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The effectiveness of intratympanic injections with methylPREDnisolon versus placebo in the treatment of vertigo attacks in MENière's disease (PREDMEN trial): a study protocol for a phase-3 multicentre, double-blinded, randomized, placebo-controlled trial

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Abstract

Introduction: Intratympanic corticosteroids are commonly used in the treatment of Menière's disease (MD). However, few and small randomized controlled trials (RCT) on the effectiveness of intratympanic corticosteroids have been performed. A recent Cochrane review suggested that a well conducted placebo-controlled RCT with a large study population is required to evaluate the effectiveness of the use of intratympanic corticosteroids in MD. The following protocol describes a phase-3 multicentre, double-blinded, randomized, placebo-controlled trial to compare the effectiveness of methylprednisolone (62.5 mg/ml) to a placebo (sodium chloride 0.9%).

Methods and analysis: We aim to recruit 148 patients with unilateral MD from 6 hospitals in the Netherlands. Patients will be randomly assigned to either the methylprednisolone, or the placebo group. Two injections will be given, one at baseline and one after two weeks. Follow-up assessments will be done at 3, 6, 9 and 12 months. The primary outcome will be the frequency of vertigo attacks. Attacks will be evaluated daily with the DizzyQuest app. Secondary outcomes include hearing loss, tinnitus, health-related quality of life, use of co-interventions and escape medication, (serious) adverse events and cost-effectiveness. These will be evaluated with audiometry and multiple commonly used, validated questionnaires. For the primary and secondary outcomes mixed model analysis, estimating equation (GEE) analysis and logistic regression analysis will be used.

Ethics and Dissemination: This study was submitted via the Clinical Trials Information System, reviewed and approved by the Medical Research Ethics Committee Leiden The Hague Delft and the local institutional review board of each participating centre. All data will be presented ensuring the integrity and anonymity of patients. Results will be published in scientific journals and presented on (inter)national conferences.

Strengths and limitations:

- In this randomized placebo-controlled study both participants and clinicians will remain blinded throughout the follow-up period, therefore minimizing the risk of bias.
- The prospective design with patients daily recording their vertigo attack directly in an app, lowers the risk of missing data and recall bias.
- This study includes a rather large patient population of 148 patients.
- VM and MD share multiple features in terms of clinical presentation and other symptomatology, distinguishing between the two could be challenging and therefore could form a possible limitation in this study.
- Subanalyses on clinical subgroups of MD (autoimmune, familial, and MD + migraine) will be difficult to conduct, because many patients cannot be classified in a subgroup or are part of multiple subgroups.

Introduction

Menière's disease (MD) is a clinical condition characterized by unilateral tinnitus and aural fullness, low- to mid-frequency sensorineural hearing loss, and spontaneous episodes of vertigo that can last 20 minutes to 12 hours [1]. Patients with MD experience a worse quality of life than healthy patients due to vertigo, tinnitus hearing loss [2]. In addition, higher levels of anxiety and depression are seen in patients with MD [3].

Although its aetiology is unknown, endolymphatic hydrops (EH) is thought to be associated with MD. Almost all patients with MD have EH, but not all patients with EH have symptoms of MD. It is unknown if EH is a result of MD or a causal factor for MD [4, 5]. Until this day no effective treatment for MD has been discovered. Current treatment consists of dietary and lifestyle modifications, oral diuretics, vestibular rehabilitation for chronic imbalance, intratympanic therapy, and/or ablative surgery [1]. With intratympanic gentamicin and intratympanic corticosteroid injections the drug is directly delivered into the middle ear, from where it will be absorbed in the inner ear. Unlike gentamicin, corticosteroid therapy does not carry a risk of causing hearing loss. Therefore, it is currently the first step of standard care in the treatment of MD [1]. Although the mechanism of action of steroids on the inner ear remains speculative it may improve cochlear blood flow and stabilize the vascular endothelium which enhances fluid homeostasis by up regulation of cochlear ion gene expression [6]. Recently, a Cochrane review was published evaluating the use of intratympanic corticosteroids in MD [7]. In this review, 10 randomized controlled trials (RCTs) and quasi-RCTs comparing intratympanic corticosteroids, all using dexamethasone, compared to either placebo or no treatment were included. The authors found that the evidence for the use of dexamethasone is uncertain. Intratympanic dexamethasone injection may marginally reduce the frequency of vertigo attacks. Regarding hearing and tinnitus improvement was seen, but without statistical significance.

The most commonly intratympanically administered corticosteroids are dexamethasone and methylprednisolone [1]. Phillips et al. [8] determined the efficacy of intratympanic OTO-104 (a sustained-released dexamethasone hydrogel) for the treatment of MD, in three double blind, placebo-

controlled RCTs, with a total of 165, 174 and 148 patients respectively. OTO-104 showed numerically larger decreases in definitive vertigo days compared with placebo across all three studies. However, in only one study this difference was statistically significant. Pharmacokinetic studies show that dexamethasone-phosphate has molecular and pharmacokinetic characteristics that render its use as a local therapy for hearing disorders which may explain its dubious effectiveness [9]. An animal study found that the concentrations of methylprednisolone are higher and have longer duration in perilymph and endolymph compared to dexamethasone and hydrocortisone, and therefore could be a more effective drug [10]. Typically soluble forms of methylprednisolone are administered and expected to be less permeable through the membranous boundaries compared to the less polar forms. However, there is no data whether these soluble forms are metabolized to the base form in the ear and if they are, at what rate [9]. Despite the fact that little is known about the pharmacokinetics of methylprednisolone, there are clinical indications of its effectiveness [11, 12]. Cao et al. [12] performed a literature review and demonstrated that methylprednisolone is more effective than dexamethasone in a clinical setting.

Although in the last decade, there is an increasing tendency and emerging evidence for the use of intratympanic steroids, no large RCT on the effectiveness of intratympanic methylprednisolone in MD has been conducted [13]. A meta-analysis published in 2021 included eight studies comparing intratympanic gentamicin to intratympanic corticosteroids, in which gentamicin appeared to be superior in terms of control of vertigo attacks [14]. However, gentamicin is known to be ototoxic and can induce hearing loss. Patel et al. [15] compared intratympanic gentamicin injections to methylprednisolone injections in a double-blind RCT with a 24-month post-treatment follow-up. Vertigo attacks decreased in both groups, indicating a treatment effect. However, no placebo group was involved and the sample size was relatively small (n=60).

In conclusion, there is a need of solid evidence on the effectiveness of intratympanic steroids in MD. Until now the effectiveness of methylprednisolone has not been investigated by means of a placebo controlled RCT. Therefore a well conducted RCT with a large study population and a long follow-up

period is now required to evaluate the effectiveness of intratympanic methylprednisolone in MD. In this protocol we present the methods of a phase-3 multicentre, double-blinded, randomized, placebo-controlled trial evaluating the effectiveness of intratympanic injections with methylprednisolone versus placebo in the treatment for MD patients.

Methods

Trial design

In this phase 3, multicentre, double-blind, placebo-controlled randomized trail the effect of two intratympanic methylprednisolone sodium succinate 62.5 mg/ml (Solu-Medrol in Act-O-Vial, Pfizer BV) injections 14 days apart is compared to two placebo (i.e., sodium-chloride 0.9%) injections with the same time interval on vertigo attacks in patients with MD. Parallel groups will be randomly assigned to one of both arms and outcomes will be measured during a one year follow-up period.

Study subjects

Patients with MD will be recruited by six participating sites in the Netherlands and will be approached by their own ENT specialist and informed about this trail. After a one week reflection period, informed consent forms can be signed. Baseline and outcome data will be extracted from participants' electronic medical records and collected in the cloud-based clinical data management platform Castor EDC (version v2023.1.0.1, LUMC).

In- and exclusion criteria

In order to be eligible for the study a study subject needs to have unilateral, definite MD according to the diagnostic criteria derived from the American Academy Otolaryngology Head and Neck Surgery, Classification Committee of the Bárány Society, European Academy of Otology and Neurotology and International Classification of Vestibular Disorders published in 2015 [16]. The criteria for definite MD are:

Two or more spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours,

AND

Audiometrically documented low- to medium-frequency sensorineural hearing loss in one ear,

defining the affected ear on at least one occasion before, during or after one of the episodes of vertigo,

AND

Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear (not better accounted for by another vestibular diagnosis).

Other inclusion criteria are:

- Age ≥ 18 years at the start of the trial.
- ≥ 4 vertigo attacks over the last 6 months.
- Willing to adhere to daily completion of study questionnaires using the DizzyQuest app and to the follow-up assessments.

Potential study subject who meets any of the following criteria will be excluded:

- Bilateral MD.
- Severe disability (e.g. neurological, orthopedic, cardiovascular) or serious concurrent illness that might interfere with treatment or follow-up.
- Active additional neuro-otologic disorders that may mimic MD (e.g. vestibular migraine (VM) , recurrent vestibulopathy, phobic postural vertigo, vertebro-basilar TIAs, acoustic neuroma).
- Otitis media with effusion based on tympanogram results.
- History of intratympanic injections with corticosteroid less than 6 months ago.
- History of intratympanic injections with gentamicin or ear surgery for treating MD.
- Pregnant women or nursing women.

Sample size

A sample size calculation was performed based on a power (1-β) of 80% and a type 1 error (α) of 5% and based on recommendations as summarized in the Clinical Practice Guideline for Menière's disease [1]. An expected proportion of subjects achieving vertigo control of 87.5% was assumed for methylprednisolone treatment compared to an assumed 67.5% for placebo, i.e. a difference in treatment effect of 20%. In each arm 74 patients will be included, giving a total sample size of 148. Loss of follow up is estimated to be 10%. In total, over the six participating centres, 340 MD patients

yearly visit the Otolaryngology department and will be screened for the trial. It is expected that 15% will meet the inclusion criteria and will be willing to participate. This will result in approximately 50 eligible patients for inclusion per year.

Randomization and blinding

Subjects will be randomly assigned to either methylprednisolone or placebo with a 1:1 allocation as per computer-generated random sequence, stratified by site generated by Castor EDC. Blinding will be maintained until all subjects have finished their treatment phases. All study participants, participating medical professionals, and outcome assessors will be blinded. The independent epidemiologist and pharmacy personnel will both be unblinded during randomization and therapy allocation.

Study procedure

After a one week reflection period and agreement with trial participation by means of signing the informed consent, a patient will be seen at the study site. Patients will receive an intratympanic injection with either methylprednisolone or placebo at day 1 and day 15 with a window of three days. At baseline, results of Magnetic Resonance Imaging (MRI) must be available to make sure other causes of disease are ruled out [17]. To assess the vestibular function of the horizontal semicircular canals, the caloric test and video Head Impulse test (vHIT) will be performed. To evaluate the anterior and posterior semi-circular canals, the vHIT will be conducted at baseline in order to assess the presence of vestibular hypofunction or areflexia.

During a follow-up period of one year two telephone contacts will take place at 3 and 6 months to assess possible (serious) adverse events, DizzyQuest app compliance and the use of escape medication or co-interventions. A physical follow-up visit in the outpatient clinic will be scheduled at 6 and 12 months. During these outpatient clinic visits additional audiometry and multiple questionnaires concerning tinnitus, dizziness and quality of life will be filled-in. An overview of follow-up moments of

the corresponding outcomes and a flowchart of the study procedure are presented in table 1 and figure 1, respectively.

Outcome measures

Vertigo: The primary outcome measure will be defined by the class of vertigo as defined by the AAO HNS 1995 guideline. The class of vertigo is defined by the average number of attacks per month during 6 and 12 months after treatment divided by the number of attacks 6 months before treatment times 100. As a result the following class of vertigo is defined:

- A: Complete control of vertigo = 0
- B: Substantial control of vertigo = 1-40
- C: Limited control of vertigo = 41- 80
- D: Insignificant control of vertigo = 81 – 120'
- E: Worse control of vertigo > 120

Moreover, the daily attack vertigo frequency will be monitored with the aid of the DizzyQuest app (Psymate 2)[18, 19]. The DizzyQuest app will be used to track the primary outcome measure, the frequency of dizziness attacks. Patients will answer daily questionnaires about their health and wellbeing and patients can report vertigo attacks at any time using the Dizzy quest app. Additionally, the Dizziness Handicap Inventory (DHI) questionnaire will be administered at baseline, after six months, and after a year to assess how dizziness affects daily life [20]. The effect of the injections in the DHI will be reported as raw data, as well as change in handicap category (mild handicap, moderate handicap or severe handicap) related to improvement, unchanged or worsened.

The following secondary outcomes will be measured

Hearing: Pure tone audiometry will be performed at baseline, after six months, and after a year. In line with the guideline of AAO HNS 1995 guideline[17], we will use the four-tone audiometry at 0.5, 1, 2

and 3 kHz and we will assess the word recognition scores, low-frequency hearing loss, and average scores for the four tones.

Tinnitus: The Tinnitus Functional Index (TFI) measures the impact of tinnitus on daily life [21]. This survey will be administered at baseline, after six months, and after a year. One point decrease of increase will be defined as improved or worsened tinnitus respectively [22].

Quality of life: Apart from the DHI and TFI, the EuroQol 5 dimension (EQ-5D) and EuroQol – Visual Analog Scale (EQ-VAS) questionnaires will be used to measure quality of life at baseline, after six and twelve months [23, 24]. These questionnaire are standardized tests of health status that are used in economic and clinical evaluations

Use of escape medication and co-interventions: In case participants remain suffering from intolerable vertigo attacks, the use of metoclopramide and co-interventions such as intratympanic injections of gentamicin or methylprednisolone will be allowed and documented during the follow up period. This will be based on experience of participants vertigo frequency and shared decision making.

Adverse events

Adverse events, serious adverse events and suspected unexpected serious adverse reactions will be inquired at each study visit and be registered throughout the trial in Castor EDC. Each adverse event must be reported within 24 hours after the physicians' knowledge. In the event that patient safety is compromised, patients can be unblinded.

Cost-effectiveness

Cost-effectiveness will be assessed from both a healthcare and societal cost-utility perspective, where cost per avoided vertigo attack and cost per Quality Adjusted Life Year (QALY), respectively, will be

used as the metrics. MD -related medical expenses, other healthcare expenses, and the cost of lost productivity will all be included in the estimated societal cost, which will be calculated using the iMTA Medical Consumption Questionnaire (iMCQ) and IMTA Productivity Cost Questionnaire (IPCQ).

Statistical analysis

Ordinal regression using mixed model analysis will be used to analyse the primary outcome (i.e., class of vertigo). In addition, generalized estimating equation (GEE) analysis of the actual vertigo attacks recorded using the DizzyQuest app will be used to estimate the incidence rate ratio (IRR) for comparison between the methylprednisolone and placebo groups. A decrease of 100% is considered total control of vertigo episodes, while a reduction of >40% is considered a substantial and thus clinically relevant reduction [17].

Mixed model analysis will be used to analyse differences in the questionnaire scores (DHI, TFI, FLS, eQ-5D/VAS, iMCQ, iPCQ) between the two groups. Logistic regression analysis will be used to analyse the remaining secondary outcomes (incidence of escape interventions, hearing loss, and adverse events). A reduction in hearing of 10 decibels or a 15% change in word recognition will be regarded as a clinically significant difference [17].

Subgroup analyses will be performed with regard to sex, duration of the disease and the type of MD (delayed MD, familial MD, and autoimmune MD). Two sensitivity analyses will be carried out in addition to the intention to treat analysis: a per protocol analysis in which patients who received additional co-interventions to achieve vertigo control are excluded; and an as-treated analysis in which participants who received additional co-interventions are analysed.

In order to evaluate the average costs and outcomes between the methylprednisolone and placebo groups for the cost-effectiveness analysis, intention-to-treat and net-benefit analysis will be used. For all statistical analysis, multiple imputation to adjust for missing data will all be used [25]. QALYs will be calculated using the Dutch tariff for the EuroQoL EQ-5D-5L [23] and as sensitivity analysis the visual

analogue scale valuing health, with power-transformation [26]. All outcomes with corresponding statistical analysis methods are summarized in Table 2. A p-value < 0.05 will be considered as statistically significant for all analyses and will be performed using SPSS version 25 or higher (SPSS Chicago Illinois, USA).

Patient and public involvement

The PREDMEN trial is supported by the Dutch Association for the hard of hearing, and more specifically its Committee Dizziness and Balance (Commissie Duizeligheid en Evenwicht van Hoormij-NVVS) and the Dutch association for psychological health care and social services for patients with SNHL and tinnitus (GGMD). Both organizations are involved in the realization of the trial, the writing process and implementation of trial results. Moreover, they will serve as a sounding board for MD patients participating in this trial and one patient representative will be a member of the steering committee. In line with their suggestions, patients will be involved in every stage of the research.

Ethics and Dissemination

Ethics

The PREDMEN trial was submitted via the Clinical Trial Information System (CTIS), with CTIS number: *2023-503340-13-00*, reviewed by the Medical Review Research Ethics Committee Leiden The Hague Delft (MREC LDD), and authorized for execution in the Netherlands under the European Clinical Trial Regulation (ECTR), with ClinicalTrials.gov ID: *NCT05851508.* Additionally, the institutional research board of each participating centre individually reviewed and approved the study. The study is conducted in accordance with the principles outlined in the Declaration of Helsinki (October 2013), the Medical Research Involving Human Subjects Act (WMO, 26 February 1998), the International Conference on Harmonization Good Clinical Practice (ICH GCP, November 2016) guidelines, and any other applicable guidelines, regulations, and Acts.

Patient safety

Minor complications such as intratympanic membrane perforation (3-38%) and otitis media (7%) can occur [27, 28] Safety risk will be comparable to normal clinical practice and it is not expected that significant adverse events will be seen in the intervention arm. ENT specialists are experienced with intratympanic injections due to its application in patients with sudden deafness. Since the intervention is characterized as a low risk profile study, no Data Safety Monitoring Board (DSMB) is required [29]. The sponsor will submit a report on the safety of each investigational medicinal product used in the clinical trial through CTIS. Interim analysis will be performed on the primary endpoint when 50% of the patients have been randomized and completed a follow-up of 6 months, where comparability of baseline characteristics will be assessed. In this analyses, differences in vertigo control between the two study arms should not be greater than 45%. In addition, if the difference in vertigo control reveals to be clinically significant (i.e. >20%), but ≤ 20% of the participants in methylprednisolone

reach vertigo control, the study will be terminated because of convincing effect of the treatment in the intervention arm.

Data safety

The handling of personal data complies with the Dutch Personal Data Protection Act (AVG). All data collected for the trail, including but not limited to demographic data, audiological questionnaires, and data from the DizzyQuest app will be entered in a ISO 9001 and ISO 27001:2005 certified Castor® EDC database (electronic CRF). Data will be protected with a unique subject identification code which is linked to a pass-word protected subject identification list. Only members of the study team, who will be documented on the site signature and delegation log per site, will have access to the study data. The sponsor and investigator will keep a clinical trial master file which will contain the essential documents relating to the clinical trial.

Dissemination

A summary of the results of this study will be submitted to CTIS within one year after termination of the trial. Results will also be published in scientific journals and presented on (inter)national conferences. All information that will be presented will be done so in a way that integrity and anonymity of patients is ensured. All data will be stored for 25 years after the last subject has had the last study visit.

