

Intratympanic Sustained-Exposure Dexamethasone Thermosensitive Gel for Symptoms of Ménière's Disease: Randomized Phase 2b Safety and Efficacy Trial

*Paul R. Lambert, †John Carey, ‡Anthony A. Mikulec, and §Carl LeBel,
on behalf of the Otonomy Ménière's Study Group

*Department of Otolaryngology—Head and Neck Surgery, Medical University of South Carolina, Charleston, South Carolina;
†Department of Otolaryngology—Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland;
‡St. Louis University, St. Louis, Missouri; and §Otonomy, Inc, San Diego, California

Objective: To evaluate safety and efficacy of a single intratympanic injection of OTO-104, sustained-exposure dexamethasone, in patients with unilateral Ménière's disease.

Study Design: Randomized, double-blind, placebo-controlled, Phase 2b study over 5 months.

Setting: Fifty-two academic and community otolaryngology centers.

Patients: One hundred fifty four patients (77 per group) aged 18 to 85 years inclusive.

Intervention: Single intratympanic injection of OTO-104 (12 mg dexamethasone) or placebo.

Main Outcome Measures: Efficacy (vertigo) and safety (adverse events, otoscopy, audiometry, tympanometry).

Results: Primary endpoint (change from baseline in vertigo rate at Month 3) was not statistically significant (placebo [−43%], OTO-104 [−61%], $P=0.067$). Improvements with OTO-104 were observed in prospectively defined secondary endpoints number of days with definitive vertigo, (Month 2 [$P=0.035$], Month 3 [$P=0.030$]), vertigo severity (Months 2–3, $P=0.046$) and daily vertigo counts (Month 2, $P=0.042$,

and in some Short Form-36 (SF-36) subscales (Month 2 bodily pain $P=0.039$, vitality $P=0.045$, social functioning $P=0.025$). No difference in tinnitus loudness or tinnitus handicap inventory (THI-25) was observed. OTO-104 was well tolerated; no negative impact on safety compared with placebo. Persistent tympanic membrane perforation was observed in two OTO-104 treated patients at study end.

Conclusion: OTO-104 was well-tolerated, did not significantly affect change from baseline in vertigo rate, but did reduce number definitive vertigo days, vertigo severity, and average daily vertigo count compared with placebo during Month 3. Results provide insight into analyzing for a vertigo treatment effect and support advancing OTO-104 into Phase 3 clinical trials for the treatment of Ménière's disease symptoms. **Key Words:** Corticosteroid—Dexamethasone—Intratympanic—Ménière's disease—Tinnitus—Tinnitus handicap inventory—Vertigo.

Otol Neurotol 37:1669–1676, 2016.

Affecting approximately 0.2% of the population (1), Ménière's disease is a chronic idiopathic syndrome of the inner ear that is characterized by fluctuating hearing loss, tinnitus, aural fullness, and spontaneous vertigo episodes lasting 20 minutes or more (2). Temporal bone studies have associated the disease with endolymphatic hydrops, leading to speculation that it may arise from disruption in the balance between endolymph production and absorption (3,4).

There is no cure for Ménière's disease. The disease may eventually result in irreversible sensorineural hearing loss at all frequencies in the affected ear and seriously impair a patient's quality of life (5,6). Treatments for the disease tend to focus on relieving vertigo, the most debilitating symptom associated with the disease. A reduction in inner ear fluid volume may reduce hydrops and associated clinical symptoms, which is why physicians routinely prescribe low-salt diet and diuretics (1,7). Treatments addressing symptoms may include systemic medications (anticholinergics, antihistamines, phenothiazines, benzodiazepines, corticosteroids), surgical treatments (endolymphatic sac surgery, vestibular neurectomy, labyrinthectomy), non-surgical partial ablation (intratympanic [IT] gentamicin), or low-pressure devices. Administration of aqueous corticosteroid formulations via repeat IT injections (8–10) has been associated with clinical improvement in patients with Ménière's disease.

Address correspondence and reprint requests to Paul R. Lambert, M.D., Medical University of South Carolina, Charleston, SC 29425; E-mail: lambertp@musc.edu

P.L., J.C., and A.M. have received financial compensation from Otonomy, Inc., in the past but not related to their roles as investigators in this study. C.L. is currently an employee of Otonomy, Inc. and was involved the trial design and operation for the trial. The trial and analyses were financially supported by Otonomy, Inc.

DOI: 10.1097/MAO.0000000000001227

OTO-104 is a suspension of dexamethasone in a buffered solution containing the thermoreversible glycol polymer, poloxamer 407. It is intended for IT application over the round window niche, gels within seconds at body temperature, and is designed to provide a sustained-exposure of dexamethasone to the inner ear. In preclinical studies, IT injection of dexamethasone solution showed limited perilymph exposure while OTO-104 provided sustained perilymph dexamethasone exposure (11). In a Phase 1b trial in 44 patients with Ménière's disease, a single IT injection of OTO-104 was found to be well tolerated and associated with a reduction in change from baseline in vertigo rate 3 months after treatment compared with placebo (12). This report presents the assessment of safety and efficacy in a larger Phase 2b study of OTO-104 in patients with unilateral Ménière's disease.

