressant effect of PH10 may have started on Study Day 1. However, the rapid onset of efficacy of PH10 needs to be further evaluated using an appropriate study design. One of the exciting things that is occurring in the treatment of depression is the emergence of medications with novel mechanisms and novel delivery systems. PH10 shares its intranasal delivery with esketamine, an NMDA channel blocker recently approved for treatment-resistant depression (Kim, Farchione, Potter, Chen, & Temple, 2019). However, esketamine is active systemically while PH10 is active locally on peripheral nasal chemosensory receptors. In addition, PH10 differs from esketamine in PH10's more benign adverse event profile; esketamine at present has to be administered in medically supervised settings.

Given its steroidal chemical structure, PH10 can be classified as a neuroactive steroid. Another synthetic neuroactive steroid, SAGE-217, has recently demonstrated rapid antidepressant effects (Gunduz-Bruce et al., 2019). However, unlike SAGE-217, PH10 is not a direct GABA modulator and so far does

not seem to be sedating (out of 30 subjects that completed the study, only one reported mild sedation). In conclusion, ultra-low doses of intranasal PH10 may be effective for MDD, may have a rapid onset of efficacy, appear safe and well tolerated, do not induce sedation, and most importantly, may represent a new antidepressant mechanism of action. The findings need to be replicated in larger samples.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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