The Safety and Efficacy of PF-04958242 in Age-Related Sensorineural Hearing Loss: A Randomized Clinical Trial

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IMPORTANCE To our knowledge, this is the first study to assess the potential to pharmacologically improve auditory function in adults with age-related sensorineural hearing loss.

OBJECTIVE To explore the potential for the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid potentiator mechanism to affect auditory function in individuals with mild to moderate age-related sensorineural hearing loss.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, placebo-controlled, single-dose, 3-way crossover study was conducted in 3 academic ear, nose, and throat clinics and 2 private clinical research centers between December 22, 2011, and February 26, 2013. Participants were 50- to 75-year-old men and women of nonchildbearing potential with mild to moderate sensorineural hearing loss.

INTERVENTIONS Three single doses of PF-04958242, an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate-positive allosteric modulator, and placebo.

MAIN OUTCOMES AND MEASURES Pure-tone average, speech discrimination score, and speech in noise testing change from baseline at 1 and 5 hours after a single dose of PF-04958242.

RESULTS The treatment was safe and well tolerated. The estimates for the primary endpoint change from baseline in pure-tone average compared with placebo at 1 hour were -0.77 (95% CI, -2.14 to 0.59) and 0.37 (95% CI, -0.97 to 1.72) for 0.27 and 0.35 mg, respectively. At 5 hours the estimates were -0.57 (95% CI, -2.43 to 1.29) and -0.56 (95% CI, -2.45 to 1.33) for 0.27 and 0.35 mg, respectively. No significant change from baseline was demonstrated compared with placebo in the primary or secondary study end points at 1 or 5 hours after receiving treatment.

CONCLUSIONS AND RELEVANCE To our knowledge, this clinical trial is the first study of a pharmacologic treatment for age-related sensorineural hearing loss and provides information with regard to study design, end points, variability, data characteristics, and operational feasibility to guide the design of future hearing loss trials.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01518920

Original Investigation

Published online May 21, 2015.
The prevalence of hearing loss doubles with each age decade such that nearly two-thirds of all adults older than 70 years have clinically significant hearing loss. Epidemiologic studies have demonstrated that hearing loss is independently associated with impaired cognitive and physical functioning in older adults; these findings have prompted a recent Institute of Medicine workshop on hearing loss and its effect on healthy aging. Age-related hearing loss (presbycusis) is the result of multiple cumulative lifetime insults to the cochlea in addition to genetic influences and is characterized by pathological changes in the cochlear hair cells and stria vascularis, as well as synaptic and neuronal degeneration of the spiral ganglion neurons. Current treatments for presbycusis are limited and focus primarily on devices such as hearing aids. However, the use of hearing aids among adults with clinically significant hearing impairment is less than 20%; this low rate of use is likely related to issues of cost, perceived benefit, convenience, and stigma. In contrast with other chronic age-related conditions, such as hypertension and arthritis, there are currently no pharmacologic therapies to potentially symptomatically treat presbycusis.

In auditory processing, the amino acid neurotransmitter glutamate mediates virtually all excitatory neurotransmissions in the mammalian brain. In response to glutamate, postsynaptic AMPA receptors produce a rapid membrane depolarization that mediates the majority of excitatory neurotransmission in the central nervous system and removes the magnesium block from co-localized N-methyl-D-aspartate receptor-gated ion channels that allow calcium influx into the cell. AMPA receptor-mediated signaling plays a critical role throughout the neuroaxis of the auditory processing pathway, from the ribbon synapse to the brainstem cochlear nucleus and higher cortical auditory processing centers. In addition, several genes related to AMPA and the glutamate system have been implicated in inherited types of sensorineural hearing loss.

PF-04958242 is a potent and highly selective positive allosteric modulator of AMPA receptors (an AMPA potentiator) that represents a mechanistically novel approach to the treatment of sensorineural hearing loss. AMPA potentiators, in contrast to AMPA agonists, have an effect on AMPA-mediated glutamate signaling only when the endogenous ligand glutamate is released into the synapse and therefore have no effect in the absence of glutamate. Preclinical evidence suggests that an AMPA potentiator, in contrast to an AMPA agonist, promotes synaptic transmission and plasticity without corrupting spatial and temporal information.

