Pernix Therapeutics Holdings, Inc. Announces Positive Interim Results from a Phase IV Study to Assess and Compare the Effects of Silenor 6 mg and zolpidem 10 mg on Balance, Cognitive Performance, and Arousability

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The interim results of this head-to-head comparison demonstrate that Silenor 6 mg is statistically significantly superior to zolpidem 10 mg on all measures analyzed thus far

MORRISTOWN, NJ – (BUSINESS WIRE) – November 12, 2015 – Pernix Therapeutics Holdings, Inc. (NASDAQ: PTX), a specialty pharmaceutical company, today announced positive interim results from a Phase IV Study assessing the effects of a nighttime administration of Silenor 6 mg, zolpidem 10 mg, and placebo on arousability, gait/balance, and cognitive performance in healthy volunteers. The study assessed the effects of a single dose of Silenor 6 mg compared with matching placebo and a single dose of zolpidem 10 mg compared to its matching placebo at the respective Tmax (amount of drug present at the maximum serum concentration) in normal healthy adult male volunteers (n=39). The interim results of this head-to-head comparison demonstrate that Silenor 6 mg is statistically significantly superior to zolpidem 10 mg on all measures analyzed. The results also indicate that subjects taking Silenor 6 mg did not have impairment on any of these measures and were comparable to placebo. Further, Silenor 6 mg and both placebo groups were superior to zolpidem on all measures, indicating that zolpidem subjects had significant difficulty waking up, difficulty in their ability to walk, difficulty with balance, and experienced memory impairment.

“As expected, Silenor demonstrated no evidence of impairment on the measures assessing gait and balance, in contrast to the significant impairment in those taking zolpidem 10 mg. The totality of these interim results further support the safety of Silenor, even at the higher dose (6 mg), and calls into question the use of zolpidem given the significant risks associated with impaired gait and balance in older adults,” stated Heith Durrence, PhD, Sleep Expert and Medical Director at Pernix Therapeutics. “One of the most interesting findings in the study was that over half (20) of the zolpidem group did not wake up at 110 decibels. This is just below the level at which pain begins (120 dB), and the equivalent of using a power saw three feet away.”

The objectives of this Phase IV, randomized, double-blind, placebo-controlled, four-arm crossover study were:

- To determine the absolute and relative effects at Tmax of Silenor 6 mg and zolpidem 10 mg versus placebo on arousability, ataxia/balance and cognitive performance in healthy adult male volunteers;
- To compare effects on arousability, ataxia/balance, and cognitive performance of Silenor 6 mg relative to placebo and zolpidem 10 mg relative to placebo; and
- To assess the safety of Silenor 6 mg and zolpidem 10 mg.

Subjects who met screening criteria were randomly assigned to a treatment sequence order that involved both the study drug and the time subjects were awakened using a crossover study design. These four sequences included Silenor 6 mg with a middle-of-the-night awakening at 4 hours, zolpidem 10 mg with a middle-of-the-night awakening at 1.5 hours, placebo with a middle-of-the-night awakening at 4 hours, and placebo with a middle-of-the-night awakening at 1.5 hours. These times match the Tmax of zolpidem (1.5 hours) and Silenor (4 hours). The rationale for this is that Tmax represents the time of most elevated risk for a hypnotic in terms of balance, arousability, and memory. The ability to awaken to an external noise (arousability) was assessed using the Auditory Awakening Threshold test (AAT). Once the Auditory Awakening Threshold was completed, subjects performed a Tandem Walk assessment followed by the Berg Balance Scale (BBS) and finally by Free Recall Memory testing. The co-primary endpoints were the AAT data and step offs on the Tandem Walk. For this interim analysis, 39 subjects completed the study; these data are reported.

