Management of Eustachian Tube Dysfunction With Nasal Steroid Spray

A Prospective, Randomized, Placebo-Controlled Trial

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Objective: To determine the efficacy of intranasal aqueous triamcinolone acetonide in treating the tympanometric signs and symptoms of eustachian tube dysfunction, such as otitis media with effusion and negative middle ear pressure.

Design: Randomized, placebo-controlled, double-blind prospective clinical trial.

Setting: Tertiary referral clinic.

Patients: Adults (≥18 years) and children (6-17 years) presenting with otitis media with effusion, negative middle ear pressure, or both.

Interventions: The 2 treatment arms consisted of aqueous triamcinolone or matching placebo administered once daily intranasally for 6 weeks. All subjects underwent tympanometry, otologic examination, and completion of a symptom questionnaire before and after treatment.

Main Outcome Measures: Resolution of abnormal tympanometry and change in symptom scores (severity and frequency).

Results: Ninety-one patients presenting from September 1, 2005, through December 31, 2008, with otitis media with effusion or with negative middle ear pressure were enrolled and randomly assigned to treatment or placebo in a double-blind manner. No statistically significant difference in normalization of abnormal tympanometric signs was demonstrated with the active treatment arm compared with placebo on either a per-patient basis (19% vs 32%; P = .18) or a per-ear basis (22% vs 35%; P = .15). There was also no significant difference in the overall postsudy symptom score between the 2 treatment arms, after adjusting for the prestudy overall symptom score in an analysis of covariance model (P = .27).

Conclusion: These findings do not support the use of intranasal steroid sprays to treat the manifestations of eustachian tube dysfunction.

Trial Registration: clinicaltrials.gov Identifier: NCT00279916


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This study attempts to determine whether intranasal aqueous triamcinolone acetonide (TAA-AQ) has an effect on the clinical manifestations of ETD, such as OME and NMEP. This is a novel effort to prospectively study patients (both adults and children 6 years or older) who have reached eustachian tube anatomic maturity. Also, by analyzing the rates of spontaneous short-term resolution of OME and NMEP within a control (placebo) group, this study may improve understanding of the natural history of this clinical entity.

**METHODS**

Approval for this study was obtained from the Mayo Clinic Institutional Review Board. Adults (≥18 years) and children (6-17 years) presenting to the Department of Otorhinolaryngology at Mayo Clinic (Rochester, Minnesota), with OME, NMEP, or both were candidates for enrollment in this study. Signed informed consent regarding the study's goals, rationale, risks, design, and voluntary nature was obtained.

**PART I**

Are you experiencing current dizziness or balance problems? Yes or No (circle one)

Are you experiencing current ringing in your ear(s)? Yes or No (circle one)

Are you experiencing current tinnitus (as measured by a thermometer)? Yes or No (circle one)

Are you experiencing current daily drainage from either ear? Yes or No (circle one)

Have you ever had pressure equalization tubes placed in either ear? Yes or No (circle one)

If yes, please indicate which ear

Have you been flying in an airplane within the last week? Yes or No (circle one)

Do you have a history of any of the following medical conditions or therapies?

- Cholestrectoma (ear)? Yes or No (circle one)
- Nasoparyngeal mass or tumor? Yes or No (circle one)
- Cancer? Yes or No (circle one)
- Allergic rhinitis? Yes or No (circle one)
- Systemic steroids? Yes or No (circle one)
- Immunodeficiency? Yes or No (circle one)
- Cystic fibrosis? Yes or No (circle one)
- Previous ear surgery other than pressure equalization tube placement? Yes or No (circle one)
- If yes, please indicate type of surgery including note of which ear
- Adenoidectomy? Yes or No (circle one)
- Neuromuscular disease? Yes or No (circle one)
- History of allergic rhinitis? Yes or No (circle one)
- If yes, do you suffer from allergic symptoms always or only during certain seasons?
- Are you currently taking any antibiotics, decongestants, or nasal sprays? Yes or No (circle one)
- If yes, please list medications
- Do you currently smoke tobacco products? Yes or No (circle one)
- If no, are you exposed to smoke tobacco products in the household, car, or other living environment? Yes or No (circle one)

**PART II**

Please indicate the FREQUENCY and SEVERITY at which you have been experiencing the following symptoms OVER THE PAST WEEK (circle one):