Contributors

all authors contributed to the conception of the trial, writing of the protocol, and performed an intellectual content revision. The final draft was read and approved by all authors.

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Competing interests

No competing interest was declared.

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Tables

Table 1. Overview of follow-up moments of the corresponding outcomes

Moment in trial	*Type of follow up*	*Outcomes*
From moment of inclusion unit 1 year follow up		Daily questionnaire in Dizzy quest app
Baseline	First intratympanic injection	Baseline parameters MRI Otoscopy Audiometry: PTA and SDS Vestibular testing: vHIT, caloric testing Questionnaires: DHI, TFI, FLS, EQ-5D/VAS, iMCQ, iPCQ
2 weeks	Second intratympanic injection	Otoscopy Complications Use of co-interventions Use of escape medication (S)AE
3 months, 9 months	Telephone consult	Complications Use of co-interventions Use of escape medication (S)AE
6 months, 12 months	Consult in outpatient clinic	Otoscopy Complications Audiometry: PTA and SDS Questionnaires: DHI, TFI, FLS, EQ-5D/VAS, iMCQ, iPCQ Use of co-interventions Use of escape medication (S)AE

Abbreviations: DHI, Dizziness Handicap Index; EQ 5D, EuroQol 5D; FLS, Functional Level Scale; HIT, Head Impulse Test; iMCQ, iMTA Medical Consumption Questionnaire; iPCQ, iMTA Productivity Cost; Questionnaire; MRI, Magnetic Resonance Imaging; PTA, Pure Tone Average; SDS, speech discrimination score; (S)AE, (Serious) Adverse Event, TFI, Tinnitus Functional Index

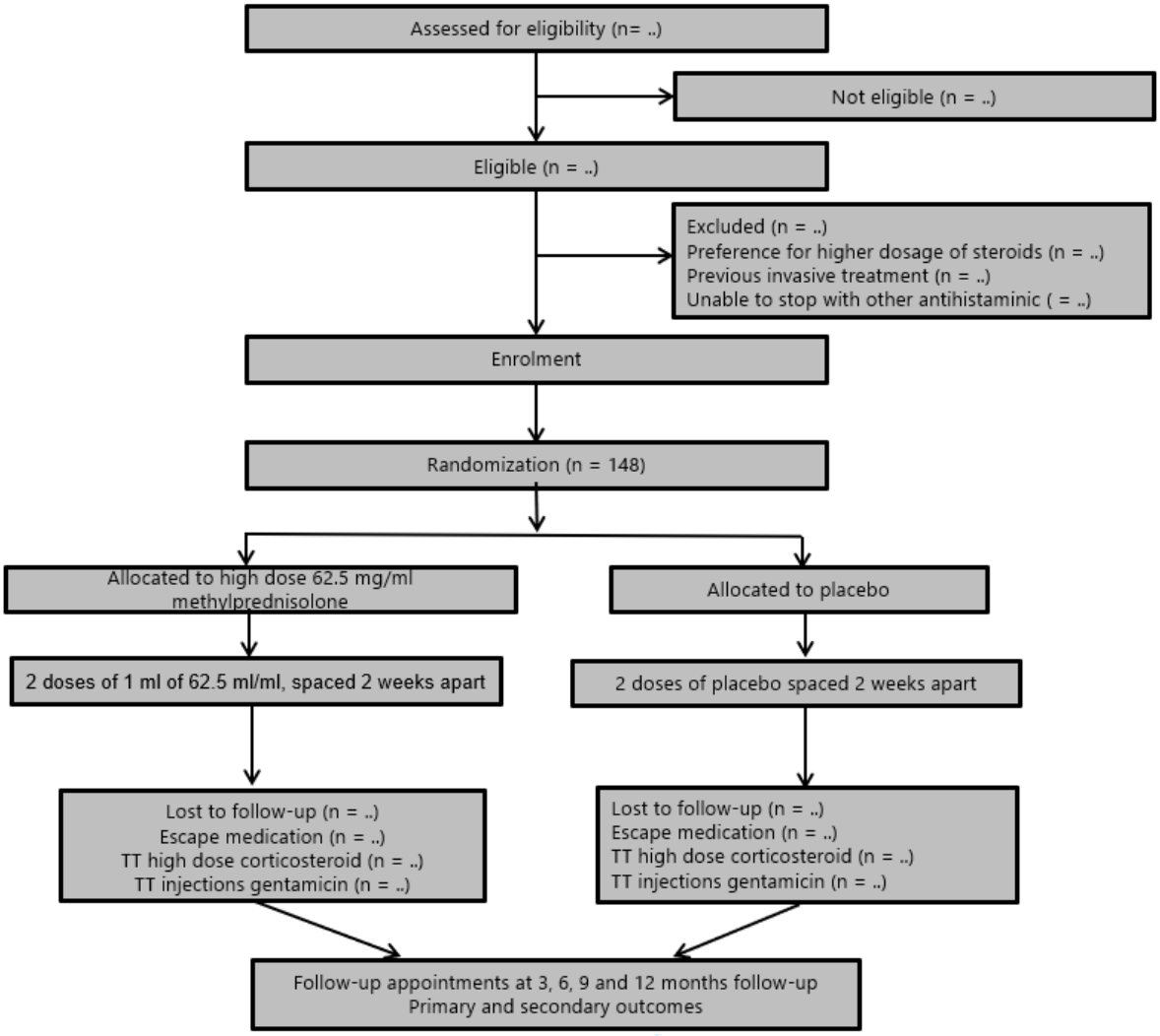
463 **Table 2 Outcomes with corresponding statistical analysis method**

	Outcome	*Type of data*	*Analysis*
Primary outcome	Number of spontaneous vertigo attacks, lasting more than 20 minutes	Count	Generalized estimating equation
	AAO HNS (1995) class of vertigo		Mixed model analysis
Secondary outcomes	Hearing (PTA; 0.5, 1, 2, 3 kHz and SDS)	Continuous	Logistic regression analysis
	Tinnitus (TFI)	Categorical	Mixed model analysis
	Quality of life (DHI, TFI, FLS, eQ-5D/VAS)	Categorical	Mixed model analysis
	Use of escape medication and co-interventions	Count	Logistic regression analysis
	(S)AE	Binary	Logistic regression analysis
	Cost effectiveness (iMCQ, iPCQ)	Categorical	Mixed model analysis

Abbreviations: DHI, Dizziness Handicap Index; EQ 5D, EuroQol 5D; FLS, Functional Level Scale; iMCQ, iMTA Medical Consumption Questionnaire; iPCQ, iMTA Productivity Cost; Questionnaire; PTA, Pure Tone Average; SDS, speech discrimination score; (S)AE, (Serious) Adverse Event, TFI, Tinnitus Functional Index

464

Figure 1. flowchart of the study procedure.



Reporting checklist for randomised trial.

Based on the CONSORT guidelines.

Instructions to authors

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		Reporting Item	Page Number
Title and Abstract			
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	2
Introduction			
Background and objectives	#2a	Scientific background and explanation of rationale	4-5
Background and objectives	#2b	Specific objectives or hypothesis	5-6
Methods			
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	7

Trial design	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7
Participants	#4a	Eligibility criteria for participants	7-8
Participants	#4b	Settings and locations where the data were collected	7
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	10-11-12
Sample size	#7a	How sample size was determined.	8-9
Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	14-15
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	9
Randomization - Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size)	9
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	9-10
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	9

Blinding	#11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	12-13
Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12-13
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	10-11-12
Results			
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	21
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	21
Recruitment	#14a	Dates defining the periods of recruitment and follow-up	19
Recruitment	#14b	Why the trial ended or was stopped	N/A
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	21
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10-11-12
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	20
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	20
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	14
Discussion			

Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	3
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Registration	#23	Registration number and name of trial registry	14
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings	N/A
Other information			
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Registration	#23	Registration number and name of trial registry	14
Protocol	#24	Where the full trial protocol can be accessed, if available	N/A
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	16

BMJ Open

The effectiveness of intratympanic injections with methylPREDnisolon versus placebo in the treatment of vertigo attacks in MENière's disease (PREDMEN trial): a study protocol for a phase-3 multicentre, double-blinded, randomized, placebo-controlled trial

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The effectiveness of intratympanic injections with methylPREDnisolon versus placebo in the treatment of vertigo attacks in MENière's disease (PREDMEN trial): a study protocol for a phase-3 multicentre, double-blinded, randomized, placebo-controlled trial

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Abstract

Introduction: Intratympanic corticosteroids are commonly used in the treatment of Menière's disease (MD). However, few and small randomized controlled trials (RCT) on the effectiveness of intratympanic corticosteroids have been performed. A recent Cochrane review suggested that a well conducted placebo-controlled RCT with a large study population is required to evaluate the effectiveness of the use of intratympanic corticosteroids in MD. The following protocol describes a phase-3 multicentre, double-blinded, randomized, placebo-controlled trial to compare the effectiveness of methylprednisolone (62.5 mg/ml) to a placebo (sodium chloride 0.9%).

Methods and analysis: We aim to recruit 148 patients with unilateral MD from 6 hospitals in the Netherlands. Patients will be randomly assigned to either the methylprednisolone, or the placebo group. Two injections will be given, one at baseline and one after two weeks. Follow-up assessments will be done at 3, 6, 9 and 12 months. The primary outcome will be the frequency of vertigo attacks. Attacks will be evaluated daily with the DizzyQuest app. Secondary outcomes include hearing loss, tinnitus, health-related quality of life, use of co-interventions and escape medication, (serious) adverse events and cost-effectiveness. These will be evaluated with audiometry and multiple commonly used, validated questionnaires. For the primary and secondary outcomes mixed model analysis, estimating equation (GEE) analysis and logistic regression analysis will be used.

Ethics and Dissemination: This study was submitted via the Clinical Trials Information System, reviewed and approved by the Medical Research Ethics Committee Leiden The Hague Delft and the local institutional review board of each participating centre. All data will be presented ensuring the integrity and anonymity of patients. Results will be published in scientific journals and presented on (inter)national conferences.

Strengths and limitations:

- In this randomized placebo-controlled study both participants and clinicians will remain blinded throughout the follow-up period, therefore minimizing the risk of bias.
- The prospective design with patients daily recording their vertigo attack directly in an app, lowers the risk of missing data and recall bias.
- This study includes a rather large patient population of 148 patients.
- VM and MD share multiple features in terms of clinical presentation and other symptomatology, distinguishing between the two could be challenging and therefore could form a possible limitation in this study.
- Subanalyses on clinical subgroups of MD (autoimmune, familial, and MD + migraine) will be difficult to conduct, because many patients cannot be classified in a subgroup or are part of multiple subgroups.

Introduction

Menière's disease (MD) is a clinical condition characterized by tinnitus and aural fullness, low- to mid-frequency sensorineural hearing loss, and spontaneous episodes of vertigo that can last 20 minutes to 12 hours [1]. Patients with MD experience a worse quality of life than healthy patients due to vertigo, tinnitus and hearing loss [2]. In addition, higher levels of anxiety and depression are seen in patients with MD [3].

Although its aetiology is unknown, endolymphatic hydrops (EH) is thought to be associated with MD. Almost all patients with MD have EH, but not all patients with EH have symptoms of MD. It is unknown if EH is a result of MD or a causal factor for MD [4, 5]. Until this day there is no agreement as to the ideal treatment of MD, due to the lack of evidence for the effect of various therapies. Current treatment consists of dietary and lifestyle modifications, oral diuretics, vestibular rehabilitation for chronic imbalance, intratympanic therapy, and/or ablative surgery [1]. With intratympanic gentamicin and corticosteroid injections the drug is directly delivered into the middle ear, from where it will be absorbed in the inner ear. Unlike gentamicin, corticosteroid therapy does not carry a risk of causing hearing loss. Therefore, it is currently the first step of standard care in the treatment of MD [1]. Although the mechanism of action of steroids on the inner ear remains speculative, it may improve cochlear blood flow and stabilize the vascular endothelium which enhances fluid homeostasis by upregulation of cochlear ion gene expression [6]. Recently, a Cochrane review was published evaluating the use of intratympanic corticosteroids in MD [7]. In this review, 10 randomized controlled trials (RCTs) and quasi-RCTs comparing intratympanic corticosteroids, all using dexamethasone, compared to either placebo or no treatment were included. The authors found that the evidence for the use of dexamethasone is uncertain. Intratympanic dexamethasone injection may marginally reduce the frequency of vertigo attacks. Regarding hearing and tinnitus, improvement was seen, but without statistical significance.

The most commonly intratympanically administered corticosteroids are dexamethasone and methylprednisolone [1]. Phillips et al. [8] determined the efficacy of intratympanic OTO-104 (a

sustained-released dexamethasone hydrogel) for the treatment of MD, in three double blind, placebo-controlled RCTs, with a total of 165, 174 and 148 patients respectively. OTO-104 showed numerically larger decreases in definitive vertigo days compared with placebo across all three studies. However, in only one study this difference was statistically significant. Pharmacokinetic studies show that dexamethasone phosphate has molecular and pharmacokinetic characteristics that complicate its use as a topical therapy for hearing disorders, which may explain its questionable effectiveness. [9]. An animal study found that the concentrations of methylprednisolone are higher and have longer duration in perilymph and endolymph compared to dexamethasone and hydrocortisone, and therefore could be a more effective drug [10]. Typically soluble forms of methylprednisolone are administered and expected to be less permeable through the membranous boundaries compared to the less polar forms. However, there is no data whether these soluble forms are metabolized to the base form in the ear and if they are, at what rate [9]. Despite the fact that little is known about the pharmacokinetics of methylprednisolone, there are clinical indications of its effectiveness [11, 12]. Cao et al. [12] performed a literature review and demonstrated that methylprednisolone is more effective than dexamethasone in a clinical setting.

Although in the last decade, there is an increasing tendency and emerging evidence for the use of intratympanic steroids, no large RCT on the effectiveness of intratympanic methylprednisolone in MD has been conducted [13]. A meta-analysis published in 2021 included eight studies comparing intratympanic gentamicin to intratympanic corticosteroids, in which gentamicin appeared to be superior in terms of control of vertigo attacks [14]. However, gentamicin is known to be ototoxic and can induce hearing loss. Patel et al. [15] compared intratympanic gentamicin injections to methylprednisolone injections in a double-blind RCT with a 24-month post-treatment follow-up. Vertigo attacks decreased in both groups, indicating a treatment effect. However, no placebo group was involved and the sample size was relatively small (n=60).

In conclusion, there is a need of solid evidence on the effectiveness of intratympanic steroids in MD. Until now the effectiveness of methylprednisolone has not been investigated by means of a placebo

controlled RCT. Therefore a well conducted RCT with a large study population and a long follow-up period is now required to evaluate the effectiveness of intratympanic methylprednisolone in MD. In this protocol we present the methods of a phase-3 multicentre, double-blinded, randomized, placebo-controlled trial evaluating the effectiveness of intratympanic injections with methylprednisolone versus placebo in the treatment for MD patients.

Methods

Trial design

In this phase 3, multicentre, double-blind, placebo-controlled randomized trial the effect of two intratympanic methylprednisolone sodium succinate 62.5 mg/ml (Solu-Medrol in Act-O-Vial, Pfizer BV) injections 14 days apart is compared to two placebo (i.e., sodium-chloride 0.9%) injections with the same time interval on vertigo attacks in patients with MD. Parallel groups will be randomly assigned to one of both arms and outcomes will be measured during a one year follow-up period.

Study subjects

Patients with MD will be recruited by six participating sites in the Netherlands and will be approached by their own ENT specialist and informed about this trial. After a one week reflection period, informed consent forms can be signed. Baseline and outcome data will be extracted from participants' electronic medical records and collected in the cloud-based clinical data management platform Castor EDC (version v2023.1.0.1, LUMC).

In- and exclusion criteria

In order to be eligible for the study a study subject needs to have unilateral, definite MD according to the diagnostic criteria derived from the American Academy Otolaryngology Head and Neck Surgery, Classification Committee of the Bárány Society, European Academy of Otology and Neurotology and International Classification of Vestibular Disorders published in 2015 [16]. The criteria for definite MD are:

Two or more spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours,

AND

Audiometrically documented low- to medium-frequency sensorineural hearing loss in one ear, defining the affected ear on at least one occasion before, during or after one of the episodes of vertigo,

AND

Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear (not better accounted for by another vestibular diagnosis).

Other inclusion criteria are:

- Age ≥ 18 years at the start of the trial.
- ≥ 4 vertigo attacks over the last 6 months.
- Willing to adhere to daily completion of study questionnaires using the DizzyQuest app and to the follow-up assessments.

Study subjects who meets any of the following criteria will be excluded:

- Bilateral MD.
- Severe disability (e.g. neurological, orthopedic, cardiovascular) or serious concurrent illness that might interfere with treatment or follow-up.
- Active additional neuro-otologic disorders that may mimic MD (e.g. vestibular migraine (VM) , recurrent vestibulopathy, phobic postural vertigo, vertebro-basilar TIAs, acoustic neuroma).
- Otitis media with effusion based on tympanogram results.
- History of intratympanic injections with corticosteroid less than 6 months ago.
- History of intratympanic injections with gentamicin or ear surgery for treating MD.
- Pregnant women or nursing women.

Sample size

A sample size calculation was performed based on recommendations as summarized in the Clinical Practice Guideline for Menière's disease [1]. An expected proportion of subjects achieving vertigo control of 87.5% was assumed for methylprednisolone treatment compared to an assumed 67.5% for placebo, i.e. a difference in treatment effect of 20%. With a statistical power (1-β) of 80% and a type 1 error (α) of 5%, 67 patients per group are required. With an estimated 10% loss-to-follow-up, 74 patients will be included in each arm, giving a total sample size of 148. In total, over the six

participating centres, 340 MD patients yearly visit the Otolaryngology department and will be screened for the trial. It is expected that 15% will meet the inclusion criteria and will be willing to participate. This will result in approximately 50 eligible patients for inclusion per year.

Randomization and blinding

Subjects will be randomly assigned to either methylprednisolone or placebo with a 1:1 allocation as per computer-generated random sequence, stratified by site generated by Castor EDC. Blinding will be maintained until all subjects have finished their treatment phases. All study participants, participating medical professionals, and outcome assessors will be blinded. The independent epidemiologist and pharmacy personnel will both be unblinded during randomization and therapy allocation.

Study procedure

After a one week reflection period and agreement with trial participation by means of signing the informed consent, a patient will be seen at the study site. Standard inquiries about the patient's demographics, family history, and medical history—particularly regarding any history of auto-immune disease and migraine—are made at the informed consent visit. Thereafter patients will receive an intratympanic injection with either methylprednisolone or placebo at day 1 and day 15 with a window of three days. The patient is lying down in supine position with their head rotated to the side and prior to the intratympanic injection the eardrum will be anesthetized. Thereafter, a myringotomy is being performed and a small spinal puncture needle is passed through the tympanic membrane to inject fluid into the middle ear cavity at the level of the round window. The patient is then required to remain on their side without swallowing for thirty minutes.

At baseline, results of Magnetic Resonance Imaging (MRI) must be available to make sure other causes of disease are ruled out [17]. To assess the vestibular function of the horizontal semicircular

canals, the caloric test and video Head Impulse test (vHIT) will be performed. To evaluate the anterior and posterior semi-circular canals, the vHIT will be conducted at baseline in order to assess the presence of vestibular hypofunction or areflexia.

