Ebselen for Protection and Treatment of NIHL Enters Clinical Testing

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US Hearing Loss—Background

- Irreversible Cell Loss
  - Auditory hair cells, supporting cells and nerve

- Leading Causes
  - Noise (>10MM)
    - Occupational (military, manufacturing) and recreational (music, sports)
  - Tinnitus (>12MM)
    - Noise exposure and ototoxic drugs
  - Drugs (>3MM)
    - Cancer chemotherapy and antibiotics (>200 Rx)
  - Age-related (>30MM)
    - Highly correlated with noise exposure

- Over 40MM Patients & Growing…With No Approved Drugs

- Large Unmet Need

References: NIH and CDC
Inner Ear and Organ of Corti
Hair Cell Injury, Defense, and Loss

Kopke et al., 2001
Importance of GPx activity in hearing and noise

Figure 2. Specific activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx) in guinea pig cochlea (medial fraction containing organ of Corti), retina and cortex. (Data from Pierson and Gray, 1982.)

Figure 10. Permanent threshold shifts (PTS) of 2-month-old GPx1 mice 14 days after broadband noise exposure in Exp. V. GpX1 KO mice developed approximately 15-20 dB more PTS than GpX1 WT mice at 10 and 20 kHz.

McFadden et al., 2001
GPx1 expression in rat SV 5h after noise

Normal no noise       Noise + vehicle       Noise + ebselen

Ratio of GPx1 intensity/area:

- Blue - normal
- Grey - noise + vehicle
- Red - noise + ebselen

* p<0.05
*** p<0.001
Ebselen (SPI-1005): A Potent GPx Mimic

Second-order rate constant
8 x 10^6 M⁻¹·s⁻¹ per tetramer

Second-order rate constant
2 x 10^6 M⁻¹·s⁻¹ per molecule
SPI-1005 Mechanisms of Action

Kil et al., 2006
Otoprotection across all frequencies
SPI-1005 4 mg/kg
ABR at 9 wks post noise

![Graph showing ABR threshold shift across different stimulus frequencies and time points post noise exposure.]

- Control
- 3 day
- 7 day
- 14 day

Key:
- * p<0.05
- ** p<0.01
- *** p<0.001
SPI-1005 reduces OHC loss in rat
4 mg/kg PO SPI-1005 BID x 3 days or 14 days vs. controls
3 Weeks post noise
Otoprotection with ebselen by multiple groups

- Pourbakht and Yamasoba (2003)
  - 10 and 30 mg/kg oral reduced PTS in Guinea pigs
  - Reduced OHC loss

- Yamasoba et al. (2005)
  - 10 mg/kg oral prevented TTS in Guinea pigs
  - Reduced swelling of afferent dendrites in spiral ganglia below IHCs

- Park et al. (2006)
  - 10 mg/kg prevented TTS
  - Decreased iNOS and NT in SV, SL, and SG
Toxicology—no significant safety issues for SPI-1005

- Acute oral toxicity in rat and mini-pig
  - Single dose up to 2000 mg/kg showed no dose limiting toxicities

- 28 day oral toxicity in rat, mini-pig, and monkey
  - Repeated dosing up to 2000 mg/kg/day showed no dose limiting toxicities

- Genotoxicity
  - AMES assay (potential for mutagenicity)—Negative
  - Mammalian Chromosome Aberration assay in Chinese Hamster Ovary Cells (potential for clastogenicity)—Negative
  - Mouse Micronucleus assay (potential to induce micro nuclei in bone marrow)—Negative
Summary of preclinical observations for SPI-1005

- Effective at low oral doses (8-10 mg/kg/day)
- Reduces TTS, PTS, and OHC loss in rats and guinea pigs
- Protects sensory and non-sensory cochlear structures
- Shows an extremely low toxicity profile
Phase 1 clinical protocol for SPI-1005

- Objectives
  - Evaluate safety and tolerability
  - Establish single dose PK
    - ADME for ebselen and major metabolites in plasma, urine
    - Total Se levels in plasma

- Study Design
  - Randomized, double-blind, placebo-controlled, single ascending dose
  - Drug product
    - 200 mg ebselen in oral capsule, matching placebo
  - Dose levels
    - 200, 400, 800, or 1600 mg
    - Dose escalation permitted based on safety and tolerability
Phase 1 protocol (continued)

- **Subjects**
  - M & F healthy volunteers, age 19-50 yrs
  - 32 enrolled, dosed, completed study, and data analyzed
  - 4 dose groups, 8 subjects each
    - 2 subjects received placebo in each dose group
    - 6 subjects received SPI-1005 in each dose group