Auditory Awakening Threshold Background

Measures of auditory arousal threshold have been performed in numerous studies. At the appropriate time (1.5 or 4 hours after bedtime), a tone was played for 3 seconds starting at 30 decibels (dB). The tone was increased in increments of 5 dB

until the subject responded by pressing a button. If an awakening was not achieved at 110 dB, the subjects were awakened by the research personnel. Points of reference measured in dB according to the Center for Disease Control and Prevention's National Institute for Occupational Safety and Health approximate that 30 dB is equivalent to a soft whisper and 110 dB is equivalent to someone shouting in your ear or a power saw at 3 feet away.[1]

Auditory Awakening Threshold Results

- Subjects taking Silenor 6 mg had little difficulty waking up, were not significantly different than placebo, and were significantly easier to wake up than the zolpidem group ($p<0.0001$)
- Silenor subjects required an average of 83 dB to wake up, the two placebo groups took 85 and 77 dB to wake up
- Subjects taking zolpidem 10 mg needed greater stimulation to wake up
- The zolpidem group required an average of 102 dB to be woken up; the median was 110 dB, which means that more than half of those taking zolpidem did not wake up with the highest dB tone
- 20 zolpidem subjects did not wake up at the highest db level of sound stimuli, while only 2 Silenor subjects did not wake up

This is the first study to assess the ability to wake up in the middle-of-the-night in subjects taking either zolpidem or Silenor. The AAT data indicate that subjects taking Silenor were no different than placebo in terms of ability to wake up. Conversely, subjects taking zolpidem had difficulty waking up, and were significantly worse than Silenor and both placebo groups. The level of impairment in arousability with zolpidem was not trivial. These impairments in zolpidem subjects may have potentially serious consequences. For example, those taking zolpidem may have difficulty waking up to noises like a baby crying (120 dB at 4' away) or a smoke detector (average of 85 dB), a potentially serious issue.

Tandem Walk Background

Tandem Walk is a method of walking where the toes of the back foot touch the heel of the front foot at each step. The Tandem Walk test quantifies characteristics of gait as the subject walks heel to toe from one end of a beam to another. The primary endpoint was the number of steps off the beam during the walk. A secondary parameter was time to completion of the walk across the beam. This measure reflects ability to walk in the middle of the night, and is predictive of ability to walk. Impairments in gait are particularly more troublesome as people age and awakenings increase. All subjects were required to complete the gait test 5 times in screening without stepping off the beam.

Tandem Walk Results

- Silenor had no evidence of balance issues, was not different than placebo, and was statistically significantly superior compared to zolpidem ($p<0.0001$); subjects taking Silenor also took significantly less time to walk across the beam than zolpidem and were no different than placebo
- Silenor subjects stepped off the beam an average of 1.5 times, and took 5.0 seconds to walk across the beam; the two placebo groups stepped off 1.2 and 0.9 times and required 4.8 and 4.7 seconds to walk across
- Zolpidem subjects experienced significant balance impairment, and also took significantly longer to walk across the beam than all other groups
- Zolpidem subjects stepped off the beam an average of 7.5 times, and took 6.4 seconds to walk across the beam
- Zolpidem had 470% more steps off the beam than Silenor

The Tandem Walk data indicate that subjects taking Silenor were no different than placebo in terms of ability to walk across the beam and the speed of completion. Conversely, subjects taking zolpidem were impaired in their ability to walk, and took longer to walk across the beam. This has potentially important safety implications for older adults with numerous nighttime awakenings, and suggests Silenor may be a safer option than zolpidem in terms of risks in the middle-of-the-night for issues like falling. It is important to note that subjects were healthy young adult males, thus these gait impairments are likely to have a larger impact as the age of the person increases.

Berg Balance Scale Background

The Berg Balance Scale (BBS) is a widely used clinical test of a person's static and dynamic balance abilities. For functional balance tests, the BBS is generally considered to be the gold standard.

Berg Balance Scale Results (note lower results equal greater impairment)

- Silenor had no evidence of balance issues, was no different than placebo, and was statistically significantly better than Zolpidem ($p<0.0001$)
- Silenor subjects scored an average of 54.3 on the BBS; the two placebo groups scored 54.9 and 55.2
- Zolpidem produced significant impairments in balance
- Zolpidem subjects scored an average of 51.5 on the BBS

The BBS data indicate that subjects taking Silenor were no different than placebo with respect to balance. Conversely, subjects taking zolpidem had significant impairments in both static balance and balance while moving. Though these data do not directly assess falls, BBS data are predictive of falls. Falls represent a serious health risk, particularly in elderly adults, and can be life-altering for patients if the fall results in a broken hip. Zolpidem has previously demonstrated that it is associated with hip breaks.[2,3] The current study supports these data and suggests an increased risk for falls in patients taking zolpidem. Silenor has not been associated with any of these issues in any study, including the current one.