During a follow-up period of one year, overall wellbeing and vertigo attacks are being assessed daily with the aid of the DizzyQuest app. Two telephone contacts will take place at 3 and 6 months to assess possible (serious) adverse events, DizzyQuest app compliance and the use of escape medication or co-interventions. A physical follow-up visit in the outpatient clinic will be scheduled at 6 and 12 months. During these outpatient clinic visits additional audiometry and multiple questionnaires concerning tinnitus, dizziness and quality of life will be filled-in. An overview of follow-up moments of the corresponding outcomes and a flowchart of the study procedure are presented in table 1 and figure 1, respectively.

Outcome measures

Vertigo: The primary outcome measure will be defined by the class of vertigo as defined by the AAO HNS 1995 guideline. The class of vertigo is defined by the average number of attacks per month during 6 and 12 months after treatment divided by the number of attacks 6 months before treatment times 100. As a result the following class of vertigo is defined:

- A: Complete control of vertigo = 0
- B: Substantial control of vertigo = 1-40
- C: Limited control of vertigo = 41- 80
- D: Insignificant control of vertigo = 81 – 120'
- E: Worse control of vertigo > 120

Moreover, the daily attack vertigo frequency will be monitored with the aid of the DizzyQuest app (Psymate 2)[18, 19]. The DizzyQuest app will be used to track the primary outcome measure, the frequency of dizziness attacks. Patients will answer daily questionnaires about their health and wellbeing and patients can report vertigo attacks at any time using the Dizzy quest app. Additionally,

the Dizziness Handicap Inventory (DHI) questionnaire will be administered at baseline, after six months, and after a year to assess how dizziness affects daily life [20]. The effect of the injections in the DHI will be reported as raw data, as well as change in handicap category (mild handicap, moderate handicap or severe handicap) related to improvement, unchanged or worsened.

The following secondary outcomes will be measured

Hearing: Pure tone audiometry will be performed at baseline, after six months, and after a year. In line with the guideline of AAO HNS 1995 guideline[17], we will use the average scores of four-tone audiometry at 0.5, 1, 2 and 3 kHz and we will assess the word recognition scores as the percent correct score at the presentation level in decibel. A decrease of ≥ 10 dB or a change in word recognition score of ≥ 15% points is considered clinically significant.

Tinnitus: The Tinnitus Functional Index (TFI) measures the impact of tinnitus on daily life [21]. This survey will be administered at baseline, after six months, and after a year. One point decrease of increase will be defined as improved or worsened tinnitus respectively [22].

Quality of life: Apart from the DHI and TFI, the EuroQol 5 dimension (EQ-5D) and EuroQol – Visual Analog Scale (EQ-VAS) questionnaires will be used to measure quality of life at baseline, after six and twelve months [23, 24]. These questionnaire are standardized tests of health status that are used in economic and clinical evaluations

Use of escape medication and co-interventions: In case participants remain suffering from intolerable vertigo attacks, regardless of which group they are allocated to, the use of metoclopramide and co-interventions such as intratympanic injections of gentamicin or methylprednisolone will be allowed and documented during the follow up period. This will be based on experience of participants vertigo

frequency and shared decision making. If patients receive additional treatment, they will not be unblinded.

Adverse events

Patients will be informed that Adverse Events, Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions must be reported as soon as possible to their ENT-surgeon or research nurse. Additional queries are made at 3, 6, 9, and 12 months to ensure that they did not fail to report occurrences. These events will be registered throughout the trial in Castor EDC. Each serious adverse event must be reported to the sponsor within 24 hours after the physicians' knowledge. In the event that patient safety is compromised, patients can be unblinded.

Cost-effectiveness

Cost-effectiveness will be assessed from both a healthcare and societal cost-utility perspective, where cost per avoided vertigo attack and cost per Quality Adjusted Life Year (QALY), respectively, will be used as the metrics. MD -related medical expenses, other healthcare expenses, and the cost of lost productivity will all be included in the estimated societal cost, which will be calculated using the iMTA Medical Consumption Questionnaire (iMCQ) and IMTA Productivity Cost Questionnaire (IPCQ).

Statistical analysis

Ordinal regression using mixed model analysis will be used to analyse the primary outcome (i.e., class of vertigo). In addition, generalized estimating equation (GEE) analysis of the actual vertigo attacks recorded using the DizzyQuest app will be used to estimate the incidence rate ratio (IRR) for comparison between the methylprednisolone and placebo groups. A decrease of 100% is considered total control of vertigo episodes, while a reduction of >40% is considered a substantial and thus clinically relevant reduction [17].

Mixed model analysis will be used to analyse differences in the questionnaire scores (DHI, TFI, FLS, eQ-5D/VAS, iMCQ, iPCQ) between the two groups. Logistic regression analysis will be used to analyse the remaining secondary outcomes (incidence of escape interventions, hearing loss, and adverse events). A reduction in hearing of 10 decibels or a 15% change in word recognition will be regarded as a clinically significant difference [17].

Subgroup analyses will be performed with regard to sex, duration of the disease and the type of MD (delayed MD, familial MD, and autoimmune MD). These subgroups will be defined as described in Frejo et al [25]. Two sensitivity analyses will be carried out in addition to the intention to treat analysis: a per protocol analysis in which patients who received additional co-interventions to achieve vertigo control are excluded; and an as-treated analysis in which participants who received additional co-interventions are analysed.

In order to evaluate the average costs and outcomes between the methylprednisolone and placebo groups for the cost-effectiveness analysis, intention-to-treat and net-benefit analysis will be used. For all statistical analysis, multiple imputation to adjust for missing data will all be used[26]. QALYs will be calculated using the Dutch tariff for the EuroQoL EQ-5D-5L [23] and as sensitivity analysis the visual analogue scale valuing health, with power-transformation [27]. All outcomes with corresponding statistical analysis methods are summarized in Table 2. A p-value < 0.05 will be considered as statistically significant for all analyses and will be performed using SPSS version 25 or higher (SPSS Chicago Illinois, USA).

Patient and public involvement

The PREDMEN trial is supported by the Dutch Association for the hard of hearing, and more specifically its Committee Dizziness and Balance (Commissie Duizeligheid en Evenwicht van Hoormij-NVVS) and the Dutch association for psychological health care and social services for patients with SNHL and tinnitus (GGMD). Both organizations are involved in the realization of the trial, the writing process and implementation of trial results. Moreover, they will serve as a sounding board for MD

patients participating in this trial and one patient representative will be a member of the steering committee. In line with their suggestions, patients will be involved in every stage of the research.

Ethics and Dissemination

Ethics

The PREDMEN trial was submitted via the Clinical Trial Information System (CTIS), with CTIS number: *2023-503340-13-00*, reviewed by the Medical Review Research Ethics Committee Leiden The Hague Delft (MREC LDD), and authorized for execution in the Netherlands under the European Clinical Trial Regulation (ECTR), with ClinicalTrials.gov ID: *NCT05851508.* Additionally, the institutional research board of each participating centre individually reviewed and approved the study. The study is conducted in accordance with the principles outlined in the Declaration of Helsinki (October 2013), the Medical Research Involving Human Subjects Act (WMO, 26 February 1998), the International Conference on Harmonization Good Clinical Practice (ICH GCP, November 2016) guidelines, and any other applicable guidelines, regulations, and Acts.

Patient safety

Minor complications such as persistent membrane perforation (5.9%) and otitis media (7%) can occur [7, 28, 29] Safety risk will be comparable to normal clinical practice and it is not expected that significant adverse events will be seen in the intervention arm. ENT specialists are experienced with intratympanic injections due to its application in patients with sudden deafness. Since the intervention is characterized as a low risk profile study, no Data Safety Monitoring Board (DSMB) is required [30]. The sponsor will submit a report on the safety of each investigational medicinal product used in the clinical trial through CTIS. Interim analysis will be performed on the primary endpoint when 50% of the patients have been randomized and completed a follow-up of 6 months, where comparability of baseline characteristics will be assessed. In this analyses, differences in vertigo control between the two study arms should not be greater than 45%. In addition, if the difference in vertigo control reveals to be clinically significant (i.e. >20%), but ≤ 20% of the participants in methylprednisolone

reach vertigo control, the study will be terminated because of convincing effect of the treatment in the intervention arm.

Data safety

The handling of personal data complies with the Dutch Personal Data Protection Act (AVG). All data collected for the trial, including but not limited to demographic data, audiological questionnaires, and data from the DizzyQuest app will be entered in a ISO 9001 and ISO 27001:2005 certified Castor® EDC database (electronic CRF). Data will be protected with a unique subject identification code which is linked to a pass-word protected subject identification list. Only members of the study team, who will be documented on the site signature and delegation log per site, will have access to the study data. The sponsor and investigator will keep a clinical trial master file which will contain the essential documents relating to the clinical trial.

Dissemination

A summary of the results of this study will be submitted to CTIS within one year after termination of the trial. Results will also be published in scientific journals and presented on (inter)national conferences. All information that will be presented will be done so in a way that integrity and anonymity of patients is ensured. All data will be stored for 25 years after the last subject has had the last study visit.

Contributors

all authors contributed to the conception of the trial, writing of the protocol, and performed an intellectual content revision. The final draft was read and approved by all authors.

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Competing interests

No competing interest was declared.

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Tables

Table 1. Overview of follow-up moments of the corresponding outcomes

Moment in trial	*Type of follow up*	*Outcomes*
From moment of inclusion unit 1 year follow up		Daily questionnaire in Dizzy quest app
Baseline	First intratympanic injection	Baseline parameters MRI Otoscopy Audiometry: PTA and SDS Vestibular testing: vHIT, caloric testing Questionnaires: DHI, TFI, FLS, EQ-5D/VAS, iMCQ, iPCQ
2 weeks	Second intratympanic injection	Otoscopy Complications Use of co-interventions Use of escape medication (S)AE
3 months, 9 months	Telephone consult	Complications Use of co-interventions Use of escape medication (S)AE
6 months, 12 months	Consult in outpatient clinic	Otoscopy Complications Audiometry: PTA and SDS Questionnaires: DHI, TFI, FLS, EQ-5D/VAS, iMCQ, iPCQ Use of co-interventions Use of escape medication (S)AE

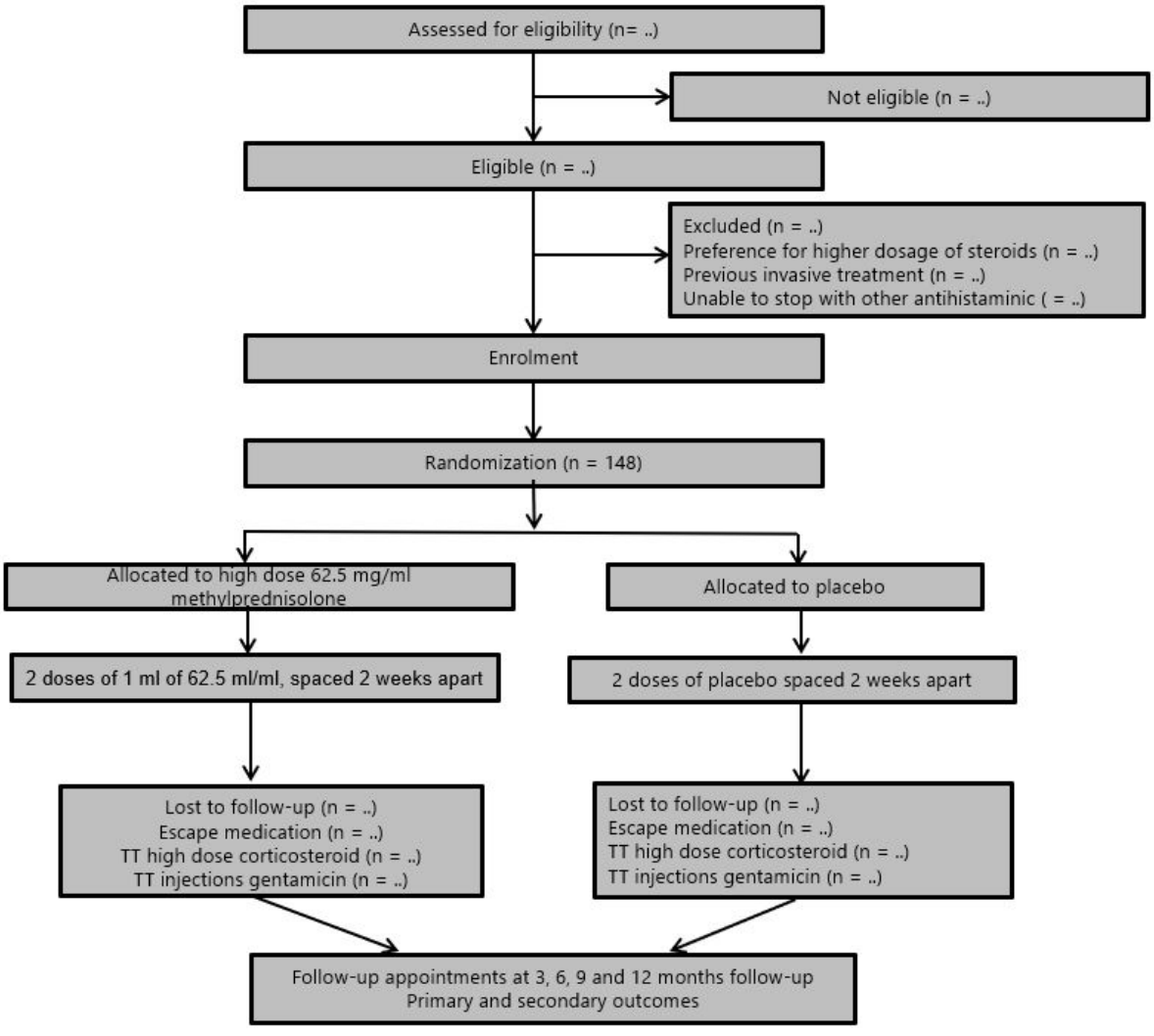
Abbreviations: DHI, Dizziness Handicap Index; EQ 5D, EuroQol 5D; FLS, Functional Level Scale; HIT, Head Impulse Test; iMCQ, iMTA Medical Consumption Questionnaire; iPCQ, iMTA Productivity Cost; Questionnaire; MRI, Magnetic Resonance Imaging; PTA, Pure Tone Average; SDS, speech discrimination score; (S)AE, (Serious) Adverse Event, TFI, Tinnitus Functional Index

Table 2 Outcomes with corresponding statistical analysis method

	Outcome	*Type of data*	*Analysis*
Primary outcome	Number of spontaneous vertigo attacks, lasting more than 20 minutes	Count	Generalized estimating equation
	AAO HNS (1995) class of vertigo		Mixed model analysis
Secondary outcomes	Hearing (PTA; 0.5, 1, 2, 3 kHz and SDS)	Continuous	Logistic regression analysis
	Tinnitus (TFI)	Categorical	Mixed model analysis
	Quality of life (DHI, TFI, FLS, eQ-5D/VAS)	Categorical	Mixed model analysis
	Use of escape medication and co-interventions	Count	Logistic regression analysis
	(S)AE	Binary	Logistic regression analysis
	Cost effectiveness (iMCQ, iPCQ)	Categorical	Mixed model analysis

Abbreviations: DHI, Dizziness Handicap Index; EQ 5D, EuroQol 5D; FLS, Functional Level Scale; iMCQ, iMTA Medical Consumption Questionnaire; iPCQ, iMTA Productivity Cost; Questionnaire; PTA, Pure Tone Average; SDS, speech discrimination score; (S)AE, (Serious) Adverse Event, TFI, Tinnitus Functional Index

Figure 1. flowchart of the study procedure.



Subject information for participation in medical scientific research

PREDMEN trial: treatment of Menière's disease with injection of anti-inflammatory drugs (methylprednisolone) into the middle ear.

A multicenter, double-blind, randomized, placebo-controlled trial to compare the efficacy of intratympanic injections of methylPREDnisolone with placebo in the treatment of vertigo attacks in MENière's disease (PREDMEN trial).

Introduction

Dear Sir/Madam,

With this information letter, we would like to ask you if you would like to participate in medical scientific research. Participation is voluntary. You are receiving this letter because you have Menière's disease. This information letter informs you of what this research is about, what it means for you, and what the advantages and disadvantages are. It is a lot of information. Please read the information and decide if you want to participate. If you want to participate, please fill out the form found in Appendix D.

Ask your questions

You can make your decision with the information you find in this information letter. In addition, we encourage you to:

- Ask questions to the researcher giving you this information.
- Talk to your partner, family, or friends about this study.
- For contact information, see Appendix A.
- Read the information at www.rijksoverheid.nl/mensenonderzoek.

1. General information

Leiden University Medical Center (LUMC) has set up this study in collaboration with the Apeldoorn Dizziness Center. Researchers, who may also be doctors or nurses, are conducting the research in different hospitals.

Participants in a medical-scientific study are often called subjects. Both patients and people who are healthy can be subjects.

The number of participants needed in this study is 148. The medical ethics review committee Leiden Hague Delft (METC-LDD) has approved this study.

Subject Information

2. What is the purpose of the study?

With this study, we want to determine whether anti-inflammatory drugs work well against vertigo attacks in Menière's disease. To do so, we will compare the effect of injections of methylprednisolone (an anti-inflammatory drug) through the eardrum in the ear (intratympanic injections) and compare this with the effect of iinjections with a placebo. A placebo is a drug with no active ingredient, a "fake" drug.

3. What is the background of the study?

In patients who suffer from Menière's disease to a severe degree, if a wait-and-see policy is not sufficient, treatment with intratympanic therapy is sometimes chosen. This treatment can involve an anti-inflammatory or an antibiotic (gentamicin) injection. There is evidence that intratympanic injections with gentamicin can reduce dizziness symptoms, the disadvantage of this treatment is that there is a risk of hearing loss. Intratympanic injections with an anti-inflammatory are also given and are safe because no hearing loss occurs. However, there is no hard evidence for the effectiveness of these anti-inflammatory injections. Therefore, with this study, we want to investigate the effectiveness of intratympanic injections with methylprednisolone (an anti-inflammatory drug).

Alternative therapies such as diuretic medications or surgical treatments are not proven effective and are therefore not offered in this study.

4. How does the examination proceed?

How long will the study last?

Are you participating in the study? Then it will take about 1 year in total.

Step 1: Are you suitable to participate?

First, we want to know if you are suitable to participate. To determine this, the researcher or doctor will review your medical file and may ask you some questions about your medical history.

Step 2: the treatment

We will treat you twice with an intratympanic injection (either placebo or methylprednisolone).

For this study, we will make 2 groups:

- Group 1. People in this group will receive intratympanic injections with placebo.
- Group 2. The people in this group will receive intratympanic injections with methylprednisolone.

Lottery will determine which treatment you receive. Neither you nor the researcher will know which group you are in. However, if it is important to your health, this can be looked up.

Step 3: examinations and measurements

Subject Information

The study requires you to visit the hospital a total of 5 times in 1 year. A visit takes about 45 minutes to a maximum of 2 hours. You will then be called twice more to see how you are doing.