- **Clinical evaluation**
  - Physical exams, orthostatic vital signs, 12-lead ECGs, Adverse Events* (AEs), hematology, chemistry, and UAs
  - Confined to clinic through 72h post-dose
  - Follow-up:
    - Clinic visit on post-dose day 7
    - Telephone on post-dose day 14

*Medical Dictionary for Regulatory Activities (MeDRA) v.9 For international uniformity in classification, retrieval, presentation, and communication of medical information*
**Safety and tolerability**

- No treatment or dose related trends seen for AEs, clinical labs, ECGs, and physical exam findings
- No serious AEs reported

<table>
<thead>
<tr>
<th>Group</th>
<th>Rx</th>
<th>Subjects with AEs possibly related to Rx</th>
<th>Subjects with no AEs or AEs unrelated to Rx</th>
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<tr>
<td>1</td>
<td>200 mg</td>
<td>67%</td>
<td>33%</td>
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<td>50%</td>
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<tr>
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<tr>
<td>All SPI-1005 Subjects</td>
<td>38%</td>
<td>63%</td>
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</tr>
<tr>
<td>All Placebo Subjects</td>
<td>38%</td>
<td>63%</td>
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Plasma ebselen and Se concentrations correlate in a dose dependent manner.
Phase 2 clinical study of SPI-1005

- **Inclusion/Exclusion Criteria**
  - Normal, healthy volunteers, aged 18-24 years, stationed at US military training bases will participate in this clinical trial.
  - Additional inclusion criteria limit volunteers to subjects with normal hearing, unremarkable otologic history, and willingness to comply with study requirements.

- **Study Arms**
  - Subjects (80) will be divided into four groups of 20 each. Each group will receive 200 mg capsules of SPI-1005 at one of three dose levels (200 mg, 400 mg, and 600 mg bid), or matching placebo for a period of 14 days during the live fire exercises.
  - Weapons training will begin the day following the first dose of study drug or placebo and continue for 3-5 days. Noise exposure will be restricted to the weapons training environment during the course of the study and all subjects will be monitored for proper use of their required military hearing protection.
Phase 2 clinical study of SPI-1005

➤ Safety

• The side effect profile of SPI-1005 will be determined by examining the toxicities and AEs that are attributable to the study drug.

• The safety parameters will include an evaluation of the clinical signs and symptoms from physical exam, the incidence of AEs, abnormal laboratory findings (hematology, clinical chemistry, urinalysis), and vital signs.

• Tolerability of SPI-1005 will be evaluated by the presence of toxicities associated with SPI-1005 administration at each of the dose levels.

This study will be run in accordance with the ethical principles set forth by the World Medical Association Declaration of Helsinki (2004).
Phase 2 clinical study of SPI-1005

➢ Efficacy

• The incidence and severity of NIHL will be analyzed for each group at time points that evaluate temporary and permanent hearing threshold shift (TTS and PTS).

• The primary efficacy endpoint of this study is a significant reduction in the incidence of HL using current military standards for Significant Threshold Shift (STS) criteria (e.g., an average shift greater than 10 dB at 2000, 3000, and 4000 Hz compared to baseline testing in the same ear) at either TTS or PTS intervals.

• A secondary endpoint is a significant reduction in the severity of HL, determined by measuring at least a 10 dB reduced hearing threshold shift at one of the tested frequencies, occurring at either the TTS or PTS time points.
Phase 2 clinical study of SPI-1005

- An additional efficacy endpoint
  - Analysis of reported tinnitus using the Tinnitus Handicap Inventory (THI). Raw THI scores will be determined for each treatment or placebo group, averaged per group, and compared for a significant reduction in mean score.

- Data management and Biostatistics
  - Contracted to CRO, data set locked for analysis by plan.
  - Analysis of variance will be used to test for significant differences between treatment and placebo groups for each of the endpoints.
Phase 2 clinical study of SPI-1005

- Being performed under CRADA with Naval Medical Center San Diego, P.I. Capt. Ben Balough.

- Study is IRB and FDA reviewed and approved.

- Currently recruiting for this study.
FDA Approved Phase 2 study of SPI-3005
Chemoprotection

- Ph-II for the Prevention of Ototoxicity
  - Platinum chemotherapy for advanced non-small cell lung ca and H&N squamous cell carcinomas
  - 80 total volunteers: 200, 400, 600 mg BID, po x 3 days x 3-4 cycles
  - Pure-tone audiometry (using SRO criteria), DPOAE, and tinnitus handicap inventory
  - Goal is to reduce the incidence/severity of HL
  - NCRAR at the Portland VA. PI Stephen Fausti
References

- Park YH, Rha KS, Park C II. Effect of ebselen on noise induced cochlear damage. ARO Mid-Winter Meeting, 2006.