Clinical Study

Evaluation of the Ototoxicity Potential of Once-Daily, Single-Entity Hydrocodone in Patients with Chronic Pain: Results of Two Phase-3 Clinical Studies

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Background: Use/misuse of the opioid combination hydrocodone-acetaminophen has been associated with permanent hearing loss. Although reports have been rare, this potential effect can have significant detrimental effect on patients' overall quality of life. To date, the ototoxic effect of hydrocodone alone has not been systematically investigated.

Objective: In this report, we aimed to evaluate the potential ototoxicity of a novel, single-entity, once-daily, extended-release hydrocodone tablet (Hysingla® ER; HYD).

Study Design: Clinical study.

Setting: Audiology clinics in US.

Methods: Results from 1207 patients in two phase 3 clinical studies were evaluated: A placebo-controlled study with an enriched enrollment, randomized withdrawal design in patients with chronic low back pain, and an open-label, long-term, safety study in patients with chronic nonmalignant and non-neuropathic pain.

Comprehensive audiologic assessments (comprising pure-tone air-conduction audiometry in the conventional [0.25-8 kHz] and ultra-high [10-16 kHz] frequencies, pure-tone bone-conduction audiometry, tympanometry, speech reception thresholds, and word recognition) were conducted at baseline and end-of-studies; air-conduction audiometry was conducted periodically during the studies. All audiologic assessments were performed in audiology clinics in the United States by licensed audiologists. The primary endpoint was changes from baseline in pure-tone air-conduction thresholds in the conventional frequencies during the studies. These trials are registered with ClinicalTrials.gov, identifiers NCT01400139 and NCT01452529

Results: During the studies, mean changes from baseline in air-conduction thresholds were clinically unremarkable. Bidirectional variability across all test frequencies was observed; 82% of patients did not experience significant threshold changes during the studies, 7% had potential hearing decrement, and 10% experienced hearing sensitivity improvement. No notable differences were observed between patients receiving HYD and placebo or between different HYD doses.

Conclusion: No ototoxic signal was observed for single-entity hydrocodone tablets at the dosages and treatment durations investigated.

Key words: Audiologic monitoring, clinical trials, hydrocodone, opioids, ototoxicity monitoring, sensorineural hearing loss

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Many medications used for chronic pain treatment are potentially ototoxic (1-5). While the ototoxic effect of some analgesics is temporary (1,2), others have been reported to cause rapidly progressive and sudden sensorineural hearing loss (SNHL) that resulted in permanent, severe to profound auditory damage (3-5). As hearing loss has been linked to cognitive decline, social and occupational dysfunction, and severe adverse health conditions (6-11), it could add significant burden to patients whose quality of life has already been reduced by their chronic pain conditions (12).

The pathophysiology of rapidly progressive and sudden SNHL is poorly understood. Rapidly progressive SNHL, which develops over weeks to months, and sudden SNHL, which describes hearing losses of ≥ 30 dB over 3 consecutive test frequencies within 72 hours, have many similar features and probable causes (13,14). Some of the identifiable causes included viral and bacterial infection, trauma, vascular/hematologic and autoimmune disorders, and neoplasm (14-17). In cases of hearing loss associated with ototoxic medications, analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids have been reported to cause rapidly progressive SNHL in general, and sudden SNHL in rare cases, that may or may not be reversible with treatment (3-5, 17-21).

In the United States (US), the most frequently prescribed opioid medication is the hydrocodone-acetaminophen combination (22). Although cases of hearing loss associated with hydrocodone-acetaminophen are rare, there have been cases of self-reported severe to profound SNHL associated with the use/misuse of this medication (18-20). Most of these were anecdotal, and these patients took a wide range of hydrocodone-acetaminophen doses, with some as high as 300 mg or more per day. The resulting hearing loss in most cases was bilateral and rapidly progressive, developing over days to months. Treatment with corticosteroid was generally ineffective in these patients and most required cochlear implantation (18-20).

Whether hydrocodone alone is potentially ototoxic has not been systematically studied to date. Until recently, hydrocodone was only available in the US as an oral, immediate-release, fixed combination product with non-opiate drugs, predominately acetaminophen. Acetaminophen alone, however, is widely used in the US as an over-the-counter and prescription medication (23,24). In 2 prospective observation cohort studies that evaluated the correlation between acetaminophen use and hearing impairment based on self-reported hearing loss, it was found that regular use of acetaminophen (ie. ≥ twice/week) increased the risk of hearing loss in both men and women. The risk of hearing loss may increase with increased duration and frequency of use (25,26). Furthermore, in in vitro mouse model studies, exposure of cochlear culture and auditory cell line to acetaminophen alone, but not to hydrocodone alone, was associated with increased cell death. Cell death associated with acetaminophen was slightly potentiated with the addition of hydrocodone (27) The results from human and mouse model studies suggest that acetaminophen, rather than hydrocodone, may be the causative agent in auditory cell damage (27).

Recently, a single-entity, once-daily, extended-release hydrocodone bitartrate tablet (20-120 mg) formulated with abuse deterrent properties (HYD; Hysingla® ER, Purdue Pharma, L.P.28) has become available in the US for the management of patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment. During HYD clinical development, a comprehensive ototoxicity monitoring protocol was implemented in two phase 3 clinical studies to evaluate the potential impact of HYD on hearing. To our knowledge, this is the first report of studies that prospectively evaluated the potential ototoxic effect of a single-entity hydrocodone product in human.

Methods

Data from 2 phase 3 clinical studies were analyzed: a placebo-controlled study that evaluated the efficacy and safety of HYD in patients with moderate-to-severe chronic low back pain (LBP), and an open-label study that evaluated the long-term safety of HYD in patients with moderate-to-severe chronic nonmalignant and non-neuropathic pain.