Thus, an approach that modulates activity-dependent AMPA receptor-mediated signaling at the ribbon synapse could plausibly enhance the ability of the limited population of spiral ganglion neuron synapses to transduce sounds. The action of AMPA potentiators to potentially amplify glutamate receptor signaling while preserving the spatial and temporal information encoded in endogenous synaptic activity may make this mechanism well suited to symptomatically improve deficits in sensorineural hearing loss.

The clinical trial was a randomized, double-blind, placebo-controlled, single-dose, 3-way crossover study. The study was conducted at 5 clinical research sites, and participants were enrolled between December 22, 2011, and February 26, 2013. Participants received a single oral dose of each of the following 3 treatments in a randomized order: PF-04958242, 0.15 and 0.27 mg, and placebo prior to an amendment; and PF-04958242, 0.35 and 0.27 mg, and placebo following an amendment. The primary reason for the related protocol amendment was an adjustment of the study dosing based on a preplanned review of drug exposures, which revealed that the initially selected low dose (0.15 mg) was not attaining the projected drug concentrations intended to test the study hypothesis. There was a minimum 10-day washout interval between treatment periods. Participants attended

Methods

Participants
The final protocol, amendments, and informed consent document were reviewed and approved by the institutional review board and/or independent ethics committee at each of the investigational centers participating in the study (Johns Hopkins University, University of Texas Southwestern, Miami Research Associates, Yale University, and Anaheim Clinical Trials). The full study protocol can be found in the trial protocol in Supplement 1. Written informed consent was obtained from all participants prior to any study procedures. The study is registered with clinicaltrials.gov (NCT01518920).

Participants included men and women of non-childbearing potential between the ages of 50 and 75 years with age-related sensorineural hearing loss in the range of 30 to 60 dB averaged across 2 and 4 kHz in at least 1 ear based on pure-tone audiometry; participants were required to have symmetric hearing loss (with respect to both pure-tone audiometry and speech discrimination score [SDS]), defined as 15-dB or less difference in pure-tone threshold between ears at 2 and 4 kHz and a difference in SDS between ears of less than 20%. Individuals were excluded if they had a history of sudden hearing loss or rapidly progressive idiopathic hearing loss; had a history of hearing disorders that might affect the diagnosis, efficacy assessments, or safety of participants (eAppendix in Supplement 2); had a Tinnitus Handicap Inventory score of 38 or more; had an SDS of less than 60% in either ear; were taking concomitant medications that could affect hearing (eAppendix in Supplement 2) or concomitant medications that could affect the pharmacokinetics of the study drug, including moderate and strong inhibitors and strong inducers of CYP3A4; or had current (2 weeks prior to screening) pathological noise exposure owing to occupational, recreational, or other types of noise.

Study Design
The clinical trial was a randomized, double-blind, placebo-controlled, single-dose, 3-way crossover study. The study was conducted at 5 clinical research sites, and participants were enrolled between December 22, 2011, and February 26, 2013. Participants received a single oral dose of each of the following 3 treatments in a randomized order: PF-04958242, 0.15 and 0.27 mg, and placebo prior to an amendment; and PF-04958242, 0.35 and 0.27 mg, and placebo following an amendment. The primary reason for the related protocol amendment was an adjustment of the study dosing based on a preplanned review of drug exposures, which revealed that the initially selected low dose (0.15 mg) was not attaining the projected drug concentrations intended to test the study hypothesis. There was a minimum 10-day washout interval between treatment periods. Participants attended

PF-04958242 is a potent and highly selective positive allosteric modulator of AMPA receptors (an AMPA potentiator) that represents a mechanistically novel approach to the treatment of sensorineural hearing loss. AMPA potentiators, in contrast to AMPA agonists, have an effect on AMPA-mediated glutamate signaling only when the endogenous ligand glutamate is released into the synapse and therefore have no effect in the absence of glutamate. Preclinical evidence suggests that an AMPA potentiator, in contrast to an AMPA agonist, promotes synaptic transmission and plasticity without corrupting spatial and temporal information.