1. Fullness or pressure in your ear(s) — OVER THE PAST WEEK

   **FREQUENCY (circle one):**
   - 1 = Never
   - 2 = Rarely (once a week)
   - 3 = Occasionally (few times a week)
   - 4 = Frequently (daily)
   - 5 = Constantly

   **SEVERITY (circle one):**
   - 1 = None at all
   - 2 = Minimum severity—barely noticeable
   - 3 = Moderate severity
   - 4 = Very severe
   - 5 = Maximum severity—could not be more severe

2. Pain in your ear(s) — OVER THE PAST WEEK

   **FREQUENCY (circle one):**
   - 1 = Never
   - 2 = Rarely (once a week)
   - 3 = Occasionally (few times a week)
   - 4 = Frequently (daily)
   - 5 = Constantly

   **SEVERITY (circle one):**
   - 1 = None at all
   - 2 = Minimum severity—barely noticeable
   - 3 = Moderate severity
   - 4 = Very severe
   - 5 = Maximum severity—could not be more severe

3. Plugged sensation in your ear(s) — OVER THE PAST WEEK

   **FREQUENCY (circle one):**
   - 1 = Never
   - 2 = Rarely (once a week)
   - 3 = Occasionally (few times a week)
   - 4 = Frequently (daily)
   - 5 = Constantly

   **SEVERITY (circle one):**
   - 1 = None at all
   - 2 = Minimum severity—barely noticeable
   - 3 = Moderate severity
   - 4 = Very severe
   - 5 = Maximum severity—could not be more severe

4. Popping sensation in your ear(s) — OVER THE PAST WEEK

   **FREQUENCY (circle one):**
   - 1 = Never
   - 2 = Rarely (once a week)
   - 3 = Occasionally (few times a week)
   - 4 = Frequently (daily)
   - 5 = Constantly

   **SEVERITY (circle one):**
   - 1 = None at all
   - 2 = Minimum severity—barely noticeable
   - 3 = Moderate severity
   - 4 = Very severe
   - 5 = Maximum severity—could not be more severe

5. Dampened hearing or hearing loss worse than usual — OVER THE PAST WEEK

   **FREQUENCY (circle one):**
   - 1 = Never
   - 2 = Rarely (once a week)
   - 3 = Occasionally (few times a week)
   - 4 = Frequently (daily)
   - 5 = Constantly

   **SEVERITY (circle one):**
   - 1 = None at all
   - 2 = Minimum severity—barely noticeable
   - 3 = Moderate severity
   - 4 = Very severe
   - 5 = Maximum severity—could not be more severe

**PART I**

While enrolled in this study, have you taken any of the following medications?

- Antibiotics? Yes or No (circle one)
- Oral decongestants (ie: Sudafed, Actifed, Contac, Tylenol Cold, etc)? Yes or No (circle one)
- If yes, please indicate type and location of cancer

**PART III**

If yes, please indicate type and location of cancer

- Radiation therapy to the head and/or neck region? Yes or No (circle one)
- Nasopharyngeal mass or tumor? Yes or No (circle one)
- Cancer? Yes or No (circle one)
- If yes, please indicate type and location of cancer

**PRESTUDY EVALUATION**

A questionnaire documenting the characteristics of related symptoms and relevant medical history was completed (Figure 1, part I). Adult subjects completed the questionnaire on their own, pediatric subjects between the ages of 12 and 17 years completed the questionnaire with parental assistance, and the parents of pediatric subjects younger than 12 years completed the questionnaire on their children’s behalf. The symptom questionnaire asked each subject to use a 5-point scale to indicate the frequency (1 = never to 5 = constantly) and severity (1 = none at all to 5 = maximum severity) of 3 symptoms in the ear during the preceding week: fullness or pressure, pain, plugged sensation, popping sensation, and dampened hearing or hearing loss worse than usual (Figure 1, part II). For each subject, an overall score was derived as the sum of the mean score for frequency and the mean score for severity.