Both studies were approved by the Copernicus Group Institutional Review Board. Written informed consents were obtained from study participants or legally authorized representatives before enrollment.

Patients

Eligible participants in both studies were ≥18 years old. Patients in the placebo-controlled study had LBP for ≥3 months that was uncontrolled by their prestudy analgesics; patients in the open-label study had chronic nonmalignant and non-neuropathic pain for ≥3 months that was either controlled or uncontrolled by their prestudy analgesics. Patients were excluded from the studies if they had: uncontrolled depression or other

psychiatric disorders, pre-existing hearing-related conditions that could cause fluctuant hearing unrelated to study drug (eg. Meniere's disease, persistent middle ear infections, autoimmune inner ear disease, perilymphatic fistula, tumor of the head, neck or auditory system, or history of otologic surgery or hearing fluctuation), exposure to known ototoxic agents within 6 months before the studies (ie. cisplatin, carboplatin, vincristine, vinblastine, head/neck radiation, aminoglycoside antibiotics, or α-difluoromethylornithine) (29-34), air-conduction threshold asymmetry >20 dB in the conventional frequencies (0.25-8 kHz), air-bone gaps >10 dB, abnormal tympanograms, or other indications of middle ear abnormality. Patients with other hearing deficits were allowed.

Study Designs and Treatments

Both studies comprised a screening period and an open-label titration period when patients converted their prestudy analgesics to HYD (20, 40, 60 mg or 80 mg daily) and adjusted their HYD doses to a level (up to 120 mg daily) that was tolerable and adequate for pain control. Subsequently, patients in the placebo-controlled study were randomized to receive HYD or placebo in a 12-week double-blind period. To minimize withdrawal and prevent potential unblinding, patients randomized to the placebo group were gradually tapered to placebo during the first 2 weeks of the double-blind period. Patients in the open-label study continued HYD treatment in a 12-month maintenance period. Nonstudy analgesics were prohibited in the placebo-controlled study, while nonopioid and short-acting opioid analgesics were permitted in the open-label study.

Audiologic Assessments

All audiologic assessments were performed in the US by licensed audiologists in a sound booth meeting American National Standards Institute (ANSI) specifications using an Interacoustics AD629e audiometer with 3A insert earphones for the conventional frequencies (0.25-8 kHz) and Sennheiser HDA 200 earphones for ultra-high frequencies (10-16 kHz). Tympanometry was conducted using the GSI TympStar immittance bridge. The audiometer was calibrated before and every 6 months during the studies according to ANSI 3.6-2010. The immittance bridge was calibrated before the studies and annually.

Comprehensive audiologic assessments were conducted at screening and at end-of-studies. They comprised an otoscopic examination, bilateral air-conduction pure-tone audiometry utilizing the modified Hughson-Westlake procedure at frequencies of 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, and 16 kHz, tympanometry, speech reception thresholds (SRT), and word recognition using a 50-word list (NU-6) at 25 dB SL. Bone-conduction thresholds were tested at 0.25, 0.5, 1, 2, 3, and 4 kHz if the air-conduction threshold at that frequency was ≥15 dB. To verify response reliability, air-conduction threshold testing was repeated at 1 and 2 kHz. Responses were considered reliable if retest thresholds at both frequencies were within ±5 dB of the original response (35-37).

Additionally, bilateral air-conduction thresholds were tested at the end-of-titration period in both studies and at maintenance period month-3 and month-6 of the open-label study. Patients completed the Dizziness Handicap Inventory (DHI) and Tinnitus Handicap Inventory (THI) questionnaires at each visit (38,39). Patients with postbaseline DHI composite scores ≥31 and concurrent increases of ≥5 from baseline were discussed with an otolaryngology consultant for the studies to determine whether additional audiologic assessment was warranted.

Significant Change Criteria

Pretreatment air-conduction thresholds for each patient served as a baseline against which postbaseline thresholds were compared. Air-conduction threshold changes were considered significant if they met ≥1 of the following American Speech-Language-Hearing Association (ASHA) criteria: change of ≥20 dB from baseline at any frequency, change of ≥10 dB from baseline at 2 adjacent frequencies, or loss of response at 3 consecutive frequencies where responses were obtained at baseline (37).

Results meeting the ASHA criteria were verified with a comprehensive audiologic assessment within 24 hours (37). Patients were flagged as patients with potential hearing decrement if the changes were confirmed with no indication of middle ear abnormality. An otolaryngology consultant for the studies monitored all patients with potential hearing decrement. Follow-up audiologic assessments were performed as recommended by the otolaryngologist, generally at 1, 2, 3, 6, and >6 months until the event resolved or stabilized. Follow-up assessment results were categorized as resolved (threshold changes no longer meet the ASHA criteria), stabilized (changes of ≤10 dB from the initial finding), or progressive (changes of >10 dB from the initial finding).

To determine if changes meeting the ASHA criteria were related to true hearing changes or simple bidirectional variability in responses, postbaseline air-conduction threshold changes meeting the ASHA criteria in the reverse direction (ie. improvement of ≥20 dB from baseline at any frequency, improvement of ≥10 dB from baseline at 2 adjacent frequencies, or acquisition of responses at ≥1 frequency where responses were absent at baseline for ≥3 adjacent frequencies) were analyzed. These patients were referred to as patients with improvement in hearing sensitivity.

Statistical Analysis

Analysis Populations

Patients with baseline comprehensive audiologic assessments and ≥1 postbaseline air-conduction threshold assessment were included. To compare effect of HYD vs placebo on hearing sensitivity, data for patients who received ≥1 double-blind treatment (HYD or placebo) during the placebo-controlled study (ie. randomized safety population) were analyzed. To determine whether ototoxic signal is present in a large population with prolonged HYD exposure, data for all HYD-treated patients in both placebo-controlled and open-label studies (ie. the integrated analysis population) were pooled and analyzed.

