Feinstein Institute for Medical Research,
Hearing & Speech Center
North Shore-LIJ Health System

An open-label study of the effects of anakinra in corticosteroid-resistant subjects with autoimmune inner ear disease

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List of Abbreviations

AIED: Autoimmune Inner Ear Disease
ANC: Absolute Neutrophil Count
CBC: Complete Blood Count with differential
dB: Decibel
IL-1β: Interleukin-1 beta
IL1R2: Interleukin-1 Receptor type II
PBMC: Peripheral Blood Immune Cells
PTA: Pure Tone Average, here to include the average of 250, 500 1000, 2000 and 4000 Hertz
SMA-7: Serum Metabolic Assay-7: Includes determination of blood sodium, potassium, glucose, and creatinine
SNHL: Sensorineural Hearing Loss
SSNHL: Sudden Sensorineural Hearing Loss
TNF-α: Tumor Necrosis Factor-alpha

Study Summary

Title	A phase I/II, open-label study of the effects of anakinra in corticosteroid-resistant subjects with autoimmune inner ear disease
Short Title	A phase I/II trial of anakinra in AIED
Phase	I/II
Methodology	An open-label, phase I/II trial
Study Duration	60 months
Study Center(s)	North Shore-LIJ Health System
Objectives	To determine if anakinra treatment results in hearing improvement in corticosteroid resistant individuals with Autoimmune Inner Ear Disease
Number of Subjects	38
Diagnosis and Main Inclusion Criteria	Autoimmune Inner Ear Disease. Patients to be included are those that failed to improve their hearing in response to a 28-30 day course of corticosteroid therapy.
Study Product, Dose, Route, Regimen	Anakinra: 100 mg/day administered daily by subcutaneous injection.
Duration of administration	Administration is to occur daily for 84-day duration.
Reference therapy	None.
Statistical Methodology	A simon 2-stage design: in year 1 a minimum efficacy of 2 or more positive responses of 10 total evaluable events (patients): if this milestone is met, a response rate of 30% or greater would warrant progression to a phase II study.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

The mechanisms that control corticosteroid responsive sensorineural hearing loss remain enigmatic. For patients that experience an acute, sensorineural decline in hearing, timely corticosteroid administration may result in preservation of some or all of the hearing. Factors that contribute to these responses have not been fully characterized, but include audiometric configuration, degree of hearing loss, presence of circulating auto-antibodies to antigens such as the 68kD protein**(1)** and CTCL2**(2)**, absence of vertigo and absence of retrocochlear pathology. Interestingly, the influence of cytokine microenvironment has not been investigated to any great degree in this disorder, largely, because the events in the cochlea may not be reflected in the peripheral blood immune cells (PBMC). Potentially reversible sensorineural hearing loss (SNHL) can be divided into several sub-groups: Autoimmune Inner Ear Disease (AIED), sudden SNHL (SSNHL) and Meniere's Disease. SSNHL is usually a unilateral, isolated event. Patients with AIED usually experience multiple episodes of rapid hearing loss either concurrently or sequentially in both ears. Of those with AIED, up to 30% may have a systemic autoimmune disease **(3)**. Some patients with SSNHL are considered to have an autoimmune etiology for their disease **(4)**, although the majority of these patients have either a viral trigger of their disease. Estimates of disease prevalence for SSNHL are that there are 15,000 new cases reported per year. For AIED, it is estimated that there is only 1 case per 1,000 cases of all SNHL. However, characterization of the mechanisms involved in steroid responsive hearing loss has been difficult because of limited access to the human cochlea. Moreover, although a number of antibodies to autoantigens have been found in patients with AIED **(5)**, no single diagnostic biomarker has been identified **(6).** Some physicians have used initial responsiveness to glucocorticoids as a hallmark of this poorly defined clinical disorder **(3, 7-9)**. The durability of continued corticosteroid responsiveness for multiple declines in hearing is limited. Of the 70% **(10)** of patients who are initially steroid responsive, only 14% remain so after 34 months **(10)**. However, the mechanism(s) that govern steroid resistance in these patients is unknown. Treatment options for those that fail corticosteroids are ineffectual. Methotrexate has been shown to be no better than placebo in a large clinical trial. Similarly, in clinical trials of anti-TNF-α therapy have also shown no benefit **(11, 12)**.

Precedent for the causal role of Interleukin-1β **(**IL-1β) involvement in hearing loss exists. Macrophage ingress into the cochlea has been demonstrated in animal models of acoustic-induced trauma **(13)**. In this model, IL-1β is expressed by macrophages, and dictated many of the later adaptive immune responses **(14)**. Administration of methylprednisolone in the acoustic injury trauma model was capable of preventing cochlear hair cell loss, however, only if administered prior to, or immediately following injury **(15).** IL-1β expression was also observed in an animal model of AIED **(16)**. In this model, LPS was required in addition to antigen re-exposure to initiate cochlear Interleukin-1β (IL-1β) expression, leukocyte ingress into the cochlea and hearing loss **(23)**. Sensorineural hearing loss has been observed in the

autoinflammatory syndromes NOMID and Muckle-Wells whose hallmarks are IL-1β dysregulation. IL-1β blockade may represent an alternative method to clinically restore hearing in patients who do not respond to corticosteroid therapy. IL-1β blockade with anakinra has already been shown to reverse sensorineural hearing loss in Muckle-Wells syndrome **(17)**. Unlike these autoinflammatory disorders, AIED is likely a true autoimmune disease where cochlin has been identified as a good candidate antigen, an animal model based on cochlin reactivity has been established **(18)**, and cochlin specific T-cells have been identified in patients with clinical disease **(19).**

1.2 Investigational Agent

DESCRIPTION

Anakinra (Kineret) is a recombinant, nonglycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra). Anakinra differs from native human IL-1Ra in that it has the addition of a single methionine residue at its amino terminus. Anakinra consists of 153 amino acids and has a molecular weight of 17.3 kilodaltons. It is produced by recombinant DNA technology using an E coli bacterial expression system.

Anakinra is supplied in single use prefilled glass syringes with 27 gauge needles as a sterile, clear, colorless-to-white, preservative-free solution for daily subcutaneous (SC) administration. The solution may contain trace amounts of small, translucent-to-white amorphous proteinaceous particles. Each prefilled glass syringe contains: 0.67 mL (100 mg) of anakinra in a solution (pH 6.5) containing sodium citrate (1.29 mg), sodium chloride (5.48 mg), disodium EDTA (0.12 mg), and polysorbate 80 (0.70 mg) in Water for Injection, USP.

CLINICAL PHARMACOLOGY

Anakinra blocks the biologic activity of IL-1 by competitively inhibiting IL-1 binding to the interleukin-1 type I receptor (IL-1RI), which is expressed in a wide variety of tissues and organs.

1 IL-1 production is induced in response to inflammatory stimuli and mediates various physiologic responses including inflammatory and immunological responses. IL-1 has a broad range of activities including cartilage degradation by its induction of the rapid loss of proteoglycans, as well as stimulation of bone resorption. 2 The levels of the naturally occurring IL-1Ra in synovium and synovial fluid from rheumatoid arthritis (RA) patients are not sufficient to compete with the elevated amount of locally produced IL-1.

Pharmacokinetics

The absolute bioavailability of Anakinra after a 70 mg SC bolus injection in healthy subjects (n = 11) is 95%. In subjects with RA, maximum plasma concentrations of Anakinra occurred 3 to 7 hours after SC administration of Anakinra at clinically relevant doses (1 to 2 mg/kg; n = 18); the terminal half-life ranged from 4 to 6 hours. In RA patients, no unexpected accumulation of Anakinra was observed after daily SC doses for up to 24 weeks.

The influence of demographic covariates on the pharmacokinetics of Anakinra was studied using population pharmacokinetic analysis encompassing 341 patients receiving daily SC injection of Anakinra at doses of 30, 75, and 150 mg for up to 24 weeks. The estimated Anakinra clearance

increased with increasing creatinine clearance and body weight. After adjusting for creatinine clearance and body weight, gender and age were not significant factors for mean plasma clearance (from PDR.net).

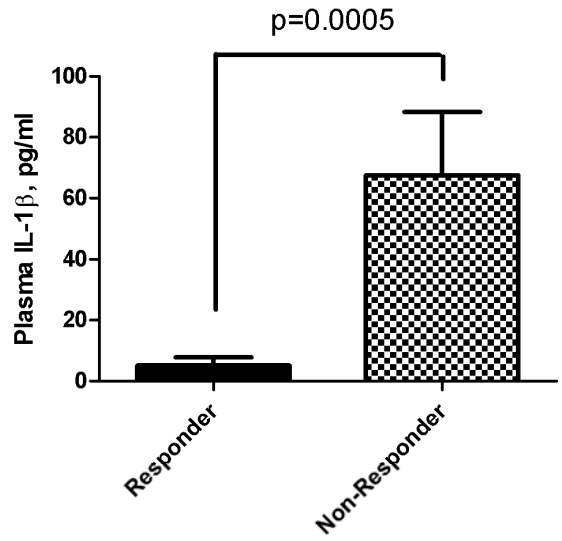
1.3 Preclinical Data

Patients with AIED are treated with corticosteroids, however, of those treated; only half respond, and fewer respond over time. Factors that influence steroid responsiveness include low basal expression of Interleukin-1 Receptor type II (IL1R2) that is strongly induced by in vitro treatment of Peripheral Blood Immune Cells (PBMC) by dexamethasone. Pre-treatment evaluation of IL1R2 expression patterns correlated with clinical response to corticosteroids ($p<0.0001$) **(20)**. Patients that are corticosteroid resistant demonstrate high basal expression levels of IL1R2, and cannot be further induced by *in vitro* corticosteroid treatment of PBMC.