You will be treated twice with an intratympanic injection, with two weeks between treatments. The treatment procedure is as follows:
You will be asked to lie on your side on the treatment table. Then a local anesthetic will be applied topically (on the eardrum). Then the ENT surgeon makes a small hole in the eardrum through which the placebo or methylprednisolone is injected. Then you must lie down for another 30 minutes, during these 30 minutes you will have to try not to swallow (During swallowing, some of the liquid may enter the throat). Thirty minutes of not swallowing may seem long, but it is doable. You can spit any excess saliva into a container.

We will be performing the following tests:

- Hearing tests, before the start of the study and 6 and 12 months after the intratympanic injections.
- Balance tests, once before the start of the study.
- During each visit, we will ask you if you have had any complaints about your health.
- You will fill out questionnaires. The questions are about dizziness, tinnitus (ringing in the ears), and quality of life. You will do this three times, before the study starts and 6 and 12 months after the intratympanic injections.
- You will complete an app daily in which you keep track of your dizziness symptoms.

Appendix C shows what actions we do at each visit, this also indicates which actions are done before the examination and which actions are part of standard care.

Step 4: follow-up check

What is different from standard care?
There is not much different in this study, compared to standard care. The physical examination, the making of an MRI, balance and hearing tests before and in the follow-up of the treatment are part of the standard care. In addition, you will return to the hospital twice for monitoring, which is also the case with regular treatment with intratympanic injections in Meniere's disease. The intratympanic injections are the same, except that, as a study participant, when you receive the injection, you do not know whether you are receiving the drug or the placebo. The duration of the consultation may be slightly longer because additional questionnaires will also be completed. In addition, as part of the study, you will report daily if you have a dizziness attack via the app.

Additional treatments during the trial
In principle, you should not take any other medication for Menière's disease during the trial. If your dizziness attacks persist frequently during the study, regardless of which group you are assigned to,

you can still be treated with an intratympanic injection of methylprednisolone, dexamethasone, triamcinolone or gentamicin in consultation with your ENT surgeon.

A middle ear injection with gentamicin is often effective in patients. Sometimes several injections are needed to achieve the desired effect. Treatment with gentamicin disables the balance organ which is irreversible. This can cause balance symptoms in the beginning. In time, this is often compensated by the balance organ on the other side.

Treatment with gentamicin can cause the same adverse effects and side effects as intratympanic corticosteroids. However, with gentamicin treatment, there is a chance that your hearing function may be reduced (20-30%) or you may lose your hearing (5-10%) in the treated ear. It is important to be aware of these serious side effects.

5. What arrangements will we make?

We will make the following agreements:

- You will not participate in any other medical scientific research during this study.
- You will come to every appointment.
- You will contact the researcher in these situations:
    - You want to start taking other medications. Even if these are homeopathic remedies, natural remedies, vitamins or drugstore remedies.
    - You are hospitalized or treated in a hospital.
    - You suddenly experience problems with your health.
    - You no longer wish to participate in the study.
    - Your phone number, address or e-mail address changes.

Can you or your partner become pregnant during the study?
Women who are pregnant or breastfeeding cannot participate in this study. Women should also not become pregnant during the study.
This is because the trial medication has the potential to affect an unborn child.

Still pregnant?
Do you become pregnant during the study? Please let the investigator know immediately. You must then stop the study as soon as possible in consultation with the researcher.

Subject Information

6. What are the possible side effects, adverse effects, or discomforts?

The therapy under investigation may result in side effects and adverse effects.

Side effects:
Since the study medication (methylprednisolone) is applied locally (in the ear) and only twice, the chance of side effects is very small. There is a small chance that a tiny hole remains in the eardrum, this hole gives a small chance of infection (less than 1%).

Adverse effects:

- The anesthesia given for the intratympanic infection may be painful.
- You may experience a brief episode of dizziness after the injection.

What are the possible discomforts of measurements during the study?
The measurements taken for the study are the same as those commonly used in standard treatment, namely hearing tests and balance tests.

7. What are the advantages and disadvantages of participating in the study?

Participating in the study can have advantages and disadvantages. Below we list them. Think about this carefully, and talk about it with others.

If you are enrolled in group 2 and receive intratympanic injections of methylprednisolone, this may reduce your Ménière symptoms, but this is not certain.

With your participation, you will help researchers gain a better understanding of the treatment of Menière's disease and, in particular, the effect of intratympanic injections with methylprednisolone.

Participating in the study may have these disadvantages or consequences:

- You may experience side effects or adverse effects of the treatment.
- Participating in the study will cost you extra time.
- You must keep the agreements associated with the study.
- After the intratympanic injection, you must remain lying down for 30 minutes and not swallow.

Don't want to participate?
You decide whether to participate in the study. Don't want to participate? Then you will receive the usual treatment for Menière's disease. Your doctor can tell you more about the treatment options available and about the advantages and disadvantages.

8. When will the study end?

When new information about the study that is relevant to you is discovered, the researcher will notify you. The researcher will then ask you if you will continue to participate.

In these situations, the study stops:

- All scheduled appointments have concluded.
- You have become pregnant.
- You want to stop the study yourself. You may do so at any time. Please notify the investigator immediately. You do not have to tell us why you want to stop. You will return to your usual treatment for Meniere's disease. The investigator may schedule one or more check-ups for your safety.
- The investigator believes it is better for you to stop. However, the investigator will still invite you for follow-up checks.
- One of the following authorities decides that the study should stop:
    - The LUMC
    - The government, or
    - The medical ethics committee reviewing the research.

What happens if you stop the study?
The researchers use the data collected up to the time of stopping.

The entire study ends when all participants are finished.

9. What happens after the research?

If, after the study is finished, you still have symptoms associated with Menière's disease, you can decide, in consultation with your attending physician, to start additional therapy, whether through injections behind the eardrum or otherwise. Which form of therapy will be started is discussed with your treating physician.

Will you receive the results of the study?
Approximately 1 year after the study is completed, the investigator will let you know the most important results of the study. The researcher may also tell you what treatment you received. Do you not want to know this? Then tell the researcher. He/she will then not tell you.

Subject Information

10. What will we do with your data?

Are you participating in the study? Then you also give us permission to collect, use and store your data.

What data do we save?

We save these data:

- your name
- your gender
- your address
- your date of birth
- data about your health
- (medical) data we collect during the study

Why do we collect, use and store your data?

We collect, use and store your data to answer the questions of this study. And to publish the results.

How do we protect your privacy?

To protect your privacy, we code your data. On all your data, we put only this code. We keep the key to the code in a secure place in the hospital. When we process your data, we always use only this code. Even in reports and publications about the study, no one can recall that it was about you.

Who can see your data?

Some individuals will be able to see your name and other personal data without a code. This may be data collected specifically for this study, as well as data from your medical record.

These are people who verify that the researchers are conducting the study properly and reliably.

These people can access your data:

- A controller working for LUMC.
- National and international supervisory authorities.

These individuals keep your data confidential. For access by these persons, we ask your permission.

The Health Care and Youth Inspectorate may access your data without your permission.

How long do we keep your data?

We keep your data in the hospital for 25 years.

May we use your data for other research?

Your data collected may also be important for other scientific research in the field of Menière's disease and its treatment. For this purpose, your data will be kept in the hospital for 25 years. In the consent form, indicate whether you agree to this. Do you not give your consent? Then you can still participate in this study. You will receive the same care.

Can you withdraw your consent to the use of your data?

You can withdraw your consent to the use of your data at any time. Please let the researcher know. This applies to the use of your data in this study and in other studies. But please note that when withdraw your consent while researchers have already collected data for a study, then they may still use these data.

Want to know more about your privacy?

- Would you like to know more about your rights in the processing of personal data? Then visit www.autoriteitpersoonsgegevens.nl.
- Do you have questions about your rights? Or do you have a complaint about the processing of your personal data? If so, please contact the person responsible for processing your personal data. For your research this is:
    - LUMC Complaints Team. See Appendix A for contact information.
- If you have complaints about the processing of your personal data, we recommend that you first discuss them with the research team. You can also go to LUMC's Data Protection Officer (see Appendix A for contact details. Or you can file a complaint with the Personal Data Authority.

Where can you find more information about the study?

The following website(s) will provide more information about the study. www.ClinicalTrials.gov and/or https://euclinicaltrials.eu. When the study finishes, the website may show a summary of the results of this study. You can find the study by searching the latter website for number 2023-503340-13-00.

11. Will you be compensated if you participate in the study?

Treatment for the study does not cost you anything and is part of standard care. If you participate in this study, you will receive a gift certificate of 25 euros at the end of the study.

12. Are you insured during the study?

Insurance has been arranged for everyone participating in this study. The insurance pays for damages caused by the study. But not for all damages. In Appendix B you will find more information about the insurance and the exceptions. It also tells you who you can report damage to.

13. We inform your family doctor

The researcher will send your GP and/or treating specialist a letter/email to let them know that you are participating in the study. This is for your own safety. If any information required for the study is

missing from your medical records, for example in the context of your medical history or about the medications you are taking, we may contact your (family) physician to request this information.

14. Do you have any questions?

Questions about the research you can directly ask at the research team .
Do you have a complaint? Please discuss it with the investigator or the doctor treating you. Would you rather not? Then go to the LUMC Complaints Team or the complaints officer of the participating center. Appendix A tells you where to find them.

15. How do you consent to the study?

You can think about this study first, but it would be nice if you could respond within a week You will then tell the researcher if you understand the information and whether or not you want to participate. Do you want to participate? Then fill out the consent form found with this information letter. You and the researcher will both get a signed version of this consent form.

Thank you for your time.

16. Attachments to this information

A. Contact details LUMC (Leiden).
B. Insurance information
C. Schedule of examination acts
D. Consent form

Subject Information

Appendix A: LUMC contact information.

Researcher:
Maud Boreel
Physician researcher, department of ENT, LUMC, Leiden
Telephone: 071-526 24 31 (available on working days from 09:00-17:00)
E-mail: predmen@lumc.nl

Complaints:
In case of complaints about the study, please contact Team Complaints of the LUMC via email: patiëntenservicebureau@lumc.nl. You can also contact Patient Service Office by phone (071-5262989; during office hours). They will handle the complaint according to the applicable agreements.

Facility Data Protection Officer:
If you have any questions about the protection of your privacy, please contact one of LUMC's Data Protection Officers (FG) at privacy@lumc.nl.

For more information about your rights:
LUMC contact details.
Albinusdreef 2
2333 ZA Leiden
Central telephone number: (071) 526 91 11
For more information about your rights see the LUMC website
https://www.lumc.nl/12367/Deelnemers-wetenschappelijk-onderzoek/

Subject Information

Appendix B: insurance information

LUMC has taken out insurance for everyone participating in the study. The insurance pays for any damage you have as a result of participating in the study. It covers damage you suffer during the study, or within 4 years of the end of your participation in the study. You must report damage to the insurer within 4 years.

Have you suffered any damage due to the study? Please report this to this insurer:

The insurer of the study is:	
Name:	Centramed
Adress:	Maria Montessorilaan 9, 2719 DB Zoetermeer
Telephonenumber:	070-3017070
Email:	info@centramed.nl
Polisnumber:	624.530.305

The insurance pays a maximum of €650,000 per person and €5,000,000 for the entire investigation (and €7,500,000 per year for all investigations by the same client).

Please note that the insurance does not cover the following damages:

- Damage due to a risk about which we have given you information in this letter. But this does not apply if the risk turned out to be greater than we thought in advance. Or if the risk was very unlikely.
- Damage to your health that would have occurred even if you had not participated in the study.
- Damage that occurs because you did not follow directions or instructions or did not follow them properly.
- Damage to the health of your children or grandchildren.
- Damage caused by a treatment method that already exists. Or by research into a treatment method that already exists.

These provisions are in the "Decree on compulsory insurance in medical scientific research with humans 2015". This decree can be found in the Government Law Database (https://wetten.overheid.nl).

Subject Information

Appendix C: Schedule of examination acts

The diagram below shows which examinations will be performed, where they will take place (hospital or telephone) and at what time point. The crosses indicate whether the examination act will take place at that time point.

Timepoint / Test / Where?	Before start study Hospital	At start study Hospital	2 weeks after start study Hospital	3 months after start study Telephonic	6 monts after start study Hospital	9 monts after start study Telephonic	12 months after start study Hospital
Explanation of research	X						
Sign consent form	X						
Requesting information about your medical history	X*						
Requesting information regarding possible side effects and the use of other medication	X*	X*	X*	X	X*	X	X*
Intratympanal injection of methylprednisolone or placebo		X	X				
Hearing tests	X*				X*		X*
Balance Tests	X*						
Completing questionnaires about quality of life, dizziness, and ringing in the ears	X				X		X
MRI scan	X*						
Fill in the Dizzy Quest app	Daily						

* These procedures are part of your standard treatment for Meniere's disease, so these procedures are not done specifically for the study, but the results of these procedures are used for the study.

Subject Information

Appendix D: Subject Consent Form

Associated with: Treatment of Meniere's disease with intratympanic methylprednisolone (PREDMEN trial)

- I have read the information letter. I was also able to ask questions. My questions have been answered well enough. I had enough time to decide if I'm going to participate.
- I know that participation is voluntary. I also know that I can decide at any time not to participate in the study. Or to stop. I know that I don't have to tell the reason why I want stop with the research
- I give the investigator permission to let my GP/specialist know that I am participating in this study.
- I give the investigator permission to request information from my general practitioner/specialist(s) about my medical data and/or about the medication I am taking.
- I give the researchers permission to collect, use and keep my data for 25 years. The investigators are only doing this to answer the research question of this study.
- I know that for the purpose of monitoring the research, some people will be able to see all my data. Those people are listed in this information letter. I give these people permission to view my data for this check.
- I know that I am not allowed to get pregnant during the study.
- The researcher discussed with me how best to avoid getting pregnant during the study.

Would you like to tick yes or no in the table below?

I give permission to keep my data for 25 years in order to use it for other research, as stated in the information letter.	Ja ☐	Nee☐
I give permission to ask me if I want to participate in a follow-up studies after this study.	Ja ☐	Nee☐
I give the researchers permission to tell me which treatment group I was in after the study.	Ja ☐	Nee☐

1. I want to participate in this study.

My name is (subject): .....

Signature:..... Date : __ / __ / __

I declare that I have fully informed this subject about the above mentioned study.

Subject Information

Will any information become available during the study that could influence the subject's consent? Then I'll notify this test subject as soon as possible.

Name of the investigator (or his/her representative):.....

Signature:..... Date:__/__/__

Additional information has been provided by:

Name:.....

Function:.....

Signature:..... Date:__/__/__

The subject will be provided with a full information letter, along with a signed version of the consent form.

Reporting checklist for randomised trial.

Based on the CONSORT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the CONSORTreporting guidelines, and cite them as:

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

		Reporting Item	Page Number
Title and Abstract			
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	2
Introduction			
Background and objectives	#2a	Scientific background and explanation of rationale	4-5
Background and objectives	#2b	Specific objectives or hypothesis	5-6
Methods			
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	7

Trial design	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7
Participants	#4a	Eligibility criteria for participants	7-8
Participants	#4b	Settings and locations where the data were collected	7
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	10-11-12
Sample size	#7a	How sample size was determined.	8-9
Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	14-15
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	9
Randomization - Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size)	9
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	9-10
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	9

Blinding	#11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	12-13
Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12-13
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	10-11-12
Results			
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	21
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	21
Recruitment	#14a	Dates defining the periods of recruitment and follow-up	19
Recruitment	#14b	Why the trial ended or was stopped	N/A
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	21
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10-11-12
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	20
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	20
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	14
Discussion			

Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	3
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Registration	#23	Registration number and name of trial registry	14
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings	N/A
Other information			
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Registration	#23	Registration number and name of trial registry	14
Protocol	#24	Where the full trial protocol can be accessed, if available	N/A
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	16

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	**Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym** A phase-3 multicentre, double-blinded, randomised, placebo-controlled trial to compare the effectiveness of intratympanic injections with methylPREDnisolon versus placebo in the treatment of vertigo attacks in MENière's disease (PREDMEN trial).
Trial registration	2a	**Trial identifier and registry name. If not yet registered, name of intended registry** Clinical trial number: 2023-503340-13-00 Clinicaltrails.gov: ID: NCT05851508
	2b	**All items from the World Health Organization Trial Registration Data Set**

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT05851508
Date of registration in primary registry	3, oktober, 2023
Secondary identifying numbers	Identifiers: NCT05851508, Unique Protocol ID: PREDMEN, Secondary ID: 10140022110009
Source(s) of monetary or material support	Stichting ZonMW: *file number: 10140022110009*
Primary sponsor	Leiden University Medical Centre
Secondary sponsor(s)	Leiden University Medical Centre
Contact for public queries	M.M.E. Boreel, MD, Leiden University Medical Centre M.M.E.Boreel@lumc.nl
Contact for scientific queries	M.M.E. Boreel, MD, Leiden University Medical Centre M.M.E.Boreel@lumc.nl
Public title	The Effectiveness of Intratympanic Methylprednisolone Injections Compared to Placebo in the Treatment of Vertigo Attacks in Meniere's Disease (PREDME
Scientific title	A Multicenter, Double-blinded, Randomised, Placebo-controlled Trial to Compare the Effectiveness of Intratympanic Injections

	MethylPREDnisolone Versus Placebo in the Treatment of Vertigo Attacks in MENière's Disease (PREDMEN Trial).
Countries of recruitment	Netherlands
Health condition(s) or problem(s) studied	Meniere's Disease (MD)
Intervention(s)	Intratympanic injection with Methylprednisolone 62.5 mg/ ml
	Placebo comparator: Intratympanic injection with saline, (sodiumchloride 0.9%)
Key inclusion and exclusion criteria	Inclusion criteria: - Unilateral, definite MD according to the diagnostic criteria derived from the American Academy Otolaryngology Head and Neck Surgery, Classification- Page 4 of 6 Committee of the Bárány Society, European Academy of Otology and Neurotology and International Classification of Vestibular Disorders - adult patients (≥ 18 years), patient hospitalized - ≥ 4 vertigo attacks over the last 6 months. - Willing to adhere to daily Dizzy quest app questionnaires and the follow-up assessments
	Exclusion criteria: - Bilateral MD - Severe disability (e.g. neurological, orthopaedic, cardiovascular) or serious concurrent illness that might interfere with treatment or follow-up. - Active additional neuro-otologic disorders that may mimic MD (e.g. vestibular migraine, recurrent vestibulopathy, phobic postural vertigo, vertebro-basilar TIAs, acoustic neuroma). - Otitis media with effusion based on tympanogram results. - History of intratympanic injections with corticosteroid less than 6 months ago. - History of intratympanic injections with gentamicin or ear surgery for treating MD. - Pregnant women and nursing women.
Study type	Interventional
	Allocation: randomised intervention model. Masking: double blind (subject, caregiver, investigator, outcomes assessor)
	Primary purpose: treatment
	Phase III
Date of first enrolment	Oktober 2023
Target sample size	148
Recruitment status	Recruiting
Primary outcome(s)	Vertigo attacks
Key secondary outcomes	Hearing loss, tinnitus, health-related quality of life, use of escape medication, adverse events, cost-effectiveness, co-interventions, overall function, impact of dizziness.

