TITLE: TREATMENT OF CLOGGED TYMPANOSTOMY TUBES: AN OFF-LAI USE OF DORNASE ALFA (PULMOZYME^{R})

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I. STUDY OBJECTIVES

Chronic otitis media (OM) is an important childhood infectious disease. Tympanostomy tubes are used to equalize the middle-ear pressure with the ambient atmospheric pressure and are efficacious as long as the lumens are patent. In a child who develops a new episode of OM following tympanostomy tube placement and is subsequently treated with oral/topical antibiotics, one of the following states will occur: patent tube, clogged tube without middle-ear effusion (MEE), or clogged tube with MEE. The clogged tube scenarios are of particular concern because they are relatively resistant to further medical treatment. Furthermore, clogged tube with effusion may result in pain and hearing impairment.

Dornase alfa (Pulmozyme^{R}) has been approved by the FDA since 1993 for the treatment of cystic fibrosis (CF). It reduces viscoelasticity of sputum by hydrolyzing DNA released by degenerating leukocytes. Since the desiccated plug of MEE in a clogged tube is laden with cellular debris and leukocytes, dornase alfa could similarly alter its viscoelasticity of the plug to re-establish the patency of the tympanostomy tube. This aim of this study is to evaluate the efficacy of dornase alfa in restoring patency in clogged tympanostomy tubes.

II. BACKGROUND

A. OTITIS MEDIA AND TYMPANOSTOMY TUBE PLACEMENT

Tympanostomy tube placement is the treatment of choice for chronic OM not responding to medical therapy. One of the main complications following tympanostomy tube placement is otorrhea. The frequency of otorrhea has been noted to involve 74.7% of the population with a mean of 2.17 episodes 12 months after insertion (Ah-Tye 2002). In a portion of these subjects with otorrhea, these tubes will become clogged. Although the frequency of this phenomenon is unknown, clinicians dread dealing with this entity because of the relative difficulty in resolving plugged tubes.

The key in treating clogged tympanostomy tubes is to understand the make-up of the blockage material itself. Reid et al (1988) reported that the lumen of plugged tubes consists of an eosinophilic material with a polymorphonuclear leukocyte infiltrate in 56% of the cases. The occurrence of luminal blockage was noted to be further associated with the presence of a MEE.

The failure to deal with plugged tubes successfully may in large part due to viscous MEE that is frequently encountered behind the plug; the so-called “glue ear” that likely was encountered during the original surgical procedure. The components within MEE responsible for its viscoelasticity have been studied. Analysis of the constituents of the MEE showed that glycoprotein and DNA but not protein or lipid were significantly higher in mucoid effusions compared to the serous effusions (Hutton, 1992). Therefore, the success in treating blocked

tubes goes beyond the dissolving the material occluding the lumen of the tube. It also involves managing mucoid MEE.

Unfortunately, a host of methods have been described to unblock clogged tube without any scientific credence and without much success. Empirically, clinicians rely on oto-topical antibiotic drops. A recent in vitro laboratory study showed vinegar and hyaluronidase solutions are more likely to clear plugged tympanostomy tubes than water and ototopical antibiotic drops (Wetine 2002). However, the ototopical drop using this combination may be of limited clinical value since the acidity of this drop would preclude compliance.

B. DORNASE ALFA

Dornase alfa (Pulmozyme^{R}) is a sterile, clear, colorless, highly purified solution of recombinant human deoxyribonuclease 1 (rhDNase), an enzyme which selectively cleaves DNA. The purified glycoprotein has a molecular weight of 37,000 daltons and its primary amino acid sequence is identical to that of the native human enzyme. The rationale behind its efficacy lies in the presence of high concentrations of extracellular DNA released by degenerating leukocytes that accumulate in response to infection present in airway secretions of patients with CF. In vitro, it hydrolyzes the DNA in sputum of CF patients and reduces sputum viscoelasticity. Administration of this drug is achieved in most CF patients by inhaling it using a nebulizer, one to two 2.5 mg ampule per day.