Primary and Supportive Analyses

Primary analyses comprised air-conduction threshold results in the conventional frequencies from the randomized safety and integrated analysis populations. Supportive analyses comprised results from air-conduction thresholds in the ultra-high frequencies, tympanometry, SRT, THI, and DHI from the randomized safety and integrated analysis populations, and results of bone-conduction thresholds and word recognition at the study level. Summary statistics were used to summarize mean and mean changes from baseline to the end-of-studies for each assessment. The incidences of potential hearing decrement and improvement in hearing sensitivity during the studies were summarized by HYD overall, HYD dose, and cumulative HYD dose at event onset for the conventional frequencies, and by HYD overall and HYD dose at event onset for the ultra-high frequencies. Pearson and Spearman association coefficients (where a coefficient of -1 indicates total negative correlation, 0 indicates no correlation, and 1 indicates total positive correlation) were used to determine the magnitude of association between HYD dose or cumulative HYD dose and the incidence of potential hearing decrement in the conventional frequencies. Prior and concomitant uses of the potentially ototoxic medications, NSAIDs, acetaminophen, phosphodiesterase type-5 inhibitors (PDE-5 inhibitors), and macrolides were summarized (1-4,21,25,26,40).

Results

Results of the efficacy and safety analyses for the placebo-controlled and open-label studies are presented elsewhere (41,42).

Patients and Treatments

The randomized safety population (N=588) comprised 296 HYD-treated and 292 placebo-treated patients from the double-blind period of the placebo-controlled study. The mean (SD) cumulative duration of double-blind treatment was 69.7 (25.22) days for the HYD group and 66.5 (27.56) days for the placebo group. The mean (SD) average daily HYD dose was 56.9 (31.76) mg for the HYD group.

The integrated analysis population (N=1207) included 302 HYD-treated patients from the titration and maintenance periods of the open-label study and 905 HYD-treated patients from the titration and double-blind periods of the placebo-controlled study. The mean (SD) cumulative HYD exposure was 95.2 (120.36) days. The mean (SD) average daily HYD dose was 48.7 (27.04) mg.

Most patients in the integrated analysis population were <65 years old, female, and white (Table1). Nine percent of the patients had pre-existing hearing conditions, including tinnitus (3.1%), bilateral deafness (1.2%), and hypoacusis (<1%). Fifty-two percent of patients had the following hearing loss risk factors (43,44): smoking (8%), diabetes (10%), hypercholesterolemia (14%), hypertension (39%), and other cardiovascular diseases (15%). No notable difference in baseline characteristics existed between the HYD and placebo groups.

As expected for patients with chronic pain, most patients in the integrated analysis population had prior exposure to the potentially ototoxic medications, NSAIDs and acetaminophen. Concomitant use of these medications decreased during the studies as nonstudy analgesics were prohibited in the placebo-controlled study. Few patients used macrolides and PDE-5 inhibitors before and concomitantly during the studies. Uses of potentially ototoxic medications before or concomitantly during the studies were balanced between the HYD and placebo groups (Table 1).

Table 1. *Demographics, baseline characteristics, and prior and concomitant potential ototoxic medication use.*

	Integrated Analysis Population	Double-blind Placebo-Controlled Study Randomized Safety Population	
	HYD (N=1207)	HYD (N=296)	Placebo (N=292)
Age n, mean (SD) (years)	1207, 49.0 (13.28)	296, 49.2 (13.51)	292, 47.9 (13.23)
Age group, n (%)			
<65 years	1060 (88)	260 (88)	261 (89)
≥ 65 years	147 (12)	36 (12)	31 (11)
≥ 75 years	27 (2)	7 (2)	2 (1)
Gender, n (%)			
Male	504 (42)	124 (42)	126 (43)
Female	703 (58)	172 (58)	166 (57)
Race, n (%)			
White	895 (74)	195 (66)	207 (71)
Black or African American	220 (18)	67 (23)	51 (17)
Other	92 (8)	34 (11)	34 (12)
Opioid Status, n (%)			
Experienced	641 (53)	131 (44)	128 (44)
Naïve	566 (47)	165 (56)	164 (56)
BMI (kg/m^2), mean (SD)	31 (7.9)	31 (7.7)	32 (7.8)
Patients with Ototoxic Medications Taken Within 30 Days Prior to Screening, n (%)			
Macrolides	6 (<1)	1 (<1)	2 (1)
PDE-5 Inhibitors	15 (1)	2 (1)	2 (1)
NSAIDs	773 (64)	191 (65)	193 (66)
Acetaminophen	636 (53)	145 (49)	142 (49)
Concomitant Ototoxic Mediation Taken During Studies, n (%)			
Macrolides	35 (3)	11 (4)	4 (1)
PDE-5 Inhibitors	16 (1)	2 (1)	2 (1)
NSAIDs[1]	517 (43)	7 (2)	2 (1)
Acetaminophen[1]	416 (35)	3 (1)	1 (<1)

PDE-5 Inhibitors=Phosphodieterase type 5 Inhibitors; NSAIDs=Nonsteroidal anti-inflammatory drugs; BMI=Body Mass Index.
1 The use of NSAIDs and acetaminophen for chronic pain treatment was prohibited for the double-blind placebo-controlled study.

Mean Changes in Air-Conduction Thresholds from Baseline

For the randomized safety and integrated analysis populations, mean air-conduction threshold changes from baseline to end-of-study in the conventional (Fig. 1) and ultra-high frequencies were generally small, bi-directional, and clinically unremarkable. No notable differences existed between the HYD and placebo groups, between the left and right ears, and among the different HYD doses. Bidirectional air-conduction threshold changes occurred across all frequencies; higher frequencies generally had larger changes.