**INCLUSION AND EXCLUSION CRITERIA**

All subjects had OME, NMEP, or both with an intact tympanic membrane as documented on otoscopic examination and
Otitis media with effusion was defined as an accumulation of fluid within the middle ear space in the absence of prominent acute inflammatory signs suggestive of infection. Adult subjects underwent otoscopic examination as well as flexible fiberoptic nasopharyngoscopy; pediatric patients underwent only otoscopic examination. Tympanograms (with external auditory canal volume measurements) were obtained from both ears. Specific exclusion criteria were tympanic membrane perforation (otoscopy), active cholesteatoma (otoscopy), acute or chronic supplicative otitis media (otoscopy), craniofacial syndromes, cleft palate, and developmental delay.

Among subjects with NMEP and tympanic membrane atelectasis, only those with type 1 retraction (mildly retracted), type 2 retraction (retracted over the incudostapedial complex), or type 3 retraction (retraction onto the promontory), as described by Dornhoffer, were considered for enrollment. Justification for exclusion of type 4 retraction (extent of retraction pocket not visualized) was based on the concern of adhesion formation, occult cholesteatoma, or both—placing these potential subjects in a poorer prognostic category that might have required imminent surgical intervention. In addition, all subjects expressed willingness to return for a scheduled follow-up evaluation at 6 weeks.

**RANDOMIZATION**

Subjects who met inclusion criteria were enrolled by the investigators and were then randomly assigned blindly by a third party (clinic pharmacy) to 1 of 2 parallel treatment arms (active treatment arm and control arm). Subjects with a type B or type C tympanogram may represent variations of ETD severity, the randomization schedule was stratified by the tympanogram result for the worse ear (type B or C) and generated using block randomization. A type A tympanogram was defined as having a peaked pressure measurement less negative than –100 kPa. Peaked tympanograms with pressure measurements more negative than –100 kPa were considered type C. Nonpeaked or flat tympanograms were considered type B. The study was double-blind for study subjects and all individuals involved in performing study-related assessments. The pharmacy oversaw the randomization, and the treatments were bottled in identical containers with the sequence concealed until all participants had been assigned.

**INTERVENTION**

Subjects aged 12 years or older in the active treatment arm received TAA-AQ (Nasacort AQ Nasal Spray; sanofi-aventis US, LLC, Bridgewater, New Jersey), 2 metered sprays in each nostril once daily (55 µg per spray), and those in the control arm received the same amount of placebo nasal spray consisting of an identical aqueous solution that lacked triamcinolone (2 sprays in each nostril once daily). Subjects younger than 12 years in the treatment arm received TAA-AQ, 1 metered spray in each nostril once daily (55 µg per spray), and those in the control arm received the same amount of matching placebo nasal spray. Subjects were instructed not to use oral or topical decongestants during the study. Intranasal TAA-AQ was chosen for its properties as an odorless aqueous preparation that was projected to cause relatively less mucosal irritation and burning compared with some other nasal steroid preparations, thereby improving the likelihood of maintaining the trial’s blinding.

**FOLLOW-UP**

At 6 weeks, subjects were asked to complete the tympanometric and quality of life questionnaire related to compliance, quality of blinding, and adverse treatment effects (Figure 1, part III). Oto logic examination and tympanometry were repeated.

**OUTCOME MEASURES**

The primary outcome measure was tympanometric normalization by 6 weeks, defined as a change in tympanogram from a pretreatment type B or C to a posttreatment type A. Our hypothesis was that administration of daily intranasal TAA-AQ would result in a higher rate of tympanometric normalization compared with the rate resulting from administration of placebo. Analysis of the primary outcome measure was based on an intent-to-treat principle; that is, subjects were analyzed according to the assigned treatment that was undertaken. Subjects who were treated with antibiotics or oral or topical decongestants or who had tympanostomy tube placement while enrolled were considered to have treatment failures in a secondary analysis of this measure. In addition, the change in the overall frequency and severity symptom score was evaluated.

**STATISTICAL ANALYSES**

The targeted sample size of 73 patients per treatment arm was determined to be sufficient to provide 80% power to detect a difference of 25% (placebo arm) vs 50% (treatment arm) in the percentage of patients with complete resolution of symptoms at 6 weeks, assuming a 10% dropout rate. The primary analysis was made on a per-subject basis. Both ears needed to have a type A result on the follow-up tympanogram for the subject to be classified as having normalization. The proportion of subjects who experienced normalization was compared between the 2 treatment arms using a χ² test. In addition, a 95% confidence interval (CI) was calculated for the difference in proportions between the 2 treatment arms. A subgroup analysis of the primary outcome was also undertaken for patients between 6 and 17 years of age. As a secondary analysis, tympanometric normalization was evaluated on a per-ear basis using all ears with type B or type C tympanogram results at baseline.