Since approval by the FDA in 1993, there have been important studies on the use of dornase alfa for the treatment of CF that include both adult and pediatric subjects with varying severity of the disease. In a 12-week randomized placebo trial in the United States, administration of dornase alfa to both pediatric and adult subjects with advanced CF showed significant improvement in pulmonary functions and dornase alfa was found to be both safe and well tolerated (McCoy 1996). In a similar international trial, dornase alfa was found to result similar improvement in pulmonary functions and have fewer dornase alfa-related and CF-related adverse events than in the U.S. study (Harms 1998). A long-term 96-week study of young children (6-10 years) with CF with mild lung function abnormalities reported significant improvement of lung functions in the dornase alfa treatment group (Quan 2001).

Off-label use of dornase alfa for the treatment of non-CF lung diseases has been reported. They include respiratory syncytial virus bronchiolitis (Nasr 2001), empyema thoracis (Simpson 2003) and plastic bronchitis (Manna 2003). In addition, the treatment of CF patients with chronic sinusitis has also been reported in retrospective study (Raynor 2000).

C. POTENTIAL EFFICACY OF DORNASE ALFA IN THE TREATMENT OF PLUGGED TYMPANOSTOMY TUBE

The rationale for dornase alfa for the treatment of plugged tympanostomy is based on the frequency of finding leukocytes in the lumen of plugged tubes and DNA in the MEE. This suggests a process of accentuated levels of extracellular DNA released by degenerating leukocytes, a picture comparable in the airway of CF patients.

D. PRELIMINARY STUDIES

1. ANIMAL STUDY

The principal investigator (KHC) is currently collaborating with Timothy T.K. Jung, MD at Loma Linda University School of Medicine in an animal study to investigate the ototoxicity of dornase alfa using the chinchilla model. Dr. Jung is a leading investigator in the field of biochemistry of the inner ear and has an animal laboratory to assess ototoxicity using auditory brainstem response (ABR) and distortion product oto-acoustic emission (DPOAE). Although animal models such as the chinchilla model have limitations in their ability to predict potential ototoxicity in humans because of species-specific factors (Chen 1999 & Hilton 2002), the chinchilla model was chosen to investigate the toxicity of dornase alfa in the inner ear due to the lack of a more suitable model.

An animal study was completed to compare the effects of saline control and 2 concentrations of dornase alfa (full-strength and 1/10 strength) on the inner ear of chinchillas. Briefly, the methodology requires the middle-ear space of an anesthetized animal to be accessed and the round window membrane, located between the middle-ear and the inner-ear, exposed. A piece of Gelfoam is placed on the round window membrane and saturated with 0.1 ml of the test solution. Hearing changes based on ABR were measured on an hourly basis up to 8 hours and DPOAE (1000Hz) was measured 2 hours into the experiment for each animal. Because animals in this model do not survive for extensive periods beyond the anesthetic period, longer-term assessment was not possible. Two-tailed Chi-square was used for statistical comparisons of the experimental groups for both the ABR and DPOAE studies.

A total of 30 animals (41 middle ears) were used. The sample size for the control, full-strength and 1/10 strength groups in the ABR study were 5, 8 and 8 respectively; whereas, in the DPOAE study, they were 6, 8 and 6 respectively. The results of the ABR study are summarized in Figure 1 which shows a progressive hearing loss over the course of the 8-hour study in all groups. Although there appeared to be a larger hearing loss in the full-strength dornase group as compared to the saline control group, the difference was not statistically significant ($P = .14$). The apparent smaller hearing loss of the 1/10 strength dornase group compared with the saline control group ($P = .20$) and the hearing loss associated with saline administration could not be readily explained; these observations likely reflect deficiencies of the study model. It is unlikely that the low-dose dornase would actually have a hearing preservation effect.

The results of the DPOAE study are summarized in Figure 2. No statistically significant differences were found between the full-strength dornase and the control group ($P = .44$) and between the 1/10 strength dornase and the control group ($P = .43$).

This preliminary study showed progressive degradation of hearing in all test groups including the control group, but no statistical differences in hearing degradation between controls and full-strength treated ears or between controls and 1/10 strength treated ears, by either ABR and DPOAE testing. Based on this study, dornase alfa appears not to have intrinsic deleterious effects on the inner ears of chinchillas. The otologic effects of dornase alfa, a recombinant form of a naturally occurring enzyme in the human body, in humans are unknown. The apparent safety of this product in an animal model commonly used to investigate ototoxicity, however, provides reassurance with regard to initiating a pilot study in humans.

Figure 1: Summary of ABR results of the saline control, full-strength dornase (Dor FS) and 1/10 strength dornase (Dor 1:10) groups over 8 hours. Hearing loss is represented in dB.