Patients with Significant Air-Conduction Threshold Changes during the Studies

Both HYD and placebo groups in the randomized safety population had similar incidences of potential hearing decrement (6% and 4%, respectively) and improvements in hearing sensitivity (9% and 10%, respectively) in the conventional frequencies (Fig. 2). Likewise for the ultra-high frequencies, the HYD and placebo groups had similar incidences of potential hearing decrement (13% and 10%, respectively) and improvements in hearing sensitivity (18% and 17%, respectively).

For the integrated analysis population, 82% of

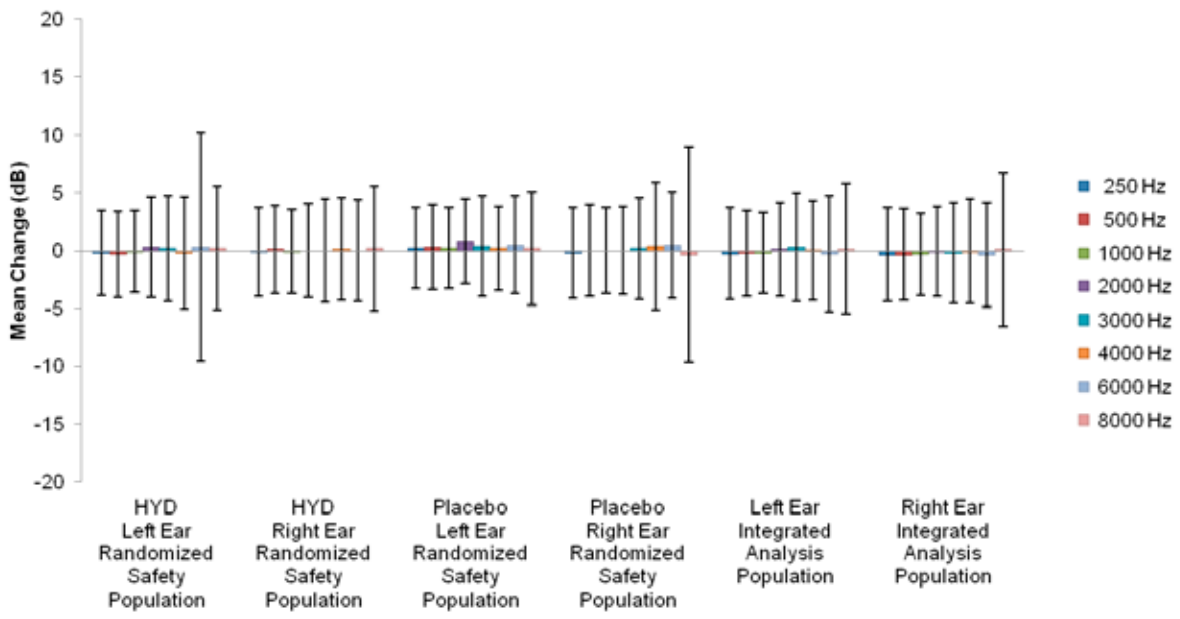

Fig. 1. *Mean changes from baseline in pure-tone air-conduction thresholds - randomized safety population and integrated analysis population.*
HYD=single-entity, once-daily, extended-release hydrocodone bitartrate tablet.
Randomized safety population comprised patients who received HYD or placebo during from the double-blind period of the placebo-controlled study.
Integrated analysis population comprised patients who received HYD during the placebo-controlled and open-label studies.

patients had no significant air-conduction threshold changes in the conventional frequencies (Fig. 2); the incidences of potential hearing decrement (7%) and improvements in hearing sensitivity (10%) were similar. For the ultra-high frequencies, 66% of patients had no significant air-conduction threshold changes; the incidence of potential hearing decrement (11%) was lower than that of improvement in hearing sensitivity (20%).

During follow-up audiologic assessments, threshold changes for all patients with potential hearing decrement had either resolved or stabilized during or after HYD treatment. No patient had threshold changes indicating progressive hearing loss.

Figures 3 and 4 present the incidences of potential hearing decrement and improvement in hearing sensitivity in the conventional frequencies by HYD dose and cumulative HYD dose at onset, respectively. No strong association was observed between HYD dose and incidence of potential hearing decrement (Pearson coefficient = 0.0679, 95% CI = 0.0049-0.1309; Spearman coefficient = 0.0702, 95% CI = 0.0049-0.1309) and between cumulative HYD dose and incidence of potential hearing decrement (Pearson coefficient=0.0306, 95% CI = -0.0245-0.0857; Spearman coefficient=0.0349, CI = -0.0163-0.0860).

Consistently, analyses of SRT, word recognition, bone-conduction thresholds, DHI, and THI results did not reveal any clinically meaningful changes.

Patients Dispositions

For the randomized safety population, 75% of patients completed the study (77% HYD; 72% placebo) and 25% discontinued treatment (23% HYD; 28% placebo). One patient from both the HYD and placebo groups discontinued treatment due to potential hearing decrement.