Thus, an approach that modulates activity-dependent AMPA receptor-mediated signaling at the ribbon synapse could plausibly enhance the ability of the limited population of spiral ganglion neuron synapses to transduce sounds. The action of AMPA potentiators to potentially amplify glutamate receptor signaling while preserving the spatial and temporal information encoded in endogenous synaptic activity may make this mechanism well suited to symptomatically improve deficits in sensorineural hearing loss. To our knowledge, this is the first clinical trial to assess the effect of a pharmacologic therapy on the treatment of age-related hearing loss and was conducted to explore the potential for this pharmacologic mechanism to affect symptoms in a population with mild to moderate age-related hearing loss.
5 planned study visits, including screening (visit 1), 3 drug administration treatment periods (including baseline and postbaseline assessments during each treatment period [visits 2-4]), and a follow-up visit (visit 5). Participants were admitted to the Clinical Research Center on each treatment period visit, underwent assessments and treatments for approximately 6 hours, and were then discharged the same day after a clinical safety assessment.

Assessments

Pure-tone Audiometry
Audiometric thresholds were tested in 5-dB increments by an audiologist. At the screening visit, air and bone conduction audiometry were performed. Air conduction audiometry was performed with insertable earphones and thresholds were obtained at 0.25-, 0.5-, 1-, 2-, 4-, and 8-KHz frequencies. Bone conduction audiometry assessed thresholds at 0.5-, 1-, 2-, and 4-KHz tones. Comparison of air conduction and bone conduction thresholds (the air-bone gap) helped to characterize the type of hearing loss. For study visits, only air conduction audiometry was performed at baseline and at postdosing assessments. Audiometric thresholds at 0.25-, 0.5-, 1-, 2-, 4-, and 8-KHz frequencies were obtained using insertable earphones and assessed at baseline and 1 and 5 hours following drug exposure. Two different pure-tone averages (PTAs) were calculated at the baseline assessment of each study visit: a conventional average of air conduction thresholds at 0.5-, 1-, and 2-KHz tones in the ear with greater hearing loss (PTA(0.5,2,4kHz)) for use in SDS presentation level determination, and an average of air conduction thresholds at 2 and 4 kHz in the ear with greater hearing loss (PTA(2-4kHz)), used as the primary study endpoint.

Speech Discrimination Score
For the baseline assessment and all postbaseline assessments during the treatment period, the SDS was measured under binaural conditions in soundfield at a presentation level of PTA(0.5,2,4kHz)+15 dB using a 50-word list of consonant-nucleus-consonant words, resulting in a submaximal achievable SDS (measured at PTA(0.5,2,4kHz)+40 dB). Subsequent assessments of the SDS at postbaseline evaluations were done at the same PTA established at the baseline assessment. The range of possible scores for the SDS is 0 to 150.

At each of the 3 treatment periods, the PTA(2-4kHz) and SDS end points were assessed at baseline (prior to drug ingestion) and at 1 hour (estimated maximal drug exposure) and 5 hours (approximately 1 half-life) following drug exposure before being discharged from the clinic.