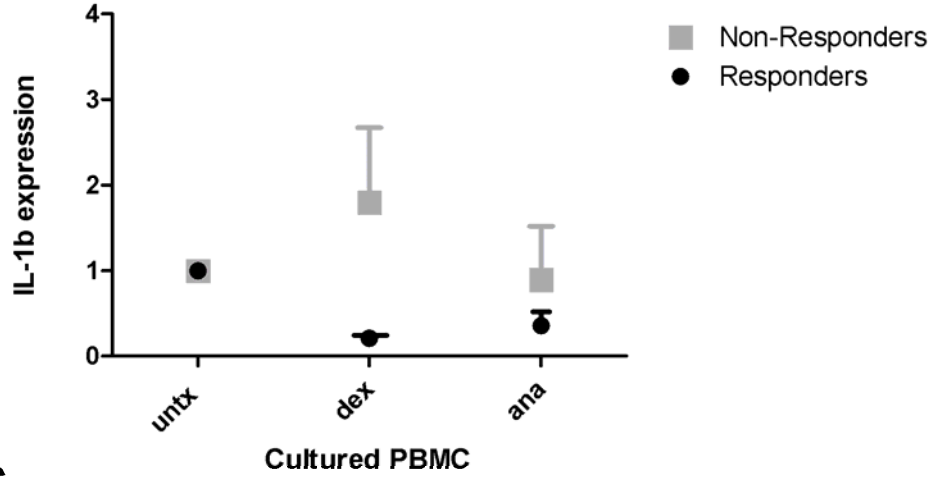
We postulated that corticosteroid resistant individuals had higher circulating levels of IL-1β than corticosteroid responsive individuals. Indeed, in a study of 43 patients, steroid non-responders demonstrated significantly higher plasma levels of IL-1β than corticosteroid responders (67.6 vs. 5.1 units ($p=0.0005$, two tailed t-test) figure 1A). Given the correlation of plasma IL-1β expression with clinical steroid response, we asked whether the PBMC from steroid responders and non-responders have altered cytokine production or release in response to anakinra. PBMC from a subset of pre-treatment clinical corticosteroid responders and pre-treatment non-responders were cultured with anakinra, and mRNA from these PBMC was assessed for IL-1β expression by Q-RT-PCR. In all responders, dexamethasone inhibited mRNA expression of IL-1β, whereas in non-responders, the effect of dexamethasone on IL-1β was variable, with no clear inhibitory pattern seen (figure 1B). When the culture supernatant was examined, IL-1β was reduced, as expected, in the dexamethasone-treated PBMC of corticosteroid responders. Notably, however, in corticosteroid non-responders, dexamethasone treatment caused a paradoxical increase in IL-1β mRNA transcription, and dexamethasone also failed to prevent IL-1β release, with high levels of IL-1β detected in the conditioned media. This failure to repress IL-1β production and release would permit the initiation of a pro-inflammatory microenvironment that precludes a steroid response.

Figure Legend:
1A: Plasma from 43 corticosteroid patients. Results were stratified to corticosteroid responsiveness as described below. Results are from 26 responders and 17 non-responders. IL-1β levels are statistically significantly elevated in corticosteroid non-responders, $p=0.0005$ (Mann-Whitney two tailed test).
1B: Pre-treatment PBMC from a minimum of 6 responders and 6 non-responders. PBMC were isolated and plated at a density of 1×10^6 cells/ml. Cells were cultured with either dexamethasone or anakinra and compared with unstimulated, cultured PBMC. RNA from these PBMC were analyzed by quantitative real time PCR for transcription of IL-1β. The mean fold change (+ SEM) observed in response to drug relative to the unstimulated PBMC level was calculated.
1C: IL-1β released into the cultured supernatant was measured by ELISA for the stimulus conditions and again compared to unstimulated, cultured PBMC.

1A



1B



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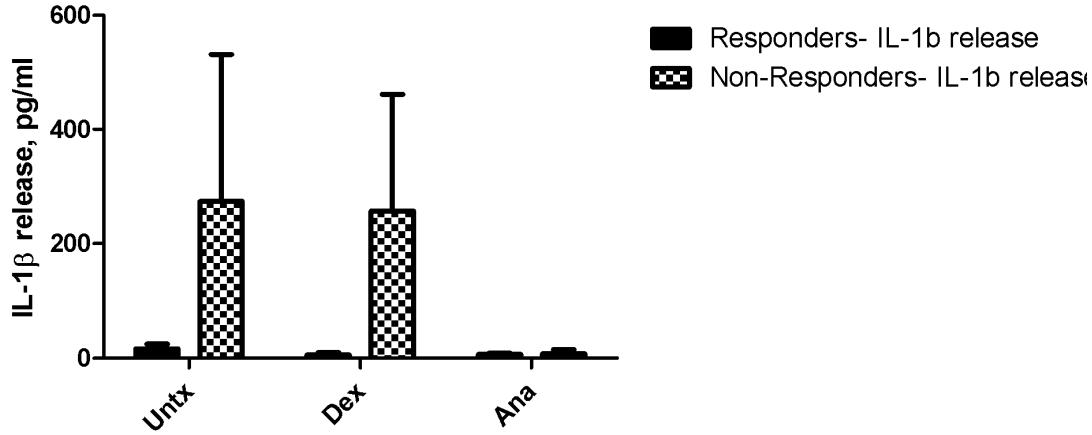


1.4 Clinical Data to Date

Clinical data available for the safety and efficacy has been established in clinical trials of rheumatoid arthritis patients. The safety and efficacy of Anakinra have been evaluated in three randomized, double-blind, placebo-controlled trials of 1790 patients ≥ 18 years of age with active rheumatoid arthritis (RA). An additional fourth study was conducted to assess safety. In the efficacy trials, Anakinra was studied in combination with other disease-modifying antirheumatic drugs (DMARDs) other than Tumor Necrosis Factor (TNF) blocking agents (studies 1 and 2) or as a monotherapy (study 3).

Study 1 involved 899 patients with active RA who had been on a stable dose of methotrexate (MTX) (10 to 25 mg/week) for at least 8 weeks. All patients had at least 6 swollen/painful and 9 tender joints and either a C-reactive protein (CRP) of ≥ 1.5 mg/dL or an erythrocyte sedimentation rate (ESR) of ≥ 28 mm/hr. Patients were randomized to Anakinra or placebo in addition to their stable doses of MTX. The first 501 patients were evaluated for signs and symptoms of active RA. The total 899 patients were evaluated for progression of structural damage.

Study 2 evaluated 419 patients with active RA who had received MTX for at least 6 months including a stable dose (15 to 25 mg/week) for at least 3 consecutive months prior to enrollment. Patients were randomized to receive placebo or one of five doses of Anakinra SC daily for 12 to 24 weeks in addition to their stable doses of MTX.

Study 3 evaluated 472 patients with active RA and had similar inclusion criteria to study 1 except that these patients had received no DMARD for the previous 6 weeks or during the study.7 Patients were randomized to receive either Anakinra or placebo. Patients were DMARD-naïve or had failed no more than 3 DMARDs.

Study 4 was a placebo-controlled, randomized trial designed to assess the safety of Anakinra in 1414 patients receiving a variety of concurrent medications for their RA including some DMARD therapies, as well as patients who were DMARD-free. The TNF blocking agents etanercept and infliximab were specifically excluded. Concurrent DMARDs included MTX, sulfasalazine, hydroxychloroquine, gold, penicillamine, leflunomide, and azathioprine. Unlike studies 1, 2 and 3, patients predisposed to infection due to a history of underlying disease such as pneumonia, asthma, controlled diabetes, and chronic obstructive pulmonary disease (COPD) were also enrolled (see ADVERSE REACTIONS: Infections).

In studies 1, 2 and 3, the improvement in signs and symptoms of RA was assessed using the American College of Rheumatology (ACR) response criteria (ACR20, ACR50, ACR70). In these studies, patients treated with Anakinra were more likely to achieve an ACR20 or higher magnitude of response (ACR50 and ACR70) than patients treated with placebo (Table 1). The treatment response rates did not differ based on gender or ethnic group. The results of the ACR component scores in study 1 are shown in Table 2.

Most clinical responses, both in patients receiving placebo and patients receiving Anakinra, occurred within 12 weeks of enrollment.