Protocol version 3 **Date and version identifier**

- Issue date: 02-05-2023
- Version 4.0

Funding	4	**Sources and types of financial, material, and other support** This project will be funded by ZonMW *file number: 10140022110009*
Roles and responsibilities	5a	**Names, affiliations, and roles of protocol contributors** Coordinating investigators: • T.D. Bruintjes, MD, PhD, prof, ENT-surgeon, department of Otorhinolaryngology Head and Neck surgery. • M.M.E. Boreel, MD, physician-researcher, department of Otorhinolaryngology Head and Neck surgery. Head of research support Leiden University Medical Centre: • B.M. Mol, PhD, Head of research support Leiden University Medical Centre Principal investigators: • B.F. van Esch, MD, PhD, ENT surgeon, Department Otorhinolaryngology and Head and Neck Surgery, Leiden University Medical Centre, The Netherlands • S.M. Winters, MD, PhD , ENT-surgeon Apeldoorn Dizziness Centre, Gelre Ziekenhuizen • W.P.A. Kelders, MD, PhD , ENT-surgeon , Rotterdam Dizziness Centre, Franciscus Gasthuis & Vlietland • R. van den Berg, MD, PhD, ENT-surgeon Department of Otorhinolaryngology, Maastricht UMC+ • H.M. Blom, MD, PhD, Professor, ENT-surgeon Department of Otorhinolaryngology, Haga Hospital • D.A. van Zuylen, MD, ENT-surgeon, Department of Otorhinolaryngology, Medisch Spectrum Twente Epidemiologist: • T. Schermer, PhD, Apeldoorn Dizziness Centre, Gelre Hospital, Apeldoorn, The Netherlands
	5b	**Name and contact information for the trial sponsor** Legal Representative of Sponsor: mw. K.G. Freriks-Bauritius Title: Management director division 3. Leiden University Medical Centre, Albinusdreef 2, 2333 ZA Leiden secretariaatbbd3enzorg@lumc.nl.
	5c	**Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities** The funding source does not have any role in this study during its execution, analysis, interpretation of the data or decision to submit results.

5d **Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)**

Coordinating investigator:

- Study planning
- Randomisation
- Responsible for trial master file
- Planning of monitor visits
- Identification Study subjects, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol and investigators brochure
- Reporting of AE/SAE/SUSAR
- Processing and analysing raw data

Coordinating investigator/PI sponsor site/head of research support LUMC:

- Design and Conduct of the PREDMEN trial
- Preparation, writing and revisions of research protocol, agreement on final protocol
- Write and review all required documents (Patient information folder, Informed Consent, Standard operating procedures etc.)
- Organisation of approval medical ethical committee
- Preparation of Investigators brochure and CRF
- Publication study reports
- Reviewing progress of study and if necessary, making changes to the protocol or other necessary documents
- Management of the budget and problems with individual centrecontracts
- Provide annual risk report

Principal investigators/Research nurse Study sites:

- Identification Study subjects, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol and investigators brochure

Epidemiologist:

- Performing interim analysis
- Processing and analysing raw data

Introduction

Background and rationale

6a **Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention**

Menière's disease (MD) is a clinical condition characterized by tinnitus and aural fullness, low- to mid-frequency sensorineural hearing loss, and spontaneous episodes of vertigo that can last 20 minutes to 12 hours [1]. Although its aetiology is unknown, endolymphatic hydrops (EH) is thought to be associated with MD and treatment is often focussed on the regulation of EH.

Current treatment of MD consists of dietary and lifestyle modifications, oral diuretics, vestibular rehabilitation for chronic imbalance, intratympanic therapy, and/or ablative surgery [1]. With intratympanic gentamicin and intratympanic corticosteroid injections the drug is directly delivered into the middle ear, from where it will be absorbed in the inner ear. Although the mechanism of action

of steroids on the inner ear remains speculative it may improve cochlear blood flow and stabilize the vascular endothelium which enhances fluid homeostasis by upregulation of cochlear ion gene expression [2]. Unlike gentamicin, corticosteroid therapy does not carry a risk of causing hearing loss. Therefore, it is currently the first step of standard care in the treatment of MD [1].

Although in the last decade, there has been an increasing tendency and emerging evidence for the use of intratympanic steroids, no large RCT on the effectiveness of intratympanic methylprednisolone in MD has been conducted. A meta-analysis published in 2021 included eight studies comparing intratympanic gentamicin to intratympanic corticosteroids, in which gentamicin appeared to be superior in terms of control of vertigo attacks [3]. However, gentamicin is known to be ototoxic and can induce hearing loss. Patel et al. compared intratympanic gentamicin injections to methylprednisolone injections in a double-blind RCT with a 24-month post-treatment follow-up [4]. Vertigo attacks decreased in both groups, indicating a treatment effect. However, no placebo group was involved and the sample size was relatively small (n=60). Recently, a Cochrane review was published evaluating the use of intratympanic corticosteroids in MD. In this review, 10 randomised controlled trials (RCTs) and quasi-RCTs comparing intratympanic corticosteroids, all using dexamethasone, compared to either placebo or no treatment were included [5]. The authors found that the evidence for the use of dexamethasone is uncertain. Intratympanic dexamethasone injection may marginally reduce the frequency of vertigo attacks. Regarding hearing and tinnitus improvement was seen, but without statistical significance.

In conclusion, there is a need of solid evidence on the effectiveness of intratympanic steroids in MD. Until now the effectiveness of methylprednisolone has not been investigated by means of a placebo controlled RCT. Therefore a well-conducted RCT with a large study population and a long follow-up period is now required to evaluate the effectiveness of intratympanic methylprednisolone in MD.

	6b	**Explanation for choice of comparators**
		Pharmacokinetic studies show that dexamethasone phosphate has molecular and pharmacokinetic characteristics that complicate its use as a topical therapy for hearing disorders, which may explain its questionable effectiveness [6]. An animal study found that the concentrations of methylprednisolone are higher and have longer duration in perilymph and endolymph compared to dexamethasone and hydrocortisone, and therefore could be a more effective drug [7]. Typically soluble forms of methylprednisolone are administered and expected to be less permeable through the membranous boundaries compared to the less polar forms. However, there is no data whether these soluble forms are metabolized to the base form in the ear and if they are, at what rate. Despite the fact that little is known about the pharmacokinetics of methylprednisolone, there are clinical indications of its effectiveness [8, 9]. Cao et al. performed a literature review and demonstrated that methylprednisolone is more effective than dexamethasone in a clinical setting [8]. Therefore we choose to compare methylprednisolone to placebo.
Objectives	7	**Specific objectives or hypotheses**
		Primary objective: To determine whether methylprednisolone (62.5 mg/ml) is superior to placebo in controlling vertigo attacks in patients with MD.
		Secondary objective: To determine whether methylprednisolone (62.5 mg/ml) is superior to placebo in controlling tinnitus, hearing, quality of life, use of escape medication, adverse events and cost-effectiveness.
Trial design	8	**Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)**

The PREDMEN study is a phase-3 multicentre, double-blinded, randomized, parallel group trial with patients suffering from MD with a total follow-up period of 12 months.

Methods: Participants, interventions, and outcomes

Study setting	9	**Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained** Six medical centres from across the Netherlands are participating in the study in order to enrol a sufficient number of patients in three years. In these centres, an ENT-surgeon, specialized in dizziness, is involved and principal investigator for the trial. The following centres are participating in the PREDMEN study: - Leiden Universitair Medisch Centrum, Leiden (sponsor site) - Apeldoorns Duizeligheidscentrum, Gelre Ziekenhuizen, Apeldoorn - Maastrichts Universitair Medisch Centrum, Maastricht - Haga-ziekenhuis, Den Haag - Medisch Spectrum Twente, Enschede - Rotterdam Duizeligheids Centrum, Rotterdam
Eligibility criteria	10	**Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)** **Inclusion criteria:** - Unilateral, definite MD according to the diagnostic criteria derived from the American Academy Otolaryngology Head and Neck Surgery, Classification- Page 4 of 6 Committee of the Bárány Society, European Academy of Otology and Neurotology and International Classification of Vestibular Disorders - Adult patient (≥ 18 years), patient hospitalized - ≥ 4 vertigo attacks over the last 6 months. - Willing to adhere to daily Dizzy quest app questionnaires and the follow-up assessments.. **Exclusion criteria**: - Bilateral MD - Severe disability (e.g. neurological, orthopaedic, cardiovascular) or serious concurrent illness that might interfere with treatment or follow-up. - Active additional neuro-otologic disorders that may mimic MD (e.g. vestibular migraine, recurrent vestibulopathy, phobic postural vertigo, vertebro-basilar TIAs, acoustic neuroma). - Otitis media with effusion based on tympanogram results. - History of intratympanic injections with corticosteroid less than 6 months ago. - History of intratympanic injections with gentamicin or ear surgery for treating MD. - Pregnant women and nursing women
Interventions	11a	**Interventions for each group with sufficient detail to allow replication, including how and when they will be administered**

Eligible patients will be randomised in equal proportion between the Methylprednisolone (62.5 mg/ml) and the Placebo (sodium chloride 0.9%). group. Intratympanic injections will be administered two times at timepoint 0 and after two weeks.

Name and description of investigational product(s):

*M*ethylprednisolone sodium succinate 62.5 mg/ml (Solu-Medrol in Act-O-Vial).

Generic name methylprednisolone sodium succinate. *Manufacture a.o.:* Pfizer B.V.; Rivium Westlaan 142 2909 LD Capelle a/d Ijssel, The Netherlands

Name and description of Placebo:

Placebo: Saline, Sodiumchloride (NaCl) 0,9% saline for injection

11b **Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)**

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw subjects from the study for urgent medical reasons. We do not anticipate any major events arising from the study intervention because the trail medicine is already widely used and the study is classified as a low risk profile study.

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

Patients cannot fail to take the medication because the intervention is an injection administered by the physician at timepoint zero and after two weeks. However, patients are obliged to complete short questionnaires on the DizzyQuest app on a daily basis. We will obtain a weekly output of the patients compliance to the app, which will aid in patient monitoring. To avoid data loss, we will contact patients who fail to report through the application and ask them to complete the questionnaires. We expect no problems assessing the other outcomes because they will be monitored throughout clinical or telephonic appointments.

11d **Relevant concomitant care and interventions that are permitted or prohibited during the trial**

Prohibited medication:

- The administration of antihistaminic drugs including betahistine is prohibited due to the risk of drug competition. The true effect of methylprednisolone could therefore be over- or underestimated

Specific permitted medication:

- In case subjects continue to suffer from vertigo attacks in a high frequency, co-interventions can be offered, in either in the placebo,- or the intervention group. Co interventions include: intratympanic injections of gentamicin, dexamethasone, methylprednisolone or triamcinolone.

- Subjects are allowed to use metoclopramide in the acute phase of vertigo

Outcomes 12 **Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended**

Primary objective(s)	**Endpoint for the primary objective(s)**	**Analysis metric primary endpoint**	**Timepoints for primary objectives:**
To determine whether intratympanic injection with 62.5 mg/ml methylprednisolone is superior to placebo in reducing the frequency of vertigo attacks in patients diagnosed with unilateral MD during one year of follow-up.	Complete or substantial control of vertigo	Measured daily with the DizzyQuest app. Categorized in class of vertigo (A-D)	Daily
Secondary objective(s), if applicable	**Endpoint(s) for secondary objective(s), if**	**Analysis metric** **Secondary endpoint**	**Timepoints for secondary objectives:**
Use of co-interventions	Use of intratympanic injections with either gentamicin, methylprednisolone dexamethasone or triamcinolone	Frequency co-intervention used	Asked at 3, 6, 9 and 12 months
Use of Escape medication	Use of metoclopramide	Frequency escape medication used	Asked at 3, 6, 9 and 12 months
Hearing	Pure tone audiometry, word recognition score.	A decrease of ≥ 10 dB or a change in word recognition score of ≥ 15% points is considered clinically significant.	Measured at baseline, after 6 and 12 months
Change in quality of life on dizziness related quality of life	Questionnaires: Dizziness handicap inventory (DHI), Functional level scale (FLS)	DHI: handicap levels: Mild handicap = 16-34 Points; Moderate handicap = 36-52 Points and Severe handicap = 54+ Points. Improved, unchanged of worsened of level. FLS: Improvement (≥ 1 point decrease), unchanged or worsened (≤ 1 point increase)	Measured at baseline, after 6 and 12 months
Change in quality of life on tinnitus	Tinnitus handicap inventory (TFI)	Improvement (≥ 1 point decrease), unchanged or worsened (≤ 1 point increase)	Measured at baseline, after 6 and 12 months
Change in quality of life in general	EQ-5D and EQ-VAS scores	Mean value, standard deviation or, if the data is skewed, the median values and the 25th and 75th percentiles.	Measured at baseline, after 6 and 12 months
Adverse events	SAE, SUSARs	Frequency SAE/SUSAR	Reported when it occurs
Incremental cost differences	Cost-effectiveness and cost-utility analysis. Medical Consumption Questionnaire (iMCQ) and IMTA productivity Cost Questionnaire (iPCQ)	Cost-effectiveness analysis (costs per prevented vertigo attack), and a cost-utility analysis (costs per QALY, calculated from the EQ-5D and EQ-VAS	Measured at baseline, after 6 and 12 months

13 **Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure**

Participant timeline

Assessments	Screening Eligibility Clinic (-8 days till day -1)	Treatment visit 1 Clinic Baseline (± 5 days)	Treatment visit 1 Clinic 2 weeks (± 5 days)	Follow-up phase Telephone 3 months (± 2 weeks)	Follow-up phase Clinic 6 months (± 2 weeks)	Follow-up phase Telephone 9 months (± 2 weeks)	End of trial Clinic 12 months (± 2 weeks)
Explanation study participation to subject	X						
Screening procedure	X						
Sign Informed Consent	X						
Inclusion/exclusion criteria	X						
Medical History	X						
Baseline parameters (sex, age, onset age of MD etc.)	X						
Concomitant medication	X			X	X	X	X
Pure Tone (PTA) and Speech Discrimination Score (SDS)	X[1,3]				X		X
Vestibular tests (caloric testing and vHIT)	X[3]						
MRI – petrous bone	X[3]						
Functional Level Scale (FLS)	X				X[2]		X
Dizziness Handicap Inventory (DHI)	X				X[2]		X
Tinnitus Functional Index (TFI)	X				X[2]		X
Generic quality of life questionnaires (EQ-5D, EQ-VAS)	X				X[2]		X
IMTA Medical Consumption Questionnaire (iMCQ) and IMTA productivity Cost Questionnaire (iPCQ)	X				X[2]		X
Randomisation	X						
Methylprednisolone or placebo		x	x				X
(S)AEs		x	x	X	X	X	X
Co intervention: injection with either methylprednisolone, dexamethasone, triamcinolone or gentamicine				Daily			
Dizzy quest app	Daily						

	14	**Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size**
Sample size calculations		The sample size calculation is based on recommendations as summarized in the Clinical Practice Guideline by Bassura et al [1]. The absolute effect on vertigo control class is expected to be 87.5% in the methylprednisolone group versus 67.5% in the placebo group. In previous studies similar high percentages of control of vertigo were seen when placebo or sham surgery was compared to an intervention. Sample size calculation was executed with the software available from DSS Research Tools (https://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/statisticalpowercalculators.aspx analyses performed with the expected 20% difference in absolute effect on vertigo and two-tailed testing). With a statistical power of 80% and a Type 1 error of 5% 67 patients per group are required. With an estimated 10% loss-to-follow-up, we aim to include 74 patients in each group.
Recruitment	15	**Strategies for achieving adequate participant enrolment to reach target sample size.** To achieve an adequate sample size, six centres in the Netherlands, with a specific department specialized in vertigo, are participating. In these centres, there is one ENT-surgeon who is in charge of the trial and recruits patients from their outpatient clinic. Presentations to inform medical professionals and to promote the study are held in these centres. When a patient is eligible, the coordinating investigator or research nurse will arrange for all of the study's requirements in order to keep the burden for the ENT-surgeons on the trial sites as low as possible. The coordinating investigator will be full-time involved in the PREDMEN-trial. Additionally, the trial will be promoted in hospitals throughout the Netherlands, national congresses, informative websites on MD, and online patient communities.
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	**Method of generating the allocation sequence (eg, computer- generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign Interventions** Subjects will be randomly assigned to either methylprednisolone or placebo with a 1:1 allocation as per computer-generated random sequence of block sizes of 2 and 4 subjects, stratified by site generated by Castor EDC ® SLL certified
Allocation concealment mechanism	16b	**Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned** Participants will be randomised using Castor EDC ® SLL certified, which is an online data management program. This program will send the randomisation code for a specific trail

		participant to the pharmacy who is preparing the medication. In this way allocation concealment will be ensured to all concealed parties (physicians, research nurses, patients, data manager, statistician etc). Trial subjects, treating physicians and outcome assessors will be blinded throughout the entire study.
Implementation	16c	**Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions** All patients who give their consent and meet the inclusion criteria will be randomised. The ENT-surgeon or Research nurse in charge of recruitment will request randomization via mail, castorEDC, or phone to the coordinating investigator. Only the coordinating investigator can randomise patients. An automated email to the pharmacy with the randomization code will then be sent. On the day of allocation, the trial pharmacist will prepare the blinded trial medication (either methylprednisolone or placebo) and give it to the ENT surgeon for injection.
Blinding (masking)	17a	**Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how** Any individual involved in the trail, except for the pharmacy staff, will be blinded. This implies that all trial subjects, treatment physicians/nurses, outcome assessors and statisticians, will remain blinded until the trial's completion.
	17b	**If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial** Emergency unblinding may occur in the following situations: in case of a medical emergency where knowledge of the blinded treatment is necessary, for the treatment of (serious) adverse event, in the event of a SUSAR (Suspected Unexpected Serious Adverse Reaction) needing expedited reporting. The investigator must document the action taken and promptly notify the sponsor. Code breaks should only occur in exceptional circumstances as mentioned above and if it is absolutely essential for further management of the participant.
Methods: Data collection, management, and analysis		
Data collection methods	18a	**Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.** Primary/Secondary outcomes: After a written informed consent is retrieved, subjects will visit the study site for the treatment with methylprednisolone/placebo at day 1 and at day 15 (with a visit window of 5 days), during a follow-up visit at 6 months, and during the end of trial visit at 12 months after first study treatment. Telephone contacts will take place at 3 and 9 monthspost-study treatment to discuss DizzyQuest app compliance and the occurrence of adverse events and use of concomitant medication. Tables presented in *question 12* and *13* display the outcome measurements collected. Training + certification: Each individual involved in the trial must be in possession of a good

clinical practice (GCP) or BROK-certificate. In order to train all trail personnel, presentations at each trial site were held during the initiation visitation to discuss all study requirements and standard operating procedures.

18b **Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols.**

Patients will be closely monitored during the entire trial. Every Monday we will receive an output of patients' DizzyQuest usage, which will help us monitor compliance of patients. To avoid data loss, we will get in contact with patients who fail to report through the application and ask them to complete the questionnaires. Additionally, patients will have in-depth conversations and be questioned about their experiences during the trial at every follow-up visit, in which we can trace and solve potential obstacles.

