UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
PURSUANT TO SECTION 13 OR 15(d) of the SECURITIES EXCHANGE ACT OF 1934

Date of Report (Date of earliest event reported): January 8, 2024

Vistagen Therapeutics, Inc.
(Exact name of registrant as specified in its charter)

NEVADA	**000-54014**	**20-5093315**
(State or other jurisdiction of incorporation)	*(Commission File Number)*	*(IRS Employer Identification Number)*

343 Allerton Ave.
South San Francisco, California 94090
(Address of principal executive offices)

(650) 577-3600
(Registrant's telephone number, including area code)

Not Applicable
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a -12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d -2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e -4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.001 per share	VTGN	Nasdaq Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (17 CFR 230.405) or Rule 12b-2 of the Securities Exchange Act of 1934 (17 CFR 240.12b-2)

Emerging Growth Company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act ☐

Item 7.01 Regulation FD Disclosure.

On January 8, 2024, Vistagen Therapeutics, Inc. began utilizing a new corporate presentation, a copy of which is attached to this Current Report on Form 8-K as Exhibit 99.1.

Disclaimer.

The information in this Current Report on Form 8-K, including the information set forth in Exhibit 99.1, is being furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "*Exchange Act*"), nor shall Exhibit 99.1 filed herewith be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits Index

Exhibit No.	Description
99.1	Vistagen Therapeutics, Inc. Corporate Presentation, dated January 2024.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

Signatures

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

Vistagen Therapeutics, Inc.

Date: January 8, 2024

By: */s/ Shawn K. Singh*
Shawn K. Singh
Chief Executive Officer


Vistagen
Innovating neuroscience to change the trajectory of global mental health
Corporate Presentation
Nasdaq: VTGN

Forward-looking Statements

This presentation contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements involve known and unknown risks that are difficult to predict and include all matters that are not historical facts. These forward-looking statements include information concerning our product candidates, development efforts, collaborations and/or potential strategic partnerships, intellectual property, financial condition, plans, development programs, prospects or future events and involve known or unknown risks that are difficult to predict. In some cases, you can identify forward-looking statements by the use of words such as "may," "could," "expect," "project," "outlook," "strategy," "intend," "plan," "seek," "anticipate," "believe," "estimate," "predict," "potential," "strive," "goal," "continue," "likely," "will," "would" and variations of these terms and similar expressions, or the negative of these terms or similar expressions. Such forward-looking statements are necessarily based upon estimates and assumptions that, while considered reasonable by us and our management, are inherently uncertain.

Our actual results or developments may differ materially from those projected or implied in these forward-looking statements, and there can be no assurance that any estimate and assumption contained within these forward-looking statements will materialize. As with all pharmaceutical products, there are substantial risks and uncertainties in the process of development and commercialization and actual results or development may differ materially from those projected or implied in these forward-looking statements. Further, there can be no guarantee that any of our drug candidates will successfully complete ongoing or, if initiated, future clinical trials, receive regulatory approval or be commercially successful, or that we will successfully replicate the results of past studies of our product candidates, including fasedienol and itruvone. Other factors that may cause such a difference include, without limitation, risks and uncertainties related to our ability to secure funding that is adequate to support our development and commercialization plans and/or to secure successful strategic global and/or regional development and commercialization partnerships; other risks and uncertainties related to delays in launching, conducting and/or completing ongoing and planned clinical trials; the scope and enforceability of our patents, including patents related to our pherine drug candidates and AV-101; fluctuating costs of materials and other resources and services required to conduct our ongoing and/or planned clinical and non-clinical trials; market conditions; the impact of general economic, industry or political conditions in the United States or internationally; and other technical and unexpected hurdles in the development, manufacture and commercialization of our product candidates. These risks are more fully discussed in the section entitled "Risk Factors" in the Company's most recent Annual Report on Form 10-K for the fiscal year ended March 31, 2023, and in the Company's Quarterly Report on Form 10-Q for the period ended September 30, 2023, as well as discussions of potential risks, uncertainties, and other important factors in our other filings with the U.S. Securities and Exchange Commission (SEC). Our SEC filings are available on the SEC's website at www.sec.gov.

Given these uncertainties, you should not place undue reliance on these forward-looking statements, which apply only as of the date of this presentation and should not be relied upon as representing our views as of any subsequent date.

We explicitly disclaim any obligation to update any forward-looking statements, other than as may be required by law. If we do update one or more forward-looking statements no inference should be made that we will make additional updates with respect to those or other forward-looking statements. Be aware that our development and commercialization plans may change at any time, without public notice, based on the kinds of risk factors described above.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. These data involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates and data.

Our Mission

Pioneering neuroscience to deliver first-in-class therapies for psychiatric and neurological disorders

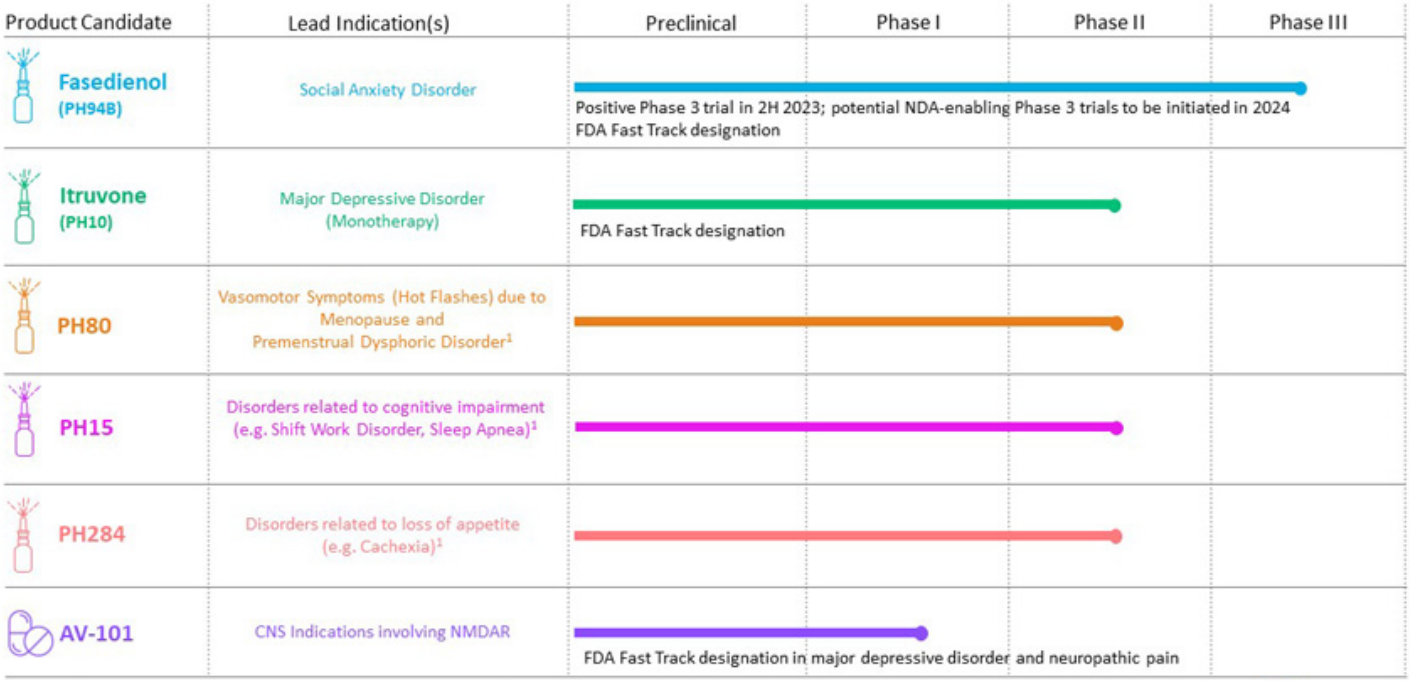
Vistagen

Investment Highlights

- Deep clinical-stage pipeline with six drug candidates targeting large markets
- Differentiated MOAs to move beyond currently approved therapies
- Lead candidate with positive Phase 3 data for acute treatment of social anxiety disorder
- Potential NDA-enabling program in social anxiety disorder funded and underway
- Experienced neuroscience product development team and clinical advisors

Vistagen

Clinical-stage Pipeline



1. Indicates U.S. IND-enabling work necessary to facilitate further Phase 2 clinical development in the U.S.

Vistagen


Vistagen
Pherines
A novel class of neuroactive therapies

Pherines

First-in-class neuroscience therapies for psychiatric and neurological disorders

- Rapidly active in minutes rather than hours or days
- Odorless and tasteless
- Favorable safety profiles observed in all clinical trials to date – do not bind to abuse-related receptors
- Locally metabolized – no need for systemic absorption or uptake by the brain
- Trigger specific receptors to activate chemosensory neurons in the mucosa lining the nasal passages, which in turn signal subgroups of olfactory bulb neurons (OBNs)
- OBN subgroups activate neural circuitry connected to deeper brain structures, including the limbic amygdala, hypothalamus, hippocampus, locus coeruleus, and prefrontal cortex
- Affect brain structures indirectly via neural circuitry instead of targeting a single gene, protein, neuron, or synapse in the brain

Vistagen


Vistagen
Fasedienol Nasal Spray
for the Acute Treatment of
Social Anxiety Disorder
Setting a new standard of care for anxiety disorders

Social Anxiety Disorder Is a Serious Mental Health Condition

SAD is not medicalized shyness. It is a chronic disorder characterized by …

Debilitating emotional and physical symptoms

- Emotional Symptoms
  - Overwhelming fear
  - Surges of anxiety
  - Extreme self-consciousness
  - Isolation leading to depression
- Physical Symptoms
  - Blushing / Sweating
  - Trembling
  - Nausea
  - Fast heartbeat / Chest discomfort
  - Shortness of breath / Dizziness

In everyday social or performance situations

Meeting new people

Presenting at work or school

Public speaking

Interviewing for a job

Eating/drinking in front of others

Making a phone call

Source: ADAA Social Anxiety Brochure 2021

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SAD Affects ~10% of the U.S. Population, with only ~20% of SAD Patients Helped by Current Pharmacotherapy

It has been over 2 decades since the current SAD therapies were approved by the FDA

Treatable Patients

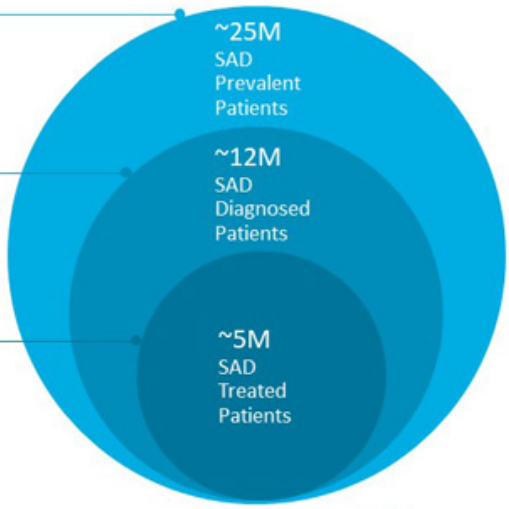
Patients suffering but unaware they may have SAD or not yet motivated to seek professional help

Underserved Patients

Patients unsatisfied with or unwilling to use current treatment options due to efficacy, side effects, or addiction potential

Existing Patients

Patients cycling through treatments, often unsatisfied with their current treatment options but without alternatives



Sources: Kantar Health. Nov 2021. National Health and Wellness Survey (NHWS), 2021. [U.S.]. Malvern, PA.