Table 1: Percent of Patients with ACR Responses in Studies 1 and 3

	Study 1 (Patients on MTX)		Study 3 (No DMARDs)		
		Kineret		Kineret	
Response	**Placebo (n = 251)**	**100 mg/day (n = 250)**	**Placebo (n = 119)**	**75 mg/day (n = 115)**	**150 mg/day (n = 115)**
a p < 0.05, Kineret versus placebo					
b p < 0.01, Kineret versus placebo					
c p < 0.001, Kineret versus placebo					
ACR20					
Month 3	24%	34%a	23%	33%	33%
Month 6	22%	38%c	27%	34%	43%a
ACR50					
Month 3	6%	13%b	5%	10%	8%
Month 6	8%	17%b	8%	11%	19%a
ACR70					
Month 3	0%	3%a	0%	0%	0%
Month 6	2%	6%a	1%	1%	1%

Table 2: Median ACR Component Scores in Study 1

	Placebo/MTX (n = 251)		Kineret/MTX 100 mg/day (n = 250)	
Parameter (median)	**Baseline**	**Month 6**	**Baseline**	**Month 6**
a Health Assessment Questionnaire; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.				
b Visual analog scale; 0 = best, 100 = worst				
c Scale 0 to 68				
d Scale 0 to 66				
Patient Reported Outcomes				
Disability index	1.38	1.13	1.38	1.00
Patient global assessment b	51.0	41.0	51.0	29.0
Pain b	56.0	44.0	63.0	34.0
Objective Measures				
ESR (mm/hr)	35.0	32.0	36.0	19.0
CRP (mg/dL)	2.2	1.6	2.2	0.5
Physician's Assessments				
Tender/painful joints	20.0	11.0	23.0	9.0
Physician global assessment	59.0	31.0	59.0	26.0
Swollen joints	18.0	10.5	17.0	9.0

A 24-week study was conducted in 242 patients with active RA on background methotrexate who were randomized to receive either etanercept alone or the combination of Anakinra and

etanercept. The ACR50 response rate was 31% for patients treated with the combination of Anakinra and etanercept and 41% for patients treated with etanercept alone, indicating no added clinical benefit of the combination over etanercept alone. Serious infections were increased with the combination compared to etanercept alone.

In study 1, the effect of Anakinra on the progression of structural damage was assessed by measuring the change from baseline at month 12 in the Total Modified Sharp Score (TSS) and its subcomponents, erosion score, and joint space narrowing (JSN) score.8 Radiographs of hands/wrists and forefeet were obtained at baseline, 6 months and 12 months and scored by readers who were unaware of treatment group. A difference between placebo and Anakinra for change in TSS, erosion score (ES) and JSN score was observed at 6 months and at 12 months (Table 3).

Table 3: Mean Radiographic Changes Over 12 Months in Study 1

	Placebo/MTX (N = 450)		**Kineret 100 mg/day/MTX (N = 449)**		**Placebo/MTX vs. Kineret/MTX**	
	Baseline	**Change at Month 12**	**Baseline**	**Change at Month 12**	**95% Confidence Interval***	**p-value****
* Differences and 95% confidence intervals for the differences in change scores between Placebo/MTX and Kineret/MTX						
** Based on Wilcoxon rank-sum test						
TSS	52	2.6	50	1.7	0.9 [0.3, 1.6]	<0.001
Erosion	28	1.6	25	1.1	0.5 [0.1, 1.0]	0.024
JSN	24	1.1	25	0.7	0.4 [0.1, 0.7]	<0.001

The disability index of the Health Assessment Questionnaire (HAQ) was administered monthly for the first six months and quarterly thereafter during study 1. Health outcomes were assessed by the Short Form-36 (SF-36) questionnaire. The 1-year data on HAQ in study 1 showed more improvement with Anakinra than placebo. The physical component summary (PCS) score of the SF-36 also showed more improvement with Anakinra than placebo but not the mental component summary (MCS). ***All data from this section is from PDR.net, search Kineret, PDR Full Label, Manufacturer, Biovitrum.***

1.5 Dose Rationale and Risk/Benefits

The recommended dose of Anakinra for the treatment of patients with rheumatoid arthritis is 100 mg/day administered daily by subcutaneous injection. Higher doses did not result in a higher response. As such, the same dosing recommendations will be used for patients with Autoimmune Inner Ear Disease. The dose should be administered at approximately the same time every day. In order to determine efficacy, hearing thresholds will be monitored by audiogram every 28 days during the 84-day trial period. In a single case study of a patient with Muckle-Wells syndrome, a three month treatment regimen of 100mg/day resulted in restoration of normal hearing to a patient with bilateral sensorineural hearing loss (PTA prior to treatment: AS: 46dB AD: 43dB, PTA post treatment AS: 11dB AD: 9dB) **(17)**.

Instructions on appropriate use should be given by the healthcare provider to the patient or caregiver. Patients or caregivers should not be allowed to administer Anakinra until the patient or

caregiver has demonstrated a thorough understanding of procedures and an ability to inject the product. After administration of Anakinra, it is essential to follow the proper procedure for disposal of syringes and needles. See the "Patient Information" insert for detailed instructions on the handling and injection of Anakinra.

Patients receiving Anakinra may experience a decrease in neutrophil counts. In the placebo-controlled studies, 8% of patients receiving Anakinra had decreases in neutrophil counts of at least 1 World Health Organization (WHO) toxicity grade compared with 2% in the placebo control group. Nine Anakinra-treated patients (0.4%) experienced neutropenia (ANC (Absolute Neutrophil Count) <1 × 109/L). For this reason, neutrophil counts will be monitored every thirty days while receiving Anakinra therapy. Therapy will be discontinued for any patient that develops moderate neutropenia (ANC<1000) (see section 9.5 Stopping Rules).

Renal insufficiency can reduce clearance of Anakinra. The mean plasma clearance of Anakinra in subjects with mild (creatinine clearance 50-80 mL/min) and moderate (creatinine clearance 30-49 mL/min) renal insufficiency was reduced by 16% and 50%, respectively. In severe renal insufficiency and end stage renal disease (creatinine clearance < 30 mL/min), mean plasma clearance declined by 70% and 75%, respectively. Less than 2.5% of the administered dose of Anakinra was removed by hemodialysis or continuous ambulatory peritoneal dialysis. For this reason, creatinine levels will be measured before and during therapy. Patients with a creatinine clearance of less than 49mL/min will not be eligible for this study. (Creatinine clearance will be measured by the following formula: [[140-age(yr)]*weight(kg)]/[72*serum Cr(mg/dL)](*0.85 for women). Patients that develop renal insufficiency while undergoing therapy (creatinine clearance of less than 49mL/min) will be prevented from continuing therapy (see section 9.5 Stopping Rules).

A 3.6 fold increase in the rate of lymphoma (a malignancy of the blood) was seen (0.12cases/100 patient years) in response to Anakinra (Patient years is the number of patients studied multiplied by the number of years studied). Patients with a history of a malignancy in the past 3 years may not be recruited for this study (see section 4.2 Exclusion Criteria).

2 Study Objectives

The purpose of this study is to determine if anakinra therapy may be an alternate therapy in patients with steroid resistant Autoimmune Inner Ear Disease.

Primary Objective
To assess the potential efficacy of anakinra in improving hearing thresholds in corticosteroid-resistant patients with Autoimmune Inner Ear Disease.

Secondary Objective
To assess the safety and tolerability of a three month course of anakinra in corticosteroid resistant patients with Autoimmune Inner Ear Disease.

Tertiary Objective
To determine if measurement of circulating or induced IL-1β expression, either prior to, during, or upon completion of therapy is predictive of clinical hearing recovery.

3 Study Design

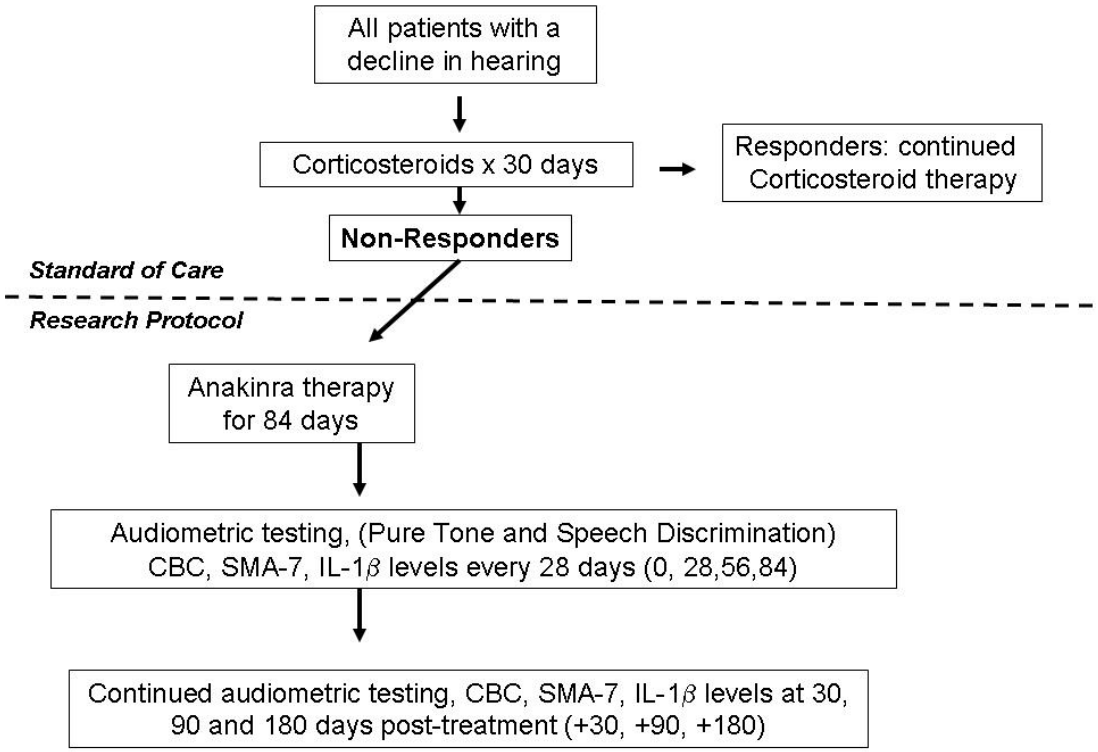
3.1 General Design

- The proposed study will be a Phase I/II, single-centered, open-label trial of Anakinra in corticosteroid resistant patients with AIED.
- Trial design:

Patient & Audiometric Criteria: All patients to be included in this phase I/II clinical trial must exhibit development of sensorineural hearing loss (SNHL) of greater than 30dB at one or more frequencies in *both* ears with evidence of active deterioration (elevated threshold) in at least one ear of 15 dB at one frequency (excluding 250 or 8kHz as a sole indicator), or 10dB at 2+ frequencies developing in >3 days but <90 days **(7)**. If after the first 10 subjects are recruited, no untoward effect on hearing is identified, subjects with unilateral hearing loss may also be included. To utilize the expanded criteria defined above, progressive sensorineural hearing loss potentially attributed to anakinra therapy cannot be observed in the first 10 evaluable patients. If progressive SNHL is observed in over 25% but less than 50% of patients receiving anakinra during the initial phase, we would NOT utilize the expanded criteria.

- This group of potential patients may include those patients previously diagnosed as sudden SNHL if they demonstrated features suspicious for of autoimmune disease (if they have a systemic autoimmune disorder, family history of autoimmune disease, or if they had previous episodes of sudden sensorineural hearing loss in the same or contralateral ear), as long as they meet the audiologic criteria defined above with the exception that the hearing loss may evolve in less than 3 days. Similarly, patients previously diagnosed as Meniere's Disease with autoimmune features may be included if they meet the audiologic criteria as defined above. Patients were excluded from study if they had evidence of retrocochlear pathology on their MRI scan.
- ***Definition of corticosteroid non-responder***: All patients must have been treated with 60mg of oral prednisone for a minimum of 7 days with a variable taper thereafter, for a minimum of 30 days in total, and response to prednisone therapy measured by audiometry before treatment and at approximately 30 days post-treatment. Audiometry will consist of a pure tone average ((PTA): here to include 250, 500, 1000, 2000, and 4000Hz) and speech discrimination score to be recorded pre and post treatment. Clinical responsiveness will be defined as either an average of 5 decibel or greater PTA improvement (as the average of five frequencies was recorded) in their post-treatment audiogram, or a greater than 12% improvement in the speech discrimination scores. In the event a patient with a pre-treatment profound SNHL demonstrates an improvement on PTA, however, no improvement in speech discrimination is noted, and the initial speech discrimination is 0%, this patient would be classified as a non-responder. Patients that received concurrent or sequential intratympanic corticosteroids may be included only if they received the 30 days of oral steroids as well.
- ***Entrance into the research protocol:*** Patients that failed to respond to corticosteroid therapy will be offered anakinra therapy as an alternate therapy to continued corticosteroid therapy. Given that anakinra is a daily subcutaneous injectable, it is unethical to perform a placebo controlled trial where a patient potentially could receive 84 consecutive days of injectable saline. Moreover, the total projected number of patients for this phase I/II trial is too low to consider a cross-over design. Thus an open-label trial design is proposed. Patients will be monitored every 28 days while on therapy

by audiogram and laboratory values. Laboratory values include a Complete Blood Count (CBC) with differential, SMA-7, HCG or UCG (for child-bearing aged females) and plasma IL-1β levels/stimulation studies. Patients will complete daily logs as to injection site reactions and other potential side effects.



3.2 Primary Study Endpoints

The primary endpoint is to determine whether those treated with anakinra for 84 days demonstrate an improved hearing threshold compared with their pre-anakinra-treatment threshold.

3.3 Primary Safety Endpoints

The safety endpoints to be measured include:

1. assessment for neutropenia,
2. assessment for development of severe new infections while on therapy,
3. assessment of injection site irritation,
4. assessment of worsening of hearing thresholds while on therapy.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Patients must have Autoimmune Inner Ear Disease, Meniere's Disease, or Sudden Sensorineural Hearing Loss with autoimmune features.

2. Age and Gender: males and females ages 13 to 75 weighing 90 lbs or greater will be recruited.
3. Patients must be capable of understanding and giving informed consent.
4. If the recruited patient is between the ages of 13 and 17, an assent will be obtained from the patient and consent from one parent/legal guardian prior to enrollment.
5. Patients must have SNHL of greater than 30dB at one or more frequencies in one or both ears with evidence of active deterioration (elevated threshold) in at least one ear of 15 dB at one frequency (excluding 250 or 8kHz as a sole indicator) on their audiogram, or 10dB at 2+ frequencies developing in >3 days but <90 days, or in the case of SSNHL, the hearing loss may evolve in less than 3 days if the patient displays features suggestive of an autoimmune disorder.
6. Patients must have previously undergone a trial of high-dose corticosteroid therapy, at 60 mg daily for a minimum of seven days, with a variable taper thereafter that consists of a total of 30 consecutive days of corticosteroid use. Patients must have demonstrated less than or equal to a 5 decibel average improvement in their PTA in response to corticosteroids as measured by their audiogram.
7. Patients may have a concurrent other autoimmune disease(s).

4.2 Exclusion Criteria

1. Patients over 75 years of age, because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.
2. Patients with evidence of retrocochlear pathology (vestibular schwannoma) or inner ear malformation (Mondini Malformation or Enlarged Vestibular Aqueduct) based on imaging.
3. Patients concurrently receiving methotrexate or TNF-antagonist therapy.
4. Patients with a diagnosis of any immunodeficiency syndrome.
5. Patients with active or chronic infections.
6. Patients currently receiving, or having received treatment for a malignancy in the past three years.
7. Patients that developed an immediate onset, profound SNHL with 0% speech discrimination scores.
8. Patients whose hearing loss coincided with significant, disabling episodes of vertigo.
9. Patients with a diagnosis of chronic renal insufficiency (a creatinine clearance of <49mL/min) or chronic renal failure.
10. Patients with evidence of neutropenia (an ANC of < 1000) prior to treatment with Anakinra.
11. Patients with known hypersensitivity to E. coli derived products.
12. Patients with latex sensitivity (the needle cover is a derivative of latex).
13. Pregnant or lactating females.
14. Children under the age of 13, as Anakinra is supplied in pre-filled syringes dosed for adult sized patients..
15. Non-English speaking patients, as the word recognition scoring is in English and is a vital component to the efficacy analysis.

4.3 Subject Recruitment and Screening

Subjects will be recruited from the practices of several Neurotologists and Otolaryngologists from the North Shore-LIJ Health System. No recruitment materials will be disseminated; however, patients within these practices with a diagnosis of AIED, SSNHL or Meniere's Disease may be sent letters informing them of this clinical trial. All patients that are treated with corticosteroids (60mg per day for 7 days with a taper thereafter to 30 days of treatment in total) will be informed of the study availability to them only if they fail to respond to corticosteroids as measured on the audiogram at approximate 30 day post-treatment interval. The study will be described to the patient. Pre-treatment laboratory tests will be performed for inclusion (CBC, SMA-7, beta HCG or UCG (if female of child-bearing age)) at visit 1 (or within 2 weeks prior). Plasma IL-1β and in vitro expression of IL-1β in PBMC and monocytes will also be measured. Patients that fail corticosteroid therapy and meet inclusion and exclusion criteria will be given the option of enrolling in this phase I/II trial and receiving Anakinra. Alternatively, they may opt to receive continued corticosteroids, or no further treatment. It is possible that a number of patients will not wish to perform daily injections for 84 days.