Speech in Noise Test
The speech in noise test (SINT) was administered using the AZBio sentences (an open set discrimination task using lists of 20 sentences presented by 3 variable speakers with an average length of 7.25 words per sentence and background noise of a 4-person multitalker babble noise) using an adaptive procedure. AZBio scores were measured under the condition of multitalker babble noise presented from in front of the participant using the same speaker as the sentences. Test sentences were presented at a 60-dB sound pressure level with multitalker babble noise at a +2-dB signal to noise ratio (SNR). With the stimulus sentences fixed at a 60-dB sound pressure level, the SNR of the multitalker babble noise was varied in 2-dB increments until the participant’s target SNR was reached (defined as the SNR at which the participant obtained a percentage correct (SD) score that was 50% [SD] of their percentage correct score in a quiet condition). The SNR obtained was the level at which all postbaseline assessments were conducted on each treatment day. Results from the SINT were analyzed using the total number of correct words repeated back by the participant, with a range of possible scores from 0 to 159. AZBio sentences were used as a direct measure of functional speech perception in noise in the soundfield under binaural conditions.13

Tinnitus Assessment
Two assessments of tinnitus were included in this study. The Tinnitus Handicap Inventory44 is a 25-item self-report questionnaire that lists subjective questions designed to identify problem areas that may be present if an individual is distressed by his or her tinnitus. Scores range from 0 to 100, with higher scores indicating more severe tinnitus; scores of 38 or higher were used as a study exclusion criterion in this study. A tinnitus severity ranking scale (linear scale from 1 to 10 on which participants rated the severity of their current tinnitus) was also used to monitor for treatment-related changes in tinnitus.

Statistical Analysis
All participants who completed at least the first treatment period were included in the efficacy data analyses. Inferential analyses for the efficacy end points included data for only the 0.27-mg and 0.35-mg treatments and placebo since there were limited data for the 0.15-mg dose. All treatment sequences are presented for the safety end points. The primary analysis for primary and secondary end points was based on the full analysis set using treatment received. The primary end point for this study was change from baseline to 1 hour after the dose in the PTA of thresholds at 2- and 4-KHz frequencies measured in the ear with greater hearing loss (determined at PTA(2-4kHz)). If the hearing loss was identical in both ears, the right ear was denoted as the ear with greater hearing loss for all efficacy end points. The model to test the primary end point was a repeated measures linear crossover model (Latin square) including fixed-effect terms for period, treatment, center, first-order carryover, time and treatment by time interaction, and baseline measures as covariates. The analysis of the key secondary end points of change from baseline to 5 hours after the dose in PTA(2-4kHz) was conducted using the same linear crossover model.

Results

Demographics and Baseline Values
Figure 1 depicts the consolidated standards of reporting trials diagram. Forty-four participants (29 men and 15 women) from 5 centers in the United States were randomized to the study. The 5 centers were Johns Hopkins University (1 participant), University of Texas Southwestern (1 participant), Miami Research Associates (25 participants), Yale University (7 participants), and Anaheim Clinical Trials (10 participants). The study participants had a mean age of 61.9 years. The baseline PTA and other demographic char-
characteristics are shown in Table 1. Three participants were randomized but did not receive treatment. Of the 41 participants who were treated, 39 completed the study. Two participants discontinued the study because they were no longer willing and/or able to comply with scheduled visits and other study procedures.

### Efficacy

The primary efficacy analysis based on the modified intent-to-treat group was conducted on actual treatment received. The modified intent-to-treat group is defined as all participants who received PF-04958242 and completed at least the first treatment period.

Summary statistics were computed for PTA2-4kHz for all PF-04958242 doses and placebo and are presented in Table 2. Least-square means and SEs for SDS change from baseline at 1 and 5 hours are shown in Figure 2B. No significant changes were observed for the PF-04958242 groups compared with baseline or placebo at either time point.

### Pharmacokinetic Results

Mean plasma PF-04958242 concentration-time profiles are presented in Figure 3. Exposure increased with dose from 0.15 mg to 0.35 mg. The highest PF-04958242 mean plasma concentration (3.38 ng/mL) was observed at 45 minutes and was below the safety exposure limit criteria currently set for this compound (4.05 ng/mL).

To explore a potential association of plasma PF-04958242 concentrations with the primary endpoint PTA, the observed plasma concentration nearest to the collection of the endpoint was plotted; no clear association was identified (eFigure in Supplement 2).