Data management

19 **Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol**

The handling of personal data complies with the Dutch Personal Data Protection Act (in Dutch: De Wet Algemene Verodering Gegevensbescherming, AVG). All data collected for the trail, including but not limited to demographic data, audiological questionnaires, data from the DizzyQuest app will be entered in a ISO 9001 and ISO 27001:2005 certified Castor® EDC (electronic CRF). Personal and medical data that needs to be collected for the trail will be extracted from electronic medical records. We will use an unambiguous subject identification code that allows identification of all the data reported for each subject. The subject code will be documented on the subject identification list which will be filed in the ISF. There will be a subject identification list per participating site. The subject identification list, and any other data/documents containing personal identifiable information, of the participating site will remain at the site and will not be shared with the sponsor (LUMC) or any other participating site. Only members of the study team, who will be documented on the site signature and delegation log per site, will have access to the study data.

Analysed and processed data will be kept in a secured folder on the ENT department network drive of the LUMC, with restricted access to only the members of the study team. Every night backups are saved by the hospital IT automatically. The digital trial master file will be saved in PaNaMa RMS the research management system of the LUMC. Any hard copy documents will be stored in a locked cabinet at the ENT department of the LUMC. The (digital) investigator site files of the participating sites will be stored according to local procedures following the applicable regulations. The blinding is safeguarded by the pharmacies of all participating trial sites. If the study will not continue, all essential documents will be maintained for at least 2 years after formal discontinuation. All data will be stored for 25 years after the last subject has had the last study visit.

Statistical methods

20a **Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol**

Ordinal regression using mixed model analysis will be used to analyse the primary outcome

(i.e., class of vertigo). In addition, generalized estimating equation (GEE) analysis of the actual vertigo attacks recorded using the DizzyQuest app will be used to estimate the incidence rate ratio (IRR) for comparison between the methylprednisolone and placebo groups.

Mixed model analysis will be used to analyse differences in the questionnaire scores (DHI, TFI, FLS, eQ-5D/VAS, iMCQ, iPCQ) between the two groups. Logistic regression analysis will be used to analyse the remaining secondary outcomes (incidence of escape interventions, hearing loss, and adverse events).

In order to evaluate the average costs and outcomes between the methylprednisolone and placebo groups for the cost-effectiveness analysis, intention-to-treat and net-benefit analysis will be used. For all statistical analysis, multiple imputation to adjust for missing data will all be used. QALYs will be calculated using the Dutch tariff for the EuroQoL EQ-5D-5L and as sensitivity analysis the visual analogue scale valuing health, with power-transformation

20b **Methods for any additional analyses (eg, subgroup and adjusted analyses)**

Subgroup analyses will be performed with regard to sex, duration of the disease and the type of MD. Two sensitivity analyses will be carried out in addition to the intention to treat analysis: a per protocol analysis in which patients who received additional co-interventions to achieve vertigo control are excluded; and an as-treated analysis in which participants who received additional co-interventions are analysed.

20c **Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)**

Missing, unused and spurious data values will be coded as '888'; ambiguous values (e.g. if two or more boxes are ticked for a single dimension) will be treated as missing data. multiple imputations will be used to account for missing data.

Methods: Monitoring

Data monitoring

21a **Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol.**
Alternatively, an explanation of why a DMC is not needed

Since the intervention is categorized a low risk profile study no Data Safety Monitor Board (DSMB) or Data Monitoring Committee (DMC) is required and patient safety and treatment efficacy will we be performed by the independent expert.

21b **Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial.**

Interim analysis will be performed on the primary endpoint when 50% of the patients have been randomized and completed a follow-up of 6 months, where comparability of baseline characteristics will be assessed. In this analyses, differences in vertigo control between the two study arms should not be greater than 45%. In addition, if the difference

in vertigo control reveals to be clinically significant (i.e. >20%), but ≤ 20% of the participants in methylprednisolone reach vertigo control, the study will be terminated because of convincing effect of the treatment in the intervention arm.

Harms 22 **Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct**

Patients will be informed that Adverse Events (AE), Serious Adverse Events (SAE) and Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported as soon as possible to their ENT-surgeon or research nurse. Additional queries are made at 3, 6, 9, and 12 months to ensure that they did not fail to report occurrences. These events will be registered throughout the trial in Castor EDC.

Each SAE must be reported to the sponsor site within 24 hours after the physicians' knowledge. A SUSAR must be reported depending on the seriousness of the reaction and will be as follows:

- In the case of fatal or life-threatening SUSARs, not later than **7 days** after the sponsor became aware of the reaction
- In the case of non-fatal or non-life-threatening SUSARs, not later than **15 days** after the sponsor became aware of the reaction
- In the case of a SUSARs which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, not later than **7 days** after the sponsor became aware of the reaction being fatal or life-threatening

The sponsor site will report the SAEs or SUSAR through the web portal of CTIS that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse event.

Auditing 23 **Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor**

Monitoring in all sites in the Netherlands will be executed by one assigned monitor of the LUMC according to the monitor plan. The monitor will visit each centre yearly. The visitation frequency can be altered based on the amount of inclusions. During the visitation the monitor will verify:

- Source data verification
- In,- and exclusion criteria
- Informed consent
- Control of the Trial Master File
- SAE's/SUSARS
- Trial procedures
- Product accountability
- Visitation of the pharmacy

The principal investigator of a participating centre receives a summary of the findings after each monitoring visit. The monitor report includes: a summary of reviewed trial data; a general description of the quality; a summary of key findings / facts, deviations and deficiencies; an overview of measures and recommendations to ensure compliance with the protocol; an "overall" conclusion.

Ethics and dissemination

Research ethics approval	24	**Plans for seeking research ethics committee/institutional review board (REC/IRB) approval** The PREDMEN trial was submitted via the Clinical Trial Information System (CTIS), with CTIS number: *2023-503340-13-00*, reviewed by the Medical Review Research Ethics Committee Leiden The Hague Delft (MREC LDD), and authorized for execution in the Netherlands under the European Clinical Trial Regulation (ECTR), with ClinicalTrials.gov ID: *NCT05851508.* Additionally, the institutional research board of each participating centre individually reviewed and approved the study. The study is conducted in accordance with the principles outlined in the Declaration of Helsinki (October 2013), the Medical Research Involving Human Subjects Act (WMO, 26 February 1998), the International Conference on Harmonization Good Clinical Practice (ICH GCP, November 2016) guidelines, and any other applicable guidelines, regulations, and Acts.
Protocol amendments	25	**Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)** Any modifications to the protocol which may impact on the conduct of the study, affecting the patients, study procedures, or significant administrative aspects will require an official amendment to the protocol. This amendment must be approved in the clinical trials information system. Minor corrections to the protocol, which have no impact on the study, will be discussed with the sponsor's research team, and these minor corrections will be reported to the clinial trials information system if a major revision is submitted.
Consent or assent	26a	**Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)** Patients will be introduced to the trail and given a patient information letter by trained research nurses, ENT-surgeons, or the coordinating investigator. After a few days, research nurses or the coordinating investigator will have an informed consent conversation with patients and answer their questions. When the patient agrees to participate in the trial, the research nurse, involved ENT-surgeon or coordinating investigator will obtain a written informed consent.
	26b	**Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable** Not applicable
Confidentiality	27	**How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial.** Source documents for this study will include hospital records and procedure reports and

		data collection forms. These documents will be used to enter data on the (e)CRFs. Data reported on the (e)CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification code. Each study site has its own investigator site file, where study specific information is stored. This ISF will be secured with password-protected access systems, available to trial personnel only. All other participant information such as signed consent forms, will be stored in locked file cabinets in areas with limited access on the trial site. DizzyQuest app: All data handling will be documented in a processing agreement between the LUMC and the company that created the DizzyQuest App (Psymate). Until a reliable internet connection is established, the user's smartphone will store the DizzyQuest app's data. The smartphone stores data that is encrypted and inaccessible to outside parties. Data will be sent to the Smart eHealth servers in Belgium when the smartphone connects to the internet. All data will be automatically removed from the smartphone after the data transfer.
Declaration of interests	28	**Financial and other competing interests for principal investigators for the overall trial and each study site** None
Access to data	29	**Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators** Only the coordinating investigators and PI of the sponsor site will have access to the entire data set. Other principal investigators will have direct access to their own site's dataset and will have access to a cleaned data set of all sites on request. To ensure confidentiality, any identifying participant information will be removed from data distributed to project team members.
Ancillary and post-trial care	30	**Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation** The study has been classified as a low risk profile study. Therefore we do not anticipate any harm from trial participation. When the trial has completed after one year, the patient will be returned to the care of his personal ENT-surgeon. However, when any harm from trial participation occurs, the sponsor has an insurance that is in accordance with the legal requirements in the Netherlands (Article 7 WMO, under 1). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

Dissemination policy	31a	**Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions .**

After completion of the trial, all patients who wish to know to which study arm they were allocated, will be informed.

Within one year from the end of a clinical trial in all Member States concerned, the sponsor will submit to the EU database CTIS a summary of the results of the clinical trial. The content of the summary of the results is set out in CTR Annex IV. It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of the summary is set out in CTR Annex V.

Furthermore, abstracts, papers and oral presentations will be submitted to several symposia and scientific papers. There will be two classes of reports of the PREDMEN trial:

A. Reports of the major outcomes of the PREDMEN trial.
B. Reports addressing in detail on aspect of the PREDMEN trial

Each paper, abstract, or oral presentation will be reviewed and approved by the sponsor's research team.

31b **Authorship eligibility guidelines and any intended use of professional writers**

Researchers who have been involved from the beginning and are certain to receive authorship will be listed as below:

Abstracts/papers/oral presentation: M.M.E. Boreel MD, B.F. van Esch, MD, PhD, B.M. Mol, MSc PhD, prof. P.P.G. van Benthem, MD, PhD, prof. T.D. Bruintjes, MD, PhD.

These arrangements for publication are based on the following merits: M.M.E. Boreel is the PhD student and is working full time on the research. B.F. van Esch is the principal investigator, B.M. Mol is head of research support, P.P.G. van Benthem is professor and the head of the Otorhinolaryngology Department and. T.D. Bruintjes is Professor Otorhinolaryngology, in particular Ménière's disease, and project leader. Other authors of participating centres will be added to the manuscript according to their participation and number of subjects they have included.

31c **Plans, if any, for granting public access to the full protocol, participant- level dataset, and statistical code**

In a period of no more than 2 years after the collection of the 1-year post randomization interviews and diaries, we will deliver a completely deidentified data set to an appropriate archive for sharing purposes. In due course, consultations will be held with the data protection officer regarding the preparation of this dataset. So that it complies with Dutch and local (LUMC) laws and regulations.

Appendices

Informed consent materials	32	**Model consent form and other related documentation given to participants and authorised surrogates** The patient information letter and informed consent form is included in the appendix.
Biological specimens	33	**Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable** Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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The effectiveness of intratympanic injections with methylPREDnisolon versus placebo in the treatment of vertigo attacks in MENière's disease (PREDMEN trial): a study protocol for a phase-3 multicentre, double-blinded, randomized, placebo-controlled trial

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The effectiveness of intratympanic injections with methylPREDnisolon versus placebo in the treatment of vertigo attacks in MENière's disease (PREDMEN trial): a study protocol for a phase-3 multicentre, double-blinded, randomized, placebo-controlled trial

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Abstract

Introduction: Intratympanic corticosteroids are commonly used in the treatment of Menière's disease (MD). However, few and small randomized controlled trials (RCT) on the effectiveness of intratympanic corticosteroids have been performed. A recent Cochrane review suggested that a well conducted placebo-controlled RCT with a large study population is required to evaluate the effectiveness of the use of intratympanic corticosteroids in MD. The following protocol describes a phase-3 multicentre, double-blinded, randomized, placebo-controlled trial to compare the effectiveness of methylprednisolone (62.5 mg/ml) to a placebo (sodium chloride 0.9%).

Methods and analysis: We aim to recruit 148 patients with unilateral MD from 6 hospitals in the Netherlands. Patients will be randomly assigned to either the methylprednisolone, or the placebo group. Two injections will be given, one at baseline and one after two weeks. Follow-up assessments will be done at 3, 6, 9 and 12 months. The primary outcome will be the frequency of vertigo attacks. Attacks will be evaluated daily with the DizzyQuest app. Secondary outcomes include hearing loss, tinnitus, health-related quality of life, use of co-interventions and escape medication, (serious) adverse events and cost-effectiveness. These will be evaluated with audiometry and multiple commonly used, validated questionnaires. For the primary and secondary outcomes mixed model analysis, estimating equation (GEE) analysis and logistic regression analysis will be used.

Ethics and Dissemination: This study was submitted via the Clinical Trials Information System, reviewed and approved by the Medical Research Ethics Committee Leiden The Hague Delft and the local institutional review board of each participating centre. All data will be presented ensuring the integrity and anonymity of patients. Results will be published in scientific journals and presented on (inter)national conferences.

Strengths and limitations:

- In this randomized placebo-controlled study both participants and clinicians will remain blinded throughout the follow-up period, therefore minimizing the risk of bias.
- The prospective design with patients daily recording their vertigo attack directly in an app, lowers the risk of missing data and recall bias.
- This study includes a rather large patient population of 148 patients.
- VM and MD share multiple features in terms of clinical presentation and other symptomatology, distinguishing between the two could be challenging and therefore could form a possible limitation in this study.
- Subanalyses on clinical subgroups of MD (autoimmune, familial, and MD + migraine) will be difficult to conduct, because many patients cannot be classified in a subgroup or are part of multiple subgroups.

Introduction

Menière's disease (MD) is a clinical condition characterized by tinnitus and aural fullness, low- to mid-frequency sensorineural hearing loss, and spontaneous episodes of vertigo that can last 20 minutes to 12 hours [1]. Patients with MD experience a worse quality of life than healthy patients due to vertigo, tinnitus and hearing loss [2]. In addition, higher levels of anxiety and depression are seen in patients with MD [3].

Although its aetiology is unknown, endolymphatic hydrops (EH) is thought to be associated with MD. Almost all patients with MD have EH, but not all patients with EH have symptoms of MD. It is unknown if EH is a result of MD or a causal factor for MD [4, 5]. Until this day there is no agreement as to the ideal treatment of MD, due to the lack of evidence for the effect of various therapies. Current treatment consists of dietary and lifestyle modifications, oral diuretics, vestibular rehabilitation for chronic imbalance, intratympanic therapy, and/or ablative surgery [1]. With intratympanic gentamicin and corticosteroid injections the drug is directly delivered into the middle ear, from where it will be absorbed in the inner ear. Unlike gentamicin, corticosteroid therapy does not carry a risk of causing hearing loss. Therefore, it is currently the first step of standard care in the treatment of MD [1]. Although the mechanism of action of steroids on the inner ear remains speculative, it may improve cochlear blood flow and stabilize the vascular endothelium which enhances fluid homeostasis by upregulation of cochlear ion gene expression [6]. Recently, a Cochrane review was published evaluating the use of intratympanic corticosteroids in MD [7]. In this review, 10 randomized controlled trials (RCTs) and quasi-RCTs comparing intratympanic corticosteroids, all using dexamethasone, compared to either placebo or no treatment were included. The authors found that the evidence for the use of dexamethasone is uncertain. Intratympanic dexamethasone injection may marginally reduce the frequency of vertigo attacks. Regarding hearing and tinnitus, improvement was seen, but without statistical significance.

The most commonly intratympanically administered corticosteroids are dexamethasone and methylprednisolone [1]. Phillips et al. [8] determined the efficacy of intratympanic OTO-104 (a

sustained-released dexamethasone hydrogel) for the treatment of MD, in three double blind, placebo-controlled RCTs, with a total of 165, 174 and 148 patients respectively. OTO-104 showed numerically larger decreases in definitive vertigo days compared with placebo across all three studies. However, in only one study this difference was statistically significant. Pharmacokinetic studies show that dexamethasone phosphate has molecular and pharmacokinetic characteristics that complicate its use as a topical therapy for hearing disorders, which may explain its questionable effectiveness. [9]. An animal study found that the concentrations of methylprednisolone are higher and have longer duration in perilymph and endolymph compared to dexamethasone and hydrocortisone, and therefore could be a more effective drug [10]. Typically soluble forms of methylprednisolone are administered and expected to be less permeable through the membranous boundaries compared to the less polar forms. However, there is no data whether these soluble forms are metabolized to the base form in the ear and if they are, at what rate [9]. Despite the fact that little is known about the pharmacokinetics of methylprednisolone, there are clinical indications of its effectiveness [11, 12]. Cao et al. [12] performed a literature review and demonstrated that methylprednisolone is more effective than dexamethasone in a clinical setting.

Although in the last decade, there is an increasing tendency and emerging evidence for the use of intratympanic steroids, no large RCT on the effectiveness of intratympanic methylprednisolone in MD has been conducted [13]. A meta-analysis published in 2021 included eight studies comparing intratympanic gentamicin to intratympanic corticosteroids, in which gentamicin appeared to be superior in terms of control of vertigo attacks [14]. However, gentamicin is known to be ototoxic and can induce hearing loss. Patel et al. [15] compared intratympanic gentamicin injections to methylprednisolone injections in a double-blind RCT with a 24-month post-treatment follow-up. Vertigo attacks decreased in both groups, indicating a treatment effect. However, no placebo group was involved and the sample size was relatively small (n=60).

In conclusion, there is a need of solid evidence on the effectiveness of intratympanic steroids in MD. Until now the effectiveness of methylprednisolone has not been investigated by means of a placebo

controlled RCT. Therefore a well conducted RCT with a large study population and a long follow-up period is now required to evaluate the effectiveness of intratympanic methylprednisolone in MD. In this protocol we present the methods of a phase-3 multicentre, double-blinded, randomized, placebo-controlled trial evaluating the effectiveness of intratympanic injections with methylprednisolone versus placebo in the treatment for MD patients.

Methods

Trial design

In this phase 3, multicentre, double-blind, placebo-controlled randomized trial the effect of two intratympanic methylprednisolone sodium succinate 62.5 mg/ml (Solu-Medrol in Act-O-Vial, Pfizer BV) injections 14 days apart is compared to two placebo (i.e., sodium-chloride 0.9%) injections with the same time interval on vertigo attacks in patients with MD. Parallel groups will be randomly assigned to one of both arms and outcomes will be measured during a one year follow-up period.

Study subjects

Patients with MD will be recruited by six participating sites in the Netherlands and will be approached by their own ENT specialist and informed about this trial. After a one week reflection period, informed consent forms can be signed. Baseline and outcome data will be extracted from participants' electronic medical records and collected in the cloud-based clinical data management platform Castor EDC (version v2023.1.0.1, LUMC).

In- and exclusion criteria

In order to be eligible for the study a study subject needs to have unilateral, definite MD according to the diagnostic criteria derived from the American Academy Otolaryngology Head and Neck Surgery, Classification Committee of the Bárány Society, European Academy of Otology and Neurotology and International Classification of Vestibular Disorders published in 2015 [16]. The criteria for definite MD are:

Two or more spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours,

AND

Audiometrically documented low- to medium-frequency sensorineural hearing loss in one ear, defining the affected ear on at least one occasion before, during or after one of the episodes of vertigo,

AND

Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear (not better accounted for by another vestibular diagnosis).

Other inclusion criteria are:

- Age ≥ 18 years at the start of the trial.
- ≥ 4 vertigo attacks over the last 6 months.
- Willing to adhere to daily completion of study questionnaires using the DizzyQuest app and to the follow-up assessments.