MATERIALS AND METHODS

Study Design

This was a randomized, double-blind, placebo-controlled, multicenter 20-week Phase 2b study conducted in North America (clinicaltrials.gov Identifier NCT01412177). This study was conducted in compliance with the applicable regulatory requirements, Declaration of Helsinki and the International Conference on Harmonisation Guidance on Good Clinical Practice and Institutional Review Board approved (Schulman IRB and Local Institutional IRBs). A Data Safety Monitoring Board conducted four periodic reviews of the safety data in a blinded manner.

Study Population

All patients were willing to comply with the protocol, and able to provide written informed consent, including agreement to privacy language within the informed consent compliant with Health Insurance Portability and Accountability Act before the initiation of any study-related procedures.

Key patient inclusion criteria were the following: ages 18 to 85 years diagnosed with definite unilateral Ménière's disease (2); patient recorded at least two definitive (a score of 2–4 from the vertigo severity scale) vertigo episodes during the 4-week lead-in period and completed at least 22 of 28 diary entries during screening; patient agreed to maintain their current treatments for Ménière's disease; women of childbearing potential had a negative pregnancy test before randomization and took adequate contraceptive precautions for the duration of the study.

Patients were excluded from the study if they had any of the following: infection in the sinuses or upper respiratory system; middle ear disease or a significant abnormality of the tympanic membrane affecting the IT injection; a history of immunodeficiency disease; previous use of IT gentamicin; previous endolymphatic sac surgery; tympanostomy tubes with evidence of perforation or lack of closure; vertiginous migraine; drop attacks; systemic or IT steroids (within 1 month previous); experience of an adverse reaction to IT injection of steroids; or women who were pregnant or lactating.

Randomization and Trial Intervention

Following the 4-week lead-in period, eligible patients were randomly assigned to receive either 12 mg OTO-104 or placebo on Day 1 using a 1:1 allocation ratio based on a computer-

generated permuted block randomization algorithm. OTO-104 was given as a single 0.2 ml IT injection of 60 mg/ml on Day 1, and patients were observed for 4 months.

Patients recorded their daily vertigo and tinnitus experiences via an interactive voice response system diary during the 4-week lead-in period and 4-month follow-up period. The daily vertigo diary (13–16) used a 5-point vertigo severity scale (0 = vertigo-free day, 1 = vertigo episode lasting <20 minutes, 2 = definitive vertigo episode lasting >20 minutes, 3 = definitive vertigo episode associated with nausea/vomiting, 4 = worst attack experienced to date).

The physician administering the study drug was blinded up to the point of injection, but differences in the opacity between placebo and OTO-104 prevented blinding beyond that point. The administering physicians were trained not to use video monitors or discuss the appearance of the injected materials that would unblind the study staff or patients.

Objectives and Endpoints

The primary efficacy endpoint, which is what the sample size was based on, was the change from baseline in vertigo rate (definitive vertigo days divided by number of days of diary entries) during the 4-week interval from Week 9 through Week 12 (Month 3) (12).

Protocol-defined secondary efficacy endpoints included the change from baseline in severity of vertigo episodes, number of definitive vertigo days, average daily count of vertigo episodes, tinnitus handicap inventory (THI-25) (17,18), tinnitus frequency, degree of tinnitus loudness, and the quality of life Short Form-36 (SF-36) (19,20).

Safety

Safety endpoints included adverse events, vital signs, clinical laboratory measurements, and the Columbia-Suicide Rating Scale (C-SSRS). Otoscopic examinations were performed in both ears at all visits. Audiometry assessments (range 250–8000 Hz) included air- and bone-conduction thresholds and pure-tone averages (PTAs) for bone and air conduction (500, 1000, and 2000 Hz frequencies) in accordance with the American-Speech-Language-Hearing Association Guidelines (21). Word recognition tests were conducted in both ears using a standardized 50 word protocol with Northwestern University Auditory Test Number Six (NU-6) compact disc. Tympanometry was used to assess mobility of the tympanic membrane using a 226 Hz probe frequency.

Statistical Analyses

The primary endpoint, change from baseline in vertigo rate at Month 3, was analyzed using a linear mixed model with repeated measures. The full model contained fixed effects for randomized treatment group (OTO-104 versus placebo), study month treatment group by study week interaction, and baseline vertigo frequency. Primary analysis consisted of a linear contrast of the simple effect among the adjusted change from baseline means (change from baseline least squared [LS] means) between OTO-104 and placebo at Month 3 at the 2-tailed 0.05 alpha level. Secondary efficacy endpoints examining vertigo frequency at Months 1, 2, and 4 were from the same primary analysis conducted for the primary endpoint using linear contrasts for each of these other time points. Number of definitive vertigo days (definitive vertigo rate) was evaluated using a Poisson generalized linear mixed model. The primary efficacy analysis population was the full analysis set of patients and the safety analyses were descriptive.