Some patients that failed corticosteroid therapy (as measured by a pre and post treatment audiogram) may be referred by non-study physicians for participation in this study. Inclusion of these patients may be considered if no greater than 30 days has elapsed since the discontinuation of corticosteroids, and that the patient received 30 days of prednisone. In the event the patient did not receive 30 days of prednisone, the patient will be treated again with 60mg of prednisone for 7 days and a variable taper to achieve 30 days of continuous therapy. Audiometry will be repeated again at the end of the treatment. If the patient is still a "non-responder", they will have the option to enroll in this study.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Some patients may be prematurely withdrawn prior to completion of the drug for several reasons. Indications for early termination of anakinra administration is (1) Development of neutropenia as defined as an ANC of <1000, (2) Development of a serious bacterial infection (pneumonia, cellulitis, septicemia) (3) Severe injection site reaction, (4) Rash consistent with an allergic reaction to Anakinra, (5) Significant worsening of hearing threshold in either ear (greater than 20dB worsening of the pure tone average) (6) Development of renal insufficiency (as determined by a creatinine clearance of <49mL/min). The patient may also self-withdraw due to intolerance of daily injections. Although abrupt termination of drug should not pose a safety issue, a greater concern exists for hearing deterioration. If this occurs, prednisone therapy will immediately be reinstituted, barring any patient contraindications to continued corticosteroid therapy. If anakinra therapy is terminated due to safety concerns, corticosteroid therapy may be recommended, only if further hearing deterioration occurs off anakinra. Also see section 9.5: Stopping Rules. If a patient is withdrawn during study treatment, a follow-up audiogram, all safety bloods and IL-1 levels will be done approximately within 30 days of the last injection.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Even if patients prematurely withdraw, or are withdrawn from the study, an analysis of all data collected through the time of withdrawal will be included for analysis. Data on the withdrawn

subjects is critical to the integrity of the final data analysis, especially for safety and tolerability issues.

5 Study Drug

5.1 Description

Anakinra is supplied in pre-filled syringes for daily subcutaneous injection. One box represents a 28 day supply. Anakinra is to be stored at 4^0C. The drug should be allowed to reach room temperature prior to injecting. One pre-filled syringe contains 100mg of anakinra suspended in solution.

5.2 Treatment Regimen

The patient will inject the entire contents (100mg) of a prefilled syringe subcutaneously after appropriately sterilizing the area to be injected with rubbing alcohol and allowing the area to dry. The patient will perform daily injections for 84 consecutive days.

5.3 Method for Assigning Subjects to Treatment Groups

This open-label trial of Anakinra will not be randomized. Given the route of drug delivery, a placebo-controlled trial is not possible. All patients that fail corticosteroid therapy will be offered Anakinra, thereby avoiding selection bias for certain patients. All enrolled patients on Anakinra will undergo audiometric testing and blood collection at 0, 28, 56 and 84 days during the treatment period. Upon cessation of treatment, audiometric testing will again be performed at +30, +90 days and +180 days. During the same visit as audiometric testing, blood will be collected for a CBC, SMA-7, and IL-1β plasma and stimulation studies.

5.4 Preparation and Administration of Study Drug

The drug, Anakinra, will be supplied by the manufacturer and stored in the LIJ pharmacy department. The pre-filled syringes do not require reconstitution or mixing. The lot number will be recorded and the box (28 syringes for a 28 day supply) dispensed by one of the study nurses. The study nurse will demonstrate to the patient how to inject the drug properly. The patient will also watch an instructional video. The patient will be given a sharps container to store the wasted syringes. These sharps containers will be returned to us for disposal.

5.5 Subject Compliance Monitoring

Patients will be given a 28 day supply of medication, record keeping materials and a sharps container. The patient will be asked to send an email (at least weekly) to the study nurse indicating the time of injection and any noted skin or other reactions while on study drug. If the study nurse has not been contacted by the enrolled subject in a 7 day period, the nurse will contact the patient by telephone to check their status. If the patient will be without email access for a given period, this information will be conveyed to the nurse prior to the period, and the patient will fill out a written log book during this period. In the event the patient does not have email access, the patient will fill out a log book daily. The study nurse will contact these patients weekly (by phone) to check their status. It is anticipated that the majority of subjects will communicate by email. Compliance will also be monitored by having the patient return the sharps container monthly. Although spent needles will not be pulled out and counted, the

volume of needles in the container can be estimated. In the event a patient is non-compliant, the patient will be contacted by the physician that enrolled the patient. The physician will determine the cause of non-compliance. For any patient that has a greater than 72 hour lapse in treatment not dictated by a physician, in most cases, these subjects will be informed that they will be withdrawn from the study.

5.6 Prior and Concomitant Therapy

Patients' concomitant medical therapies and recently completed (within the past three months) medical therapies will be recorded. All patients are required to have received oral corticosteroids to determine eligibility for enrollment. Most concomitant therapies are permissible. Medications that are contraindicated during treatment are TNF antagonists and chemotherapies.

5.7 Packaging

Anakinra will be supplied in single use, pre-filled glass syringes in a 4x7 dispensing pack of 28 syringes (one box). Each syringe contains 100mg of Anakinra. Each box should last 28 days.

5.8 Blinding of Study Drug

Not applicable.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.9.2 Storage

Anakinra should be stored in the refrigerator (36 to 46 degrees F). The drug should not be frozen or shaken. Furthermore, it should be protected from light.

5.9.3 Dispensing of Study Drug

Anakinra will be dispensed to enrolled patients by providing them with a 28 day supply and a sharps container for used syringes. The patient will complete daily logs of drug administration. Upon the completion of the 28 day course, the patient will return to the office with the filled sharps container and any unused medication. This reconciliation process will be completed before providing the patient with the next 28-day course of medication.

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

All patients will initially be treated with a 30-day course of corticosteroids. Only those patients that failed to respond to corticosteroids (as defined in section 3.1) will be approached to enroll in this clinical trial. The option to undergo treatment with Anakinra for a corticosteroid resistant hearing loss will be explained to the patient. The sponsor-investigator, Dr Vambutas, has a Conflict of Interest (COI) and will not directly consent patients from her practice. The nature of the conflict is that she and the Feinstein Institute hold a use patent for interleukin-1 antagonist therapy for autoimmune and sudden hearing loss as well as Meniere's disease. This conflict will be disclosed to all patients considering participation in this study. Any patients designated appropriate for study by the inclusion/exclusion criteria will be consented by her partner, Dr. Gerald Zahtz, who does not have a COI. The other study investigators (Dr. Gerald Zahtz and Dr. Elliot Goldofsky) have no COI and therefore will be able to consent patients from their own practices. Risks and potential benefits of anakinra therapy will be described.

6.1 Visit 1(Baseline)

Once the corticosteroid resistant patient has been identified at the end of a 28-30 day course of oral corticosteroids, enrolled patients will undergo blood testing (If the patient underwent a CBC, SMA-7 within 2 weeks prior to visit 1, those bloods will be accepted as enrollment criteria bloodwork). The audiogram taken at the end of the corticosteroid treatment will be used as the time 0 audiogram. Throughout the study, the audiologists will be blinded to the study treatment timepoint. Blood will be taken for a CBC, SMA-7, serum HCG or UCG (if female of child-bearing age) and plasma IL-1β and studies for IL-1β stimulation in PBMC (30cc). The labs will be checked: if there is no evidence of neutropenia, renal insufficiency or pregnancy, the patient will be asked to meet with study nurses for instruction for self administration of anakinra. The patient will be asked to maintain a daily log of injections, injection site reactions and any associated symptoms (fluctuating hearing, vertigo, tinnitus, headaches).

6.2 Visit 2

At 28 days post-initial Anakinra treatment the patient will return for repeat audiometric testing and provide a blood sample (30cc). The daily logs would be reviewed by the study nurses weekly. The logs would be reviewed by the clinician at the time of the visit. Injection sites would be inspected and reactions documented. The blood specimen would be used to determine the CBC with differential, SMA-7, serum HCG (for females of child-bearing age) and IL-1β plasma level and induction. The patient would be instructed to bring any remaining drug to the visit (if possible) as well as the spent syringes in the sharps container. The patient would be given a new 28 day supply of Anakinra and a new sharps container. CBC and SMA-7 results would be reviewed within 72 hours and any patients with changes in their white blood cell numbers, neutrophils numbers or creatinine values will be contacted. Any patient that develops neutropenia or renal insufficiency will be excluded from receiving further drug.

6.3 Visit 3

At 56 days post-initial Anakinra treatment the patient will return for repeat audiometric testing and provide a blood sample (30cc). The daily logs would be reviewed by the study nurses weekly. The logs would be reviewed by the clinician at the time of the visit. Injection sites would be inspected and reactions documented. The blood specimen would be used to determine the CBC with differential, SMA-7, beta HCG and IL-1β plasma level and induction. The patient would be instructed to bring any remaining drug to the visit as well as the spent syringes in the sharps container. The patient would be given a new 28 day supply of Anakinra and a new sharps container. CBC and SMA-7 results would be reviewed within 72 hours and any patients with changes in their white blood cell numbers, neutrophils numbers or creatinine values will be contacted. Any patient that develops neutropenia or renal insufficiency will be excluded from receiving further drug.

6.4 Visit 4

At 84 days post-initial treatment the patient will return for repeat audiometric testing and provide a blood sample (30cc). The daily logs would be reviewed by the study nurses weekly. The logs would be reviewed by the clinician at the time of the visit. Injection sites would be inspected and reactions documented. The blood specimen would be used to determine the CBC with differential, SMA-7, and IL-1β plasma level and induction. The patient would be instructed to bring any remaining drug to the visit as well as the spent syringes in the sharps container. CBC and SMA-7 results would be reviewed within 72 hours and any patients with changes in their white blood cell numbers, neutrophils numbers or creatinine values will be contacted.