Vistagen

Current SAD Treatments Fall Short of Physicians' Preferred Product Profile

There is no FDA-approved acute treatment for SAD

Desired Product Profile of Treatments for Social Anxiety Disorder							
Drug	Fast-acting	Non-systemic	No Long-term Side Effects	Non-sedating*	No Cognitive/ Motor Impairment	No Withdrawal Syndrome	No Abuse Potential
FDA-approved **(sertraline, paroxetine, venlafaxine)**	⊖	⊖	⊖	✓	✓	⊖	✓
Off-label (benzodiazepines)	✓	⊖	⊖	⊖	⊖	⊖	⊖
Physicians' Preferred SAD Therapy	✓	✓	✓	✓	✓	✓	✓

* Non-sedative hypnotic agents

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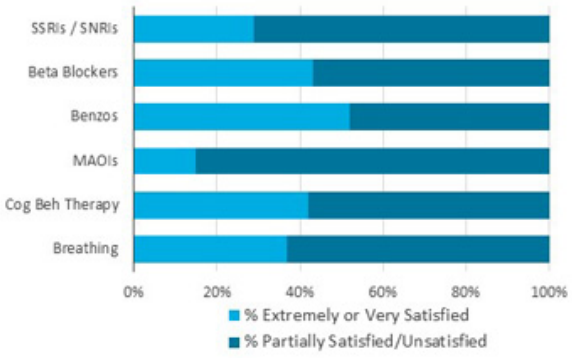
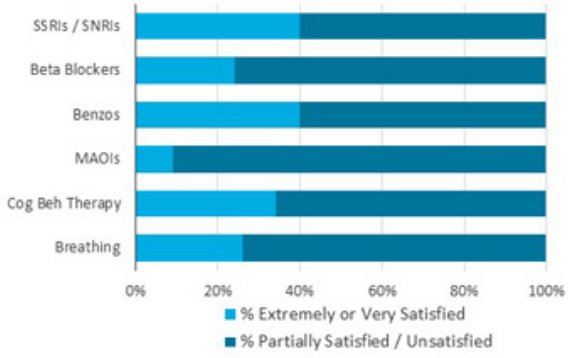
Physician Satisfaction with Therapies Currently Prescribed for Acute Episodes of SAD Is Modest

Psychiatrists (n=125)



Primary Care Physicians (n=126)

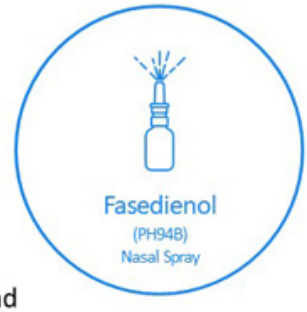


Sources: Vistagen Proprietary Market Research, Online Survey, Jan 2022

Vistagen

Fasedienol Brings New Optimism for the Acute Treatment of SAD

- De-risked potential NDA*-enabling pathway with positive results of PALISADE-2 Phase 3 trial for the acute treatment of SAD reported in 2H 2023
- Novel mechanism of action (MOA) differentiated from all approved products
- Designed for patient-tailored administration, with potential use analogous to an as-needed rescue inhaler for asthma
- No observed systemic absorption or direct activity on neurons in the brain
- Does not bind to GABA receptors to potentiate GABA
- Favorable tolerability profile and no evidence of abuse liability potential
- Successful use over time has potential to build confidence and reduce fear, anxiety, and avoidance of social anxiety stressors
- Target product profile aligns with preferences of patients and providers
- FDA Fast Track designation granted



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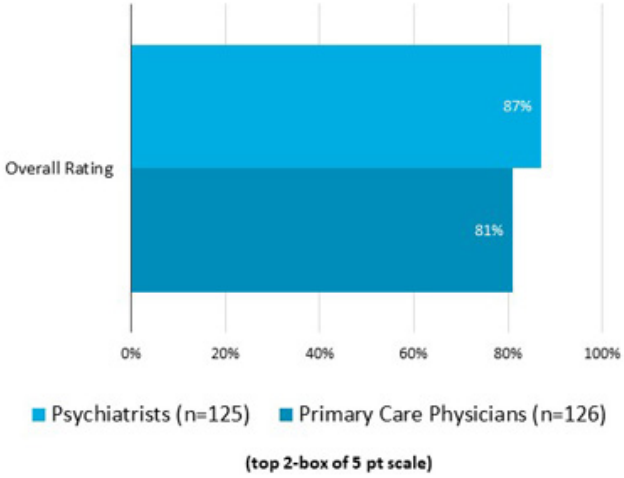
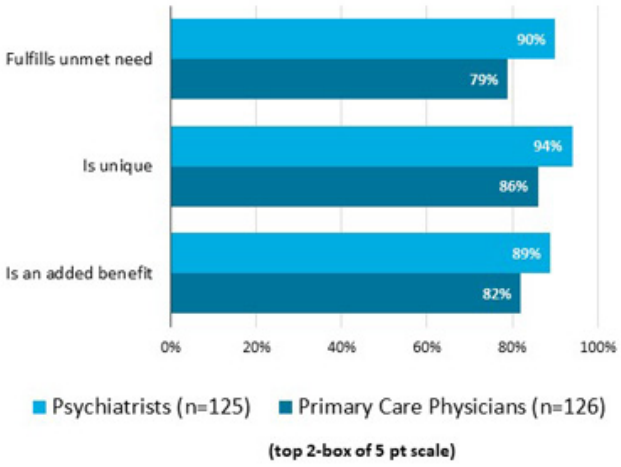
*NDA = New Drug Application

Blinded Fasedienol Target Product Profile Rated Highly by Psychiatrists and Primary Care Physicians





Sources: Vistagen Proprietary Market Research, Online Survey, Jan 2022 (n=251)

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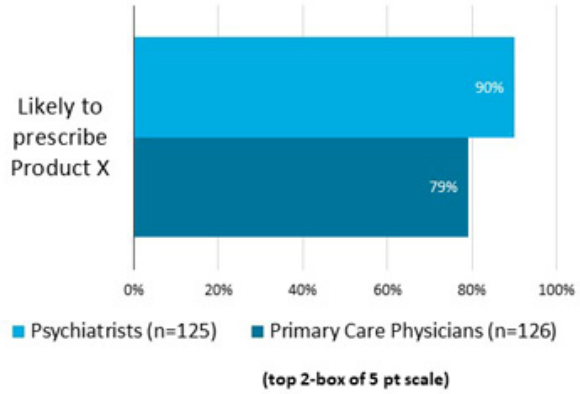
Psychiatrists and Primary Care Physicians Indicate High Intent to Prescribe a Product with Fasedienol's Profile and Note it Would Be Appropriate for the Majority of their SAD Patients



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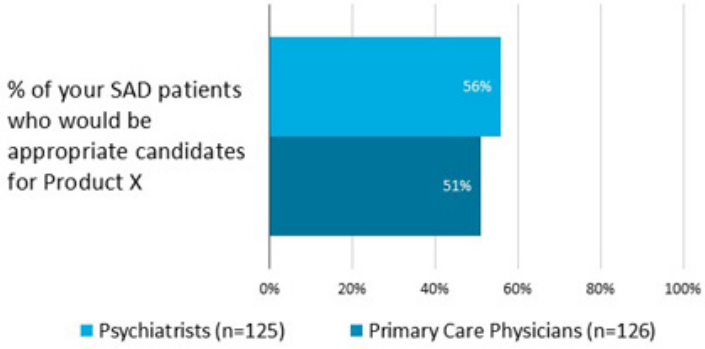
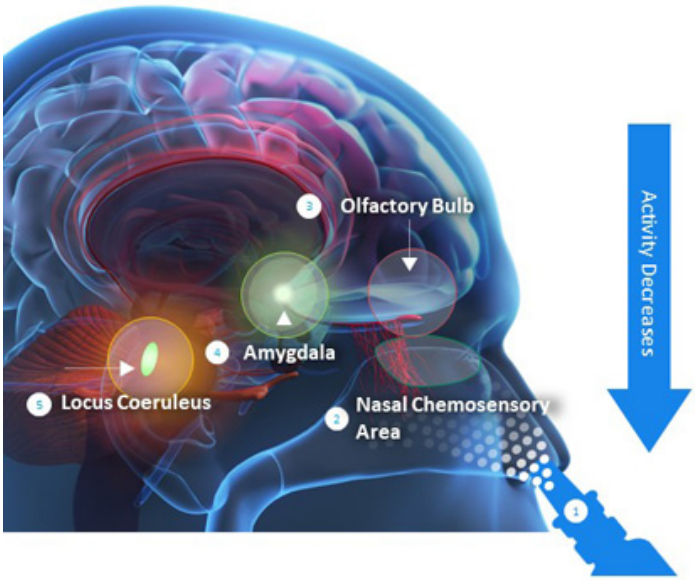


Sources: Vistagen Proprietary Market Research, Online Survey, Jan 2022 (n=251)