The comparison on the proportion of ears with normalization was evaluated on the basis of a logistic regression model that was fit using generalized estimating equations to take into account the correlation between ears of the same subject.

Finally, the responses at 6 weeks to the symptom frequency and severity questionnaire were compared between the 2 treatment arms using Wilcoxon rank sum tests. In the case of treatment failures, the subject’s data points were assigned the worst rank before calculation of the rank sum test. In addition, an overall score was derived as the sum of the mean score for frequency and the mean score for severity. The poststudy overall symptom score was compared between the 2 treatment arms, after adjusting for the prestudy overall symptom score in an analysis of covariance model.

All calculated P values were 2-sided, and P < .05 was considered statistically significant. Statistical analyses were performed using SAS, version 9.1 (SAS Institute, Inc, Cary, North Carolina).

**RESULTS**

Ninety-one subjects met the inclusion criteria and provided consent for enrollment from September 1, 2005, through December 31, 2008. Of the 91 subjects, 45 (49%) were male, and the mean (SD) age at enrollment was 41.7 (29.5) years, with a range of 6.1 to 95.8 years. The total number of patients screened during the subject recruit-
per-ear treatment outcome

Among the 37 subjects randomized to TAA-AQ with a follow-up tympanogram, a total of 55 ears had an initial tympanogram of type B or C; on follow-up, 12 ears (21.8%) had complete normalization. Among the 37 subjects randomized to placebo with a follow-up tympanogram, a total of 57 ears had an initial tympanogram of type B or C; on follow-up, 20 ears (35.1%) had complete normalization.
This difference was not statistically significant ($P = .15$). These results are summarized in Table 2.

When the subjects treated with antibiotics or oral decongestants while enrolled in the study were handled as having treatment failures (ie, incomplete resolution), then 8 of the 55 ears (15%) of subjects randomized to TAA-AQ had tympanometric normalization compared with 16 of the 57 ears (28%) of subjects randomized to placebo ($P = .16$).

**SYMPTOM QUESTIONNAIRE OUTCOMES**

Subjects who were randomized to TAA-AQ tended to have more moderate severity in fullness or pressure in their ears ($P = .07$), as well as more frequent ($P = .02$) and more severe ($P = .03$) plugged sensation in their ears, than did subjects randomized to placebo, after 6 weeks of treatment. In addition, the overall poststudy symptom score tended to be higher for subjects randomized to TAA-AQ compared with the score for those randomized to placebo ($P = .07$). After adjusting for the prestudy overall symptom score in an analysis of covariance model, the poststudy overall symptom score was not significantly different between the 2 treatment arms ($P = .27$).

**Table 3** summarizes the change (from pretreatment to posttreatment) in symptom frequency and severity after categorization of the change scores as same, better, or worse. The percentage of subjects with improved symptoms was not significantly different between the 2 treatment arms ($P > .05$, $\chi^2$ test).

**ADVERSE EVENTS**

Although both cough and nosebleeds were reported as adverse events in both arms of the study, no severe events occurred and no subject was removed from the study as a result.

**COMMENT**

The ideal treatment strategy for management of ETD in adults is not well understood. Watchful waiting may be a reasonable, conservative initial option to manage ETD in uncomplicated cases. Yet, analysis of data derived from the placebo arm of this study demonstrates that only approximately one-third of cases seemed to undergo spontaneous normalization of tympanometric findings at a 6-week follow-up interval. Notwithstanding this low rate of spontaneous resolution, severe adverse consequences of watchful waiting were not encountered. This new information about natural disease history in adults should prove valuable for patient counseling.

In 2002, van Heerbeek et al published the results reported for various medical interventions for ETD in both animal models and humans and noted a lack of data from prospective randomized, double-blind, placebo-controlled trials within the medical literature. In particular, evidence to support the use of oral decongestants and antihistamines for OME in children is lacking. Furthermore, a study by van Heerbeek et al demonstrated no effect of single-dose topical application of a nasal decongestant on ETD in children in a randomized, double-blind, placebo-controlled study using sophisticated measures of eustachian tube function.