6.5 Visit 5 (Follow-up period)

At 30 days following the discontinuation of treatment, enrolled patients will return for an audiometric evaluation and blood collection. If any patient develops a new decline in hearing during the 180 day follow-up period, standard corticosteroid therapy or retreatment with anakinra will be offered. The blood specimen would be used to determine the CBC with differential, SMA-7, and IL-1β plasma level and induction. If retreatment with anakinra is indicated, a beta HCG will also be obtained (if female) before patient resumes study medication and daily symptom logs will be restarted. A 28 day dose box of anakinra will be given free of charge to the patient if retreatment is indicated during the 180 day follow up period. At that point, a letter may be sent to the patient's insurance company for possible coverage of the drug in case a sustained use of anakinra is necessary. During the 180 follow up period, the maximum number of times a patient can receive a 28 day dose of anakinra would be 4, however, we may not be able to provide this medication free of charge for this duration.

6.6 Visit 6 (Follow up period)

At 90 days following the discontinuation of treatment, enrolled patients will return for an audiometric evaluation and blood collection. The blood specimen would be used to determine the CBC with differential, SMA-7, and IL-1β plasma level and induction.

6.7 Visit 7(End of study)

At 180 days following the discontinuation of treatment, enrolled patients will return for an audiometric evaluation and blood collection. The blood specimen would be used to determine the CBC with differential, SMA-7, and IL-1β plasma level and induction.

6.8 Interval visits

Patients may ask or need (at the discretion of the investigator) to be seen at interval visits. While audiological testing is indicated, blood specimen collection (CBC w/ diff, SMA-7, beta HCG (if indicated) and IL-1β plasma level and induction) will not be collected at these visits unless the patient is on study medication or will be resuming study medication based on the findings during the interval visit. Any patient resuming anakinra treatment during the follow-up period will be seen 28 days after the resumed medication has been started in order for the necessary blood specimens (noted above) and audiological testing to be performed. Based on that testing, the investigator may decide to either continue or stop any additional anakinra therapy.

6.9 Research Blood Sample Collection and Storage

The plasma for IL-1β and IL-1β stimulation (30 cc) will be transported by hand by the P.I. to FIMR, where it will be stored at -20C in a locked freezer until further testing is performed. The sample number corresponds to the patient ID number assigned at enrollment. Second number is assigned in a database that corresponds to both the patient ID number and the date the sample was acquired. This information is a password protected database, accessible only by research laboratory assistant.

7 Statistical Plan

7.1 Sample Size Determination & Statistical Methods

Corticosteroid resistant AIED patients currently have no therapeutic alternatives available to them. These patients that failed initial corticosteroid therapy are not expected to demonstrate a placebo effect, as they have already undergone 2 serial audiograms that demonstrated a <5dB PTA improvement in hearing for trial inclusion. A Simon 2-stage “optimal” design will be used to test the null hypothesis that the true objective response rate (RR) is 10% or less (which would not be clinically meaningful) versus the alternative hypothesis that the true response rate is 30% or greater. With a significance level of 0.05 and a power of 0.80, a maximum total of 29 evaluable patients will be required to assess the objective response rate. Ten (10) evaluable patients will be enrolled in Stage 1(R21 phase). If 1 or fewer objective responses are observed in the first 10 evaluable patients, then the trial will be terminated (do not proceed to R33). Primary milestone: If 2 or more objective responses (improvement in the PTA ≥5dB) are observed in the first 10 patients (20%), we will proceed to the R33 phase.

If the RR is 10% or less, then the expected sample size for the trial is 15 patients and the probability of early termination at the end of the R21 phase (stage 1) is 74%. Overall, a total of approximately 38 patients may be enrolled in this R21/R33 study to ensure that the specified numbers of evaluable patients are available for analysis at each stage.

Given that anakinra may cause injection site reactions, it is possible that some patients will prematurely self-terminate the study. In order to appropriately evaluate the results, 29 patients would need to complete the 84-day course of anakinra. Overall, a total of 38 patients may be enrolled in this study to ensure that the specified numbers of evaluable patients are available for analysis at each stage.

7.2 Subject Population(s) for Analysis

All-Treated Population: The analysis will be performed on all corticosteroid non-responders subsequently treated with 84 consecutive days of anakinra. The primary analysis will consist of determining whether an improvement in either audiometric threshold or speech discrimination can be achieved with anakinra in patients that did not respond to corticosteroids. The secondary analysis will be to determine whether anakinra can be administered safely for an 84 consecutive day period without significant complications in this patient population.

8 Safety and Adverse Events

8.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinically significant laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events

8.3.1 Study Sponsor Notification by Investigator

A serious adverse event must be reported to the study sponsor by telephone within 24 hours of the event. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:

Andrea Vambutas, MD
Phone: (718) 470-7550
Fax: (718) 470-4281

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor

8.3.2 EC/IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) that are related or possibly related and expected or unexpected that occur during a study or in a post-study period of reasonable duration (i.e. during follow-up), will be reported to the EC/IRB within 5 days of the PI learning of the event. Copies of each report and documentation of EC/IRB notification and receipt will be kept in the Clinical Investigator's binder.

8.3.3 FDA Notification by Sponsor

The study sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

8.4 Unblinding Procedures

Not applicable.

8.5 Stopping Rules

Patients that develop either moderate neutropenia (ANC<1000) or moderate renal insufficiency (Creatinine clearance of less than 48mL/min) will be prevented from receiving further Anakinra therapy. Allergic reaction to anakinra, severe injection site reaction, hearing deterioration of greater than 20dB PTA, or development of a serious bacterial infection will also constitute criteria for discontinuation of therapy (see section 4.4.1). The study nurses and the DSMB will be informed of these stopping rules. If greater than 25% of the total number of patients to be

recruited for this study (n=5) are prevented from completing Anakinra therapy, then the entire study will be stopped for safety concerns. Cross reference section 5.4.1.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6.1 Independent Data and Safety Monitoring Board

Because of the potential COI of the Principal Investigator and the Institution, an independent data safety monitoring board will be constructed. The function of this board will be to assess any adverse risk associated with anakinra therapy and will have the authority to review an un-blinded analysis of both safety and efficacy. The DSMB for this study be comprised of: an Otolaryngologist/Neurotologist, a Bio-Statistician, and a Rheumatologist that are not (1) associated with the study, (2) are not members of the Feinstein Institute for Medical Research. The members' names and contact information will be submitted to the IRB and maintained within the study file.

The data safety monitoring board will conference every 6 months by phone, assisted by a web based ability to review the data that is encrypted to protect the privacy of the patients. One of the study nurses will maintain a database of (1) patient logs of compliance, site reactions and symptoms, (2) adverse reactions, (3) audiometric data, (4) CBC and SMA-7 values. This will be maintained in a password required website. The DSMB will independently access this data. The PI and the study nurse will be available during the meeting times to participate in the discussion only to clarify questions raised by the DSMB. The DSMB will report their findings, in writing, to the Investigator and to the Institutional Review Board at the Feinstein Institute within one week of their meeting.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject

authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to a monitoring plan. The independent DSMB will meet every 6 months for the duration of the study. The investigator will provide data to the DSMB two weeks prior to scheduled meeting dates to allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study

related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11.1 Potential Benefits

Patients with corticosteroid resistant autoimmune hearing loss, sudden hearing loss or Meniere's disease that failed to recover hearing with prednisone may recover hearing. However this cannot be guaranteed and Anakinra may not work to recover their hearing.

This study may improve our understanding of the causes and possible treatments for these diseases or it may advance knowledge, provide information about the disease process or eventually lead to improved treatment or management.

11.2 Risks/Discomforts

- Injections site reactions: The most common adverse event in patients receiving Anakinra is injection site reactions, which is described as redness, bruising, inflammation and pain. This occurred in 71% of patients, typically in the first 4 weeks of therapy, lasting from 14-28 days (from pdr.net). Infections were identified in 39% of Anakinra treated patients and 37% of placebo treated patients. In most cases, this redness is limited and will not necessitate discontinuation of Anakinra. In prior studies of rheumatoid arthritis, most patients experienced redness during the first month of treatment.

- Serious adverse reactions: In studies in rheumatoid arthritis studies, the following serious adverse reactions were reported: 2% of adults who took Anakinra developed serious infection (cellulitis (an infection of the skin that is caused by a bacteria) pneumonia, and bone and joint infections).

- Neutropenia (a reduced white blood cell count): White blood cells help to fight infection: 8% of those treated with Anakinra experienced neutropenia as compared with 2% of patients that received a placebo.

- Lymphoma: a 3.6 fold increase in the rate of lymphoma (a malignancy of the blood) was seen (0.12cases/100 patient years) (Patient years is the number of patients studied multiplied by the number of years studied).

- Vertigo: Vertigo may be a consequence of the disease or a consequence of anakinra therapy.

- There is also the possibility that taking Anakinra could worsen hearing. If your disease worsens significantly during the study, you and/or your physician may decide to discontinue participation.

Pregnancy Risks

The risk of the study drug to an unborn baby is not well known at this time. As a result, women should not be in this study if they are pregnant, breast-feeding, or trying to become pregnant.