Vistagen

Fasedienol's Novel Proposed Mechanism of Action

Differentiated from all current therapies for anxiety disorders



Activity Decreases

1. Microgram-level intranasal dose of fasedienol is administered
2. Fasedienol engages specific peripheral receptors in nasal chemosensory neurons (NCNs)
3. Once stimulated with fasedienol, NCNs then trigger subsets of interneurons in the olfactory bulbs (OBs)
4. Neurons in the OBs then stimulate inhibitory GABAergic "Fear Off" neurons in the limbic amygdala, the main fear and anxiety center of the brain
5. The stimulation of the limbic amygdala DECREASES the activity of the sympathetic nervous system which facilitates fear extinction activity of the limbic-hypothalamic system, as well as in other parts of the brain

Sources: Monti L, and Liebowitz MR (2020). Neural circuits of anxiolytic and antidepressant pherine molecules. CNS Spectrums https://doi.org/10.1017/S109285292000190X

Vistagen

PALISADE-2 Phase 3 Trial for Acute Treatment of SAD

PALISADE-2

Public speaking challenge

Study Design

A U.S. randomized, multi-center, double-blind, placebo-controlled, single-dose administration Phase 3 trial to evaluate the efficacy, safety, and tolerability of fasedienol for the acute treatment of anxiety in adult subjects with social anxiety disorder induced by a public speaking challenge in a clinical setting

Screening Criteria

Inclusion Criteria

+ SAD diagnosis; LSAS > 70
+ HAMD < 18 at screening
+ Normal olfactory function, Quick Olfactory Test if suspected necessary
+ No recent history of COVID-19

Exclusion Criteria

— Significant psychiatric illness, use of psychotropic medication
— Suicidal behavior
— Alcohol or substance use disorder
— Significant nasal pathology

Outcome Measures

Primary Endpoint

- Change in mean SUDS scores from baseline compared to placebo

Secondary Endpoint

- Responder Rates based on Clinical Global Impression – Improvement

Vistagen

Positive PALISADE-2 Phase 3 SAD Trial Top-line Results

Clinically meaningful results across primary, secondary, and exploratory endpoints

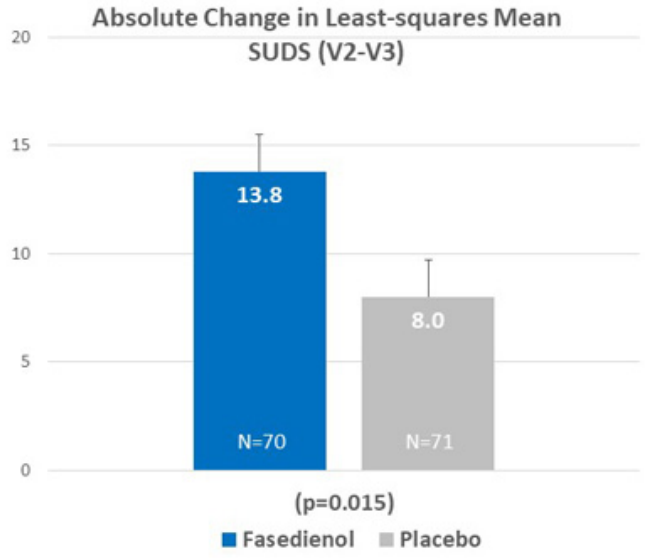
PALISADE-2 Endpoints	*P Value*
1° Met Primary Endpoint: Change in Least-squares mean SUDS scores vs. placebo (from Visit 2 to Visit 3)	**p = 0.015**
2° Met Secondary Endpoint: CGI-I proportion of responders vs. placebo (much or very much less anxious from Visit 2 to Visit 3)	**p = 0.033**
Met Exploratory Endpoint: PGI-C proportion of responders vs. placebo (much or very much less anxious from Visit 2 to Visit 3)	**p = 0.003**
Met Exploratory Endpoint: SUDS proportion of responders vs. placebo (≥20-point improvement in SUDS score from Visit 2 to Visit 3)	**p = 0.020**
Well-tolerated, consistent with fasedienol studies completed to date	

Vistagen

PALISADE-2 Primary Efficacy Endpoint: Change in Least-squares Mean SUDS Scores from V2 to V3 vs. Placebo

PALISADE-2

Met primary efficacy endpoint with a change from Baseline of 5.8 points better than placebo



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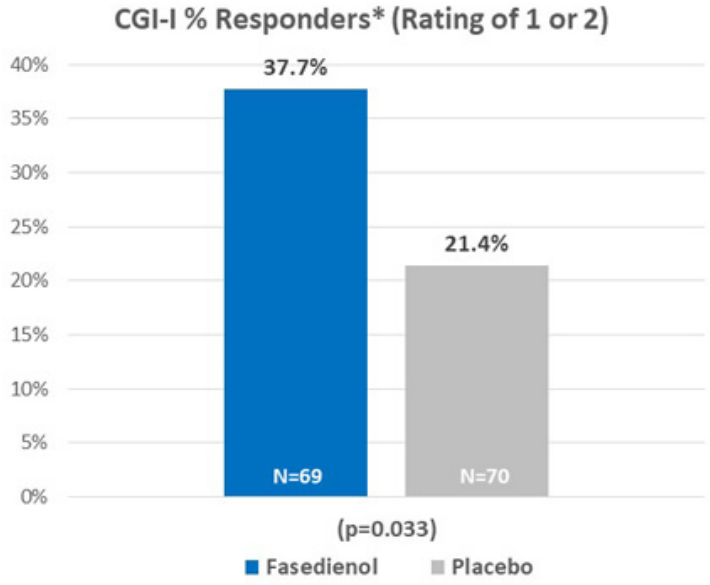
PALISADE-2 Secondary Efficacy Endpoint: CGI-I Responders vs. Placebo at V3

PALISADE-2

Met secondary efficacy endpoint with fasedienol responders 1.8 times greater than placebo



CGI-I Score

1 = Very Much Less Anxious
2 = Much Less Anxious
3 = A Little Less Anxious
4 = No Change
5 = A Little More Anxious
6 = Much More Anxious
7 = Very Much More Anxious

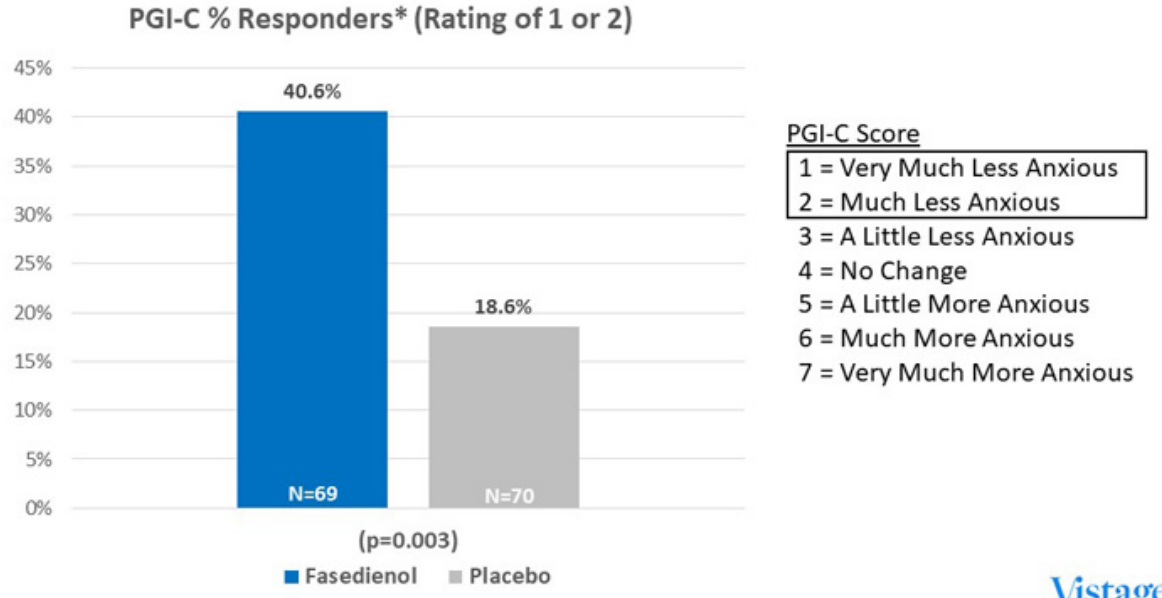
Vistagen

* In accordance with FDA-aligned, pre-specified statistical analysis plan, missing CGI-I values for one subject on placebo and one subject on fasedienol were not imputed for the ITT CGI-I responder analysis. The missing values resulted from site error and are considered missing at random.

PALISADE-2 Exploratory Endpoint: PGI-C Responders vs. Placebo at V3

PALISADE-2

Met exploratory endpoint with fasedienol responders 2.2 times greater than placebo



PGI-C Score

1 = Very Much Less Anxious
2 = Much Less Anxious
3 = A Little Less Anxious
4 = No Change
5 = A Little More Anxious
6 = Much More Anxious
7 = Very Much More Anxious

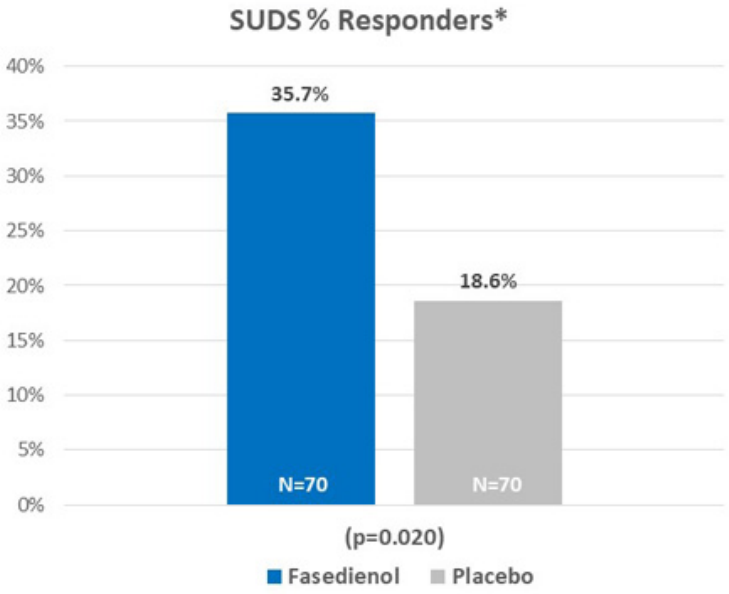
Vistagen

* In accordance with FDA aligned, pre-specified statistical analysis plan, missing PGI-C values for one subject on placebo and one subject on fasedienol were not imputed for the ITT PGI-C responder analysis. The missing values resulted from site error and are considered missing at random.

