SPI-1005 A Novel Investigational Drug For The Treatment of Meniere’s Disease

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Background
Meniere’s is a serious neurotologic disease with a U.S. prevalence of approximately 190 per 100,000 persons that is characterized by episodic vertigo, fluctuating hearing loss, and intermittent or constant tinnitus. Meniere’s is most usually unilateral and is thought to be due to a swelling and/or inflammation of the endolymphatic duct within the inner ear. The onset of Meniere’s is typically between 40-50 years of age, and is ruled in after all three symptoms have been reported and after the documentation of hearing loss (typically low frequency sensorineural hearing loss). Symptoms can last from minutes to several hours and can be incapacitating and require emergent supportive care. Patients often experience nausea, vomiting, aural pressure, dizziness, and difficulty communicating, during and after acute attacks. There are no approved drug therapies for MD. Patients with MD are managed with low salt diets, thiazide diuretics, and oral or locally injected steroids, or locally injected gentamycin. The safety and efficacy of these treatments is controversial, and involve systemic and local side effects including amylomaic-induced hearing loss and tinnitus. Some MD patients may opt for inner ear surgery which can include endolymphatic sac decompression, labyrinthectomy or neuroectomy. The dura-blight of these surgical interventions is controversial, and the side effects of hearing loss and tinnitus are also possible.

SPI-1005 is an oral capsule containing 200 mg of ebselen and three excipients. Ebselen is a novel selenoenzymatic compound (214 daltons) whose mechanism of action is as a glutathione peroxidase (GPx1) mimic (Figure 1). Under redox stress, ebselen has been shown to induce GPx expression or activity in cells and tissues. In animal studies, ebselen has been shown to reduce the swelling of the endolymphatic duct, afferent dendrites (synapses between inner hair cell and auditory neuron), and spiral edema due to acoustic trauma (Kil et al., 2007). Therefore, ebselen has both anti-inflammatory and neuroprotective properties in the inner ear. In support of this, SPI-1005 has been tested in a Phase 1 clinical trial involving normal healthy subjects (Kil et al., 2009) and in a Phase 2 clinical trial involving healthy adults at risk for developing an acute noise induced hearing loss or NIHL (Kil et al., 2017). Data from the Phase 2 study showed that SPI-1005 provided before and after a 4 hr exposure to loud music or calibrated sound challenge (SCC), reduced the incidence and severity of an acute NIHL (Figure 2). These otoprotective findings suggest that SPI-1005 may be valuable in treating patients with sensorineural hearing loss. We have now designed and conducted a Phase 1b clinical trial in patients diagnosed with Meniere’s disease.

Methods
A multi-center clinical trial was conducted for the treatment of Meniere’s Disease, Protocol Number SPI-1005-151: “A Phase 1b, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of SPI-1005 in Adults with Meniere’s Disease”. The trial was active at 3 of 4 established sites in the U.S., where 56 subjects were screened for study eligibility and participation. The study enrolled 42 adult subjects diagnosed with probable or definite Meniere’s disease (MD) using AAO-HNS 1995 criteria (40 subjects were planned) within 12 months of study participation. 40 subjects met inclusion/exclusion criteria and were randomized to placebo or one of three different doses of SPI-1005 (200, 400 or 600 mg, twice daily for 21 days) in a 1:1:1:1 ratio. Study drug (3 capsules) was administered orally in the am and pm before meals (6 cap. 3 weeks). Clinical assessments were performed at 6 visits over a 7.9 week period. 39 subjects completed the study as directed. One subject withdrew from the study after being randomized to study drug. The average age of the completed subjects was 53 yr (age range 32-72) with 22 males and 17 females. This trial was registered under NCT02635381.

Several safety assessments including physical exams, adverse event reporting, serum chemistry (Chem), and hematocrit (Hct), were performed at baseline, during the 21 day treatment period, and during the 28 day post treatment period. Several efficacy assessments were explored including pure tone audiometry, word recognition, electrocochleography, and two patient reported outcome measures of tinnitus and vertigo severity involving the Tinnitus Functional Index (TFI) and the Vertigo Symptom Scale (VSS). All these assessments were conducted at baseline, after 21 days of treatment, and following 28 days post treatment. Responder and non-responder criteria were established based on clinically relevant improvements in hearing (reduction in tinnitus and vertigo. Significant hearing improvement >10 dB reduction from baseline (0.25, 0.5, 1 and 2 kHz) Significant WNT improvement >10% increase from baseline (0.35) Significant TFI improvement >10 pt reduction from baseline (0.01) Significant VSS improvement >6 pt reduction from baseline (0.05).

Results
Safety Analysis
There have been no reported Serious Adverse Events or AE that were definitely or probably due to study drug. All AEs were mild to moderate, and are consistent with the prior existing clinical experience involving SPI-1005 treatment in Phase 1 and Phase 2 studies. No clinically relevant changes in Chemistry 20 or CBC values have been observed during 21 days of treatment (see Table).

Exploratory Efficacy Analysis
SPI-1005 treated subjects (32%) showed clinically relevant improvements (>10 dB in baseline) in low frequency hearing loss (2.5, 0.5 or 1 kHz), the frequencies of hearing that are most typically affected in MD, vs placebo treated subjects (20%). This responder vs non-responder difference was significant by Fisher’s Exact test, p-value <0.03. Improvements in low frequency hearing were as high as 35 dB. Tinnitus loudness was measured on a visual analog scale from 0-10 as part of the TFI (Question 2). Clinically relevant improvement were defined as a ≥2 reduction in tinnitus loudness (from baseline). SPI-1005 treated subjects (55%) showed clinically relevant improvements vs placebo treated subjects (30%). This responder vs non-responder difference was non-significant by Fisher’s exact test, p-value <0.27. Improvements in tinnitus loudness were as high as an 8 point reduction. Clinically relevant improvements in word recognition involving the words-in-noise test (WNT) were defined as a >50% improvement from baseline. SPI-1005 treated subjects (48%) showed clinically relevant improvements vs placebo treated subjects (30%). This responder vs non-responder difference was non-significant by Fisher’s exact test, p-value <0.48. Improvements in WNT were as high as 120%. Differences in overall TFI and VSS scores were non-significant.

Conclusions
SPI-1005 was found to be safe and well tolerated following 21 days of dosing in an adult population with Meniere’s Disease, observed and followed for a 7.9 week period while on study. The exploratory efficacy analysis indicates that SPI-1005 treated subjects had a positive response to 21 days of treatment in some critical symptoms that define MD. These initial findings warrant further investigation, and we are conducting a Phase 2b clinical trial with 120 patients. SPI-1005 has the potential to become the first medical treatment for Meniere’s disease.

References
Kil E, Pierce C, Tran H, Gu R, Lynch JD. Ebselen treatment reduces noise induced hearing loss via the mimickry and induction of glutathione peroxidase. Hear Res. 2007 Apr;226(1-2):44-51