In the integrated analysis population, 55% of patients completed HYD treatment and 45% discontinued HYD treatment. Five patients (<1%) discontinued treatment due to potential hearing decrement. The

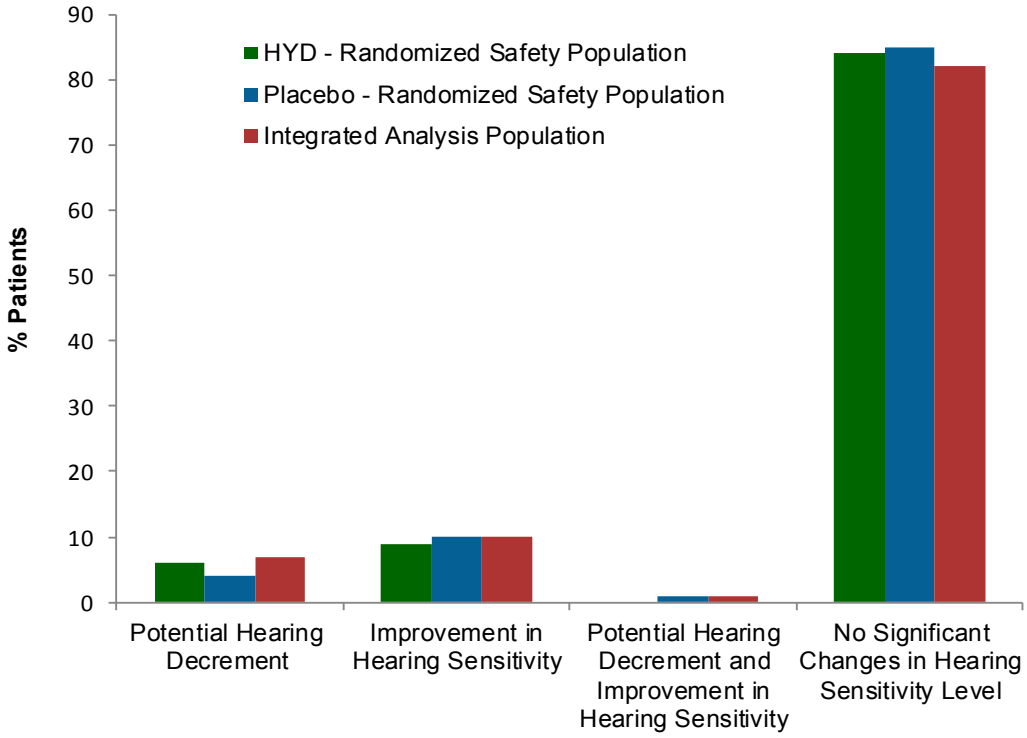

Fig. 2. *Percentage of patients with potential hearing decrement and improvement in hearing sensitivity – randomized safety population and integrated analysis population.*
HYD=single-entity, once-daily, extended-release hydrocodone bitartrate tablet.
Randomized safety population comprised patients who received HYD or placebo during from the double-blind period of the placebo-controlled study.
Integrated analysis population comprised patients who received HYD during the placebo-controlled and open-label studies.

HYD=single-entity, once-daily, extended-release hydrocodone bitartrate tablet.
Integrated Analysis Population comprised patients who received HYD during the placebo-controlled and open-label studies.
No strong association was observed between HYD dose and incidence of potential hearing decrement (Pearson coefficient=0.0679, 95% CI=0.0049-0.1309; Spearman coefficient=0.0702, 95% CI=0.0049-0.1309. A coefficient of -1 indicates total negative correlation, 0 indicates no correlation, and 1 indicates total positive correlation).

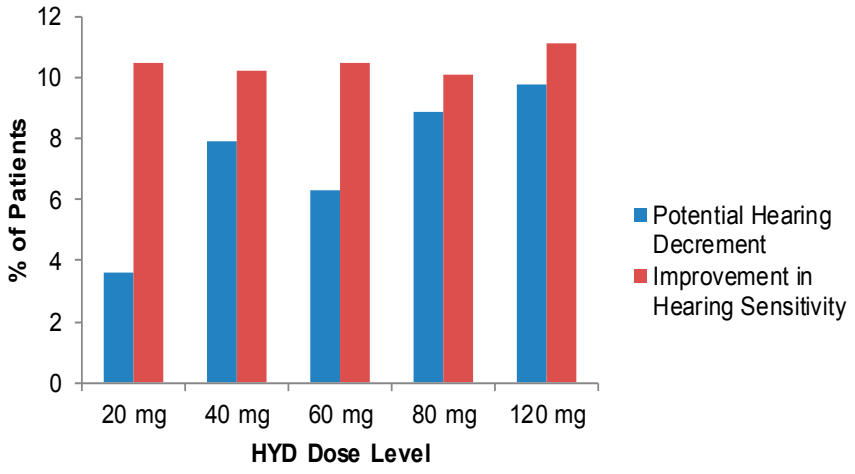

Fig. 3. *Percentage of patients with potential hearing decrement and improvement in hearing sensitivity by HYD dose at event onset – integrated analysis population.*