PALISADE-2 Exploratory Endpoint: SUDS Responders vs. Placebo at V3

PALISADE-2

Met exploratory endpoint with fasedienol responders 1.9 times greater than placebo



SUDS Responders
≥ 20-point improvement from Visit 2 baseline to Visit 3

* In accordance with FDA-aligned, pre-specified statistical analysis plan, missing V3 SUDS values for one subject on placebo were not imputed for the ITT SUDS responder analysis. The missing values resulted from site error and are considered missing at random.

Vistagen

PALISADE-2 Tolerability Profile

PALISADE-2

The tolerability profile of fasedienol was favorable and consistent with results from all fasedienol trials completed to date

- No severe or serious adverse events were reported in this trial
- There were no discontinuations due to adverse events following the single dose of fasedienol
- Adverse events were infrequent and mild or moderate in severity
- There were no treatment-emergent adverse events (TEAEs) reported above a 2% occurrence, except pyrexia in the placebo group (2.49%)

Vistagen

PALISADE Open Label Safety Study

PALISADE-LTSS

Over 30,000 doses self-administered in daily life by 481 SAD patients

Design

Long-term self-administration of 3.2 µg of fasedienol as-needed, up to 4x/day prior to anxiety-provoking social and performance stressors in daily life, with a mean study duration of 4 months, and a maximum study duration of over 10 months

Results

- Long-term self-administration of 3.2 µg of fasedienol as-needed, up to 4x/day, was well-tolerated in adult SAD patients (n=481)
- Of the 481 SAD participants in the study who received at least one dose of fasedienol, at least one treatment-emergent adverse event (TEAE) was reported by 56.8% of subjects, with 54.9% of the 481 participants reporting mild or moderate TEAEs and only 1.9% of participants reporting severe TEAEs
- Headache was the most common TEAE (17.0%; 8.7% drug-related); COVID-19 infection was reported by 11.4% (0% drug-related) of participants
- No other TEAE occurred in more than 5.0% of participants

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Fasedienol Potential U.S. NDA-enabling Phase 3 Clinical Plan*

To complement the positive results from PALISADE-2, Vistagen is preparing to initiate two additional Phase 3 clinical studies of fasedienol for the acute treatment of SAD in 2024

PALISADE-3 and PALISADE-4 Phase 3 Trials with Open-label Extension (OLE)

Design: Phase 3 Acute Treatment Public Speaking Challenge similar to PALISADE-2

Potential OLE: Up to 12 months

Timing: Preparing to begin PALISADE-3 in 1H 2024 and PALISADE-4 in 2H 2024

Target enrollment: Approximately 230 in each Phase 3 study

Vistagen believes either PALISADE-3 or PALISADE-4, if successful, together with PALISADE-2, may establish substantial evidence of the effectiveness of fasedienol in support of a potential U.S. NDA submission to the FDA for the acute treatment of anxiety in adults with SAD in 1H 2026

*Initiation of each of these Phase 3 studies is subject to FDA feedback

Vistagen

PALISADE-3 and PALISADE-4 Phase 3 SAD Trials with OLE*

PALISADE

Study Design

Randomized, multi-center, double-blind, placebo-controlled, single-dose administration Phase 3 trial to evaluate the efficacy, safety, and tolerability of fasedienol for the acute treatment of anxiety induced by a public speaking challenge in adult subjects with social anxiety disorder in a clinical setting

Criteria

Inclusion Criteria

+ Female and male subjects; age 18-65
+ SAD diagnosis; LSAS ≥ 70; HAMD<18
+ Normal olfactory function determined by Quick Olfactory Test
+ Medical and psychiatric health

Exclusion Criteria

— Nasal swab within the past four weeks
— COVID-19 diagnosis + any residual symptoms within past 4 weeks
— Drug use (incl. cannabis), heavy use of alcohol, smoking, vaping
— Other primary psychiatric disorders; receiving CNS active medications

Outcome Measures

Primary Endpoint

- Change in mean SUDS scores from V2 to V3 compared to placebo

Secondary Endpoints

Responder rates at V3 vs placebo:

- Patient Global Impression of Change
- Clinical Global Impression – Improvement

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*OLE = Open Label Extension. Vistagen is preparing to initiate these Phase 3 studies in 2024, subject to FDA feedback

Fasedienol Phase 2 Repeat Dose Study with OLE*

Study Design

Randomized, multi-center, double-blind, placebo-controlled, repeat-dose administration Phase 2B trial to evaluate the efficacy, safety, and tolerability of a repeat dose of fasedienol for the acute treatment of anxiety induced by a public speaking challenge in adult subjects with social anxiety disorder in a clinical setting

Criteria

Inclusion Criteria

+ Female and male subjects; age 18-65
+ SAD diagnosis; LSAS ≥ 70; SUDS ≥ 75 at V2
+ Normal olfactory function determined by Quick Olfactory Test
+ Medical and psychiatric health

Exclusion Criteria

— Nasal swab within the past four weeks
— COVID-19 diagnosis + any residual symptoms within past 4 weeks
— Drug use (incl. cannabis), heavy use of alcohol, smoking, vaping
— Other primary psychiatric disorders; receiving CNS active medications

Outcome Measures

Primary Endpoint

- Change in mean SUDS scores from V2 to V3 for single dose and repeat dose compared to placebo

Secondary Endpoint

Responder rates at V3 vs placebo:

- Patient Global Impression of Change
- Clinical Global Impression – Improvement

*OLE = Open Label Extension. Vistagen is preparing to initiate this Phase 2 study in 2H 2024, subject to FDA feedback

Vistagen


Vistagen
Itruvone Nasal Spray
for Major Depressive Disorder
Setting a new standard of care for depression disorders

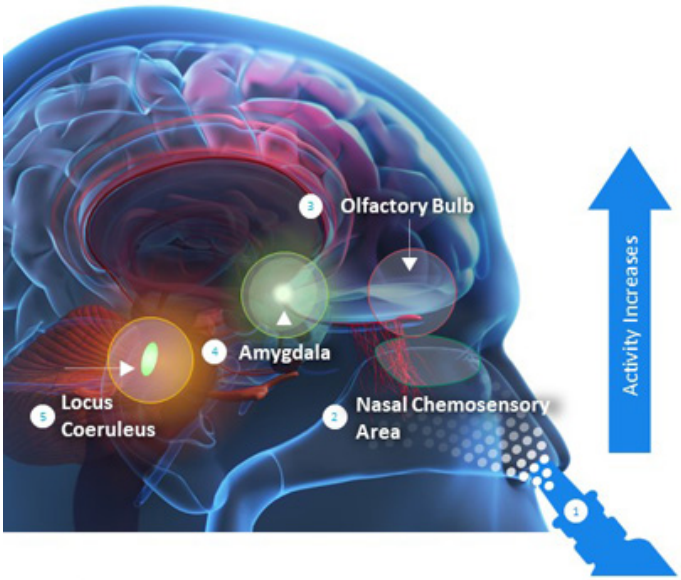
Itruvone is a Novel Potential Monotherapy for Major Depressive Disorder (MDD)

- Innovative odorless, tasteless synthetic neuroactive nasal spray
- Designed for rapid-onset antidepressant effects
- Novel and differentiated MOA from all approved antidepressants
- Observed to be non-systemic, non-sedating, non-addictive; does not not bind to GABA receptors to potentiate GABA
- Positive exploratory Phase 2A trial completed (n=30)
- Well-tolerated in all clinical studies to date
- FDA Fast Track designation granted

Vistagen

Itruvone's Novel Proposed Mechanism of Action

Differentiated from all current therapies for depression disorders



1. Microgram-level intranasal dose of itruvone is administered
2. Itruvone engages specific peripheral receptors in nasal chemosensory neurons (NCNs)
3. Once stimulated with itruvone, NCNs trigger subgroups of interneurons in the olfactory bulbs (OBs)
4. Neurons in the OBs then stimulate GABAergic and CRH neurons in the limbic amygdala
5. The stimulation of the limbic amygdala INCREASES the activity of the sympathetic autonomic nervous system and the release of catecholamines from the midbrain

Sources: Monti L, and Liebowitz MR (2020). Neural circuits of anxiolytic and antidepressant pherine molecules. CNS Spectrums https://doi.org/10.1017/S109285292000190X

Vistagen

Itruvone Antidepressant Effects in Phase 2A MDD Study

Design: Phase 2A randomized, double-blind, placebo-controlled, parallel design POC clinical study (n=30)

Dosing: 3.2 μg or 6.4 μg of itruvone or placebo i.n., 2 times per day for 8 weeks

Primary Endpoint: Change in HAMD-17 scores from baseline compared to placebo

Results:

- 6.4 μg dose significantly reduced depressive symptoms as early as one week based on HAMD-17 scores compared to placebo (p=0.022)
- 3.2 μg dose showed a trend (p=0.101)
- Strong effect sizes for both 3.2 μg and 6.4 μg vs. placebo at 1 week and at 8 weeks

Safety & Tolerability: Well-tolerated, no serious adverse events observed, no dissociative side effects, no reports of weight gain or sexual dysfunction

Results support advancement to potential Phase 2B clinical development

Rapid-onset antidepressant effects with itruvone observed in MDD study participants with minimal side effects

Sources: Monti, L., Nicolini, H., Liebowitz, M., & Hanover, R. (2019). "A Placebo Controlled Trial of PH10: Test of a New Rapidly Acting Intranasally Administered Antidepressant." *Br J Phar Med Res* 4(6): 2157-2168.