RESULTS

A total of 154 (77 in each treatment group) men and women participated in the trials between December 2013 and April 2015 (Fig. 1). The study was conducted in 52 sites in the United States. Baseline demographics were generally balanced across both groups (Table 1).

Efficacy

A single IT administration of OTO-104 was not significant at 0.05 level (-0.052 with 95% CI of $-0.108, 0.004$; $P = 0.067$) for the primary endpoint of vertigo rate as the change from baseline during Month 3. The reduction in vertigo rate from baseline during Month 3 was approximately 4.6 definitive vertigo episodes for OTO-104 patients (61% reduction) and 3.2 definitive vertigo episodes for placebo patients (43% reduction) (Fig. 2).

The number of definitive vertigo days was statistically significant different between the groups in favor of OTO-104 group at Month 2 (2.16 versus 3.11 days, $P = 0.035$) and Month 3 (1.64 versus 2.54, $P = 0.030$) (Fig. 3). Month 2 and 3 changes from baseline in vertigo severity scores were also statistically significant in favor of OTO-104, with a 14% absolute reduction and 44 to 56% relative reduction in vertigo severity (Fig. 4).

The change from baseline in average daily vertigo count over 4 months (exploratory analysis versus “protocol-defined secondary efficacy endpoints”) showed statistical significance at Month 2 (24% reduction compared with placebo, $P = 0.042$) with a reduction from

1.91 at baseline to 0.62 in the OTO-104 group. The 22% reduction in the OTO-104 group in daily vertigo count was not significantly different from placebo in Month 3 (Fig. 5).

For both the OTO-104 and placebo groups, the frequency of tinnitus, the change from baseline in tinnitus frequency, average degree of tinnitus loudness, and the THI-25 remained stable throughout the follow-up period with no statistically significant differences observed.

The highest domain (versus “the composite”) SF-36 analysis was not statistically significant at Month 3 (Fig. 6a), although certain subscales of SF-36 were statistically significantly improved in OTO-104 patients compared with placebo patients (bodily pain, vitality, social functioning, Fig. 6b).

Safety

Most adverse events were mild or moderate in severity. No treatment-emergent adverse events (TEAE) resulted in patient discontinuation from this trial. The incidence of TEAE reported was similar between the OTO-104 and placebo treatment groups (Table 2). The most frequent TEAEs more than 3% observed in the OTO-104 group were nasopharyngitis, upper respiratory tract infection, sinus headache, and headache (Table 2). Seven severe TEAE were reported in four patients (5.3%) in the OTO-104 group (pneumonia, syncope, and vertigo in [one patient each] and depressed level of consciousness, sleep apnea syndrome, and disorientation in one patient), and 11 severe TEAE were reported in seven patients (9.0%) in the placebo group.

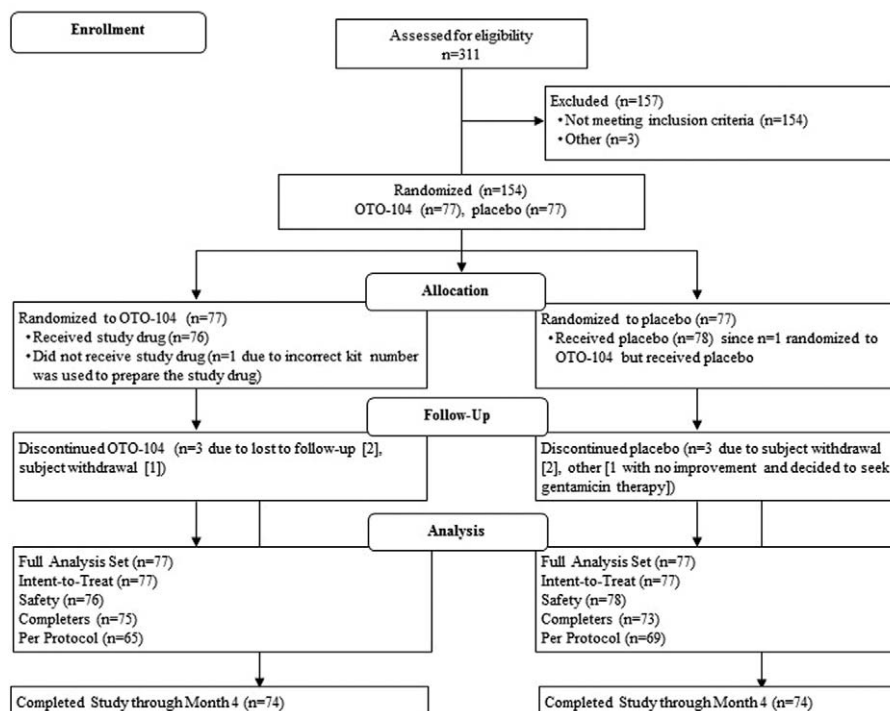


FIG. 1. CONSORT diagram. Patients were included in the treatment group to which they were randomized regardless of the actual study drug received.