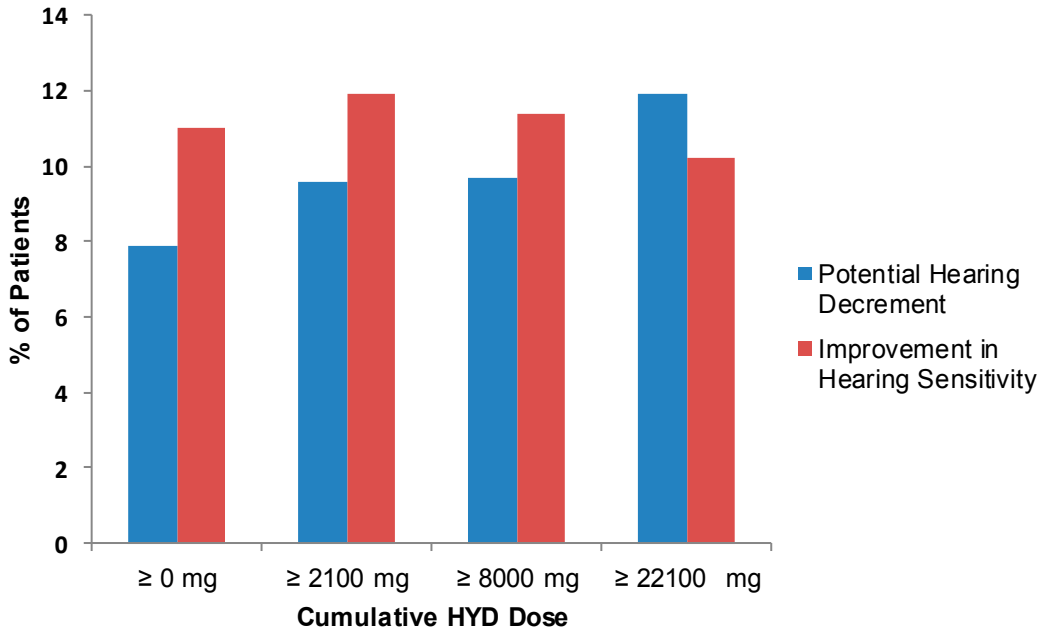

Fig. 4. *Percentage of patients with potential hearing decrement and improvement in hearing sensitivity by cumulative hyd dose at event onset – integrated analysis population.*
HYD=single-entity, once-daily, extended-release hydrocodone bitartrate tablet.
Integrated Analysis Population comprised patients who received HYD during the placebo-controlled and open-label studies.
The cumulative HYD dose is determined by the patients' daily HYD dose and duration of exposure in days. No strong association was observed between cumulative HYD dose and incidence of potential hearing decrement (Pearson coefficient=0.0306, 95% CI=-0.0245-0.0857; Spearman coefficient=0.0349, CI=-0.0163-0.0860. A coefficient of -1 indicates total negative correlation, 0 indicates no correlation, and 1 indicates total positive correlation).

ages of these patients (42 – 81 years old), HYD doses received (20 – 80 mg), and duration of HYD exposure before event onset (9-95 days) varied widely. The degree of threshold changes also varied: 3 patients had bilateral changes of 10 – 20 dB in the conventional frequencies and 10 – 40 dB in the ultra-high frequencies, one had unilateral changes of 20 dB in the conventional frequencies, and one had bilateral changes of 10-50 dB in the conventional frequencies. During poststudy follow-up audiologic examinations, threshold changes for these patients had either resolved or stabilized; no progression of threshold changes was reported.

Discussion

Analyses of audiologic testing results from 1207 chronic pain patients in two phase 3 clinical studies showed no ototoxic signal for HYD at the dosages and treatment duration investigated. Primary analyses based on pure-tone air-conduction thresholds in the conventional frequencies showed that mean threshold changes from baseline to the end-of-studies were small, bidirectional, and clinically unremarkable. Percentages of patients with improvement in hearing sensitivity were similar to those with potential hearing decrement (Fig. 2). No notable differences were observed between the HYD and placebo groups. Increased HYD dose or cumulative HYD exposure did not increase the incidence of potential hearing decrement (Figs. 3 and 4). Analyses of ultra-high frequency pure-tone air-conduction thresholds, SRT, bone-conduction thresholds, word recognition, tympanometry, THI, and DHI support the conclusions from the primary analyses.

Most patients in the studies did not experience significant air-conduction threshold changes in the conventional or ultra-high frequencies; however, bidirectional changes meeting the ASHA (potential hearing decrement) or reverse ASHA (improvement in hearing) criteria occurred for 18%-34% of patients; greater fluctuations generally occurred in the higher test frequencies. Variability in air-conduction thresholds may be

multifactorial, including unreported loud noise exposure, decreased mental concentration and fatigue due to opioid use, ongoing pain and discomfort, and learning effect due to repeat testing.

Nevertheless, analyses of air-conduction threshold changes did not reveal a pattern suggestive of ototoxicity. Specifically, previously reported cases of ototoxicity associated with hydrocodone-acetaminophen described hearing loss as rapidly progressive and permanent (18-20). This pattern was not seen in our patients. No patients with potential hearing decrement during the studies had lasting severe or profound hearing loss; their threshold changes had either resolved or stabilized at the follow-up audiologic assessments performed during or after HYD treatment. Additionally, most ototoxic medications affect ultra-high frequencies initially and then progress towards conventional frequencies (45-48). This pattern of threshold changes was not seen in patients from the studies. For patients with potential hearing decrement, most changes varied over time. Finally, most ototoxic medications are dose-dependent (49). No HYD dose-dependent threshold changes were observed in our studies (Fig. 3); increased cumulative HYD exposure did not increase the incidence of potential hearing decrement (Fig. 4).

A majority of patients in the studies used medications with ototoxic potential, including NSAIDs, acetaminophen, PDE5-inhibitors, and macrolides; however, their use was balanced between the HYD and placebo groups in the controlled study and would not have altered the conclusions. Additionally, careful monitoring of potential ototoxicity throughout the studies found no evidence of ototoxic synergism between HYD and other potentially ototoxic medications.

Serial air-conduction threshold evaluation at both conventional and ultra-high frequencies is an effective method of ototoxicity monitoring (37). As prospective assessments of hearing function provide a pretreatment control against which post-treatment results are compared, they provide a reliable method for detecting early drug-induced ototoxicity before symptomatic hearing loss (37). To our knowledge, these are the first large-scale human studies that prospectively evaluated the potential ototoxic effect of a single-entity hydrocodone product.

One limitation of the studies presented here pertains to sample size and treatment duration. As reports of rapidly progressive, severe to profound, permanent hearing loss are rare among the general population, a study population of 1207 patients with up to 12 months of maintenance treatment may not be sufficient to uncover this rare side effect. Therefore, while our study results do not warrant routine ototoxicity screening during HYD treatment, audiologic assessments would be indicated if a patient develops subjective hearing loss.

It should be noted that while no ototoxicity signal was seen for HYD, which is an extended-release, single-entity hydrocodone product, it remains to be determined whether a similar conclusion can be made for short-acting hydrocodone-containing products. Additionally, future clinical studies investigating the genetic variance for drug-metabolizing enzymes may help identify patients who are predisposed to drug-induced ototoxicity.