Study subjects who meets any of the following criteria will be excluded:

- Bilateral MD.
- Severe disability (e.g. neurological, orthopedic, cardiovascular) or serious concurrent illness that might interfere with treatment or follow-up.
- Active additional neuro-otologic disorders that may mimic MD (e.g. vestibular migraine (VM) , recurrent vestibulopathy, phobic postural vertigo, vertebro-basilar TIAs, acoustic neuroma).
- Otitis media with effusion based on tympanogram results.
- History of intratympanic injections with corticosteroid less than 6 months ago.
- History of intratympanic injections with gentamicin or ear surgery for treating MD.
- Pregnant women or nursing women.

Sample size

A sample size calculation was performed based on recommendations as summarized in the Clinical Practice Guideline for Menière's disease [1]. An expected proportion of subjects achieving vertigo control of 87.5% was assumed for methylprednisolone treatment compared to an assumed 67.5% for placebo, i.e. a difference in treatment effect of 20%. With a statistical power (1-β) of 80% and a type 1 error (α) of 5%, 67 patients per group are required. With an estimated 10% loss-to-follow-up, 74 patients will be included in each arm, giving a total sample size of 148. In total, over the six

participating centres, 340 MD patients yearly visit the Otolaryngology department and will be screened for the trial. It is expected that 15% will meet the inclusion criteria and will be willing to participate. This will result in approximately 50 eligible patients for inclusion per year.

Randomization and blinding

Subjects will be randomly assigned to either methylprednisolone or placebo with a 1:1 allocation as per computer-generated random sequence, stratified by site generated by Castor EDC. Blinding will be maintained until all subjects have finished their treatment phases. All study participants, participating medical professionals, and outcome assessors will be blinded. The independent epidemiologist and pharmacy personnel will both be unblinded during randomization and therapy allocation.

Study procedure

After a one week reflection period and agreement with trial participation by means of signing the informed consent, a patient will be seen at the study site. Standard inquiries about the patient's demographics, family history, and medical history—particularly regarding any history of auto-immune disease and migraine—are made at the informed consent visit. Thereafter patients will receive an intratympanic injection with either methylprednisolone or placebo at day 1 and day 15 with a window of three days. The patient is lying down in supine position with their head rotated to the side and prior to the intratympanic injection the eardrum will be anesthetized. Thereafter, a myringotomy is being performed and a small spinal puncture needle is passed through the tympanic membrane to inject fluid into the middle ear cavity at the level of the round window. The patient is then required to remain on their side without swallowing for thirty minutes.

At baseline, results of Magnetic Resonance Imaging (MRI) must be available to make sure other causes of disease are ruled out [17]. To assess the vestibular function of the horizontal semicircular

canals, the caloric test and video Head Impulse test (vHIT) will be performed. To evaluate the anterior and posterior semi-circular canals, the vHIT will be conducted at baseline in order to assess the presence of vestibular hypofunction or areflexia.

During a follow-up period of one year, overall wellbeing and vertigo attacks are being assessed daily with the aid of the DizzyQuest app. Two telephone contacts will take place at 3 and 6 months to assess possible (serious) adverse events, DizzyQuest app compliance and the use of escape medication or co-interventions. A physical follow-up visit in the outpatient clinic will be scheduled at 6 and 12 months. During these outpatient clinic visits additional audiometry and multiple questionnaires concerning tinnitus, dizziness and quality of life will be filled-in. An overview of follow-up moments of the corresponding outcomes and a flowchart of the study procedure are presented in table 1 and figure 1, respectively.

Outcome measures

Vertigo: The primary outcome measure will be defined by the class of vertigo as defined by the AAO HNS 1995 guideline. The class of vertigo is defined by the average number of attacks per month during 6 and 12 months after treatment divided by the number of attacks 6 months before treatment times 100. As a result the following class of vertigo is defined:

- A: Complete control of vertigo = 0
- B: Substantial control of vertigo = 1-40
- C: Limited control of vertigo = 41- 80
- D: Insignificant control of vertigo = 81 – 120'
- E: Worse control of vertigo > 120

Moreover, the daily attack vertigo frequency will be monitored with the aid of the DizzyQuest app (Psymate 2)[18, 19]. The DizzyQuest app will be used to track the primary outcome measure, the frequency of dizziness attacks. Patients will answer daily questionnaires about their health and wellbeing and patients can report vertigo attacks at any time using the Dizzy quest app. Additionally,

the Dizziness Handicap Inventory (DHI) questionnaire will be administered at baseline, after six months, and after a year to assess how dizziness affects daily life [20]. The effect of the injections in the DHI will be reported as raw data, as well as change in handicap category (mild handicap, moderate handicap or severe handicap) related to improvement, unchanged or worsened.

The following secondary outcomes will be measured

Hearing: Pure tone audiometry will be performed at baseline, after six months, and after a year. In line with the guideline of AAO HNS 1995 guideline[17], we will use the average scores of four-tone audiometry at 0.5, 1, 2 and 3 kHz and we will assess the word recognition scores as the percent correct score at the presentation level in decibel. A decrease of ≥ 10 dB or a change in word recognition score of ≥ 15% points is considered clinically significant.

Tinnitus: The Tinnitus Functional Index (TFI) measures the impact of tinnitus on daily life [21]. This survey will be administered at baseline, after six months, and after a year. One point decrease of increase will be defined as improved or worsened tinnitus respectively [22].

Quality of life: Apart from the DHI and TFI, the EuroQol 5 dimension (EQ-5D) and EuroQol – Visual Analog Scale (EQ-VAS) questionnaires will be used to measure quality of life at baseline, after six and twelve months [23, 24]. These questionnaire are standardized tests of health status that are used in economic and clinical evaluations

Use of escape medication and co-interventions: In case participants remain suffering from intolerable vertigo attacks, regardless of which group they are allocated to, the use of metoclopramide and co-interventions such as intratympanic injections of gentamicin or methylprednisolone will be allowed and documented during the follow up period. This will be based on experience of participants vertigo

frequency and shared decision making. If patients receive additional treatment, they will not be unblinded.

Adverse events

Patients will be informed that Adverse Events, Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions must be reported as soon as possible to their ENT-surgeon or research nurse. Additional queries are made at 3, 6, 9, and 12 months to ensure that they did not fail to report occurrences. These events will be registered throughout the trial in Castor EDC. Each serious adverse event must be reported to the sponsor within 24 hours after the physicians' knowledge. In the event that patient safety is compromised, patients can be unblinded.

Cost-effectiveness

Cost-effectiveness will be assessed from both a healthcare and societal cost-utility perspective, where cost per avoided vertigo attack and cost per Quality Adjusted Life Year (QALY), respectively, will be used as the metrics. MD -related medical expenses, other healthcare expenses, and the cost of lost productivity will all be included in the estimated societal cost, which will be calculated using the iMTA Medical Consumption Questionnaire (iMCQ) and IMTA Productivity Cost Questionnaire (IPCQ).

Statistical analysis

Ordinal regression using mixed model analysis will be used to analyse the primary outcome (i.e., class of vertigo). In addition, generalized estimating equation (GEE) analysis of the actual vertigo attacks recorded using the DizzyQuest app will be used to estimate the incidence rate ratio (IRR) for comparison between the methylprednisolone and placebo groups. A decrease of 100% is considered total control of vertigo episodes, while a reduction of >40% is considered a substantial and thus clinically relevant reduction [17].

Mixed model analysis will be used to analyse differences in the questionnaire scores (DHI, TFI, FLS, eQ-5D/VAS, iMCQ, iPCQ) between the two groups. Logistic regression analysis will be used to analyse the remaining secondary outcomes (incidence of escape interventions, hearing loss, and adverse events). A reduction in hearing of 10 decibels or a 15% change in word recognition will be regarded as a clinically significant difference [17].

Subgroup analyses will be performed with regard to sex, duration of the disease and the type of MD (delayed MD, familial MD, and autoimmune MD). These subgroups will be defined as described in Frejo et al [25]. Two sensitivity analyses will be carried out in addition to the intention to treat analysis: a per protocol analysis in which patients who received additional co-interventions to achieve vertigo control are excluded; and an as-treated analysis in which participants who received additional co-interventions are analysed.

In order to evaluate the average costs and outcomes between the methylprednisolone and placebo groups for the cost-effectiveness analysis, intention-to-treat and net-benefit analysis will be used. For all statistical analysis, multiple imputation to adjust for missing data will all be used[26]. QALYs will be calculated using the Dutch tariff for the EuroQoL EQ-5D-5L [23] and as sensitivity analysis the visual analogue scale valuing health, with power-transformation [27]. All outcomes with corresponding statistical analysis methods are summarized in Table 2. A p-value < 0.05 will be considered as statistically significant for all analyses and will be performed using SPSS version 25 or higher (SPSS Chicago Illinois, USA).

Patient and public involvement

The PREDMEN trial is supported by the Dutch Association for the hard of hearing, and more specifically its Committee Dizziness and Balance (Commissie Duizeligheid en Evenwicht van Hoormij-NVVS) and the Dutch association for psychological health care and social services for patients with SNHL and tinnitus (GGMD). Both organizations are involved in the realization of the trial, the writing process and implementation of trial results. Moreover, they will serve as a sounding board for MD

patients participating in this trial and one patient representative will be a member of the steering committee. In line with their suggestions, patients will be involved in every stage of the research.

Ethics and Dissemination

Ethics

The PREDMEN trial was submitted via the Clinical Trial Information System (CTIS), with CTIS number: *2023-503340-13-00*, reviewed by the Medical Research Ethics Committee Leiden The Hague Delft (MREC LDD), and authorized for execution in the Netherlands under the European Clinical Trial Regulation (ECTR).Additionally, the institutional research board of each participating centre individually reviewed and approved the study. The study is conducted in accordance with the principles outlined in the Declaration of Helsinki (October 2013), the Medical Research Involving Human Subjects Act (WMO, 26 February 1998), the International Conference on Harmonization Good Clinical Practice (ICH GCP, November 2016) guidelines, and any other applicable guidelines, regulations, and Acts.

Patient safety

Minor complications such as persistent membrane perforation (5.9%) and otitis media (7%) can occur [7, 28, 29] Safety risk will be comparable to normal clinical practice and it is not expected that significant adverse events will be seen in the intervention arm. ENT specialists are experienced with intratympanic injections due to its application in patients with sudden deafness. Since the intervention is characterized as a low risk profile study, no Data Safety Monitoring Board (DSMB) is required [30]. The sponsor will submit a report on the safety of each investigational medicinal product used in the clinical trial through CTIS. Interim analysis will be performed on the primary endpoint when 50% of the patients have been randomized and completed a follow-up of 6 months, where comparability of baseline characteristics will be assessed. In this analyses, differences in vertigo control between the two study arms should not be greater than 45%. In addition, if the difference in vertigo control reveals to be clinically significant (i.e. >20%), but ≤ 20% of the participants in methylprednisolone

reach vertigo control, the study will be terminated because of convincing effect of the treatment in the intervention arm.

Data safety

The handling of personal data complies with the Dutch Personal Data Protection Act (AVG). All data collected for the trial, including but not limited to demographic data, audiological questionnaires, and data from the DizzyQuest app will be entered in a ISO 9001 and ISO 27001:2005 certified Castor® EDC database (electronic CRF). Data will be protected with a unique subject identification code which is linked to a pass-word protected subject identification list. Only members of the study team, who will be documented on the site signature and delegation log per site, will have access to the study data. The sponsor and investigator will keep a clinical trial master file which will contain the essential documents relating to the clinical trial.

Dissemination

A summary of the results of this study will be submitted to CTIS within one year after termination of the trial. Results will also be published in scientific journals and presented on (inter)national conferences. All information that will be presented will be done so in a way that integrity and anonymity of patients is ensured. All data will be stored for 25 years after the last subject has had the last study visit.

Trial Registration

This study is registered at ClinicalTrials.gov Protocol Registration and Results System, with the registration ID: NCT05851508.

Contributors

The conception and design of the study were developed by BE, BM, PPvB, TB. The drafting of the original protocol was done by BE, BM, TB, TS. The coordination of the study was carried out by BE, BM, MB, TB. Patient recruitment and collection of data was performed by BE, MB, PPvB, TB. The statistical analysis plan was designed by TS. The present manuscript was drafted by MB. The funding was obtained by BE, BM, TB. All authors read and approved the final manuscript prior to submission for publication.

BE and TB acted as the guarantors of this study.

Funding

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Competing interests

No competing interest was declared.

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Tables

Table 1. Overview of follow-up moments of the corresponding outcomes

Moment in trial	*Type of follow up*	*Outcomes*
From moment of inclusion unit 1 year follow up		Daily questionnaire in Dizzy quest app
Baseline	First intratympanic injection	Baseline parameters MRI Otoscopy Audiometry: PTA and SDS Vestibular testing: vHIT, caloric testing Questionnaires: DHI, TFI, FLS, EQ-5D/VAS, iMCQ, iPCQ
2 weeks	Second intratympanic injection	Otoscopy Complications Use of co-interventions Use of escape medication (S)AE
3 months, 9 months	Telephone consult	Complications Use of co-interventions Use of escape medication (S)AE
6 months, 12 months	Consult in outpatient clinic	Otoscopy Complications Audiometry: PTA and SDS Questionnaires: DHI, TFI, FLS, EQ-5D/VAS, iMCQ, iPCQ Use of co-interventions Use of escape medication (S)AE

Abbreviations: DHI, Dizziness Handicap Index; EQ 5D, EuroQol 5D; FLS, Functional Level Scale; HIT, Head Impulse Test; iMCQ, iMTA Medical Consumption Questionnaire; iPCQ, iMTA Productivity Cost; Questionnaire; MRI, Magnetic Resonance Imaging; PTA, Pure Tone Average; SDS, speech discrimination score; (S)AE, (Serious) Adverse Event, TFI, Tinnitus Functional Index

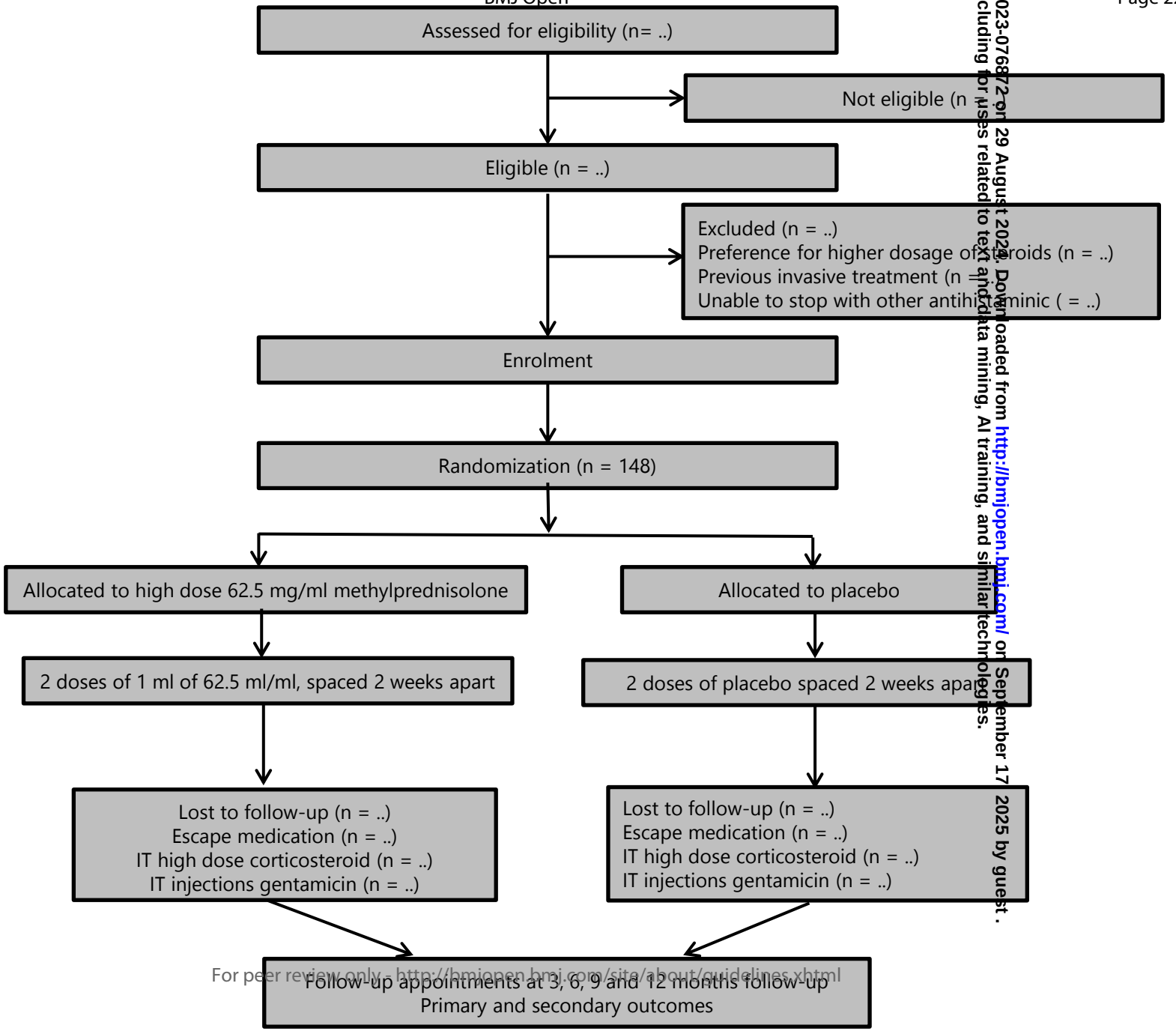
Table 2 Outcomes with corresponding statistical analysis method

	Outcome	*Type of data*	*Analysis*
Primary outcome	Number of spontaneous vertigo attacks, lasting more than 20 minutes	Count	Generalized estimating equation
	AAO HNS (1995) class of vertigo		Mixed model analysis
Secondary outcomes	Hearing (PTA; 0.5, 1, 2, 3 kHz and SDS)	Continuous	Logistic regression analysis
	Tinnitus (TFI)	Categorical	Mixed model analysis
	Quality of life (DHI, TFI, FLS, eQ-5D/VAS)	Categorical	Mixed model analysis
	Use of escape medication and co-interventions	Count	Logistic regression analysis
	(S)AE	Binary	Logistic regression analysis
	Cost effectiveness (iMCQ, iPCQ)	Categorical	Mixed model analysis

Abbreviations: DHI, Dizziness Handicap Index; EQ 5D, EuroQol 5D; FLS, Functional Level Scale; iMCQ, iMTA Medical Consumption Questionnaire; iPCQ, iMTA Productivity Cost; Questionnaire; PTA, Pure Tone Average; SDS, speech discrimination score; (S)AE, (Serious) Adverse Event, TFI, Tinnitus Functional Index

Figure 1.

Flowchart of the study procedure. IT, intratympanic.