Free Recall Memory Testing

Free recall is a commonly used assessment of memory whereby participants were presented with a total of 16 words, one at a time. The encoding period typically lasted a few minutes. Participants were asked to recall as many words as possible at two different time points: one directly after the encoding task at Tmax, and the second 15 minutes following final awakening in the morning. The number of correctly recalled words were the primary endpoint from this measure.

Free Recall Memory Testing Results

- Subjects taking Silenor 6 mg were able to recall the same amount of words as both placebo groups; further Silenor 6 mg recalled significantly more words than the zolpidem group ($p<0.0001$), both at Tmax and the following morning
- At Tmax, Silenor subjects recalled an average of 7.8 words, and the two placebo groups recalled 7.9 and 8.6 words; the following morning Silenor subjects recalled an average of 6.8 words, and the two placebo groups recalled 6.7 and 7.7 words
- Subjects taking zolpidem 10 mg appeared to have difficulty recalling words, both in the middle of the night and the following morning
- The zolpidem group recalled an average of 5.1 words at Tmax; the following morning zolpidem subjects recalled 2.0 words

The Free Recall Memory test indicated that subjects taking Silenor were no different than placebo in their ability to remember words regardless of the time of assessment. Conversely, subjects taking zolpidem had significant impairment in the ability to recall words at both time points, consistent with previous reports of anterograde amnesia. The finding of no impairment in the Silenor group compared with placebo is an important finding. These data suggest that patients taking Silenor had no evidence of memory impairment, irrespective of whether memory was assessed in the middle-of-the-night or the following morning. Finally, the highly significant differences between Silenor and zolpidem suggest that Silenor may be a better treatment option for insomnia suffers if memory impairment is a concern or the person has a neurodegenerative disease.

Future Use of Data

The interim findings from this Phase IV study will be submitted as an abstract to a medical congress. Additionally, full study results are expected in Q1 of 2016. These results will also include memory data from middle of the night awakenings and morning awakenings, safety data, and sleep data.

About Pernix Therapeutics Holdings, Inc.

Pernix Therapeutics Holdings, Inc. is a specialty pharmaceutical business with a focus on acquiring, developing and commercializing prescription drugs primarily for the U.S. market. The Company targets underserved therapeutic areas such as CNS, including neurology and psychiatry, and has an interest in expanding into additional specialty segments. The Company promotes its branded products to physicians through its Pernix sales force, uses contracted sales organizations to market its non-core, cough and cold products, and markets its generic portfolio through its wholly owned subsidiaries, Macoven Pharmaceuticals, LLC and Cypress Pharmaceutical, Inc.

To learn more about Pernix Therapeutics, visit www.pernixtx.com.

About Silenor

SILENOR® is a prescription sleep medicine that is used to treat people with insomnia who have trouble staying asleep.

- Silenor is believed to work with the natural sleep-wake cycle by selectively blocking H1 receptor, and important wake-promoting mechanism
- Silenor helps patients stay asleep – the most common sleep complaint – for up to 7 hours
- Silenor is non-addictive, with no abuse potential and no evidence of tolerance in long-term use
- Silenor has next-day residual effects comparable to placebo – even in elderly patients

Important Safety Information about Silenor

Because sleep disturbances may be caused by underlying physical and/or psychiatric disorders, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7-10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated.

Patients should only take Silenor when they are prepared to get a full night's sleep. Silenor should be taken within 30 minutes of bedtime, and patients should confine their activities after ingestion to those necessary to prepare for bed. Patients should not consume alcohol or take other drugs that cause drowsiness with Silenor. Co-administration of monoamine oxidase inhibitors (MAOIs) with Silenor has not been studied and is not recommended. Patients should not take Silenor if they have untreated narrow angle glaucoma, severe urinary retention, severe sleep apnea or hypersensitivity to any of the ingredients in Silenor. Before taking Silenor, patients should tell their doctors if they have a history of depression, mental illness or suicidal thoughts.

The most common adverse events observed in Silenor clinical trials were drowsiness, upper respiratory tract infections and nausea.

Silenor® is a registered trademark of Pernix Therapeutics Holdings, Inc.
To learn more about Silenor, visit www.silenor.com

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