STOP OTOTOXICITY: PHASE 1/2 CLINICAL TRIAL OF SPI-1005

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Background & Methods

Multi-organ side effects of aminoglycoside antibiotics are well-established. Damage to the inner ear (ototoxicity), often leads to hearing loss, tinnitus, vertigo, or disequilibrium in 40-80% of patients. Hearing loss begins in the high frequencies and progresses to the low frequencies. Outer hair cells (OHCs) are typically the first auditory sensory cell affected in the cochlea. However, injury and death of supporting cells, stria vascularis, and spiral ganglion neurons have also been shown to occur. The ototoxicity can be permanent and can progress after the cessation of aminoglycoside treatment or can be exacerbated with the use of other drugs.

Ebselen (SPI-1005), a glutathione peroxidase mimic and inducer, has novel anti-inflammatory activity and protects and repairs inner ear cells from multiple insults including noise and ototoxic drug exposures in several animal models of hearing loss and ototoxicity (Ki et al., 2007; Lynch et al., 2005; Gu et al., 2019). SPI-1005 has demonstrated safety and efficacy in a Phase 2 clinical trial involving noise induced hearing loss (Ki et al., 2017) and Meniere’s Disease (Ki et al., 2018), and is being tested in a Phase 2 clinical trial involving Bipolar disorder. The objectives of this Phase 1/2 study in Cystic Fibrosis patients were to determine the incidence and severity of ototoxicity after a single IV course of tobramycin for the treatment of acute pulmonary exacerbation (Observational) and to determine tobramycin serum levels following three oral doses of SPI-1005 (Sentinel PK).

Sentinel PK and Observational Study Design

Twenty adult CF volunteers aged 18-70 years with Acute Pulmonary Exacerbation being treated with IV tobramycin (20 mg/kg/d for 10-21 days) were enrolled. Patients underwent several audiological assessments over a 2 month period (baseline, 2 and 4 weeks after IV tobramycin treatment). The incidence and severity of cochleotoxic change, tinnitus and vertigo were assessed with five validated tests or measures. Five separate adults also received concomitant SPI-treatment (600 mg bid po x 3 doses) to assess tobramycin Cmax/Cmin. Day 1: tobramycin only. Day 2: tobramycin + SPI-1005 am/pm; Day 3: tobramycin + SPI-1005 am only. Tobramycin serum levels were sampled at 0, 1, 2, 3, 4, 6, 8, and 12 hr after each IV dose.

Audiological Assessments and Responder Criteria

Pure Tone Audiometry (PTA): A modified Hughson-Westlake procedure requires a correct response following 2 out of 3 presentations in 5-dB steps at each frequency to determine hearing sensitivity or threshold. ASHA Guidelines (1994) defines PTA, its use in determining cochleotoxicity, and recommends testing extended high frequencies (EHF) above 8 kHz. Test-retest reliability is +/5 dB within the conventional frequencies (0.25, 0.5, 1, 2, 3, 4 and 8 kHz) and at most EHF (9-16 kHz). Baseline, repeat, and follow-up testing is recommended before/after each dose and/or at 30, 60 or 90 days post treatment, if possible. Increases in hearing thresholds (+10 dB) or a loss of response at multiple frequencies from baseline are considered evidence of clinically relevant hearing loss, and can occur unilaterally or bilaterally.

Sensitive Range for Ototoxicity (SRO): PTA tests the upper octave of hearing and is defined by the highest frequency within each ear (i.e. up to 20 kHz) with a behavioral response or threshold ≤100 dB) plus the thresholds of the 6 lower frequencies determined in 1/6 octave intervals (i.e. down to 10 kHz in this example). ASHA defines cochleotoxic change as a loss of 20-dB (1 frequency), 10-dB (2 adjacent frequencies), or a loss of response (3 adjacent frequencies), from baseline, and also applies to conventional frequencies.

Distortion Product Ototoxic/Acoustic Emissions (DPOAE): An objective measure of OHF function evoked by presenting two different tones (F1 and F2 frequencies) at two different levels (L1 and L2) across a range of frequencies with fixed ratio (F2/F1=1.2) over a range of dB levels (i.e. L1/L2=65/55) in the same ear. Decreases in DPOAE amplitudes ≥25 dB are thought to be early evidence of OHF injury or ototoxicity.

Words-in-Noise Test (WINT): 35 unique monosyllabic words are presented to each ear at 7 different signal-to-noise ratios (SNR) and cover a broad range of listener with little to no ceiling or floor effect. 24, 20, 16, 12, 8, 4 and 0 SNRs are presented in descending order where 8, 4 and 0 are the most difficult SNRs. Decreases in the total WINT score of ≥10% from baseline may be early evidence of hearing loss or ototoxicity.

Tinnitus Functional Index (TFI): Validated patient reported outcome (PRO) measure of tinnitus severity over the last week involving 25 questions (overall score of 0-100). A ≥10 pt increase from baseline maybe clinically relevant. Question #2 rates Tinnitus Loudness (TL) on a visual analogue scale (0-10). A ≥22 pt increase in TL from baseline maybe clinically relevant.

Vertigo Symptoms Scale (VSS): Validated PRO measure of vertigo severity over the last month with 15 questions (overall score of 0-60). A ≥6 pt increase from baseline is clinically relevant.

Results

Clinically Relevant Changes between baseline at 2 & 4 weeks

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<tr>
<th>Subject</th>
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<th>Day 2</th>
<th>Day 3</th>
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Conclusions

In this CF population, a standard course of IV tobramycin was sufficient to cause clinically relevant hearing loss and other ototoxic symptoms including tinnitus, vertigo and loss of word recognition in the majority of patients (78-82%). The audiometric measures (PTA, SRO and DPOAE) were more sensitive to ototoxic change than the PRO measures (TFI and VSS). Patient age and the duration of IV tobramycin treatment were not obvious factors for predicting ototoxic change using these assessments or responder criteria. Oral dose of SPI-1005 did not alter IV tobramycin serum levels. These Phase 1b data (Observational and Sentinel PK) support the design of the proposed Phase 2 interventional study.

References