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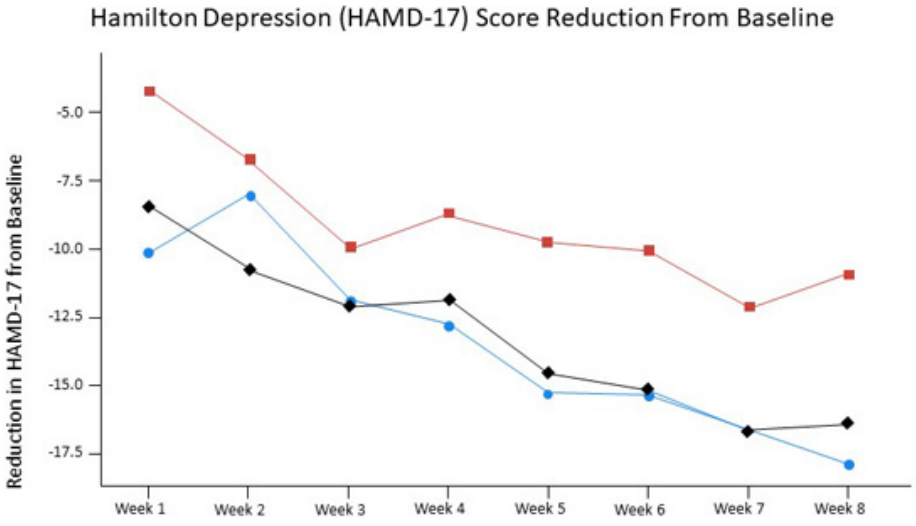
Itruvone Phase 2A MDD Study



6.4 µg dose produced rapid-onset and sustained antidepressant effects in MDD study participants with minimal side effects

Itruvone Dose	HAMD-17 Score	p (itruvone vs placebo)	Cohen's D (Effect Size)
3.2 µg (Low Dose)	-16.3	0.101	0.74
6.4 µg (High Dose)	-17.8	0.022	0.95
Placebo	-10.9	--	--

Sources: Monti, L., Nicolini, H., Liebowitz, M., & Hanover, R. (2019). "A Placebo Controlled Trial of PH10: Test of a New Rapidly Acting Intranasally Administered Antidepressant." *Br J Phar Med Res* 4(6): 2157-2168.

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Itruvone Phase 2B Clinical Plan*

Planning for potential Phase 2B development of itruvone as an innovative, non-systemic monotherapy for MDD is underway

- Potential Design: Double-blind, randomized, placebo-controlled, parallel study in approximately 200 total male and female subjects (18 to 65 years old) with a confirmed diagnosis of MDD, who are not currently taking any antidepressants
- Outpatient self-administration of 6.4 µg (3.2 µg twice daily) itruvone nasal spray over a 4-week period
- Potential Primary Efficacy Endpoint: Change from Baseline to Day 28 in the HAMD-17 Rating Scale

*Potential Initiation of this Phase 2B study in 2H 2024 is subject to FDA feedback


Vistagen
PH80 Nasal Spray
for Vasomotor Symptoms
(Hot Flashes) due to Menopause
Setting a new standard of care

PH80 Nasal Spray

Potential treatment for vasomotor symptoms (hot flashes) due to menopause and premenstrual dysphoric disorder

- Innovative, rapid-onset product candidate
- Novel and differentiated MOA from all approved products
- Taken as-needed for treatment of multiple menopausal hot flashes daily, potential use analogous to a rescue inhaler for asthma
- Expected to provide relief in the moment, as well as reduce the number and severity of hot flashes over time
- No systemic absorption or direct action on CNS neurons
- Potential safety and tolerability profile advantages over currently approved therapies
- Positive exploratory Phase 2A studies completed in menopausal hot flashes (n=36) and premenstrual dysphoric disorder (n=52)

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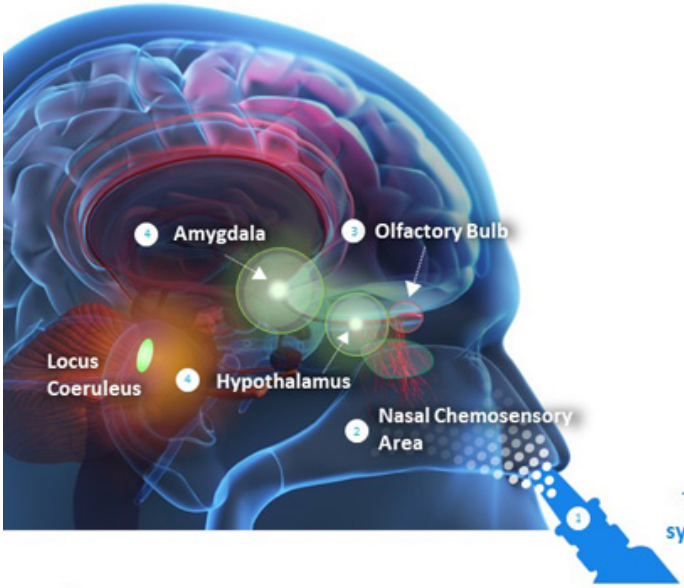
PH80's Novel Proposed Mechanism of Action

Differentiated from all currently approved VMS therapies



1. Microgram-level intranasal dose of PH80 is administered
2. PH80 engages specific peripheral receptors in nasal chemosensory neurons (NCNs)
3. Once stimulated with PH80, NCNs then trigger subgroups of neurons in the olfactory bulbs (OBs)
4. Neurons in the OBs then stimulate neurons in the limbic amygdala and the hypothalamus

Activity Decreases

The stimulation of neurons in the limbic amygdala and the hypothalamus decreases the activity of the autonomic nervous system and decreases activation of the trigeminal-vascular neural circuits

Downstream effects potentially include:

- Decreased irritability;
- Decreased muscle tension;
- Reduced core body temperature; and
- Reduced feeling of internal heat

These changes potentially affect the neural circuits involved in vasomotor symptoms (hot flashes) due to menopause, premenstrual dysphoric disorder (PMDD), and migraine

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Source: Monti L, and Liebowitz MR (2020). Neural circuits of anxiolytic and antidepressant pherine molecules. CNS Spectrums https://doi.org/10.1017/S109285292000190X

PH80 Phase 2A Study in Hot Flashes

Objective: Proof-of-principle evaluation of PH80 efficacy and tolerability for the acute management of VMS (hot flashes) due to menopause

Study Details: Randomized, double-blind, placebo-controlled, Phase 2A study. Participants self-administered PH80 (3.2 µg/dose) or placebo for 4 weeks up to 4 times daily with a dose at night if needed (up to 16 µg/day). Participants were followed up weekly during the treatment period

Participants: Menopausal women aged 45-60 (n=36) with ≥ 8 hot flashes of moderate to severe intensity per day on average for 1 week (≈ 56/week)

Outcome Measures: Daily ratings of the Number, Severity, Disruption in function (Bother), and Sweating associated with daily hot flashes, PGI-C, CGI-I, Safety, and Tolerability

Results: PH80 showed statistically and clinically significant improvement vs. placebo in the number and severity of hot flashes while also significantly reducing participant-reported disruption in function and sweating associated with hot flashes

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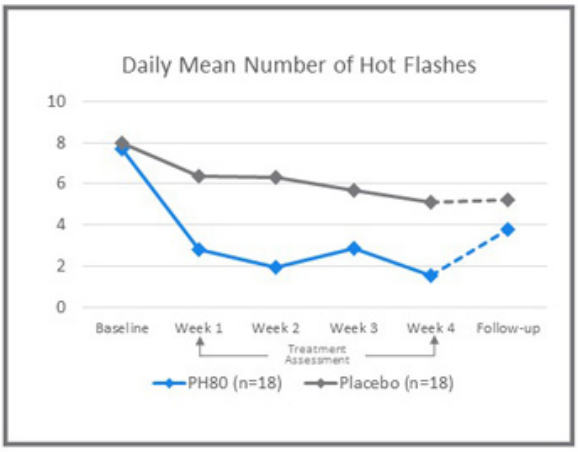
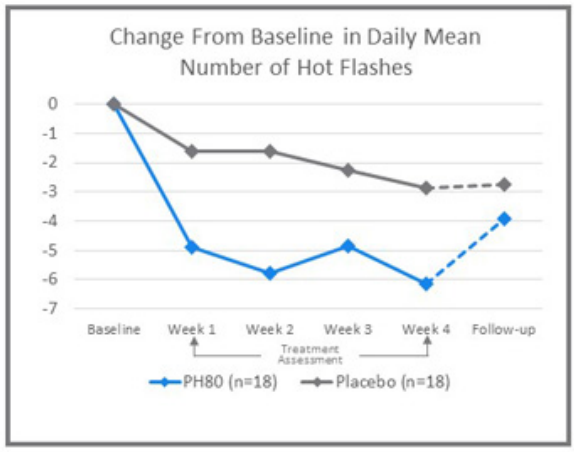
PH80 Phase 2A Study in Hot Flashes: Met Primary Efficacy Endpoint

Statistically and clinically significant improvement vs. placebo in the number of hot flashes at 1 week and maintained through 4 weeks of treatment (p<.001)





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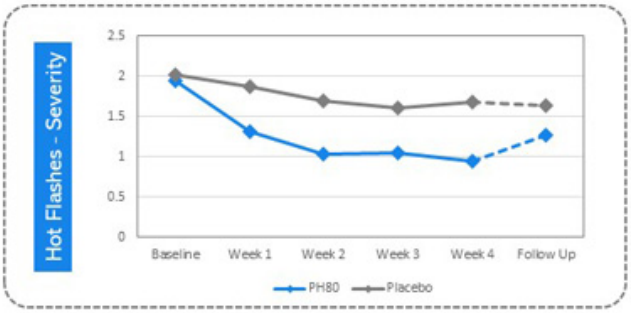
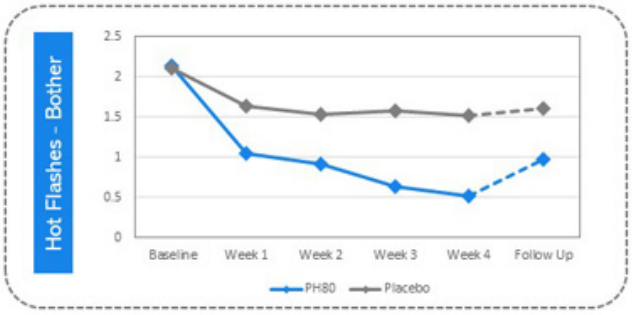
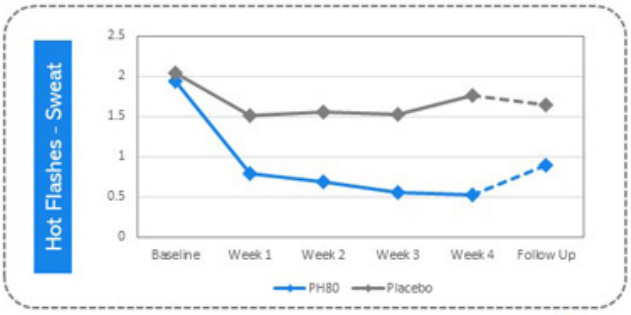
PH80 Phase 2A Study in Hot Flashes: Met Secondary Efficacy Endpoints

