Translating an oral anti-inflammatory SPI-1005 and locally injected cyclin-dependent kinase inhibitor SPI-5557 to clinic

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Disclosure:

Yes, within the last 12 months, I have/had a financial arrangement or affiliation with commercial interests related to the content of this continuing education activity that requires disclosure.

Shareholder in and Employee of Sound Pharmaceuticals
Glutathione Peroxidase (GPx) is a validated enzyme that protects and repairs inner ear cells from multiple cochlear insults

SPI-1005 – Proprietary oral capsule taken twice daily

- Contains ebselen (API), which is a potent GPx1 mimic and inducer
- Small molecule that crosses the BBB and blood cochlear barrier
- Ebselen can induce GPx1 transcription in several critical cells in the noise exposed cochlea demonstrating its redox sensitivity and additional activity as a Nrf2 activator and represents a new class of anti-inflammatory
  - Completed Phase 1 in 32 healthy volunteers
  - Completed Phase 2a in 83 subjects with acute NIHL
  - Completed Phase 1b in 40 subjects with Meniere’s Disease
  - Completed Phase 1b in 25 subjects with Cystic Fibrosis (CF)

Enrolled 125 in Phase 2b in Meniere’s Disease in the US (still blinded)

Enrolling 80 in Phase 2b in CF Aminoglycoside Ototoxicity in the US

Enrolling 60 in Phase 2 in Bipolar Disorder in the UK (Oxford)

Prepping Phase 2b in acute NIHL to enroll 180
<table>
<thead>
<tr>
<th>Drug Target</th>
<th>Product: Indication</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<th>Status/Collaborator/Funder</th>
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<tr>
<td>Glutathione Peroxidase</td>
<td>SPI-1005: Acute Noise Induced Hearing Loss</td>
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<td>Ph2a showed SPI-1005 is safe and reduced the incidence and severity of the acute NIHL <em>Lancet July 14, 2017</em></td>
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<td>Glutathione Peroxidase</td>
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<td>Phase 1b showed SPI-1005 is safe and improved chronic hearing loss and tinnitus loudness</td>
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<td>Glutathione Peroxidase/Xanthine Oxidase</td>
<td>SPI-3005: Platinum-based Ototoxicity</td>
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<td><em>In vivo</em> evidence of multi-organ protection</td>
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<td>SPI-3005: Aminoglycoside-based Ototoxicity</td>
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<td>Phase 1b shows high incidence of ototoxicity after IV tobramycin</td>
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<td>p27Kip1</td>
<td>SPI-5557: Regeneration</td>
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<td><em>In vivo</em> evidence of regeneration and improvement in hearing</td>
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High GPx1 vs GPx2, GPx3 or GPx4 expression in several critical cochlear structures

Ebselen treatment reduces noise induced hearing loss via the mimicry and induction of glutathione peroxidase. Kil J, Pierce C, Tran H, Gu R, Lynch ED. Hear Res. 2007
SPI-1005 Reduces both Temporary and Permanent Threshold Shifts

SPI-1005 Reduces Strial Edema and Endolymphatic Hydrops following acute noise exposure

(A) Blue – No Noise control cochlea
(B) Grey -- Noise + Placebo
(C) Red -- Noise + SPI-1005

- GPx1 (Green) increased in SPI-1005 treated cochlea 5 hrs post-noise
- SPI-1005 induces GPx1 in organ of Corti, spiral ganglia and stria vascularis
SPI-1005 reduces neural injury and deafferentation in a Guinea pig model of acute NIHL

Yamasoba et al., Ebselen prevents noise-induced excitotoxicity and Temporary Threshold Shift (TTS). Neuroscience Letters. 2005
Clinical Trial Site: University of Florida, Gainesville

Indication: Prevention of Noise Induced Temporary Threshold Shift

Principal Investigator: Colleen Le Prell

SPI-1005-202: Calibrated Sound Challenge (CSC)

- Volunteers age 18-31 years with up to 24 dB hearing loss
- 80 subjects exposed to CSC (loud music x 4 hours via iPod and insert earphones)
- Oral dosing of 0, 200, 400 and 600 mg capsules twice daily x 4 days
- Baseline hearing tests (n=2) prior to dosing and CSC
- Multiple follow-up hearing tests (n=6) after CSC and at 1 and 7 days post-CSC
- Primary Endpoint: Reduction of Hearing Loss at 4 kHz (most affected frequency in NIHL)
- Secondary Endpoints: Reduction in Hearing Loss at multiple frequencies (4, 6 and 8 kHz)
Oral administration of SPI-1005 (200, 400 and 600 mg bid x 4 days) showed highly significant and clinically relevant improvements in hearing at several time points post-noise exposure when compared to placebo.

- **Primary Endpoint:**
  - >50% reduction in NIHL severity at 4 kHz (400 mg p<0.01)

- **Secondary Endpoints:**
  - >50% reduction in NIHL severity at 3, 4 and 6 kHz (400 mg p<0.01)
  - >50% reduction in NIHL severity at 4, 6 and 8 kHz (200 and 400 mg p<0.01, 600 mg p<0.05)
  - >50% reduction in NIHL severity at all frequencies (200 and 400 mg p<0.01)

- **Post-hoc Analysis:**
  - >50% reduction in STS > 10 dB HL (200 and 600 mg p<0.05)

- **Excellent safety and tolerability in CSC exposed population:**
  - No adverse events related to study drug
  - CBC unchanged
  - Chemistry-20 unchanged
Clinical Trial Sites: Seattle, MUSC, New York Otology, House Clinic