### Safety

PF-04958242 was safe and well tolerated in this study. Forty-four participants were randomized, 41 received treatment, 39 completed the study, and 5 discontinued the study. Two participants discontinued the study during the between-treatment washout phase because they were no longer willing and able to comply with scheduled visits and other study procedures. Three participants discontinued after randomization but prior to receiving treatment. No participants discontinued owing to an adverse event (AE). There were no reports of death, serious AEs, or severe AEs. Most of the reported AEs were mild; of 4 moderate-severity AEs, pyrexia was the only one judged to be possibly related to the study treatment.

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**Table 1. Demographic Characteristics and Baseline Audiometric Assessments**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Sex, No.</td>
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<tr>
<td>Male</td>
<td>29</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
</tr>
<tr>
<td>Age, y, mean (SD) [range]</td>
<td>61.9 (6.8) [54-70]</td>
</tr>
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<td>Race, No.</td>
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<tr>
<td>White</td>
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<tr>
<td>Black</td>
<td>3</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
</tr>
<tr>
<td>Body mass index, mean (SD) [range]</td>
<td>30.2 (7.1) [20.7-60.6]</td>
</tr>
<tr>
<td>Baseline PTA2-4kHz, mean (SD) [range]</td>
<td></td>
</tr>
<tr>
<td>Treatment period 1</td>
<td>46.3 (10.7) [30.0-67.5]</td>
</tr>
<tr>
<td>Treatment period 2</td>
<td>44.7 (12.4) [25.0-67.5]</td>
</tr>
<tr>
<td>Treatment period 3</td>
<td>43.9 (12.6) [22.5-65.0]</td>
</tr>
</tbody>
</table>

Abbreviation: PTA2-4kHz, the average of air conduction thresholds at 2 and 4 kHz in the ear with greater hearing loss.

* Calculated as weight in kilograms divided by height in meters squared.
* Measured in 41 participants.
* Measured in 39 participants.
Table 2. Descriptive Summary of Baseline and Mean Change From Baseline at 1 and 5 Hours for PTA2-4kHz, SDS, and SINT Score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PF-04958242, 0.15 mg (n = 10)</th>
<th>PF-04958242, 0.27 mg (n = 39)</th>
<th>PF-04958242, 0.35 mg (n = 30)</th>
<th>Placebo (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTA2-4kHz</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean (SD) [range]</td>
<td>36.75 (8.74) [25.0 to 50.0]</td>
<td>45.06 (12.29) [22.5 to 67.5]</td>
<td>47.92 (10.97) [27.5 to 65.0]</td>
<td>44.88 (12.10) [22.5 to 67.5]</td>
</tr>
<tr>
<td>Change from baseline at 1 h, mean (SD) [range]</td>
<td>-1.00 (2.41) [-7.50 to 0]</td>
<td>-1.79 (2.69) [-7.50 to 2.50]</td>
<td>-0.58 (2.43) [-5.00 to 5.00]</td>
<td>-1.13 (2.33) [-7.50 to 2.50]</td>
</tr>
<tr>
<td>Change from baseline at 5 h, mean (SD) [range]</td>
<td>-1.50 (2.42) [-7.50 to 0]</td>
<td>-1.73 (2.44) [-7.50 to 2.50]</td>
<td>-1.58 (3.74) [-17.50 to 2.50]</td>
<td>-1.19 (4.46) [-25.00 to 2.50]</td>
</tr>
<tr>
<td>SDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean (SD) [range]</td>
<td>143.9 (2.81) [140.00 to 148.00]</td>
<td>142.50 (7.21) [120.00 to 150.00]</td>
<td>140.90 (6.53) [127.00 to 150.00]</td>
<td>141.60 (6.06) [128.00 to 150.00]</td>
</tr>
<tr>
<td>Change from baseline at 1 h, mean (SD) [range]</td>
<td>0.50 (4.55) [-10.00 to 6.00]</td>
<td>0.10 (3.71) [-10.00 to 11.00]</td>
<td>-1.40 (5.95) [-17.00 to 8.00]</td>
<td>0.50 (4.45) [-10.00 to 9.00]</td>
</tr>
<tr>
<td>Change from baseline at 5 h, mean (SD) [range]</td>
<td>-0.60 (2.99) [-4.00 to 5.00]</td>
<td>-1.00 (3.90) [-20.00 to 5.00]</td>
<td>-1.80 (6.39) [-22.00 to 9.00]</td>
<td>-0.60 (4.99) [-17.00 to 10.00]</td>
</tr>
<tr>
<td>SINT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean (SD) [range]</td>
<td>68.79 (13.47) [51.62 to 94.01]</td>
<td>69.23 (19.86) [24.73 to 108.56]</td>
<td>70.84 (17.84) [24.12 to 109.09]</td>
<td>68.88 (18.10) [31.80 to 97.59]</td>
</tr>
<tr>
<td>Change from baseline at 1 h, mean (SD) [range]</td>
<td>3.47 (7.84) [-10.30 to 15.94]</td>
<td>1.83 (13.69) [-20.78 to 41.06]</td>
<td>-2.16 (17.12) [-47.26 to 30.63]</td>
<td>1.14 (18.46) [-29.04 to 70.45]</td>
</tr>
<tr>
<td>Change from baseline at 5 h, mean (SD) [range]</td>
<td>4.27 (15.0) [-17.25 to 30.53]</td>
<td>4.43 (18.43) [-47.83 to 28.15]</td>
<td>-8.68 (20.77) [-57.27 to 41.06]</td>
<td>-3.22 (19.26) [-58.12 to 39.00]</td>
</tr>
</tbody>
</table>