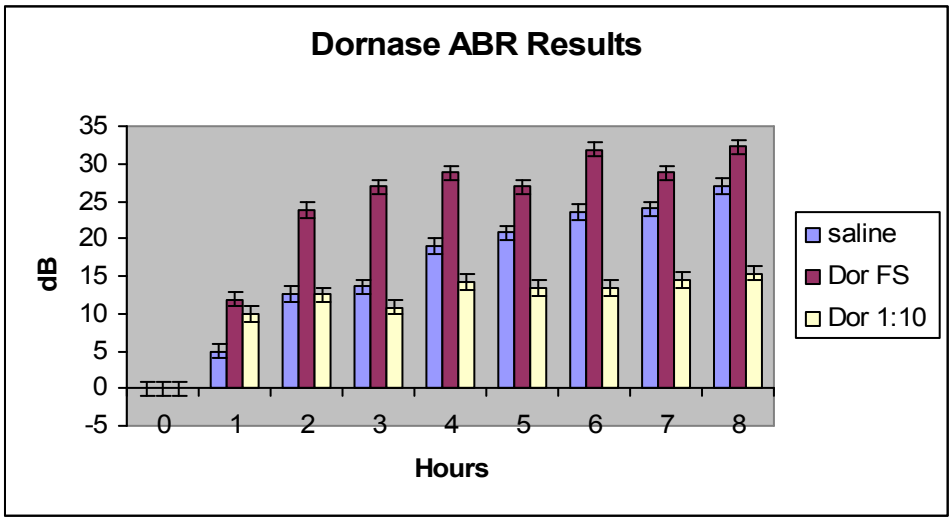
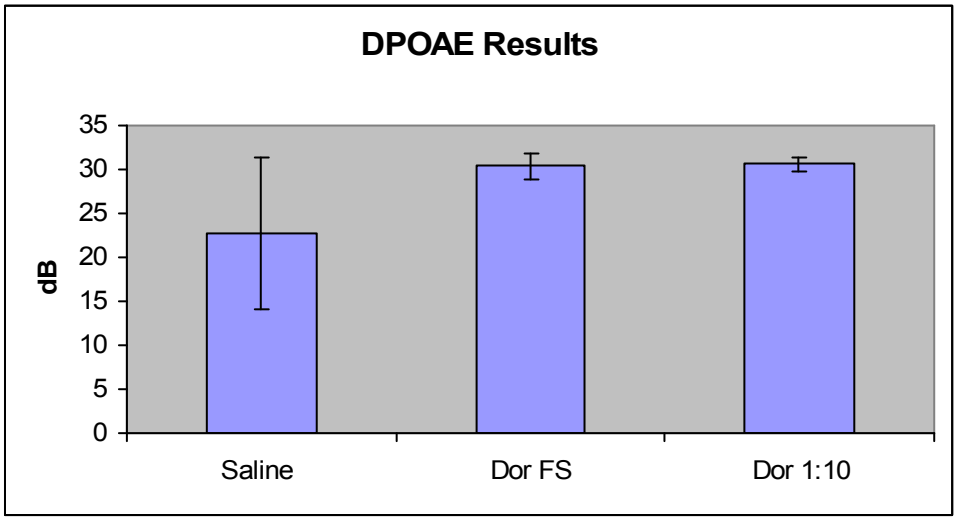


Figure 2: Summary of DPOAE results of the saline control, full-strength dornase (Dor FS) and 1/10 strength dornase (Dor 1:10) 2 hours into the experiment measured at 1000 Hz. Hearing loss is represented in dB.



2. HUMAN EXPERIENCE

Dornase alfa at one-tenth concentration was used in 1 subject with primary ciliary dyskinesia with clogged tympanostomy tubes in the clinical setting for compassionate reasons following informed consent by KHC in 2004. Children with ciliary dyskinesia have MEE so thick that it constantly clogs their tympanostomy tubes despite repeated medical treatment as in the case of this patient. The mother of this patient was informed of the findings of the ongoing animal study and agreed to the off-label use of dornase alfa (1/10 concentration) 5 drops twice a

day for 10 days. She noticed ear drainage within the treatment period, suggesting that the treatment resulted in clearing the clogged tubes to allow drainage of the MEE to the external ear canals.