Publications prospectively addressing the effect of nasal steroids on ETD are limited. Thomas et al systematically reviewed the existing prospective data in 2006 relating to the treatment of OME in children using oral or nasal steroids for the Cochrane Database. They concluded that combined therapy with antibiotics and nasal steroids in children may have short-term benefit compared with antibiotics alone but based this on the findings of a single prospective study. They also concluded that data to support the use of nasal steroids alone were insufficient because they were based on the findings in a...
The frequency and severity of each of these 5 symptoms were rated by each subject (Figure 1, part II) before starting the study and after 6 weeks.

Table 3. Summary of Change in Symptom Scores

<table>
<thead>
<tr>
<th>Criterionb</th>
<th>Intranasal Aqueous Triamcinolone Acetonide (n=38)</th>
<th>Placebo (n=40)</th>
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</thead>
<tbody>
<tr>
<td>Fullness or pressure in ears</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>Better 11 (28.9) 18 (45.0)</td>
<td>Same 17 (44.7) 17 (42.5)</td>
</tr>
<tr>
<td></td>
<td>Worse 10 (26.3) 5 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>Better 13 (34.2) 18 (45.0)</td>
<td>Same 14 (36.8) 13 (32.5)</td>
</tr>
<tr>
<td></td>
<td>Worse 11 (28.9) 9 (22.5)</td>
<td></td>
</tr>
<tr>
<td>Pain in ears</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>Better 11 (28.9) 8 (20.0)</td>
<td>Same 17 (44.7) 23 (57.5)</td>
</tr>
<tr>
<td></td>
<td>Worse 10 (26.3) 9 (22.5)</td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>Better 9 (23.7) 6 (15.0)</td>
<td>Same 19 (50.0) 25 (62.5)</td>
</tr>
<tr>
<td></td>
<td>Worse 10 (26.3) 9 (22.5)</td>
<td></td>
</tr>
<tr>
<td>Plugged sensation in ears</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>Missing 0 1</td>
<td>Better 10 (26.3) 14 (35.9)</td>
</tr>
<tr>
<td></td>
<td>Same 13 (34.2) 21 (53.8)</td>
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<td></td>
<td>Worse 15 (39.5) 4 (10.3)</td>
<td></td>
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<tr>
<td>Severity</td>
<td>Missing 0 1</td>
<td>Better 15 (39.5) 14 (35.9)</td>
</tr>
<tr>
<td></td>
<td>Same 8 (21.1) 16 (41.0)</td>
<td></td>
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<tr>
<td></td>
<td>Worse 15 (39.5) 9 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Popping sensation in ears</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>Missing 0 1</td>
<td>Better 11 (28.9) 8 (20.5)</td>
</tr>
<tr>
<td></td>
<td>Same 14 (36.8) 18 (46.2)</td>
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<td></td>
<td>Worse 13 (34.2) 13 (33.3)</td>
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<tr>
<td>Severity</td>
<td>Missing 0 2</td>
<td>Better 9 (23.7) 6 (15.8)</td>
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<tr>
<td></td>
<td>Same 17 (44.7) 19 (50.0)</td>
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<tr>
<td></td>
<td>Worse 12 (31.6) 13 (34.2)</td>
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<td>Dampered hearing/loss worse than usual</td>
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<tr>
<td>Frequency</td>
<td>Missing 0 1</td>
<td>Better 16 (42.1) 16 (41.0)</td>
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<td></td>
<td>Same 14 (36.8) 15 (38.5)</td>
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<td></td>
<td>Worse 10 (26.3) 10 (25.6)</td>
<td></td>
</tr>
</tbody>
</table>

Data are given as number (percentage) of responses to that question.

b The frequency and severity of each of these 5 symptoms were rated by each subject (Figure 1, part II) before starting the study and after 6 weeks using a 5-point scale to indicate the frequency (1 = never to 5 = constantly) and severity (1 = none at all to 5 = maximum severity). The change was categorized as “same” if the same response was provided by the subject during both assessments, “better” if a more favorable response (less frequent or less severe) was provided after 6 weeks, or “worse” if a more unfavorable response (more frequent or more severe) was provided after 6 weeks.