PH80 also significantly reduced participant-reported severity, disruption in function (Bother), and sweating associated with hot flashes during the treatment period as compared with placebo







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PH80 Phase 2A Study in Premenstrual Dysphoric Disorder (PMDD)

Objective: Proof-of-principle evaluation of PH80 efficacy and tolerability for the acute management of the symptoms of PMDD

Study Details: Randomized, double-blind, placebo-controlled, exploratory Phase 2A study. Subjects who did not respond to placebo at a screening visit returned after the onset of symptoms during the next menstrual cycle. At the second study visit, subjects were randomized to receive either 0.9 µg PH80 nasal spray or placebo, self-administered at home as-needed, up to 4 times per day for 6 consecutive days

Participants: Women aged 18-40 (n=52) with at least 1 year of experiencing PMDD symptoms and Premenstrual Tension Scale (PMTS) score ≥ 10. Individuals with relevant pre-existing conditions or use of SSRIs were excluded

Outcome Measures: Penn Daily Symptom Report (DSR), Premenstrual Tension Scale (PMTS), PGI-C, CGI-I, Safety, and Tolerability

Results: PH80 showed statistically and clinically significant improvement vs. placebo in symptoms of PMDD at study endpoint after 6 days of treatment (during the critical days of the menstrual period) based on DSR (p=0.008) and PMTS (p=0.006) and was well-tolerated with no serious adverse events

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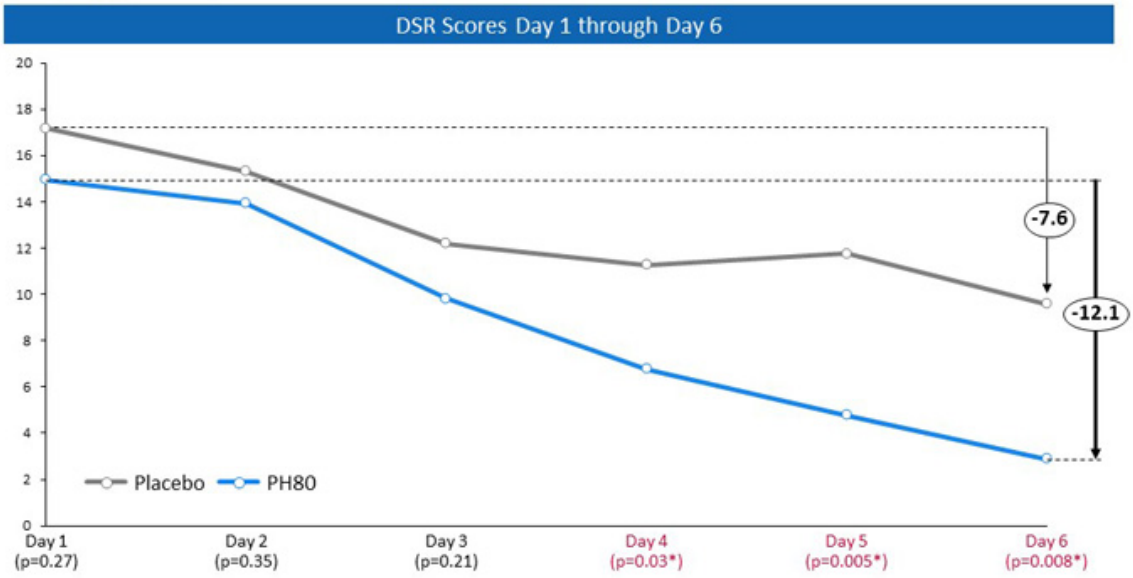
PH80 Phase 2A Study in PMDD: Met Primary Efficacy Endpoint

PH80 treatment resulted in significant separation in PMDD DSR scores vs placebo from Day 4 through Day 6 (p=.008)



* Denotes Statistical Significance

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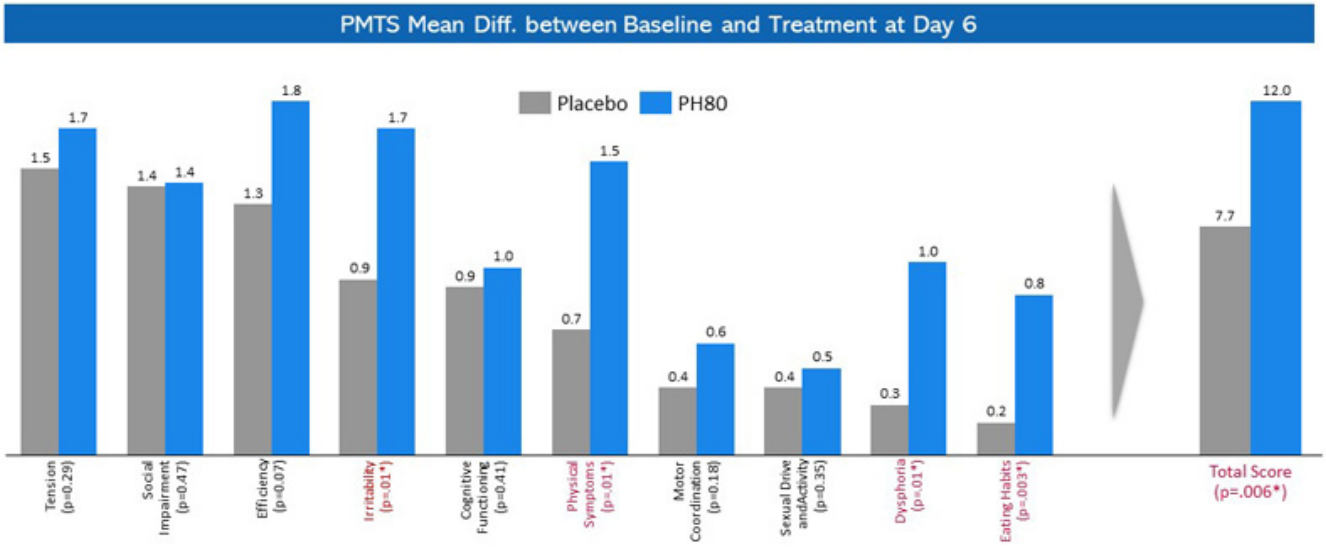
PH80 Phase 2A Study in PMDD: Met Primary Efficacy Endpoint

PH80 resulted in clinically significant reduction in PMTS from baseline vs Placebo (p=.006)



* Denotes Statistical Significance

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PH15 Nasal Spray
for Acute Treatment of
Cognitive Impairment
caused by Mental Fatigue
Setting a new standard of care

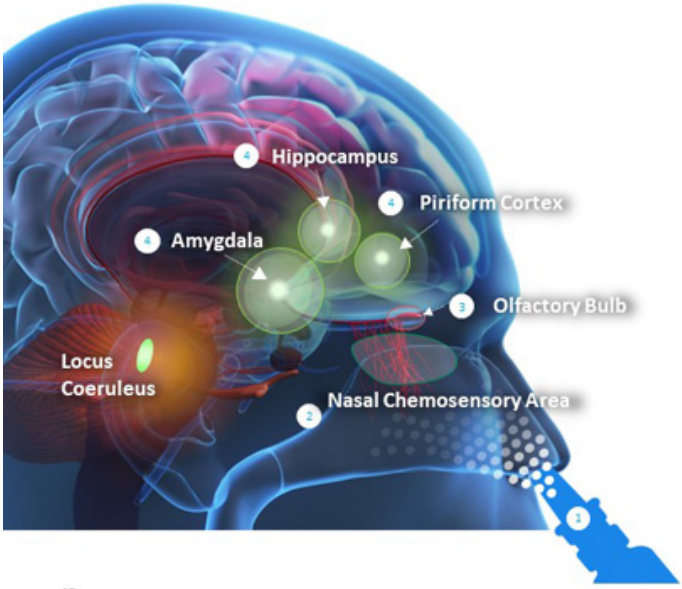
PH15 Nasal Spray

Potential for improvement of cognitive impairment caused by mental fatigue

- Novel and differentiated MOA provides potential new treatment for acute improvement of cognition and disorders that cause sleep deprivation and ensuing fatigue and cognitive impairment (e.g., Shift Work Disorder, Sleep Apnea, and Narcolepsy)
- Rapid-onset
- No systemic absorption
- No direct activity on neurons in the brain

PH15 Novel Proposed Mechanism of Action

Differentiated from all currently approved therapies



1. Microgram-level intranasal dose of PH15 is administered
2. PH15 engages specific peripheral receptors in nasal chemosensory neurons (NCNs)
3. Once stimulated with PH15, NCNs then trigger subgroups of neurons in the olfactory bulbs (OBs)
4. Neurons in the OBs then directly stimulate neurons in several areas of the basal forebrain including the hippocampus, amygdala, and piriform cortex

Activity Increases

Increased activity in the hippocampus is responsible for improvement in cognitive function

Increased activity in the limbic amygdala in turn increases activity in the cerebral cortex, leading to improved psychomotor function

Sources: Monti L, and Liebowitz MR (2020). Neural circuits of anxiolytic and antidepressant pherine molecules. CNS Spectrums https://doi.org/10.1017/S1092852920001901X

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PH284 Nasal Spray
for Acute Treatment of
Wasting Syndrome (Cachexia)
Setting a new standard of care

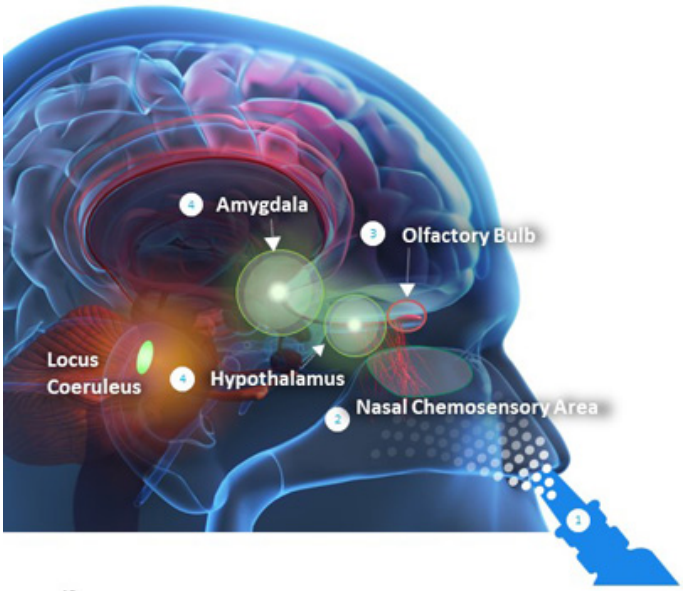
PH284 Nasal Spray

Potential acute treatment for wasting syndrome (cachexia)