III. METHODS

The study is a randomized clinical trial and the length of each subject's participation in the study is 3 months. Patients will be seen at entry, 14 days and 3 months post-treatment. A total of 40 subjects with clogged tubes will be stratified into sub-groups with MEE (N=20) and without MEE (N=20). Random assignment will occur within sub-groups to either traditional or experimental treatment. Traditional treatment will consist of ofloxicin (Floxin^{R}) otic drop at 5 drops twice a day for 7 days. Experimental treatment will consist of instillation of full-strength dornase alfa, 5 drops twice a day for 7 days. The primary outcome of the study is patency of the tympanostomy tube at the day-14 visit. The secondary outcomes of the study include the presence or absence of drainage in the ear canal and fluid in the middle ear at the day-14 visit.

The patency of the tubes will be assessed by otoscopy and tympanometry at all three visits. Audiograms will be performed on all subjects at the entry, Day 14 visit and 6-week visit. All subjects will undergo a final audiogram at the 3-month visit.

The otolaryngologist will be blinded to the treatment medication. Medications will be dispensed through the Research Pharmacy at The Children's Hospital. A standard randomization table, stratified for the two subgroups, will be used by the research pharmacist to dispense the study medications. Parents will be asked to use the otic drops by placing the affected ear upward with the child's head tilted or with the patient in a recumbent position. The subject will then stay in that position for 1 minute after the parent pumps the tragal area to ensure maximum penetration of the ear drop to the medial end of the external ear canal. A piece of cotton will be placed in the ear canal to ensure the ear drop not running out, prior to allowing the patient to get up or applying drops to the opposite ear in a child with bilateral clogged tubes.

Treatment failure will be subject to the discretion of the principal investigator and sub-investigators. Options for plugged tubes include clearing the tube lumen mechanically using surgical instrumentation under the operating microscope in the office. For those that failed mechanical clearing, replacement of tube may be required. For those that have persistent drainage, treatment using non-study medications may be required.

A. Recruiting Methods

Patients will be recruited from The Children's Hospital Ear, Nose and Throat Clinic. Patients who have acute otitis media who have undergone tube placement within the previous 12 months, between the ages of 1 year and 18 years, all ethnic groups, and both sexes will be eligible. The study will involve the use of protected health information. The study site will gain permission from each subject to use their protected health information by written authorization. All subjects will be identified by the treating physician at the subject's chosen treatment institution (The Children's Hospital).

B. Consent Procedure

All potential subjects that are identified by the PI and/or designee that meet the inclusion/exclusion criteria will be given the opportunity to participate. Parents/guardians/patients will be given the consent/assent during the screening visit. They will be given the opportunity to review the consent/assent and ask questions about the study. Parents/guardians/patients will be asked to summarize in their own words what participation in this research study involves and that they are comfortable with the risks and benefits of participating in the research study. Any additional questions they have will also be answered by the principal investigator prior to signing the consent/assent. Once the consent/assent form is signed, a copy will be provided to the parent/guardian/patient and a copy will be placed in the participant's medical record at The Children's Hospital. All subjects will be consented by the Principal Investigator and/or designee who have received appropriate training as established by the Colorado Multiple Institutional Review Board. Non-English speaking patients will be able to participate in the study. The COMIRB short-form consent in conjunction with the approved English version and the assistance of the translation service will be used for non-English speaking families.

C. Authorization Procedure

Authorization will be obtained by the treating physician and/or designee at time of consent for study. A signed and dated copy of the authorization form will be provided to the subject and another copy placed in the participant's medical record at The Children's Hospital. All subject's information will be coded by initials and study number. The study site coordinator is the only individual who will hold the information capable to link the subject to a particular study number. The study site coordinator's information is in a locked office at all times.

D. Inclusion and Exclusion Criteria

All subjects from age 1 to 18 years who have undergone tube placement in the previous 12 months will be included in the study. Subjects with middle-ear fluid on entry into the study will be required to have had a prior normal hearing test All subjects with symptoms of an acute otitis media (otalgia or otorrhea), sensorineural hearing loss, cranio-facial syndromes, cystic fibrosis, prior ear surgery except tube placement, sensitivity to fluoroquinolones and presence of granulation tissue in the lumen of the tympanostomy tubes will be excluded.