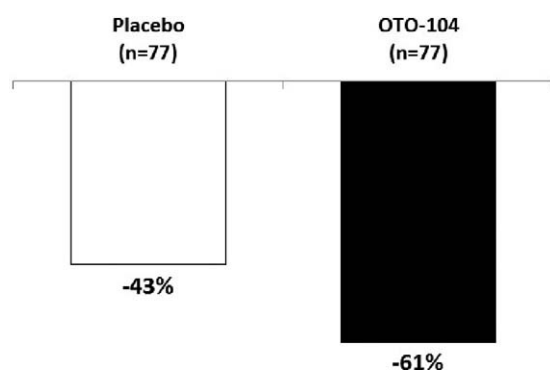
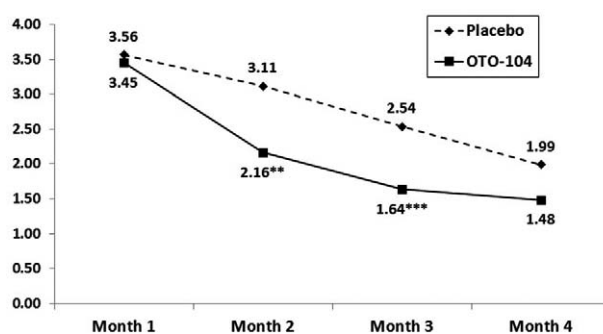
TABLE 1. Demographic and baseline characteristics

	OTO-104 (N = 77)	Placebo (N = 77)
Patients completing study, n (%)	75 (97.4%)	73 (94.8%)
Age, years, mean (SD)	54.8 (11.04)	55.3 (12.48)
Gender (male/female)	35/42 (45.5%/54.5%)	39/38 (50.6%/49.4%)
Race, n (%)		
White	70 (90.9%)	74 (96.1%)
Black or African American	3 (3.9%)	1 (1.3%)
Asian	0	1 (1.3%)
Native American/ Canadian	1 (1.3%)	0
Not applicable	1 (1.3%)	0
Other	2 (2.6%)	1 (1.3%)
Ethnicity, n (%)		
Hispanic or Latino	4 (5.2%)	2 (2.6%)
Not Hispanic or Latino	71 (92.2%)	75 (97.4%)
Unknown	2 (2.6%)	0
Duration of Ménière's disease, n (%)		
≤5 years	48 (62.3%)	47 (61.0%)
6–10 years	11 (14.3%)	19 (24.7%)
11–15 years	12 (15.6%)	9 (11.7%)
>15 years	6 (7.8%)	2 (2.6%)
Baseline vertigo frequency, mean	0.282	0.251

Baseline vertigo frequency is defined as the proportion of definitive vertigo days during the 1-month lead-in period.

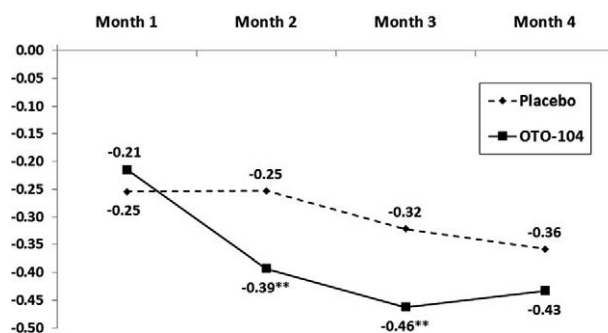
The incidence of abnormal otoscopic findings for the auricle, meatus, or middle ear was low, ranging from 0 to 2.7%. Shifts from normal to abnormal tympanic membrane findings in the treated ear were at least twice as common in OTO-104 group as in the placebo group at each visit. Number and percentage of OTO-104 patients with tympanic membrane perforation decreased over time: Month 1 (n = 10, 13.3%), Month 2 (n = 5, 6.7%), and Months 3 and 4 (n = 2, 2.7%).

At baseline, most patients had a tympanometry category of A in both the treated ear (98.7% OTO-104; 97.4% placebo) and non-treated ear (94.7% OTO-104; 94.9% placebo). The proportions of OTO-104

**FIG. 2.** Percent change in vertigo rate during Month 3 from baseline (full analysis set). $P=0.067$.**FIG. 3.** Number of definitive vertigo days over 4 months* (secondary endpoint). *Prospectively defined poisson regression statistical model used to assess rate of definitive vertigo days within each monthly period. ** $P=0.035$, *** $P=0.030$.

patients with categories of B (small/normal) and B (large) in the treated ear increased to 4.1 and 8.1%, respectively, at Month 1, consistent with the presence of tympanic membrane perforation following study drug injection. Evaluated by otoscopy at the end of the study, two OTO-104 patients had tympanometry findings consistent with perforations: one perforation was considered a pinhole perforation and the other perforation was rated $\leq 25\%$ of the tympanic membrane.