Abbreviations: PTA2-4kHz, the average of air conduction thresholds at 2 and 4 kHz in the ear with greater hearing loss; SDS, speech discrimination score; SINT, speech in noise testing.

Figure 2. Placebo-Corrected Change in Primary and Secondary End Points

The types of AEs that were reported with PF-04958242 were consistent with those seen earlier in the clinical program in participants aged 18 to 55 years. A summary of AEs is provided in the eTable in Supplement 2. Dizziness was the only all-causeality AE reported by more than 1 participant per treatment arm (0.27 mg, 2 participants; 0.35 mg, 1 participant; and placebo, 1 participant) and diarrhea was the only treatment-related AE reported by more than 1 participant per treatment arm (placebo, 2 participants; and 0.35 mg, 1 participant).

Absolute values and change from the baseline values for the Tinnitus Severity Scale data demonstrated that no PF-04958242 dose exhibited a difference from placebo, consistent with the compound not being associated with an increase in tinnitus symptoms in AE reporting.

There were no clinically significant changes in laboratory test values, vital signs, or electrocardiogram results during treatment with PF-04958242.

Discussion

The results of this trial demonstrate that a single dose of PF-04958242 was not associated with any significant change in primary or secondary end points compared with placebo. This study represents, to our knowledge, the first clinical trial to examine the effect of a pharmacologic intervention on treatment of age-related hearing loss. As such, it provides useful information with regard to study design, end points, variability, data characteris-
tions, and operational feasibility to guide the design of future hearing loss trials. Development of this novel study was made possible through active collaboration between industry and academic investigators that resulted in a timeline from initial concept discussion to start of the randomized clinical trial of 9 months, representing a highly efficient approach to drug development that may serve as a model for subsequent efforts to assess potential treatments in areas of unmet medical need with novel treatment approaches.

The rationale for selection of the AMPA target is the essentially universal expression of AMPA receptors throughout the auditory system. In particular, previous work has clearly established that AMPA receptors mediate cochlear afferent signaling at the ribbon synapse, which is the key interface in neural transmission between the inner hair cell and spiral ganglion nerve. A treatment aimed at the AMPA subtype glutamate channel might be hypothesized to provide near-immediate symptomatic improvement in synaptic relay. This hypothesis led to the rationale and interest in examining this mechanism following a single dose of PF-04958242.