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Author Contributions

All authors had full access to the data, were involved in the analysis and interpretation of data, and take full responsibility for the integrity of the data and for the accuracy of the data analysis. All authors were involved in the drafting of the manuscript and the critical revision of the manuscript for important intellectual content. Drs. Campbell, Kutz, Shoup, Wen, Lynch, and Ripa were involved in the concept and design of this analysis. Drs. Wen and Lynch supervised the study and were responsible for the acquisition of data. Dr. He was responsible for the statistical analysis.

Drs. Campbell, Kutz, and Shoup served as paid consultants to Purdue Pharma L.P. during the design, planning, and execution of the studies, and during the preparation of this manuscript. Drs. Lynch, He, and Ripa are full-time employees of Purdue Pharma L.P. Dr. Wen was a full-time employee of Purdue Pharma L.P during the design, planning, and execution of the studies, and during the preparation of this manuscript.

Role of Sponsor

The originally submitted manuscript went through the standard publication review process at Purdue Pharma L.P.

References

1. Seligmann H, Podoshin L, Ben-David J, Fradis M, Goldsher M. Drug-induced tinnitus and other hearing disorders. *Drug Saf* 1996; 14:198-212.
2. Jung TT, Rhee CK, Lee CS, Park YS, Choi DC. Ototoxicity of salicylate, nonsteroidal anti-inflammatory drugs, and quinine. *Otolaryngol Clin North Am* 1993; 26:791-810.
3. Ahmad S, Bhanji A, Pal S, Karim M. Irreversible sensorineural hearing loss:An unusual side effect of non-steroidal anti-inflammatory drugs. I*nt J Clin Pharmacol Ther* 2010; 48:514-516.
4. McKinnon BJ, Lassen LF. Naproxen-associated sudden sensorineural hearing loss. *Mil Med* 1998; 163:792-793.
5. Rigby MH, Parnes LS. Profound hearing loss associated with oxycodone-acetaminophen abuse. *J Otolaryngol Head Neck Surg* 2008; 37:E161-162.
6. Lin FR, Yafe K, Xia J, Xue QL, Harris TB, Purchase-Helzner E, Satterfield S, Ayonayon HN, Ferucci L, Simonsick EM, Health ABC Study Group. Hearing loss and cognitive decline in older adults. *JAMA Intern Med* 2013; 173:293-299.
7. Gurgel RK, Ward PD, Schwartz S, Norton MC, Foster NL, Tschanz JT. Relationship of hearing loss and dementia:a prospective, population-based study. *Otol Neurotol* 2014; 35:775-781.
8. Olusanya BO, Ruben RJ, Parving A. Reducing the burden of communication disorders in the developing world:an opportunity for the millennium development project. *JAMA* 2006; 296:441-444.
9. Dalton DS, Cruickshanks KJ, Klein BE, Klein R, Wiley TL, Nondahl DM. The impact of hearing loss on quality of life in older adults. *Gerontologist* 2003; 43:661-668.
10. Campbell VA, Crews JE, Moriarty DG, Zack MM, Blackman DK. Surveillance for sensory impairment, activity limitation, and health-related quality of life among older adults:United States, 1993-1997. *MMWR CDC Surveill Summ* 1999; 48:131-156.
11. Mohr PE, Feldman JJ, Dunbar JL, McConkey-Robbins A, Niparko JK, Rittenhouse RK, Skinner MW. The societal costs of severe to profound hearing loss in the United States. *Int J Technol Assess Health Care* 2000; 16:1120-1135.
12. Lamé IE, Peters ML, Vlaeyen JW, Kleef Mv, Patijn J. Quality of life in chronic pain is more associated with beliefs about pain, than with pain intensity. *Eur J Pain* 2005; 9:15-24.
13. De Kleyn A. Sudden complete or partial loss of function of the octavus-system in apparently normal persons. *Acta Otolaryngol (Stockh)* 1944; 32:407-429.
14. Schreiber BE, Agrup C, Haskard DO, Luxon LM. Sudden sensorineural hearing loss. *Lancet* 2010; 375:1203-1211.
15. Kishimoto I, Yamazaki H, Naito Y, Shinohara S, Fujiwara K, Kikuchi M, Kanazawa Y, Tona R, Harada H. Clinical features of rapidly progressive bilateral sensorineural hearing loss. *Acta Otolaryngol* 2014; 134:58-65.
16. Chau JK, Lin JR, Atashband S, Irvine RA, Westerberg BD. Systematic review of the evidence for the etiology of adult sudden sensorineural hearing loss. *Laryngoscope* 2010; 120:1011-1021.
17. Sara SA, Teh BM, Friedland P. Bilateral sudden sensorineural hearing loss:review. *J Laryngol Otol* 2014; 128:S8-15.
18. Ho T, Vrabec JT, Burton AW. Hydrocodone use and sensorineural hearing loss. *Pain Physician* 2007; 10:467-472.
19. Friedman RA, House JW, Luxford WM, Gherini S, Mills D. Profound hearing loss associated with hydrocodone/acetaminophen abuse. *Am J Otol* 2000; 21:188-191.
20. Oh AK, Ishiyama A, Baloh RW. Deafness associated with abuse of hydrocodone/acetaminophen. *Neurology* 2000; 54:2345.
21. Kyle ME, Wang JC, Shin JJ. Impact of nonaspirin nonsteroidal anti-inflammatory agents and acetaminophen on sensorineural hearing loss:a systematic review. *Otolaryngol Head Neck Surg* 2015; 152:393-409.
22. IMS Institute for Healthcare Informatics:Medicine use and shifting costs of healthcare:A review of the use of medicines in the United States in 2013. www.imshealth.com/portal/site/imshealth/menuitem.762a961826aad98f53c753c71ad8c22a/?vgnextoid=2684d47626745410VgnVCM10000076192ca2RCRD&vgnextchannel=736de5fda6370410VgnVCM10000076192ca2RCRD&vgnextfmt=default Accessed December 2, 2015
23. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States:the Slone survey. *JAMA* 2002; 287:337-344.
24. Food and Drug Administration Acetaminophen Overdose and Liver Injury - Background and Options for Reducing Injury, 2009. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM164897.pdf. Accessed December 2, 2015.
25. Curhan SG, Eavey R, Shargorodsky J, Curhan GC. Analgesic use and the risk of hearing loss in men. *Am J Med* 2010; 123:231-237.
26. Curhan SG, Shargorodsky J, Eavey R, Curhan GC. Analgesic use and the risk of hearing loss in women. *Am J Epidemiol* 2012; 176:544-554.
27. Yorgason JG, Kalinec GM, Luxford WM, Warren FM, Kalinec F. Acetaminophen ototoxicity after acetaminophen/hydrocodone abuse:evidence from two parallel in vitro mouse models. *Otolaryngol Head Neck Surg* 2010; 142:814-819, 819.e1-2.
28. HYSINGLA™ ER (hydrocodone bitartrate) extended release tablets for oral use, CII [package insert]. Purdue Pharma L. P., Stamford, CT. 2015.
29. Forge A, Schacht J. Aminoglycoside antibiotics. *Audiol Neurootol* 2000; 5:3-22.
30. Lugassy G Shapira A. Sensorineural hearing loss associated with vincristine treatment. *Blut* 1990; 61:320-321.
31. Schweitzer VG. Ototoxicity of chemotherapeutic agents. *Otolaryngol Clin North Am* 1993; 26:759-789.
32. Moss PE, Hickman S, and Harrison BR. Ototoxicity associated with vinblastine. *Ann Pharmacother* 1999; 33:423-425.
33. Kalcioglu MT, Kuku I, Kaya E, Oncel S, and Aydogdu I. Bilateral hearing loss during vincristine therapy: A case report. *J Chemother* 2003; 15:290-292.
34. Croghan MK, Aickin MG, Meyskens FL. Dose-related alpha-difluoromethylornithine ototoxicity. *Am J Clin Oncol* 1991; 14:331-335.
35. Fausti SA, Henry JA, Helt WJ, Phillips DS, Frey RH, Noffsinger D, Larson VD, Fowler CG. An individualized, sensitive frequency range for early detection of ototoxicity. *Ear Hear* 1999; 20:497-505.
36. Campbell KC, Kelly E, Targovnik N,