To assess the possible adverse effects of IT gel treatments on sensorineural and conductive hearing mechanisms, BC as well as AC thresholds were evaluated. The OTO-104 and placebo groups showed no significant differences with respect to the types and incidences of shifts in AC and BC in the treated ear at Month 4. Incidences of air bone gap improvement of more than 10 dB in the treated ear of OTO-104 patients at Month 4 was 6.1% at 500 Hz, 4.3% at 1000 Hz, and 1.4% at 2000 Hz. In the placebo patients those values were 13.7, 7.9, and 2.7%, respectively. The incidences of air bone gap worsening in the treated ear of OTO-104 patients at Month 4 were 13.6% at 500 Hz, 8.6% at 1000 Hz, and 1.4% at 2000 Hz. In the placebo patients those values

**FIG. 4.** Change from baseline in vertigo severity score over 4 months* (secondary endpoint). *Prospectively defined data reported as change from baseline in vertigo severity score (total reported average vertigo score divided by the number of diary entries over the respective 28-day reporting period using a 5 point severity scale). ** $P=0.046$.

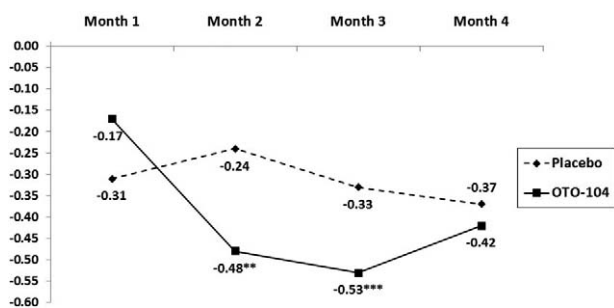


FIG. 5. Change from baseline in average daily vertigo count over 4 months* (exploratory analysis). *Data reported as change from baseline in average daily vertigo count (average number of vertigo episodes reported in daily diary divided by the number of diary entries in each respective study month). ** $P=0.042$, *** $P=0.065$.

were 6.8, 6.6%, and 0, respectively. Again, these differences were not statistically significant. There were no significant differences in word recognition at any time point (Month 1–4) between the OTO-104 and placebo groups.

The OTO-104 and placebo groups showed no notable treatment differences in post-baseline C-SSRS, laboratory test results or vital signs.

DISCUSSION

In this randomized, double-blind, placebo-controlled trial in Ménière’s disease, a single IT injection of 12 mg OTO-104 was associated with reductions in various vertigo outcome measures. While the primary efficacy analysis did not achieve statistical significance, multiple prospectively defined secondary vertigo endpoints (number of definitive vertigo days, vertigo severity, average daily vertigo count) were statistically significant at Months 2 and 3 (Figs. 3–5). Definitive vertigo days and vertigo severity appear to be the most sensitive measures that reflect a potential treatment effect of OTO-104. These results are consistent with the previously reported Phase 1b study with OTO-104 (12), and provide further evidence that intratympanic steroids can provide reductions in vertigo (8–10,22,23). The observation that statistically