Women of childbearing age should use birth control for the entire duration of the anakinra treatment. Hormonal methods (birth control pill, etc.), double-barrier methods (condoms with spermicidal, sponge with spermicidal, or diaphragm with spermicidal), or abstinence may be used.

12 Study Finances

12.1 Funding Source

This study will be financed from a grant from the National Institute of Deafness and other Communication Disorders at the National Institute of Health. Additional funding will be provided by the Otolaryngology Foundation of the North Shore-LIJ Health System.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Feinstein Institute for Medical Research investigators will follow the University conflict of interest policy.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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North Shore-Long Island Jewish Health System
The Feinstein Institute for Medical Research
Long Island Jewish Medical Center Campus
Department of Otolaryngology

Consent for Participation in a Phase I Study to evaluate the efficacy and safety of Anakinra in Corticosteroid-Resistant Autoimmune Inner Ear Disease

Principal Investigator: Andrea Vambutas, M.D.

Co-Investigators: Elliot Goldofsky, M.D., Gerald Zahtz, M.D.

Sponsor: **National Institute on Deafness & Other Communication Disorders, NIH**

Introduction:
This consent form is written from the point of view of a research subject. If consent will be obtained from the parent or legal guardian of a minor, the words "you" and "your" should be read as "your child."

You are being asked to participate in a research study. The following information will explain the purpose of the study, what you will be asked to do, and the potential risk and benefits. It will also explain that you do not have to be in this study to receive medical care. You should ask questions before deciding whether you wish to participate, or at any time during the course of the study. You will be told of any new findings that may influence your decision to continue to participate.

Financial Disclosure:
The Feinstein Institute for Medical Research and Dr. Andrea Vambutas, an investigator on this study, hold a patent for use of IL1R2 as a biologic marker for steroid sensitive hearing loss and for the use of Anakinra for the treatment of Autoimmune Inner Ear Disease, Sudden Sensorineural Hearing Loss and Meniere's Disease. If Anakinra is found to be effective, Dr Vambutas and the Feinstein Institute may benefit financially.

Purpose of Study:
You are being asked to participate in this research study because you have autoimmune hearing loss (which includes sudden sensorineural hearing loss and Meniere 's disease) that is resistant to corticosteroids. Corticosteroids (like prednisone) are used to treat the inflammation (swelling) that causes your hearing loss. Since you are resistant to corticosteroids, it means that the medication that is typically used to treat your condition, no longer works for you.

This research study involves the use of an investigational medication called anakinra (Kineret). We are studying anakinra because previous research suggests that a cytokine (a protein) in the body called interleukin-1 (IL-1) may be responsible for resistance to corticosteroids. In the laboratory setting, the researchers have found that anakinra may reduce IL-1 in the immune cells involved in your condition. However, we do not know if it will work in humans.

The purpose of this study is to find out the effectiveness in anakinra when used in those with your condition. About 38 people will participate in this study.

In this research study, anakinra is an investigational drug. This means that anakinra is not approved by the United States Food and Drug Administration (FDA) for the treatment of Autoimmune Hearing Loss. Anakinra is approved by the FDA for the treatment of rheumatoid arthritis.

Expected Duration of Subject's Participation:
If you agree to be in this study, your participation will be for 9-12 months. Thirty eight (38) participants will be enrolled in this study.

Description of Procedures:
To be considered for entry into this study, you need to have already had a sudden decline in hearing that your doctor felt should be treated with prednisone (a corticosteroid). After having received 28-30 days of corticosteroids, you did not experience any hearing improvement as a result of this treatment.

If you agree to participate in this study, you will be offered the study drug which is administered by an injection that is given under the skin (subcutaneous). The study drug, Anakinra, 100 mg, will be administered once a day for three 28 day cycles (a total of 84 days). You will be instructed on the administration by a nurse and an instructional video. You will need to store the drug in a refrigerator.

If you are a female who is able to become pregnant, you will have a pregnancy blood test (about 2 teaspoons) to confirm that you are not pregnant at the time you begin the study drug. You will have a pregnancy test prior to commencing this study and at each visit while continuing study medication.

Visit 1:
Before you are entered into the study:

- To be included in this study, you will need to have adequate blood counts and kidney function. Therefore a complete blood count and kidney blood tests will be drawn before you start the injections. If you are a female of child-bearing age, you must have a negative pregnancy test prior to starting the injections.
- You will also have blood drawn to measure your IL-1 level and IL-1 associated proteins. We will refer to all of these studies as "IL-1 level". The total amount of blood that will be drawn at this visit will be about 3 tablespoons.

If you are included in this study, you will:

- Receive a 28 day supply of the study drug along with a container to discard the used needles (sharps container)
- Undergo instruction on the study drug
- Be given a log to record information about the study drug
- Be instructed to return any remaining drug and the sharps container with the used need

During your participation:

- If you take the study drug, you will complete daily logs to confirm that you have taken the study medication and to monitor for injection site reaction and other symptoms associated with receiving this medication. You will need to give these logs to the study nurse at daily to weekly intervals. This can be done by email, by fax or regular mail.
- **Every 14 days** (only if your white blood count is borderline low)
  Your complete blood count (including a neutrophil count) will be monitored every 28 days to check for neutropenia (decrease in white blood cell count). If your prior white blood cell count was slightly low, but not low enough to prevent you from participating in this study, your white blood cell count will be monitored every 14 days for the duration of the 84 days on Anakinra. The total amount of blood taken to monitor your complete blood count will be about 2 teaspoons during these 14 day intervals.

Visit 2:
After you receive the first 28 days of the study drug, you will return to the office for:

- A hearing test
- Blood testing to monitor your blood count, pregnancy test (if female of child-bearing age), IL-1 levels and kidney function. The total amount of blood taken at this visit will be about 3 tablespoons.
- Review of your daily logs
- Injection site(s) examination for site reactions
- Bring in unused study medication and sharps container.

If you continue in the study, at this visit, you will:

- Be provided with the next 28 day supply of medication and a sharps container.
- Continue to monitor any reactions you are experiencing in these next 28 days
- Continue to complete your daily logs.

If you are withdrawn from the study while still on anakinra, a follow-up audiogram, safety bloods and IL-1 levels (about 3 tablespoons) will be done within approximately 30 days of your last injection.

Visit 3:
At 56 days after you start the study drug, you will return to the office for:

- A hearing test
- Blood testing to monitor your blood count, pregnancy test (if female of child-bearing age), IL-1 levels and kidney function. The total amount of blood taken at this visit will be about 3 tablespoons.
- Review of your daily log
- Injection site(s) examination for site reactions.
- Bring in unused study medication and sharps container.

If you continue in the study, at this visit, you will:

- Be provided with the next 28 day supply of medication and a sharps container.

- Continue to monitor any reactions you are experiencing in these next 28 days
- Continue to complete your daily logs

Visit 4:
At 84 days after you start the study drug, you will return to the office for:
- A hearing test
- Blood testing to monitor your blood count, IL-1 levels and kidney function. The total amount of blood taken at this visit will be about 3 tablespoons.
- Injection site(s) examination for site reactions
- Return unused study drug and sharps container

Follow-Up Period:
Visit 5 - At 30 days after you stop your study drug you will return to the office for:
- A hearing test
- Blood testing to monitor your blood count, IL-1 levels and kidney function. The total amount of blood taken at this visit will be about 3 tablespoons.

Visit 6 - At 90 days after you stop your study drug you will return to the office for:
- A hearing test
- Blood testing to monitor your blood count, IL-1 levels and kidney function. The total amount of blood taken at this visit will be about 3 tablespoons.

Visit 7 - At 180 days after you stop your study drug you will return to the office for:
- A hearing test
- Blood testing to monitor your blood count, IL-1 levels and kidney function. The total amount of blood taken at this visit will be about 3 tablespoons.

If you develop a new worsening in your hearing loss in the 180 day follow-up period, you will be offered corticosteroid therapy which is the standard medical treatment for your condition, or you may be restarted on anakinra therapy. A 28 day dose box of anakinra will be given free of charge to you if retreatment is indicated. At that point, a letter may be sent to your insurance company for possible coverage of the drug in case a continued use of anakinra in necessary. During the 180 follow up period, the maximum number of times you can receive a 28 day dose of anakinra would be 4 times. If retreatment with anakinra is indicated, a pregnancy test (if female of child-bearing age) will also be done along with the normal follow-up period blood testing before you resume the study medication. Daily logs will also be resumed. Follow-up (interval) visits will be scheduled after 28 days if you need to be retreated with anakinra. A hearing test and blood testing to monitor your blood count, IL-1 levels and kidney function will be done at each interval visit. If continued treatment on anakinra is needed, a pregnancy test (if female of child-bearing age) will also be done at the interval visit.

Possible Benefits:
Patients with corticosteroid resistant autoimmune hearing loss, sudden hearing loss or Meniere's disease that failed to recover hearing with prednisone may recover hearing. However this cannot be guaranteed and Anakinra may not work to recover your hearing.

This study may improve our understanding of the causes and possible treatments for your disease or it may advance knowledge, provide information about the disease process or eventually lead to improved treatment or management.