STUDY WEAKNESSES

The study enrolled 91 rather than the targeted 146 subjects because of a slow rate of subject recruitment. Although the observed rate for complete resolution in the placebo arm was close to what was anticipated (observed 32.4%, anticipated 24.3%), the rate in the TAA-AQ arm was considerably lower than anticipated (observed 18.9%, anticipated 50%). The 95% CI for the difference (TAA-AQ minus placebo) in the observed proportions was –33.2% to 6.2%. Accordingly, the calculated upper range of possible improvement after treatment that could have been undetected by this study is a mere 6%, which is such a small difference that it likely would not provide most clinicians with motivation to treat ETD with TAA-AQ. We note that published data relating to the natural history of ETD and NMEP on which to base our pre-study outcome predictions were sparse.

A second weakness relates to the secondary outcomes, wherein we analyzed the results of a nonvalidated eustachian tube symptom questionnaire (to our knowledge, a validated tool does not yet exist) that also did not demonstrate beneficial treatment effects. We candidly acknowledge that the definitive meaningfulness of these secondary outcomes is in question because they are derived from a nonvalidated questionnaire.

We also acknowledge that nasal septal deviation, turbinate hypertrophy, and adenoid hypertrophy, which could have had a negative effect on drug delivery in some cases, were not assessed.

Finally, this study intentionally did not seek to exclusively include or exclude subjects with allergic rhinitis.
nitis. Twelve percent of all subjects reported a history of allergic rhinitis, yet subjects were not formally evaluated for confirmation or quantification. However, the number of subjects with self-reported allergic rhinitis was actually slightly higher in the control arm (17% vs 7% in the treatment arm); therefore, it is unlikely that this factor could account for the failure of the active study medication to show a treatment benefit.

Given the inflammatory nature of allergic rhinitis and the established potential negative effect on eustachian tube function, it is certainly possible that nasal steroids may have a role in treating patients with ETD who fall within this specific subcategory. Newer intranasal steroid preparations, such as TAA-AQ, are efficacious and generally safe, as demonstrated in large studies dealing with allergic rhinitis. Future research efforts looking specifically at the impact of nasal steroids on ETD in subjects with established allergic rhinitis are needed.

STUDY STRENGTHS

First, despite the study’s shortcomings, this is to our knowledge the first prospective placebo-controlled study dealing with the effect of nasal steroid sprays on ETD in adults and relatively older children—a patient group that has been generally neglected in clinical trial efforts to study ETD. Second, the primary outcome measure evaluated in this study (tympanogram normalization) is one that is both objective and clinically relevant insofar as tympanometry is commonly used by physicians to evaluate ETD. Finally, the placebo arm of this study provides valuable prospectively acquired data related to the natural history of ETD in older children and adults that is otherwise scarce in the medical literature.

In conclusion, topical intranasal application of TAA-AQ did not increase the likelihood of normalization of the tympanometric manifestations of ETD at 6 weeks in a study group of subjects aged 6 years or older. On the basis of responses to a pretreatment and posttreatment questionnaire, it also appears unlikely to improve ETD-related symptom complaints. Finally, our data portray a natural history of OME and NME in this population that undergoes spontaneous resolution by 6 weeks in only approximately one-third of subjects. The study medication was well tolerated without any unexpected adverse effects or serious adverse events reported.

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Author Contributions: Dr Orvidas had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gluth, McDonald, and Orvidas.
Acquisition of data: Gluth, McDonald, Bauch, Beatty, and Orvidas.
Analysis and interpretation of data: Gluth, Beaver, Bauch, and Orvidas.
Drafting of the manuscript: Gluth, McDonald, and Weaver.
Critical revision of the manuscript for important intellectual content: Gluth, Bauch, Beatty, and Orvidas.
Statistical analysis: Weaver.
Obtained funding: Gluth and Orvidas.
Administrative, technical, and material support: McDonald, Bauch, and Orvidas.
Study supervision: Gluth, McDonald, Bauch, Beatty, and Orvidas.

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Additional Contributions: Complete editorial control of manuscript preparation, review, and approval was independently maintained by the authors, who take complete responsibility for its content, although courtesy access to manuscript contents was afforded to sanofi-aventis US, LLC during the manuscript preparation process. All statistical calculations were independently undertaken by the authors at Mayo Clinic, Rochester, Minnesota.