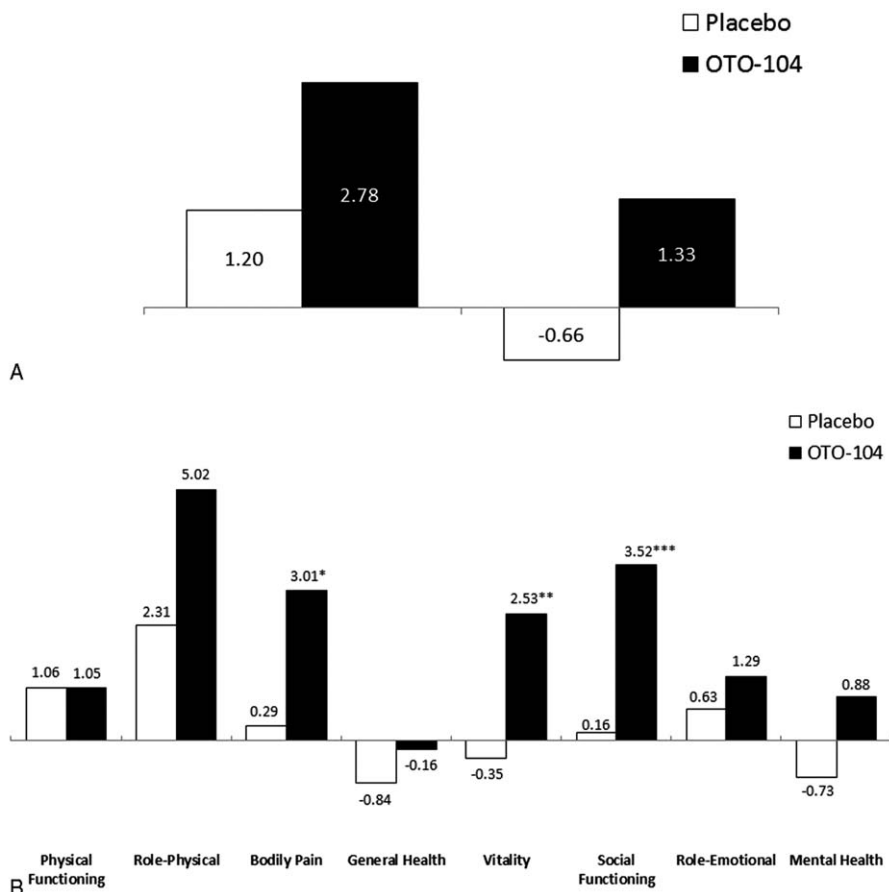


FIG. 6. A, Summary level of the SF-36 change from baseline at Month 3—general health questionnaire (exploratory analysis). B, SF-36 general health questionnaire change from baseline at Month 3, subscales. * $P=0.039$, ** $P=0.045$, *** $P=0.025$. SF-36 indicates Short Form-36.

TABLE 2. Treatment emergent adverse events occurring with more than 3% incidence (safety analysis set)

Preferred Term for Adverse Event	Number of Patients (%)	
	OTO-104 (N=76)	Placebo (N=78)
Total patients with any treatment emergent adverse event	42 (55.3%)	45 (57.7%)
Nasopharyngitis	7 (9.2%)	5 (6.4%)
Upper respiratory tract infection	5 (6.6%)	5 (6.4%)
Urinary tract infection	1 (1.3%)	5 (6.4%)
Headache	4 (5.3%)	3 (3.8%)
Hypertension	2 (2.6%)	4 (5.1%)
Sinus headache	3 (3.9%)	0
Ear pain	1 (1.3%)	3 (3.8%)
Diarrhea	2 (2.6%)	3 (3.8%)
Drug hypersensitivity	0	3 (3.8%)

n = number of patients reporting at least one adverse event with preferred term; (%) = percentage of patients among treatment group (N).

If a patient experienced more than one episode of an adverse event, the patient is counted once for that preferred term.

Preferred term is based on the Version 16.1 of the MedDRA coding dictionary.

significant improvement in SF-36 subscales following OTO-104 dosing is notable given the quality of life challenges experienced by patients with Ménière's disease (5,6).

Animal models have shown that a single IT injection of OTO-104 may have advantages over IT corticosteroid solutions (11). The poloxamer-based formulation has both sustained-release and muco-adhesive properties that provides a sustained inner ear dexamethasone concentration. In guinea pigs and sheep (13), for example, it has been shown that a single middle ear injection of OTO-104 achieves significant inner ear drug levels for 2 to 3 months. We hypothesize that after IT injection, the thermosensitive poloxamer positions and maintains dexamethasone microparticles at the round window niche, providing a depot for sustained drug diffusion into the inner ear. This is in contrast to the high variability and transient exposure of steroid concentration in the inner ear observed following IT injection of solution-based formulations in patients (24,25). It is estimated that poloxamer, based on tracer studies, is eliminated within 2 weeks after injection (13).

There were no statistical or clinically meaningful treatment differences on otoscopy, audiometry, tympanometry, word recognition, vital signs, clinical laboratory evaluations or the C-SSRS. The safety assessments in this study support the position that intratympanic administration of corticosteroids are well tolerated and no new risks were identified (9,26,27). Persistent tympanic membrane perforations were observed in two OTO-104 treated patients (2.7%) at the end of study, consistent with perforations seen following IT administration of an aqueous solution of a glucocorticoid steroid (22,28).

In the current study, no changes were observed in tinnitus loudness or THI-25 between OTO-104 and

placebo, unlike what was observed in the Phase 1b study (12) where an OTO-104 treatment effect was observed with THI-25. The reason for this is unclear, but in general, patients were less impaired from a tinnitus perspective in the current study than what was seen in the Phase 1b study.

OTO-104 may provide advantages over steroid solutions that are not FDA-approved for Ménière's disease. Following administration of OTO-104, patients were able to sit upright immediately and did not need to remain laterally recumbent for up to 30 minutes with no talking or swallowing as is generally required following administration of solution. This offers patient acceptance and convenience advantages over current clinical practice which frequently includes multiple IT injections of steroid solution per course of treatment.

Like all studies, this large Phase 2 trial had limitations. Vertigo and tinnitus endpoints were monitored as efficacy endpoints, while hearing function and tympanometry were measures of safety. While it would be of interest to assess whether hearing function was improved in the OTO-104 treatment group compared with placebo, the study design did not enable this comparison. A stratification design that balances treatment groups on the basis of low frequency hearing function would be ideal, however, the fluctuating nature of this measure in Meniere's disease patients would require a significantly larger study than the present study.