Indication: Treatment of Meniere’s disease (Hearing Loss, Tinnitus, Vertigo)

Investigators: May Huang, Paul Lambert, Sujana Chandrasekhar, William Slattery

SPI-1005-151: Randomized, Double Blinded, Placebo-Controlled Trial

- Volunteers age 18-70 years with Meniere’s Disease
- 40 adult subjects dx by AAO-HNS 1995 Criteria in the last 12 months
- Oral dosing of 0, 200, 400 and 600 mg capsules twice daily x 21 days
- Baseline and repeat PTA/WINT, electrocochleography (ECochG), and patient reported outcomes (PROs) for Tinnitus and Vertigo severity, over a 2 month period
- Primary Endpoint: Safety and Pk
- Secondary Endpoints: PTA/WINT, ECochG, TFI or VSS
Oral dosing for 21 days is well tolerated with no adverse events due to study drug.

- No clinically relevant changes in Chemistry-20 or CBC values.
- Pure tone audiometry (PTA) and word recognition scores (WRS) show some agreement.
- Improvements were as high as 35 dB in low frequency (.25, .5, or 1kHz) hearing:
  - Significant hearing improvement of >10 dB in 52% of actives.
  - Significant improvement in 10% of placebos.
  - p-value is 0.02 by Fisher’s Exact Test.

Improvements were as high as 120% over baseline WRS:
  - Significant WINT improvement of >10% in 48% of actives.
  - Significant improvement in 40% of placebos.
  - p-value is 0.48 by Fisher’s Exact Test.

- Both PTA/WINT improvements are significant and greater in actives vs placebos.
- Improvement in low frequency hearing may precede an improvement in WRS.
Male Age 64: 400mg BID SPI-1005

Right Ear

Left Ear
Clinical Trial Sites: MUSC, UMiami, UPenn, and UTSW

Goal: Incidence and severity of ototoxicity following IV tobramycin

Principal Investigator: Patrick Flume

SPI-3005-501: Observational study

- CF volunteers age 18-70 years with Acute Pulmonary Exacerbation
- 20 adult subjects being treated with IV tobramycin 10 mg/kg/d for 10-21 days
- Baseline and two follow-up PTA/WINT/DPOAE, TFI, & VSS over 2 month period
- Primary Endpoint: Incidence and severity of cochleotoxic change
- Secondary Endpoints: Incidence and severity of tinnitus or vertigo
Female Age 26: 11 Days IV Tobramycin

Right Ear

Left Ear
SPI-1005 (three oral doses of 600 mg) did not significantly serum tobramycin levels (Cmax and Cmin) in adult patients receiving once daily IV tobramycin (10 mg/kg)

- Cmax average 27 mg/L (20-35) and Cmin average 0.7 mg/L (0.3 to 1.6) without SPI-1005
- Cmax average 27.5 mg/L (13-39) and Cmin average 1.4 mg/L (0.3 to 4.0) with SPI-1005

PTA and DPOAEs showed a robust level of cochleotoxicity at 2 weeks (89%/82%) and 4 weeks (93%/80%) post-treatment with IV tobramycin (10 mg/kg) for 10-21 days

- SRO (89%/87%) was more sensitive than Conventional (33%/27%) PTA at 2/4 weeks post
- DPOAEs (82%/80%) were equally unilateral/bilateral (40%/40%) at 2/4 weeks post
- Subject age and days of IV tobramycin did not appear to be strong predictors of ototoxicity

WINT showed decreases at 2 weeks (17%) and 4 weeks post (40%)

TFI showed increases at 2 weeks (12%) and 4 weeks post (8%)

VSS showed increases at 4 weeks post (8%)

Audiometric assessments (PTA/DPOAE) were more sensitive than PRO assessments (TFI/VSS)
0.5mM Tobramycin  

0.05 mM Ebselen  

200 mg/kg Tobramycin  

20 mg/kg Ebselen
Proprietary gene therapy and siRNA (SPI-5557) that inhibit p27Kip1 can stimulate cellular regeneration. Cell cycle protein (p27Kip1) key to inhibition of cell division or cellular regeneration in the inner ear was identified in mice, rats and Guinea pigs by Sound Pharmaceuticals. Non-regenerating inner ear cells can divide in p27Kip1 knock out mice and differentiate into new: Hair cells, Supporting cells, Neurons. Scanning electron micrographs provided by Dr. T. Yamasoba, University of Tokyo.
Cellular regeneration in p27Kip1 knockout mice was independently confirmed by Sound Pharmaceuticals, the Fred Hutchinson Cancer Research Center and the House Ear Institute.

Gu et al, ARO 2003
White et al, Nature 2006
World Congress on
Endoscopic Ear Surgery 3.0
June 13-15, 2019
BOSTON RENAISSANCE WATERFRONT HOTEL

Pre-clinical Optimization 2017-2019
• Optimization
  • Formulation of siRNA delivery
  • Improvements in hearing in the majority of animals injected

IND Enabling Studies 2019-20
• Pharm/Tox
  • Genotoxicity (AMES, MNA, CHO)
  • Systemic delivery (intravenous)
  • Local delivery (inner ear)
  • Complete Safety Pharmacology

• CMC
  • GMP production
  • Stability (lyophilized and suspended)
  • Method development & validation

IND filing Ph1/2 Safety & Efficacy 2020-2021
• General
  • Single local injection, dose escalating
  • 24 adult patients with severe to profound hearing loss

• Endpoints
  • Improvement in hearing thresholds
  • Improvement in speech discrimination
  • Tolerability