E. Selection of Study Population

Subjects of both genders regardless of ethnicity will be enrolled. If subjects with bilateral clogged tubes are encountered and are eligible based on inclusion and exclusion criteria, both ears will be enrolled.

F. Number and distribution of subjects among experimental groups

Approximately 40 subjects should be enrolled and treated with the study medication in this study. It is planned to recruit this sample in 1 center. We shall not enroll beyond this recommended maximum number of subjects without written approval from the sponsor followed by the notification and approval to the IRB. Enrollment into the screening and treatment phase of the study will be stopped by the sponsor when the anticipated or actual subject numbers have been achieved at the study site.

G. Estimated Duration of Study

The study will consist of a treatment phase of 7 days followed by a follow up phase of 11 weeks. The duration of each subject's participation is expected to be 12 weeks, with subject recruitment proposed to start in November 2006 and end in June 2007 and with the last patient out in October 2007. The study end is defined as the date for the last patient visit.

H. Examinations, Laboratory Tests, Procedures and Follow-Up Visits

A total of 4 visits will be required. Otologic examination and audiograms will be performed at each visit. Tympanograms are obtained during the entry and 14-day visits. Audiologic testing will be performed at entry, day-14 visit, 6-week visit and 3-month visit and will proceed as follows:

- Children under the age of 3 years of age will be given VRA with insert earphones (visual reinforced audiometry). Children who fail to complete VRA will not enter the study since ear-specific information cannot be obtained.
- Children who are 3 years of age or older and children under 3 years of age who are developmentally precocious will undergo CPA (conditioned play audiometry).
- Older children (≥ 6 years of age) will undergo standard air and bone audiometry. A change in threshold greater than 15 dB in 2 frequencies will be defined in this study as significant hearing loss.

The principal and sub-investigators will ultimately determine if the change in hearing threshold is attributable to the investigational medication.

Floxin otic (the comparative medication) will be stored at room temperature per package insert and will be instilled directly from the bottle by the parent/caretaker. Dornase alfa will be kept in the refrigerator and the parent/caretaker will be asked to withdraw the medication from the bottle using single-use medication droppers provided by the study coordinator. The parent/caretaker will be asked to hand-warm the medication dropper (dornase alfa group) and the medication bottle (ofloxacin group) for 1 minute prior to use to minimize vestibular effects from cold ear drops.

Schematic chart of events

Clinical Procedures	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
	Day 1 visit	Day 14 visit	6 week visit	3 month visit
Informed Consent	X			

Medical History	X			
Physical Examination	X	X	X	X
Otologic Exam	X	X	X	X
Audiogram	X	X	X	X
Medication Dispensing	X			
Medication Collection		X		
Adverse Event Collection	X	X	X	X
Concomitant Medication Collection	X	X	X	X

I. Drugs, Devices or Instruments

Twenty subjects will receive with Floxin Otic and 20 subjects will receive topical instillation of Pulmozyme to the ears.

J. Protected Health Information HIPAA

Recruitment Authorization Form A will be used by the one of the patient's primary caregivers to obtain patient consent to share their PHI with the principal investigator and research staff if the principal investigator has not already been involved in care. HIPAA Research Authorization Form B will be used to obtain patient's consent specifying with whom his/her PHI will be shared. In this study, sponsor will be privy to this information along with central Laboratory, the FDA, and COMIRB.

Patients are able to access their medical records according to hospital protocol but may not have access to all of their research records during or after the study.

All electronic study materials from The Children's Hospital will be stored on space allocated on a hospital network server that is backed up nightly and has a verified procedure for restoration of data. This network has an emergency power supply and disaster recovery plan in case of power failure or catastrophic events.

Data collected on paper forms will be kept in the Clinical Trials Organization locked office- and stored at the research coordinator's cubicle. Study data will be managed using REDCap (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium which includes University of Colorado–Denver and was initiated at Vanderbilt University. The database is hosted at the University of Colorado–Denver Development and Informatics Service Center (DISC), which will be used as a central location for data processing and management. REDCap data collection

projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the *DISC*. This iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap also includes a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. REDCap is flexible enough to be used for a variety of types of research and provides an intuitive user interface for database and survey design and data entry.

Source documentation including the patient's birth date, date of diagnosis, date of study entry, diagnosis, the results of the pretreatment and end of therapy evaluations, including the extent of disease evaluation (history, physical examination and imaging studies), and baseline laboratory values will be stored in locked cabinets in locked rooms. Only the PI and study coordinator will have physical access to these documents.