Hughes L, Van Saders C, Gottleib AB, Dorr MB, Leighton A. Audiologic monitoring for potential ototoxicity in a phase I clinical trial of a new glycopeptide antibiotic. *J Am Acad Audiol* 2003; 14:157-168

37. American Speech-Language-Hearing Association. Audiologic Management of Individuals Receiving Cochleotoxic Drug Therapy [Guidelines]. 1994. www.asha.org/policy/GL1994-00003/. Accessed December 2, 2015.
38. Jacobson GP, Newman W. Development of the Dizziness Handicap Inventory. *Arch Otolaryngol Head Neck Sur.* 1990; 116:424-427.
39. Newman CW, Jacobson GP, Spitzer JB. Development of the Tinnitus Handicap Inventory. *Arch Otolaryngol Head Neck Surg* 1996; 122:143-148.
40. Khan AS, Sheikh Z, Khan S. Viagra deafness-Sensorineural hearing loss and phosphodiesterase-5 inhibitors. Laryngoscope 2011; 121:1049-1054.
41. Wen W, Sitar S, Lynch SY, He E, Ripa S. A multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of single-entity, once-daily hydrocodone tablets in patients with uncontrolled moderate to severe chronic low back pain. *Expert Opin Pharmacother* 2015; 16:1593-1606.
42. Wen W, Taber L, Lynch SY, He E, Ripa S. 12-Month safety and effectiveness of once-daily hydrocodone tablets formulated with abuse-deterrent properties in patients with moderate to severe chronic pain. *J Opioid Manag* 2015; 11:4;339-356.
43. Agrawal Y, Platz EA, Niparko JK. Prevalence of hearing loss and differences by demographic characteristics among US adults:data from the National Health and Nutrition Examination Survey, 1999-2004. *Arch Intern Med* 2008; 168:1522-1530.
44. Gates GA, Cobb JL, D'Agostino RB, Wolf PA. The relation of hearing in the elderly to the presence of cardiovascular disease and cardiovascular risk factors. *Arch Otolaryngol Head Neck Surg* 1993; 119:156-161.
45. Fausti SA, Rappaport BZ, Schechter MA, Frey RH, Ward TT, Brummett RE. Detection of aminoglycoside ototoxicity by high-frequency auditory evaluation:selected case studies. *Am J Otolaryngol* 1984; 5:177-182.
46. Fausti SA, Schechter MA, Rappaport BZ, Frey RH, Mass RE. Early detection of cisplatin ototoxicity. Selected case reports. *Cancer* 1984; 53:224-231.
47. Fausti SA, Henry JA, Schaffer HI, Olson DJ, Frey RH, McDonald WJ. High-frequency audiometric monitoring for early detection of aminoglycoside ototoxicity. *J Infect Dis* 1992; 165:1026-1032.
48. Rappaport BZ, Fausti SA, Schechter MA, Frey RH. A prospective study of high-frequency auditory function in patients receiving oral neomycin. *Scand Audiol* 1986; 15:67-71.
49. D'Alonzo BJ, Cantor AB. Ototoxicity:Etiology and issues. *J Fam Pract* 1983; 16:489-494.