PF-04958242 was safe and well tolerated. There were no severe or serious AEs during this study. Most of the AEs that were reported were mild or moderate in severity. Tinnitus Severity Scale data demonstrated that the compound was not associated with an increase in tinnitus symptoms.

Neither primary dose of PF-04958242 (0.27 and 0.35 mg) resulted in significant changes from the baseline in PTA, SDS, or SINT scores at 1 or 5 hours after the dose compared with placebo. The results of the exploratory analysis for the primary end point with the addition of age and sex as covariates were similar to those observed for the primary analysis. The primary doses of PF-04958242 resulted in drug exposures consistent with those observed for the primary analysis. The primary doses of PF-04958242 were safe and well tolerated. There were no severe or serious AEs during this study. Most of the AEs that were reported were mild or moderate in severity. Tinnitus Severity Scale data demonstrated that the compound was not associated with an increase in tinnitus symptoms.

Exposure increased with dose from 0.15 mg to 0.35 mg. The highest PF-04958242 mean plasma concentration (3.38 ng/mL) was observed at 45 minutes and was below the safety exposure limit criteria currently set for this compound (4.05 ng/mL, dashed line). Data points are means; error bars, SDs.

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Potential Contributors to the Lack of Efficacy Signal

The lack of a significant pharmacologic effect could be owing to several factors. The population selected was individuals with mild to moderate (30- to 60-dB) hearing loss. The state of the glutamate system in relation to the degree of hearing loss is not known, and it is possible that a more severe degree of hearing loss is required to demonstrate a clinical meaningful effect based on the state of glutamatergic signaling deficits.

Somewhat related to this factor is the observed baseline SDS. Following calculation of the PTA at 0.5- to 2-kHz, this study assessed the SDS at the PTA at 0.5- to 2-kHz + 15 dB. This assessment resulted in a mean SDS of 140 to 143, with a maximum achievable value of 150. Thus, the ceiling effect may have prevented any demonstration of improvement. A future study design may wish to consider conducting the SDS test at PTA at 0.5- to 2-kHz or PTA at 0.5- to 2-kHz + 5 dB.

In this study, only a single dose of PF-04958242 was administered and assessed. Although it was hypothesized that the effect of an ion channel modulator would likely be rapid, repeated drug exposure may be necessary to develop an effect throughout the auditory circuit, which may be related to impaired plasticity in an older population or to a more impaired circuit (eg, fewer inner hair cells, glutamate, or neurites). It is also possible that greater or more prolonged drug exposure is required. The preclinical data obtained with PF-04958242 demonstrate full equilibration with the brain compartment, and it is conceivable that the blood-cochlear barrier behaves as a different compartment, although this scenario seems unlikely. A maximum tolerated dose has not been achieved with PF-04958242.

It is also possible that the need to have sufficient, but not excessive or toxic, glutamate effects at the ribbon synapse is a formidable challenge. That said, PF-04958242 is a positive allosteric modulator and thus its role is to augment the effect of the release of glutamate at the synapse in a time-coherent and spatially coherent manner, not to increase the glutamate levels at the ribbon synapse or at other synapses throughout the auditory system.

The auditory circuit is extremely complex and involves both peripheral and central components. It would be expected to have multiple redundancies that may mitigate any attempt to alter the circuit through intervention of a single mechanism. Conversely, it is possible that other neurotransmitters have a more significant role in the auditory circuitry.

Finally, the end points in this study were psychoacoustic measures that are several steps removed from the direct effect of an AMPA potentiator, and it is possible that inclusion of end points that assess more proximal signals to the ribbon synapse may demonstrate treatment effects that are not evident at the behavioral level (eg, evoked potentials).