- Innovative, fast-acting therapy for appetite enhancement
- Intranasal administration, taken before meals
- Potential to increase subjective feelings of hunger and caloric intake in patients diagnosed with wasting syndrome, a severe consequence of many chronic diseases and advanced cancer
- Favorable tolerability and promising clinical activity
- Novel and differentiated MOA targets a neuronal circuit associated with appetite stimulation instead of a single gene, protein, neuron, or synapse, which may have therapeutic potential in wasting syndrome (cachexia)

PH284 Novel Proposed Mechanism of Action

Differentiated from current treatment options



1. Microgram-level intranasal dose of PH284 is administered
2. PH284 engages specific peripheral receptors in nasal chemosensory neurons (NCNs)
3. Once stimulated with PH284, NCNs then trigger subsets of neurons in the olfactory bulbs (OBs)
4. Neurons in the OBs then stimulate neurons in the amygdala and the arcuate nucleus of the hypothalamus

Activity Increases

The stimulation of neurons in the arcuate nucleus of the hypothalamus increases activity of aguti-related peptide (AGRP) neurons and neuropeptide Y (NPY) neurons, which increase appetite and decrease energy expenditure

Both are key regulators of feeding, energy balance, and metabolic homeostasis

Sources: Monti L, and Liebowitz MR (2020). Neural circuits of anxiolytic and antidepressant pherine molecules. CNS Spectrums https://doi.org/10.1017/S1092852920001901X

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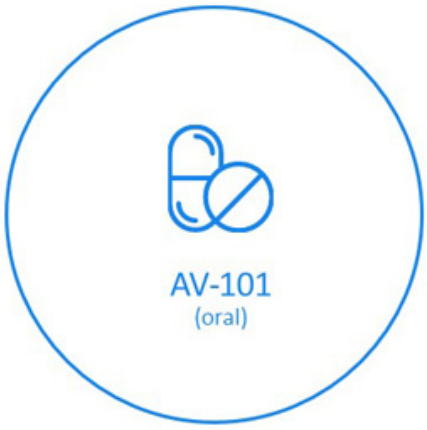
AV-101
for Potential Phase 2A Development
Setting a new standard of care for disorders involving the NMDA receptor

AV-101 for Multiple Disorders

Designed to inhibit (but not block) NMDA receptor activity

- Oral prodrug of 7-Cl-KYNA, a potent and selective full antagonist at the glycine site of the NMDA receptor
- Inhibition of the NMDA receptor, without fully blocking the receptor like ketamine and other NMDAR antagonists, is thought to reduce the side effect burden
- Well-tolerated in all clinical studies to date
- FDA Fast Track designations granted for adjunctive treatment of MDD and treatment of neuropathic pain
- Assessing go forward opportunities for collaborative Phase 2 development




Levodopa-Induced Dyskinesia
Associated with Parkinson's therapy


Seizures


Suicidal Ideation


Neuropathic Pain


Major Depressive Disorder

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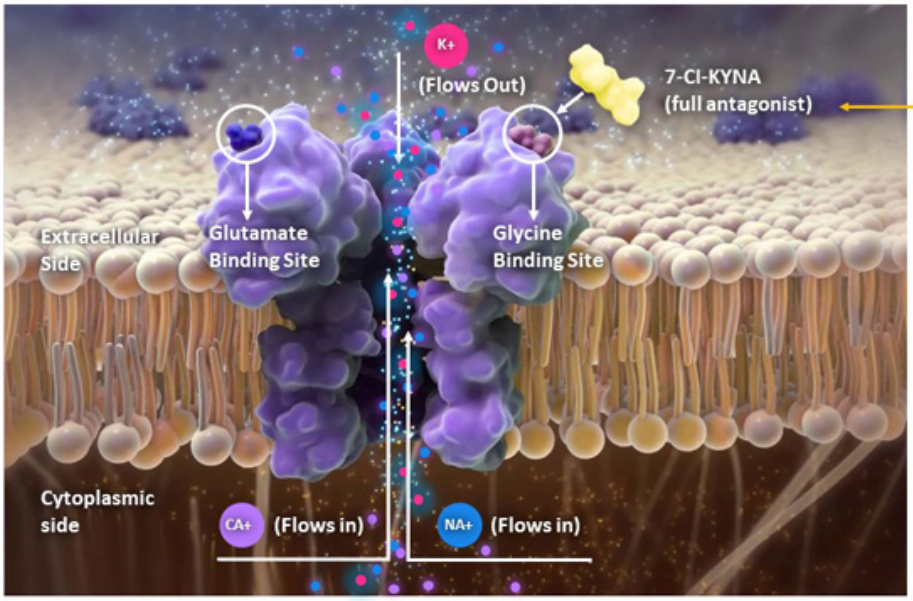
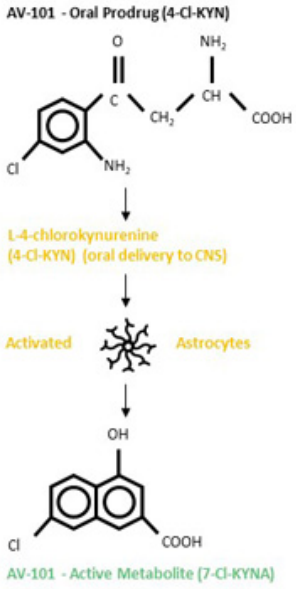
AV-101's Proposed I Mechanism of Action





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Distinguished Clinical and Regulatory Advisors

Representing Premier Institutions and Deep CNS and Regulatory Expertise

Maurizio Fava, M.D.

Professor of Psychiatry, Harvard Medical School; Director, Division of Clinical Research, Massachusetts General Hospital (MGH) Research Institute; and Executive Vice Chair of the Department of Psychiatry

Thomas Laughren, M.D.

Director (retired), U.S. Food and Drug Administration (FDA) Division of Psychiatry Products, Office of New Drugs, Center for Drug Evaluation and Research (CDER)

Michael Liebowitz, M.D.

Former Columbia University psychiatrist, director and founder of the Anxiety Disorders Clinic at the New York State Psychiatric Institute; current Managing Director of The Medical Research Network LLC

Sanjay Mathew, M.D.

Vice Chair for Research and Professor of Psychiatry and Behavioral Sciences at Baylor College of Medicine; Staff Psychiatrist at the Michael E. DeBakey VA Medical Center

Gerard Sanacora, Ph.D., M.D.

Professor of Psychiatry, Yale School of Medicine; Director, Yale Depression Research Program; Co-Director, Yale-New Haven Hospital Interventional Psychiatry Service

Mark Wallace, M.D.

Professor of Clinical Anesthesiology, Chair of the Division of Pain Medicine, Medical Director and Director at the University of California, San Diego

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Vistagen
Fasedienol Nasal Spray
for Social Anxiety Disorder
Additional Information
Setting a new standard of care for anxiety disorders

Subjective Units of Distress Scale (SUDS)

Primary efficacy endpoint in PALISADE Phase 3 trials for acute measurement

The SUDS measures the self-reported intensity of anxiety and/or distress in patients with SAD

Patients are asked to rate their level of anxiety/distress on a scale of 0-100

Physiological signs of distress such as sweating, shaking, increased heart rate or respiration, and gastrointestinal distress may be present at a score of 70, and are present at a score of 80

We believe SUDS has become the standard for acute measurement of anxiety, now leveraged in several recent clinical trials

100	Highest anxiety/distress that you have ever felt
90	Extremely anxious/distressed
80	Very anxious/distressed; can't concentrate
70	Quite anxious/distressed; interfering with functioning
60	Moderate-to-strong anxiety or distress
50	Moderate anxiety/distress; uncomfortable, but can still function
40	Mild-to-moderate anxiety or distress
30	Mild anxiety/distress; no interference with functioning
20	Minimal anxiety/distress
10	Alert and awake, concentrating well
0	No distress; totally relaxed

Sources: Oxford Clinical Psychology. © Oxford University Press, 2014

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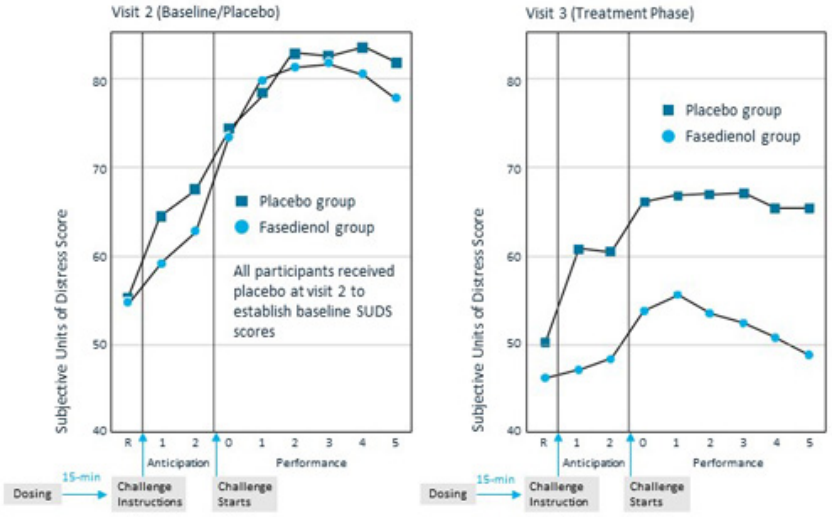
Fasedienol Efficacy in Phase 2 Public Speaking Challenge Trial

Minute-by-minute SUDS scores



Fasedienol rapidly reduced anxiety in response to public speaking challenge		
	Active Group	Placebo Group
Mean Difference	26.7	14.0
Standard Deviation	21.6	16.3
Number of Subjects	45	46
t = 3.16	p = 0.002	Cohen's d (Effect Size)0.66

Subject is told they will have to give a 5-minute speech without notes to an audience of 3 role-players and have 2 minutes to prepare.