CONCLUSIONS

In conclusion, data from this clinical trial suggest that a single IT injection of OTO-104 reduces certain vertigo outcome measures after 3 months in patients with Ménière's disease. These findings support advancing OTO-104 into Phase 3 clinical trials for the treatment of Ménière's disease.

Acknowledgments: The authors thank the patients and their caregivers, the clinical trial site staff members, trial coordinators, nursing and supporting staff, the Rho, Inc. project managers, trial monitors, statisticians, and remaining members of the trial teams for their participation in this trial.

The authors express their sincere gratitude to the following principal investigators who participated in the trials:

Ansley, J., Carolina Ear, Nose and Throat Center, Orangeburg, SC.

Antonelli, P., University of Florida Health, Gainesville, FL.

Bryarly, R., Lovelace Scientific Resource, Austin, TX.

Carey, J., John Hopkins University School of Medicine, Baltimore, MD.

Chan, E., Michigan Ear Institute, Novi, MI.

Crawford, J., Madigan Army Medical Center, Tacoma, WA.

DeVenecia, R., Massachusetts Eye and Ear Infirmary, Boston, MD.

Douglis, F., Douglis Medical Research, Conroe and Spring, TX.

Gantz, B., University of Iowa Health Care, Iowa City, IA.

Gluth, M., University of Chicago, Chicago, IL.

Gold, S., Charlotte Eye, Ear, Nose, Throat Associates, Charlotte, NC.

Hammerschlag, P., New York University School of Medicine, New York, NY.

Kaylie, D., Duke Otolaryngology Head and Neck Surgery Clinic, Durham, NC.

Kim, H-O., The New York Eye and Ear Infirmary, New York, NY.

Kutz, W., UT Southwestern Medical Center, Dallas, TX.

Labadie, R., Vanderbilt University, Nashville, TN.

Lalwani, A., Columbia University Medical Center, New York, NY.

Lambert, P., Medical School of South Carolina, Charleston, SC.

Lanier, B., Central California Clinical Research, Fresno, CA.

Lansford, B., NEA Baptist Clinic, Jonesboro, AR.

Major, S., Advanced Research Institute, Ogden, UT.

Manthei, S., Westfield Nevada Eye and Ear, Henderson, NV.

Mattox, D., Emory University, Atlanta, GA.

Maxwell, K., Piedmont ENT Associates, Winston-Salem, NC.

McElveen, J., Carolina Ear & Hearing Clinic, Raleigh, NC.

McFeely, W., North Alabama ENT Associates, Huntsville, AL.

Micco, A., NMF Otolaryngology, Chicago, IL.

Mikulec, A., St. Louis University, St. Louis, MO.

Miller, S., Intermountain Ear Nose & Throat Specialist, Salt Lake City, UT.

Mitskavich, M., Coastal ENT, Neptune, NJ.

Moss, J., Charlotte Eye, Ear, Nose, and Throat Associates, Matthews, NC.

Munzer, E., ENT and Allergy Associates, New Windsor, NY.

Nguyen, Q., University of California San Diego, San Diego, CA.

Nguyen-Huynh, A., Oregon Health & Science University, Portland, OR.

Novak, M., Carle Foundation Hospital, Urbana, IL.

Roebuck, J., South Texas Ear Nose and Throat, Beaumont, TX.

Romett, J., Colorado ENT & Allergy, Colorado Springs, CO.

Rosenbloom, J., Alamo ENT, LLC, San Antonio, TX.

Samy, R., University of Cincinnati, Cincinnati, OH.

Shohet Ear Associates, Newport Beach and Seal Beach, CA.

Silverstein, H., Silverstein Institute, Sarasota, FL.

Staecker, H., University of Kansas Medical Center, Kansas City, KS.

Strasnick, B., EVMS Otolaryngology, Norfolk, VA.

Vambutas, A., NS-LIJ Health System, Hearing & Speech Center, New Hyde Park, NY.

Welsh, D., Advanced ENT and Allergy, Louisville, KY.

Wetmore, S., West Virginia University Hospitals, Morgantown, WV.

Widick, M., Ear, Nose and Throat Associates of South Florida, Boca Raton, FL.

Medical Writing support: The authors thank Donna Simcoe of Simcoe Consultants, Inc. funding provided by Otonomy, Inc. for development of an early draft of the manuscript based on conversations with the authors.