Study Strengths and Limitations

A strength of this study is that, as the first study of the pharmacologic treatment of age-related sensorineural hearing loss, it pro-

Figure 3. Observed Total PF-04958242 Plasma Concentration Time Profiles Following a Single Oral Dose

PF-04958242 Plasma Concentration, ng/mL

Dose

0.15 mg

0.27 mg

0.35 mg

Nominal Time After Dose, h

0.75 1 2 3 4 5

0

1

2

3

4

5

Exposure increased with dose from 0.15 mg to 0.35 mg. The highest PF-04958242 mean plasma concentration (3.38 ng/mL) was observed at 45 minutes and was below the safety exposure limit criteria currently set for this compound (4.05 ng/mL, dashed line). Data points are means; error bars, SDs.
vides useful information with regard to study design, end points, variability, data characteristics, and operational feasibility to guide the design of future hearing loss trials. A limitation of this study is that, owing to the absence of sufficient treatment literature in age-related sensorineural hearing loss with the study end points to provide data while designing the study, a conservative approach for powering this clinical trial was used. For future trials with a similar population and end points, the study design approach might assume a lower variance for the primary end point.

Conclusions
This trial assessed several key end points related to hearing. Future studies could include additional assessment of physiological function at the ribbon synapse using auditory brainstem response or distortion products of otoacoustic emissions. Indeed, studies by Kujawa and Liberman and others suggest that both low-level noise and hearing loss related to presbycusis may directly affect the ribbon synapse and the inner hair cell auditory nerve synapse, with the first evidence of pathological symptoms being a synaptopathy. In both circumstances, this scenario results in changes in auditory brainstem response wave I amplitude, which may also be a better way to assess a population in the clinic receiving acute treatment doses.

Selection of individuals with a greater breadth of hearing loss and/or studying participants for a greater duration of drug therapy would also provide for a more comprehensive profile, as would the assessment of alternative outcome assessments.

REFERENCES
2. Gallacher J, Ilubaera V, Ben-Shlomo Y, et al. Administrative, technical, or material support: Bednar, DeMartinis, Bowditch, Gaudreault, Zumpano, Lin. Study supervision: Bednar, DeMartinis, Lin. ConFLICT of Interest Disclosures: Drs Bednar and Lin had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Bednar, DeMartinis, Bowditch, Zumpano, Lin. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: Bednar, DeMartinis, Bowditch, Gaudreault, Zumpano, Lin. Statistical analysis: Bowditch, Zumpano, Lin. Administrative, technical, or material support: Bednar, DeMartinis, Bowditch, Gaudreault, and Ms Zumpano are employees of Pfizer, Inc. Dr Lin and Mr Bowditch were compensated for their work according to the contracts made for their participation as investigators in the study and for initial consultations in the concept and design of the study. Dr Lin and Mr Bowditch did not receive compensation for their contributions to this manuscript. No other disclosures were reported. Funding/Support: This study was sponsored by Pfizer Inc. Role of the Funder/Sponsor: Pfizer Inc had a role in the design and conduct of the study, collection, management, analysis, and interpretation of the data; preparation, review, approval of the manuscript; and the decision to submit the manuscript for publication. Previous Presentation: This study was presented in part at the 2015 Association for Research in Otolaryngology meeting; February 22, 2015; Baltimore, Maryland.
Additional Contributions: Mark Milad, PharmD, Milad Pharmaceutical Consulting, contributed to the study design and conduct. Barbara Evans, RN, provided administrative support. We thank the additional investigators of the study for recruiting and assessing patients: John Carey, MD, Johns Hopkins Medical Institute, Howard Schwartz, MD, Miami Research Associates, Elias Michaelides, MD, Yale School of Medicine, Peter Rolland, MD, University of Texas Southwestern Medical Center, and Peter Winkle, MD, Anaheim Clinical Trials. None of the individuals listed in this section were compensated for their contributions to this manuscript. Each of the investigators listed in this section were compensated for conducting the clinical study, either individually (Schwartz, Winkle), or through their institution (Carey, Michaelides, Rolland). Pfizer directly compensated Evans as an employee of Pfizer, Inc, and Milad as a consultant for supporting the design, conduct, and analysis of the study.