K. Data and Safety Monitoring Plan

A binary representation of the primary (patency of the tympanostomy tube) and secondary (presence of canal drainage and presence of middle-ear fluid) outcomes for the overall study population and within the two subgroups for the 14-day, 6-week and 3-month visits will be tabulated. Comparisons will employ the Chi-Square test, or, where appropriate, the Fisher Exact test. Results from this study can be used to perform sample size estimates for larger trials.

The investigators do not intend to obtain audiometric testing during therapy because ear drops in the ear canal will cause conductive hearing loss and will confound the findings; therefore, hearing threshold changes will only be detected at the day-14 visit. However, we would allow audiometric testing at any time during the study, including during the 7-day treatment period, for the individual(s) whose parent/caregiver suspects a significant change in hearing. The definition for a significant change in hearing threshold is deigned as change of hearing threshold greater than 15 dB in 2 frequencies. If this event were to be detected during the treatment phase, the study medication will be stopped. All subjects diagnosed with sensorineural hearing loss as determined by the principal or sub-investigators during the treatment or follow-up phase of the study will be followed clinically and have repeat audiologic testing until their hearing threshold stabilizes. This would constitute an adverse event and the instructions listed in Appendix A will be followed. Subjects with continuation of hearing loss at the 3-month visit compared with the baseline audiologic examination (due to middle-ear effusion) will be followed clinically and repeat audiologic testing at a time when the patient is free of effusion.

The determination of sensorineural hearing loss attributable to the study drug is solely based on a change in hearing threshold between audiograms.Hearing loss is a summation of conductive hearing loss (in this study it would be due to middle-ear fluid) and sensorineural hearing loss (in this study it would be due to ototoxic effects of the study drug). If one can control for the conductive component, any deterioration of hearing would be attributable to ototoxic effects of the study drug.

There are 4 potential scenarios for presence or absence of middle-ear fluid between the start and end of the study period for each of the subjects. The scenarios are: (1) no fluid at either the start or during the study period; (2) fluid at both the start and during the study period; (3) fluid at the start and no fluid during the study period; and (4) no fluid at the start and fluid during the study period. In the first scenario, no conductive hearing loss is expected and any hearing deterioration would represent sensorineural hearing loss solely due to ototoxic effects of the study drug. In the second scenario, conductive hearing loss from the middle-ear fluid should be relatively stable and any further hearing deterioration would again be due to ototoxic effects of the study drug. The third and fourth scenarios are more challenging. In the third scenario, the conductive hearing loss improves due to resolution of the middle-ear fluid. The determination of sensorineural hearing loss attributable to the study drug can only be compared between the first hearing test obtained after resolution of the middle-ear effusion with a prior hearing test that shows normal hearing threshold. Therefore, subjects with middle-ear fluid on entry into the study will be required to have had a prior normal hearing test. In the fourth scenario, the conductive hearing loss occurs during the course of the study. In this unlikely occurrence, the investigator will obtain additional hearing test(s) at a time when the middle-ear fluid resolves. Any hearing deterioration that is detected after resolution of middle ear fluid will be attributed to study drug.

Any new sensorineural hearing loss detected among subjects in the experimental group during the course of the study will be attributed to study drug. No other reasons for development of sensorineural hearing loss are anticipated during this short study. Likewise, if sensorineural hearing loss is identified in the experimental group but not in the control group, it will be reasonable to implicate the study drug as the etiology of this hearing loss.

If two subjects from the experimental group were to develop sensorineural hearing loss attributable to the study medication either during treatment or follow-up phase of the study, the entire study will be stopped. The instructions listed in Appendix A will be followed as well.

Genentech has a stringent set of guidelines in terms of recording, assessing and reporting adverse events to Genentech, the IRB and FDA (see Appendix A). The principal investigator will comply with the guidelines established by Genentech.

L. Data Safety Monitoring Board

The investigators have no plans for an interim analysis since this is a pilot study of 40 subjects. The person responsible for stopping the trial if 2 more subjects were to develop sensorineural hearing loss attributable to the study medication is the principal investigator. The principal investigator will monitor all audiograms on all subjects on a weekly basis.