REFERENCES

1. Barritt L. Ménière's disease. *XPharm: Compr Pharmacol Ref* 2008;3:1-6.
2. Committee on Hearing and Equilibrium. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Ménière's disease. *Otol-Head Neck Surg* 1995;113:181-5.
3. Shea JJ. Classification of Ménière's disease. *Otol Neuro* 1993;14:224-9.
4. Paparella MM. Pathogenesis of Ménière's disease and Ménière's syndrome. *Acta Otolaryngol Suppl* 1984;406:10-25.
5. Anderson JP, Harris JP. Impact of Ménière's disease on quality of life. *Otol Neurotol* 2001;22:888-94.
6. Porter M, Boothroyd RA. Symptom severity, social supports, coping styles, and quality of life among individuals' diagnosed with Ménière's disease. *Chronic Illn* 2015;11:256-66.
7. Semaan MT, Megerian CA. Contemporary perspectives on the pathophysiology of Ménière's disease: implications for treatment. *Curr Opin Otol Head Neck Surg* 2010;18:392-8.
8. Gupta BBP, Lalchandama K. Molecular mechanisms of glucocorticoid action. *Curr Sci* 2002;83:1103-11.
9. Garduño-Anaya MA, De Toledo HC, Hinojosa-González R, Panebianese C, Ríos-Castañeda LC. Dexamethasone inner ear perfusion by intratympanic injection in unilateral Ménière's disease: a two-year prospective, placebo-controlled, double-blind, randomized trial. *Otol-Head Neck Surg* 2005;133:285-94.
10. Bolease-Aguirre MS, Lin FR, Della Santina CC, Minor LB, Carey JP. Longitudinal results with intratympanic dexamethasone in the treatment of Ménière's disease. *Otol Neurotol* 2008;29:33-8.
11. Piu F, Wang X, Fernandez R, et al. OTO-104: a sustained-release dexamethasone hydrogel for the treatment of otic disorders. *Otol Neurotol* 2011;32:171-9.
12. Lambert PR, Nguyen S, Maxwell KS, et al. A randomized, double-blind, placebo-controlled clinical study to assess safety and clinical activity of OTO-104 given as a single intratympanic injection in patients with unilateral Ménière's disease. *Otol Neurotol* 2012;33:1257-65.
13. Gates GA. Clinimetrics of Ménière's disease. *Laryngoscope* 2000;110:8-11.
14. Gates GA, Green JD, Tucci DL, Telian SA. The effects of trans-tympanic micropressure treatment in people with unilateral Ménière's disease. *Arch Otol Head Neck Surg* 2004;130:718-25.
15. Gates GA, Verrall AM. Validation of the Ménière's disease patient-oriented symptom-severity index. *Arch Otol Head Neck Surg* 2005;131:863-7.
16. Gates GA, Verrall AM, Green JD, Tucci DL, Telian SA. Meniett clinical trial: long-term follow-up. *Arch Otol Head Neck Surg* 2006;132:1311-6.
17. Newman CW, Jacobson GP, Spitzer JB. Development of the tinnitus handicap inventory. *Arch Otol Head Neck Surg* 1996;122:143-8.
18. Newman CW, Sandridge SA, Jacobson GP. Psychometric adequacy of the tinnitus handicap inventory (THI) for evaluating treatment outcome. *J Am Acad Audiol* 1998;9:153-60.
19. Ware JE, Snow KK, Kosinski M, Gandek B. *SF-36 Health Survey: Manual and Interpretation Guide*. Lincoln, RI: QualityMetric Inc; 1993.

20. Ware J, Kosinski M, Keller S. *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. Health Assessment Lab.; 1994
21. American Speech-Language-Hearing Association. Guidelines for Manual Pure-Tone Threshold Audiometry [Guidelines]; 2005. Available at: <http://www.asha.org/policy/GL2005-00014.htm>. Accessed 20, 2015.
22. Herraiz C, Plaza G, Aparicio JM, et al. Transtympanic steroids for Ménière's disease. *Otol Neurotol* 2010;31:162–7.
23. Phillips JS, Westerberg B. Intratympanic steroids for Ménière's disease or syndrome. *Cochrane Database Syst Rev* 2011; 6:CD008514.
24. Bird PA, Begg EJ, Zhang M, Keast AT, Murray DP, Balkany TJ. Intratympanic versus intravenous delivery of methylprednisolone to cochlear perilymph. *Otol Neurotol* 2007;28:1124–30.
25. Bird PA, Murray DP, Zhang M, Begg EJ. Intratympanic versus intravenous delivery of dexamethasone and dexamethasone sodium phosphate to cochlear perilymph. *Otol Neurotol* 2011; 32:933–6.
26. Silverstein H, Farrugia M, Van Ess M. Dexamethasone inner ear perfusion for subclinical endolymphatic hydrops. *Ear Nose Throat J* 2009;88:778–85.
27. Kitahara T, Kubo T, Okumura S, Kitahara M. Effects of endolymphatic sac drainage with steroids for intractable Ménière's disease: a long-term follow-up and randomized controlled study. *Laryngoscope* 2008;118:854–61.
28. Rauch SD, Halpin DF, Antonelli PJ, et al. Oral vs intratympanic corticosteroid therapy for idiopathic sudden sensorineural hearing loss: a randomized trial. *JAMA* 2011;305:2071–9.