Possible Risks of Blood Drawing:
Puncturing of a vein when blood is taken may cause discomfort and bruising at the site of the puncture.

Possible Risks/Discomforts of Anakinra:

- Injections site reactions: The most common adverse event in patients receiving Anakinra is injection site reactions, which is described as redness, bruising, inflammation and pain. This occurred in 71% of patients, typically in the first 4 weeks of therapy, lasting from 14-28 days (from pdr.net). Infections were identified in 39% of Anakinra treated patients and 37% of placebo treated patients In most cases, this redness is limited and will not necessitate discontinuation of Anakinra. In prior studies of rheumatoid arthritis, most patients experienced redness during the first month of treatment.

- Serious adverse reactions: In studies in rheumatoid arthritis studies, the following serious adverse reactions were reported: 2% of adults who took Anakinra developed serious infection (cellulitis (an infection of the skin that is caused by a bacteria) pneumonia, and bone and joint infections).

- Neutropenia (a reduced white blood cell count): White blood cells help to fight infection: 8% of those treated with Anakinra experienced neutropenia as compared with 2% of patients that received a placebo.

- Lymphoma: a 3.6 fold increase in the rate of lymphoma (a malignancy of the blood) was seen (0.12cases/100 patient years) (Patient years is the number of patients studied multiplied by the number of years studied).

- Vertigo: Vertigo may be a consequence of your disease or a consequence of anakinra therapy. If you experience dizziness (vertigo), drive at your own risk, and avoid activities that place you or others at risk of injury.

- There is also the possibility that taking Anakinra could worsen your hearing. If your disease worsens significantly during the study, you and/or your physician may decide to discontinue participation.

Pregnancy Risks

The risk of the study drug to an unborn baby is not well known at this time. As a result, women should not be in this study if they are pregnant, breast-feeding, or trying to become pregnant.

If you are a woman of childbearing age, you should use birth control for the entire duration of the anakinra treatment. Hormonal methods (birth control pill, etc.), double-barrier methods

(condoms with spermicidal, sponge with spermicidal, or diaphragm with spermicidal), or abstinence may be used. Your doctor will discuss these with you.

If you think that you are pregnant or if you become pregnant during the study, please notify the study doctor immediately.

Recording of side effects:
You will be given log sheets to keep a record of when you take your study drug and any potential side effects which will be emailed at least weekly to the study coordinator while you are on anakinra. Should you have any significant adverse reactions after taking the medication, call the nurse or your doctor to report it immediately.

Alternative Treatments:
You may choose not to participate in this research study and continue to receive standard medical care, which is continued corticosteroid therapy.

Costs/Compensation:
The study medication will be supplied to you at no cost during the course of the study. You will receive a 28-day supply each time you come in for your scheduled interval evaluation for a total of 84 days of the study drug. Commercial laboratory tests for your complete blood count, kidney function and pregnancy tests will be billed to your insurance by the reference laboratory used. In the event that payment is denied, the study sponsor will cover the cost of the test. All IL-1 testing will be provided to you at no cost.

In the event you have an initial favorable response to anakinra, and relapse in the absence of drug, we will provide one additional month of therapy if you choose to be restarted on anakinra. In the event you require a longer duration of treatment, with you permission, we will send a letter to your insurance carrier requesting coverage for this therapy.

Compensation for Research-Related Injury:
If you are hurt from being in the study, you will receive medical care and treatment as needed from the North Shore Long Island Jewish Health System. However, you will be responsible for the costs of such medical treatment, directly or through your medical insurance and/or other forms of medical coverage. No money will be given to you.

Voluntary Participation:
Your participation in this study is totally voluntary. You may choose not to participate and continue to receive standard care. If you do not join the study, you will not be penalized. If you join the study, you may withdraw at any time without prejudice to your future care at North Shore-Long Island Jewish Health System. If you decide to leave the study, tell the study doctor. The quality of your medical care will be the same, whether you join, refuse to join, or decide to leave the study.

Confidentiality:
If you agree to be in this study, we will collect health information that identifies you. We may collect the results of tests, questionnaires and interviews. We may also collect information from your medical record. We will only collect information that is needed for the research. This

information is called protected health information (PHI) and has been described in this consent form. If you sign this consent form, you are giving us permission to collect, use and share your health information. This permission is called authorization. You cannot be in this study if you do not give us permission to use and share your protected health information (PHI).

Study records that identify you will be kept private. You will not be identified in study records or publications disclosed outside the North Shore-Long Island Jewish Health System, except as detailed below.

Investigators may share the results of your study tests and procedures with the National Institute of Health, Food and Drug Administration, and the Data Safety Monitoring Board.

In addition, your records may be reviewed in order to meet federal or state research regulations. Reviewers may include representatives from related government oversight agencies and the NS-LIJ Institutional Review Board (IRB- the committee that reviews research at this institution). If your research record is reviewed by any of these groups, they may also need to see your entire medical record. Please be aware that once private information is disclosed, it is subject to re-disclosure by the recipient and can no longer be considered protected.

If your research records are used for decisions related to your clinical care, then you have the right to review this information and request changes. This is limited to information about your treatment, and does not include information related to procedures or tests that are for research purposes only. You may access this information only after the study analysis is complete. You have the right to know who has and who will see your records. To request this information, or for any questions related to your health information, you may contact the Research Privacy Officer at 516-562-2018.

If you change your mind about being in the study, you may withdraw at any time. If you want us to stop collecting your health information, you need to send a letter to the researcher at the following address:

Andrea Vambutas, M.D.
Medical Director, Apelian Cochlear Implant Program
Section Head, Neurotology
Department of Otolaryngology
Long Island Jewish Medical Center
Hearing and Speech Center
430 Lakeville Road
New Hyde Park, NY 11042

Your letter needs to say that you have changed your mind and do not want the researcher to collect and share your health information. You may also need to leave the research study if we cannot collect any more health information. We may still use the information we have already collected. We need to know what happens to everyone who starts a research study, not just those people who stay in it.

The information that is collected for research will be analyzed for many years and it is not possible to know how long this analysis and follow-up will take. Therefore, you are allowing access to this information indefinitely.

Data from this study may be used in medical publications or presentations. The information will be de-identified so that individual subjects cannot be recognized and the information will no longer be considered Protected Health Information (PHI).
If the study reveals evidence of child abuse or other public health concerns, it will be shared with the appropriate authorities.

Contacts for Questions/Access to Consent Form:
If you have any questions about the study or any questions about side effects or injury from the research, you may call Dr. Andrea Vambutas, and Dr. Gerald Zahtz at (718) 470-7550, or Dr. Elliot Goldofsky at (516) 482-3223. For questions on your rights as a research subject, you may call the Office of the Institutional Review Board (the committee that oversees research at the Institution) at (516)-719-3100. A copy of this signed consent form will be given to you.

[Signature Page Follows]

Summation/Signatures: You have read the above description of the research study. You have been told of the risks and benefits involved and all your questions have been answered to your satisfaction. Furthermore, you have been assured that a member of the research team will answer any future questions that may arise. You voluntarily agree to join this study and know that you can withdraw from the study at any time without penalty. By signing this form, you have not given up any of your legal rights.

Subject's Printed Name

Subject's Signature Date
(If subject is 18 years old or older)

For children under 18 years of age:

Printed Name of Parent/Legal Guardian Signature of Parent/Legal Guardian Date

Printed Name of Parent/Legal Guardian Signature of Parent/Legal Guardian Date

Note: The second parental/legal guardian signature is not required

Witness's Signature Date

Witness's Printed Name (preferably someone not connected with the research)

Physician's Statement and Signature: In addition to advising the above subject of other forms of treatment and therapy which are appropriate, I have offered an opportunity for further explanation of the risks and discomforts which are, or may be associated with this study and to answer any further questions relating to it.

Physician's Signature Date

Physician's Printed Name

ASSENT BY MINOR SUBJECT TO PARTICIPATE IN RESEARCH

I have been asked to join this research study. I have the right to find out what will or might happen to me if I am in the study. I have the right to tell my parent(s)/legal guardian and the doctor whether I do or do not want to participate. I will be asked my permission to remain in this study once I turn 18.

My parent(s)/legal guardian will also be asked to give permission for me to be in this study.

Dr. _____ and my parent(s)/legal guardian have explained what I will have to do in the study.

Dr. _____ and my parent(s)/legal guardian have also explained any discomforts, risks and inconveniences I may experience if I am in the study.

I agree to use effective birth control whether I am a male or a female.

If I am female, I have been told that I will be asked to discuss sexual activity and birth control in private and my parents will only be involved in the discussion if I want them to be there.

If I am female, I have been told that I will have pregnancy testing if I am able to have a child and the results will be kept private and not shared with my parents without my permission. I have been told that I need to remain pregnancy free throughout the study.

I have asked any questions I had, and all my questions have been answered.

Check one:

_____ I agree to participate in this study.

_____ I do not agree to participate in this study.

_____ _____
Subject's Name Subject's Age

_____ _____
Subject's Signature Date

_____ _____
Witness Signature Date

_____
Relationship of Witness to Subject

All procedures, risks and discomforts have been explained to the subject.

_____ _____
Physician's Signature Date