M. Monitoring

It is understood that the sponsor may contact and visit the investigator intermittently and that he/she will be allowed, on request, to inspect the various records of the trial (CRFs and other pertinent data) provided that patient confidentiality is maintained in accord with TCH requirements. It will be the monitor's responsibility to inspect the CRF at regular intervals

throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them.

The sponsor monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of primary efficacy and safety endpoints. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

The monitor/co-monitor must have direct access to all source documents needed to verify the entries on the CRF. This includes the patient medical record for data verification. The investigator will permit trial-related audits and regulatory quality assurance inspections providing direct access to source/data documents.

The investigator must ensure that patients' anonymity will be maintained. Although the sponsor will be able to see the name and address of the patient while visualizing the medical record for data verification, all documents including CRFs or other documents submitted to the sponsor, patients will not be identified by their names, but by the patient/randomization number. The investigator must keep a patient identification code list showing the randomization number, the patient's name, date of birth and address, or any other locally accepted identifiers. Documents identifying the patients (e.g., patients' signed informed consent forms) should not be sent to the sponsor and should be kept by the investigator in strict confidence.

The investigator and co-investigators agree to cooperate with the monitor/co-monitor to ensure that any problems detected in the course of these monitoring visits are resolved. If the patient is hospitalized or dies in a hospital other than the study center, the investigator is in charge of contacting this hospital in order to document this SAE.

The investigator shall supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

IV. RISKS

A. Subjects

A serious potential risk for the subjects is the development of sensorineural hearing loss with the use of dornase alfa topically in the ear. The investigators have used the industry standard to test for ototoxicity based on ABR and DPOAE testing in the chinchilla model and have found no clear evidence of such toxicity. No statistical difference between ears treated with saline control and full-strength dornase alfa was observed. Because this is the first trial for such a use, some side effects may be unknown.

Other adverse reactions to ototopical drops may occur and they can be gleaned from the package insert of the comparative treatment drug, Floxin otic. The types and frequencies of the

most common adverse reactions include: taste perversion (7%), earache (1%), pruritis (1%), paraesthesia (1%), rash (1%) and dizziness (1%).

B. Investigators/Institutions

There are no known risks to investigators.

V. BENEFITS

There is no guarantee that subjects will benefit directly from this research. Information obtained during the course of this clinical research study may contribute to a better understanding of tympanostomy tubes. Regardless of any individual benefit, the knowledge gained from this study may contribute to information that would allow the use of Dornase Alfa (Pulmozyme®) in later treatment for children with clogged typanostomy tubes.

If the treatment (conventional or experimental) is successful, the subject's tympanostomy tube will become unplugged. In addition to restoring the function of the tympanostomy tube, it may result in improvement of hearing and a decrease in the chance for future infections.

VI. FUNDING

This research is funded by Genentech the manufacturer of the study drug. The study drug, the research visits, and all procedures related to the study will be provided free of charge. Third-party payers will only be charged for the initial office visit resulting in entry into the study.

The following will be paid for by the study if obtained during the study visits and as defined by protocol:

- Medical History
- Concomitant Medication Collection
- Physical Exam-Complete
- Vital Signs, Height and Weight
- Adverse Event Collection
- Otologic Examination
- Audiogram
- Pharmacy:
    1. Study Drug Dispensing
    2. Study Drug Accountability

Subject Reimbursement

Subjects will be paid up $25.00 per visit for out of pocket expenses incurred with transportation or parking associated with the clinic visit. This out of pocket reimbursement will be made in the form of cash or check after each visit is completed.

VII. SPECIAL CONSENT ISSUES

Non-English speaking patients will be able to participate in the study. The COMIRB short-form consent in conjunction with the approved English version and the assistance of the translation service will be used for non-English speaking families. At the time of consenting, the hospital translation services would be contacted and translation services would translate the consent form to the patient. Through the assistance of translation services and the study doctor and/or study coordinator, the family's questions would be answered. The families would also be questioned if they understood the study and the consenting process. Only when all questions have been answered and the family is comfortable with the study and consent form would signatures be obtained on both the English version of the consent and the short form.

VIII. BIOLOGICAL SPECIMENS/GENETIC TESTING

There are no specimens being collected for genetic testing in this study.

IX. VERTEBRATE ANIMALS

No applicable

X. CONSORTIUM/CONTRACTUAL ARRANGEMENT

Not applicable

XI. LITERATURE CITED

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