Source: Liebowitz, MR, Salman, E, Nicolini, H, Rosenthal, N, Hanover, R, Monti, L (2014). Effect of an acute intranasal aerosol dose of PH94B on social and performance anxiety in women with social anxiety disorder. *Am. J. Psychiatry* 171:675-682.

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Liebowitz Social Anxiety Scale (LSAS)

Primary Efficacy Endpoint for Over Time Measurement

The LSAS is a 24-item clinician-rated scale used to assess how SAD impacts a patient's life across a variety of situations
13 situations pertain to performance (P) and 11 pertain to social situations (S)

- Assesses both the patient's social anxiety in situations as well as avoidance of those situations
- Each item describes a situation about which the patient must answer two questions, one about fear and one about avoidance

Situation	Fear or Anxiety 0 = none 1 = mild 2 = moderate 3 = severe	Avoidance 0 = never 1 = occasionally 2 = often 3 = usually
1. Telephoning in public (P)		
2. Participating in small groups (P)		
⋮	⋮	⋮
23. Giving a party (S)		
24. Resisting a high pressure sales person (S)		

- Scored by summing the item ratings. Below are the suggested interpretations for various score ranges.

Greater than 110: Very severe social anxiety

90–110: Severe social anxiety

70–90: Marked social anxiety

50–70: Moderate social anxiety

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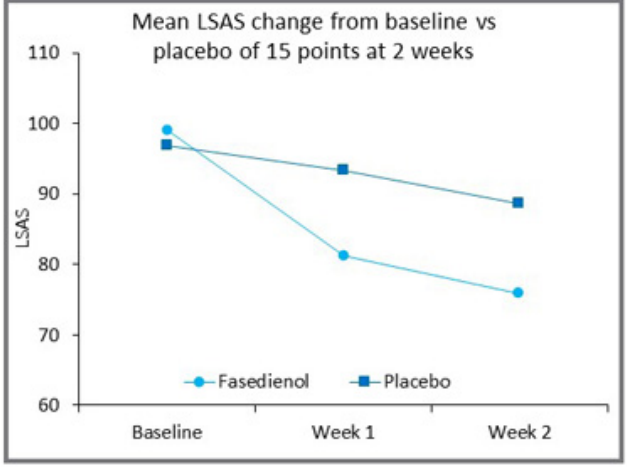
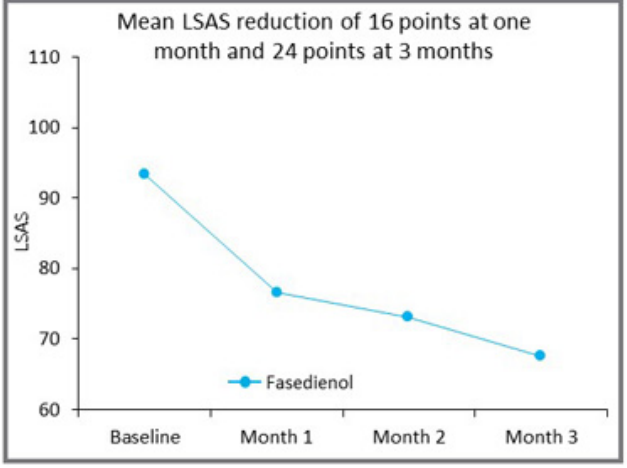
Fasedienol Efficacy Over Time as Measured by the LSAS

Fasedienol used as-needed over time has demonstrated reduction of LSAS scores in two trials

Phase 2 Crossover Study



PALISADE Open-label Safety Study



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Fasedienol Phase 1/1b Data

Well tolerated with reduction in autonomic biomarkers, increased electrical activity, and anxiety effects

Observed Reduction in Autonomic Biomarkers

Statistically significant reduction in heart rate, respiratory rate, and electrodermal activity was observed in both men and women in several studies. Intranasal 0.4 µg fasedienol also significantly increased the amplitude of the electrogram of nasal receptors (EGNR) recorded from the nasal chemosensory epithelium in both men and women.

Increased Electrical Activity of the Nasal Chemosensory Epithelium

Dose dependent increase in electrical activity of the nasal chemosensory epithelium using EGNR was observed in healthy male and female volunteers after ascending doses of fasedienol. Maximal EGNR amplitude was observed at 3.2 µg dose in both men (n=10) and women (n=10). Doses higher than 6.4 µg and up to 12.8 µg were observed not to increase EGNR amplitude and had minimal effect on the duration of the EGNR response.

Efficacy Signal in Anxiety

Observation of rapid decrease in anxiety 30 min after intranasal fasedienol administration in participants with generalized anxiety led to the identification of SAD as the ideal clinical path forward based on input from Dr. Michael Liebowitz.

Sources: **Data on file;** Monti L, and Liebowitz MR (2020). Neural circuits of anxiolytic and antidepressant pherine molecules. CNS Spectrums https://doi.org/10.1017/S109285292000190K; **2023, Human Psychopharmacology: Clinical and Experimental**

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Fasedienol Reduction in Autonomic Biomarkers: Study Results

"Physiologic biomarkers show reduced autonomic nervous system activity after intranasal administration of fasedienol in normal healthy volunteers"

- Three similarly designed Phase 1 studies were conducted in healthy volunteers (n=64; 32 male, 32 female) in a placebo-controlled crossover study design
- Doses ranging from 0.2 µg to 0.4 µg were administered across these studies using an experimental nasal spray device[1] that delivered low microgram doses of fasedienol or placebo locally and topically directly to the receptor area, decreasing the amount of study medication needed to activate the chemosensory receptors below the quantity administered with the metered spray pump used in clinical studies
- Physiologic biomarkers of respiratory rate, heart rate, and electrodermal activity were measured in each of the 3 studies before and after administration of placebo or study medication while subjects were in a resting (no stimulation) state lying comfortably on a medical bed
- **All the physiologic measures of autonomic activity were observed to be transiently and significantly reduced in all 3 studies after intranasal administration of fasedienol, showing a reproducible sympatholytic-like effect consistent with the anxiolytic effect**

Sources: Data on file; Monti L, and Liebowitz MR (2020). Neural circuits of anxiolytic and antidepressant pherine molecules. CNS Spectrums https://doi.org/10.1017/S109285292000190X; 2023, Human Psychopharmacology: Clinical and Experimental

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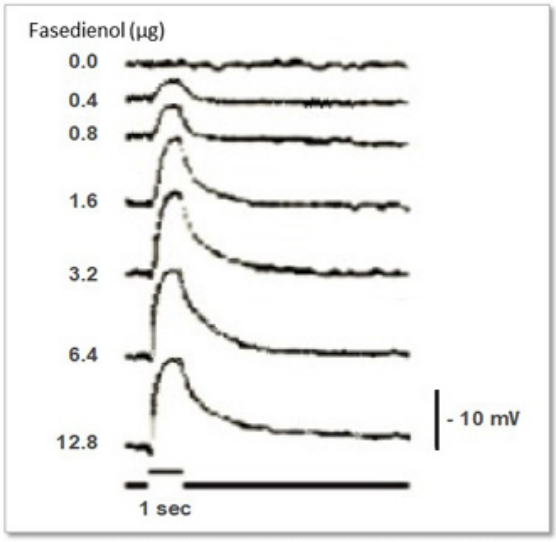
Fasedienol Electrogram of Nasal Receptors (EGNR): Study Results

Dose response led to selection of the effective dose to use in clinical trials



Dose-dependent electrical depolarization of human nasal chemosensory receptor cells in response to fasedienol

The traces show the summated response (EGNR) recorded from the nasal chemosensory receptor area in a representative human volunteer during intranasal administration of fasedienol at the quantities shown at left. Calculated 50% effective dose, ED_{50}= 1 µg

Fasedienol 3.2 µg was observed to be an EGNR response of maximal amplitude. Higher doses (6.4 µg and 12.8 µg) were observed not to produce a significant increase of EGNR amplitude and were observed to minimally increase the duration of the EGNR response

Fasedienol 3.2 µg was selected as the effective dose to use in clinical trials

Source: Monti L, and Liebowitz MR (2020). Neural circuits of anxiolytic and antidepressant pherine molecules. CNS Spectrums https://doi.org/10.1017/S109285292000190X

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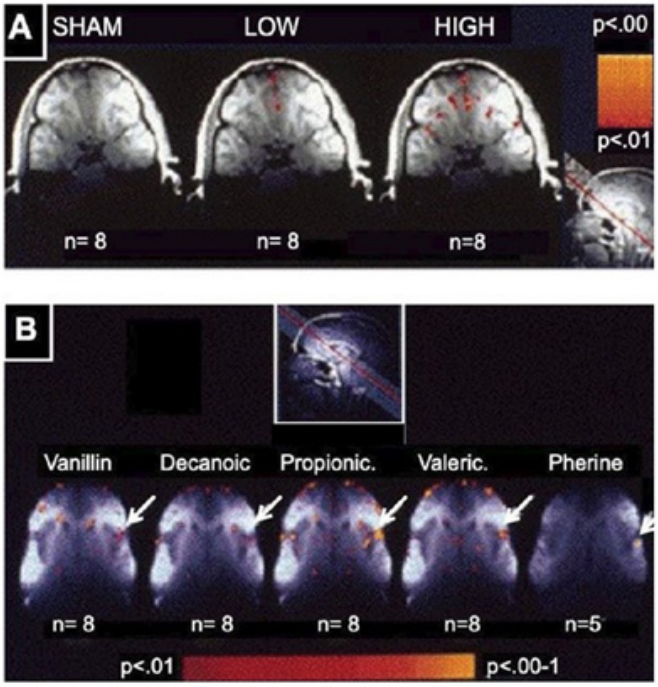
Fasedienol Dose-dependently Activates Cortical Brain Regions



Selective and dose-dependent brain activation induced by odorless pherine fasedienol (A) is different from control (SHAM) and brain activation induced by primary odors shown in (B). The results are averaged functional MRI images from human healthy volunteers (n = 8). Warmer colors on the color bars correspond to increased brain activation

Chemosensory receptor target engagement with fasedienol leads to selective activation of cortical brain regions and fasedienol is odorless based on lack of activation in brain areas activated by odors

Vistagen

Source: Monti L, and Liebowitz MR (2020). Neural circuits of anxiolytic and antidepressant pherine molecules. CNS Spectrums https://doi.org/10.1017/S109285292000190X