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	**Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym** A phase-3 multicentre, double-blinded, randomised, placebo-controlled trial to compare the effectiveness of intratympanic injections with methylPREDnisolon versus placebo in the treatment of vertigo attacks in MENière's disease (PREDMEN trial).
Trial registration	2a	**Trial identifier and registry name. If not yet registered, name of intended registry** Clinical trial number: 2023-503340-13-00 Clinicaltrails.gov: ID: NCT05851508
	2b	**All items from the World Health Organization Trial Registration Data Set**

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT05851508
Date of registration in primary registry	3, oktober, 2023
Secondary identifying numbers	Identifiers: NCT05851508, Unique Protocol ID: PREDMEN, Secondary ID: 10140022110009
Source(s) of monetary or material support	Stichting ZonMW: *file number: 10140022110009*
Primary sponsor	Leiden University Medical Centre
Secondary sponsor(s)	Leiden University Medical Centre
Contact for public queries	M.M.E. Boreel, MD, Leiden University Medical Centre M.M.E.Boreel@lumc.nl
Contact for scientific queries	M.M.E. Boreel, MD, Leiden University Medical Centre M.M.E.Boreel@lumc.nl
Public title	The Effectiveness of Intratympanic Methylprednisolone Injections Compared to Placebo in the Treatment of Vertigo Attacks in Meniere's Disease (PREDME
Scientific title	A Multicenter, Double-blinded, Randomised, Placebo-controlled Trial to Compare the Effectiveness of Intratympanic Injections

	MethylPREDnisolone Versus Placebo in the Treatment of Vertigo Attacks in MENière's Disease (PREDMEN Trial).
Countries of recruitment	Netherlands
Health condition(s) or problem(s) studied	Meniere's Disease (MD)
Intervention(s)	Intratympanic injection with Methylprednisolone 62.5 mg/ ml
	Placebo comparator: Intratympanic injection with saline, (sodiumchloride 0.9%)
Key inclusion and exclusion criteria	Inclusion criteria: - Unilateral, definite MD according to the diagnostic criteria derived from the American Academy Otolaryngology Head and Neck Surgery, Classification-Page 4 of 6 Committee of the Bárány Society, European Academy of Otology and Neurotology and International Classification of Vestibular Disorders - adult patients (≥ 18 years), patient hospitalized - ≥ 4 vertigo attacks over the last 6 months. - Willing to adhere to daily Dizzy quest app questionnaires and the follow-up assessments
	Exclusion criteria: - Bilateral MD - Severe disability (e.g. neurological, orthopaedic, cardiovascular) or serious concurrent illness that might interfere with treatment or follow-up. - Active additional neuro-otologic disorders that may mimic MD (e.g. vestibular migraine, recurrent vestibulopathy, phobic postural vertigo, vertebro-basilar TIAs, acoustic neuroma). - Otitis media with effusion based on tympanogram results. - History of intratympanic injections with corticosteroid less than 6 months ago. - History of intratympanic injections with gentamicin or ear surgery for treating MD. - Pregnant women and nursing women.
Study type	Interventional
	Allocation: randomised intervention model. Masking: double blind (subject, caregiver, investigator, outcomes assessor)
	Primary purpose: treatment
	Phase III
Date of first enrolment	Oktober 2023
Target sample size	148
Recruitment status	Recruiting
Primary outcome(s)	Vertigo attacks
Key secondary outcomes	Hearing loss, tinnitus, health-related quality of life, use of escape medication, adverse events, cost-effectiveness, co-interventions, overall function, impact of dizziness.

Protocol version 3 **Date and version identifier**

- Issue date: 02-05-2023
- Version 4.0

Funding	4	**Sources and types of financial, material, and other support** This project will be funded by ZonMW *file number: 10140022110009*
Roles and responsibilities	5a	**Names, affiliations, and roles of protocol contributors** Coordinating investigators: • T.D. Bruintjes, MD, PhD, prof, ENT-surgeon, department of Otorhinolaryngology Head and Neck surgery. • M.M.E. Boreel, MD, physician-researcher, department of Otorhinolaryngology Head and Neck surgery. Head of research support Leiden University Medical Centre: • B.M. Mol, PhD, Head of research support Leiden University Medical Centre Principal investigators: • B.F. van Esch, MD, PhD, ENT surgeon, Department Otorhinolaryngology and Head and Neck Surgery, Leiden University Medical Centre, The Netherlands • S.M. Winters, MD, PhD , ENT-surgeon Apeldoorn Dizziness Centre, Gelre Ziekenhuizen • W.P.A. Kelders, MD, PhD , ENT-surgeon , Rotterdam Dizziness Centre, Franciscus Gasthuis & Vlietland • R. van den Berg, MD, PhD, ENT-surgeon Department of Otorhinolaryngology, Maastricht UMC+ • H.M. Blom, MD, PhD, Professor, ENT-surgeon Department of Otorhinolaryngology, Haga Hospital • D.A. van Zuylen, MD, ENT-surgeon, Department of Otorhinolaryngology, Medisch Spectrum Twente Epidemiologist: • T. Schermer, PhD, Apeldoorn Dizziness Centre, Gelre Hospital, Apeldoorn, The Netherlands
	5b	**Name and contact information for the trial sponsor** Legal Representative of Sponsor: mw. K.G. Freriks-Bauritius Title: Management director division 3. Leiden University Medical Centre, Albinusdreef 2, 2333 ZA Leiden secretariaatbbd3enzorg@lumc.nl.
	5c	**Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities** The funding source does not have any role in this study during its execution, analysis, interpretation of the data or decision to submit results.

5d **Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)**

Coordinating investigator:

- Study planning
- Randomisation
- Responsible for trial master file
- Planning of monitor visits
- Identification Study subjects, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol and investigators brochure
- Reporting of AE/SAE/SUSAR
- Processing and analysing raw data

Coordinating investigator/PI sponsor site/head of research support LUMC:

- Design and Conduct of the PREDMEN trial
- Preparation, writing and revisions of research protocol, agreement on final protocol
- Write and review all required documents (Patient information folder, Informed Consent, Standard operating procedures etc.)
- Organisation of approval medical ethical committee
- Preparation of Investigators brochure and CRF
- Publication study reports
- Reviewing progress of study and if necessary, making changes to the protocol or other necessary documents
- Management of the budget and problems with individual centrecontracts
- Provide annual risk report

Principal investigators/Research nurse Study sites:

- Identification Study subjects, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol and investigators brochure

Epidemiologist:

- Performing interim analysis
- Processing and analysing raw data

Introduction

Background and rationale

6a **Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention**

Menière's disease (MD) is a clinical condition characterized by tinnitus and aural fullness, low- to mid-frequency sensorineural hearing loss, and spontaneous episodes of vertigo that can last 20 minutes to 12 hours [1]. Although its aetiology is unknown, endolymphatic hydrops (EH) is thought to be associated with MD and treatment is often focussed on the regulation of EH.

Current treatment of MD consists of dietary and lifestyle modifications, oral diuretics, vestibular rehabilitation for chronic imbalance, intratympanic therapy, and/or ablative surgery [1]. With intratympanic gentamicin and intratympanic corticosteroid injections the drug is directly delivered into the middle ear, from where it will be absorbed in the inner ear. Although the mechanism of action

of steroids on the inner ear remains speculative it may improve cochlear blood flow and stabilize the vascular endothelium which enhances fluid homeostasis by upregulation of cochlear ion gene expression [2]. Unlike gentamicin, corticosteroid therapy does not carry a risk of causing hearing loss. Therefore, it is currently the first step of standard care in the treatment of MD [1].

Although in the last decade, there has been an increasing tendency and emerging evidence for the use of intratympanic steroids, no large RCT on the effectiveness of intratympanic methylprednisolone in MD has been conducted. A meta-analysis published in 2021 included eight studies comparing intratympanic gentamicin to intratympanic corticosteroids, in which gentamicin appeared to be superior in terms of control of vertigo attacks [3]. However, gentamicin is known to be ototoxic and can induce hearing loss. Patel et al. compared intratympanic gentamicin injections to methylprednisolone injections in a double-blind RCT with a 24-month post-treatment follow-up [4]. Vertigo attacks decreased in both groups, indicating a treatment effect. However, no placebo group was involved and the sample size was relatively small (n=60). Recently, a Cochrane review was published evaluating the use of intratympanic corticosteroids in MD. In this review, 10 randomised controlled trials (RCTs) and quasi-RCTs comparing intratympanic corticosteroids, all using dexamethasone, compared to either placebo or no treatment were included [5]. The authors found that the evidence for the use of dexamethasone is uncertain. Intratympanic dexamethasone injection may marginally reduce the frequency of vertigo attacks. Regarding hearing and tinnitus improvement was seen, but without statistical significance.

In conclusion, there is a need of solid evidence on the effectiveness of intratympanic steroids in MD. Until now the effectiveness of methylprednisolone has not been investigated by means of a placebo controlled RCT. Therefore a well-conducted RCT with a large study population and a long follow-up period is now required to evaluate the effectiveness of intratympanic methylprednisolone in MD.

	6b	**Explanation for choice of comparators**
		Pharmacokinetic studies show that dexamethasone phosphate has molecular and pharmacokinetic characteristics that complicate its use as a topical therapy for hearing disorders, which may explain its questionable effectiveness [6]. An animal study found that the concentrations of methylprednisolone are higher and have longer duration in perilymph and endolymph compared to dexamethasone and hydrocortisone, and therefore could be a more effective drug [7]. Typically soluble forms of methylprednisolone are administered and expected to be less permeable through the membranous boundaries compared to the less polar forms. However, there is no data whether these soluble forms are metabolized to the base form in the ear and if they are, at what rate. Despite the fact that little is known about the pharmacokinetics of methylprednisolone, there are clinical indications of its effectiveness [8, 9]. Cao et al. performed a literature review and demonstrated that methylprednisolone is more effective than dexamethasone in a clinical setting [8]. Therefore we choose to compare methylprednisolone to placebo.
Objectives	7	**Specific objectives or hypotheses**
		Primary objective: To determine whether methylprednisolone (62.5 mg/ml) is superior to placebo in controlling vertigo attacks in patients with MD.
		Secondary objective: To determine whether methylprednisolone (62.5 mg/ml) is superior to placebo in controlling tinnitus, hearing, quality of life, use of escape medication, adverse events and cost-effectiveness.
Trial design	8	**Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)**

The PREDMEN study is a phase-3 multicentre, double-blinded, randomized, parallel group trial with patients suffering from MD with a total follow-up period of 12 months.

Methods: Participants, interventions, and outcomes

Study setting	9	**Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained** Six medical centres from across the Netherlands are participating in the study in order to enrol a sufficient number of patients in three years. In these centres, an ENT-surgeon, specialized in dizziness, is involved and principal investigator for the trial. The following centres are participating in the PREDMEN study: - Leiden Universitair Medisch Centrum, Leiden (sponsor site) - Apeldoorns Duizeligheidscentrum, Gelre Ziekenhuizen, Apeldoorn - Maastrichts Universitair Medisch Centrum, Maastricht - Haga-ziekenhuis, Den Haag - Medisch Spectrum Twente, Enschede - Rotterdam Duizeligheids Centrum, Rotterdam
Eligibility criteria	10	**Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)** **Inclusion criteria:** - Unilateral, definite MD according to the diagnostic criteria derived from the American Academy Otolaryngology Head and Neck Surgery, Classification- Page 4 of 6 Committee of the Bárány Society, European Academy of Otology and Neurotology and International Classification of Vestibular Disorders - Adult patient (≥ 18 years), patient hospitalized - ≥ 4 vertigo attacks over the last 6 months. - Willing to adhere to daily Dizzy quest app questionnaires and the follow-up assessments.. **Exclusion criteria**: - Bilateral MD - Severe disability (e.g. neurological, orthopaedic, cardiovascular) or serious concurrent illness that might interfere with treatment or follow-up. - Active additional neuro-otologic disorders that may mimic MD (e.g. vestibular migraine, recurrent vestibulopathy, phobic postural vertigo, vertebro-basilar TIAs, acoustic neuroma). - Otitis media with effusion based on tympanogram results. - History of intratympanic injections with corticosteroid less than 6 months ago. - History of intratympanic injections with gentamicin or ear surgery for treating MD. - Pregnant women and nursing women
Interventions	11a	**Interventions for each group with sufficient detail to allow replication, including how and when they will be administered**

Eligible patients will be randomised in equal proportion between the Methylprednisolone (62.5 mg/ml) and the Placebo (sodium chloride 0.9%). group. Intratympanic injections will be administered two times at timepoint 0 and after two weeks.

Name and description of investigational product(s):

*M*ethylprednisolone sodium succinate 62.5 mg/ml (Solu-Medrol in Act-O-Vial).

Generic name methylprednisolone sodium succinate. *Manufacture a.o.:* Pfizer B.V.; Rivium Westlaan 142 2909 LD Capelle a/d Ijssel, The Netherlands

Name and description of Placebo:

Placebo: Saline, Sodiumchloride (NaCl) 0,9% saline for injection

11b **Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)**

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw subjects from the study for urgent medical reasons. We do not anticipate any major events arising from the study intervention because the trail medicine is already widely used and the study is classified as a low risk profile study.

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

Patients cannot fail to take the medication because the intervention is an injection administered by the physician at timepoint zero and after two weeks. However, patients are obliged to complete short questionnaires on the DizzyQuest app on a daily basis. We will obtain a weekly output of the patients compliance to the app, which will aid in patient monitoring. To avoid data loss, we will contact patients who fail to report through the application and ask them to complete the questionnaires. We expect no problems assessing the other outcomes because they will be monitored throughout clinical or telephonic appointments.

11d **Relevant concomitant care and interventions that are permitted or prohibited during the trial**

Prohibited medication:

- The administration of antihistaminic drugs including betahistine is prohibited due to the risk of drug competition. The true effect of methylprednisolone could therefore be over- or underestimated

Specific permitted medication:

- In case subjects continue to suffer from vertigo attacks in a high frequency, co-interventions can be offered, in either in the placebo,- or the intervention group. Co interventions include: intratympanic injections of gentamicin, dexamethasone, methylprednisolone or triamcinolone.

- Subjects are allowed to use metoclopramide in the acute phase of vertigo

Outcomes 12 **Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended**

Primary objective(s)	**Endpoint for the primary objective(s)**	**Analysis metric primary endpoint**	**Timepoints for primary objectives:**
To determine whether intratympanic injection with 62.5 mg/ml methylprednisolone is superior to placebo in reducing the frequency of vertigo attacks in patients diagnosed with unilateral MD during one year of follow-up.	Complete or substantial control of vertigo	Measured daily with the DizzyQuest app. Categorized in class of vertigo (A-D)	Daily
Secondary objective(s), if applicable	**Endpoint(s) for secondary objective(s), if**	**Analysis metric** **Secondary endpoint**	**Timepoints for secondary objectives:**
Use of co-interventions	Use of intratympanic injections with either gentamicin, methylprednisolone dexamethasone or triamcinolone	Frequency co-intervention used	Asked at 3, 6, 9 and 12 months
Use of Escape medication	Use of metoclopramide	Frequency escape medication used	Asked at 3, 6, 9 and 12 months
Hearing	Pure tone audiometry, word recognition score.	A decrease of ≥ 10 dB or a change in word recognition score of ≥ 15% points is considered clinically significant.	Measured at baseline, after 6 and 12 months
Change in quality of life on dizziness related quality of life	Questionnaires: Dizziness handicap inventory (DHI), Functional level scale (FLS)	DHI: handicap levels: Mild handicap = 16-34 Points; Moderate handicap = 36-52 Points and Severe handicap = 54+ Points. Improved, unchanged of worsened of level. FLS: Improvement (≥ 1 point decrease), unchanged or worsened (≤ 1 point increase)	Measured at baseline, after 6 and 12 months
Change in quality of life on tinnitus	Tinnitus handicap inventory (TFI)	Improvement (≥ 1 point decrease), unchanged or worsened (≤ 1 point increase)	Measured at baseline, after 6 and 12 months
Change in quality of life in general	EQ-5D and EQ-VAS scores	Mean value, standard deviation or, if the data is skewed, the median values and the 25th and 75th percentiles.	Measured at baseline, after 6 and 12 months
Adverse events	SAE, SUSARs	Frequency SAE/SUSAR	Reported when it occurs
Incremental cost differences	Cost-effectiveness and cost-utility analysis. Medical Consumption Questionnaire (iMCQ) and IMTA productivity Cost Questionnaire (iPCQ)	Cost-effectiveness analysis (costs per prevented vertigo attack), and a cost-utility analysis (costs per QALY, calculated from the EQ-5D and EQ-VAS	Measured at baseline, after 6 and 12 months

13 **Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure**

Participant timeline

Assessments	Screening Eligibility Clinic (-8 days till day -1)	Treatment visit 1 Clinic Baseline (± 5 days)	Treatment visit 1 Clinic 2 weeks (± 5 days)	Follow-up phase Telephone 3 months (± 2 weeks)	Follow-up phase Clinic 6 months (± 2 weeks)	Follow-up phase Telephone 9 months (± 2 weeks)	End of trial Clinic 12 months (± 2 weeks)
Explanation study participation to subject	X						
Screening procedure	X						
Sign Informed Consent	X						
Inclusion/exclusion criteria	X						
Medical History	X						
Baseline parameters (sex, age, onset age of MD etc.)	X						
Concomitant medication	X			X	X	X	X
Pure Tone (PTA) and Speech Discrimination Score (SDS)	X[1,3]				X		X
Vestibular tests (caloric testing and vHIT)	X[3]						
MRI – petrous bone	X[3]						
Functional Level Scale (FLS)	X				X[2]		X
Dizziness Handicap Inventory (DHI)	X				X[2]		X
Tinnitus Functional Index (TFI)	X				X[2]		X
Generic quality of life questionnaires (EQ-5D, EQ-VAS)	X				X[2]		X
IMTA Medical Consumption Questionnaire (iMCQ) and IMTA productivity Cost Questionnaire (iPCQ)	X				X[2]		X
Randomisation	X						
Methylprednisolone or placebo		x	x				X
(S)AEs		x	x	X	X	X	X
Co intervention: injection with either methylprednisolone, dexamethasone, triamcinolone or gentamicine				Daily			
Dizzy quest app	Daily						

	14	**Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size**
Sample size calculations		The sample size calculation is based on recommendations as summarized in the Clinical Practice Guideline by Bassura et al [1]. The absolute effect on vertigo control class is expected to be 87.5% in the methylprednisolone group versus 67.5% in the placebo group. In previous studies similar high percentages of control of vertigo were seen when placebo or sham surgery was compared to an intervention. Sample size calculation was executed with the software available from DSS Research Tools (https://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/statisticalpowercalculators.aspx analyses performed with the expected 20% difference in absolute effect on vertigo and two-tailed testing). With a statistical power of 80% and a Type 1 error of 5% 67 patients per group are required. With an estimated 10% loss-to-follow-up, we aim to include 74 patients in each group.
Recruitment	15	**Strategies for achieving adequate participant enrolment to reach target sample size.** To achieve an adequate sample size, six centres in the Netherlands, with a specific department specialized in vertigo, are participating. In these centres, there is one ENT-surgeon who is in charge of the trial and recruits patients from their outpatient clinic. Presentations to inform medical professionals and to promote the study are held in these centres. When a patient is eligible, the coordinating investigator or research nurse will arrange for all of the study's requirements in order to keep the burden for the ENT-surgeons on the trial sites as low as possible. The coordinating investigator will be full-time involved in the PREDMEN-trial. Additionally, the trial will be promoted in hospitals throughout the Netherlands, national congresses, informative websites on MD, and online patient communities.
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	**Method of generating the allocation sequence (eg, computer- generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign Interventions** Subjects will be randomly assigned to either methylprednisolone or placebo with a 1:1 allocation as per computer-generated random sequence of block sizes of 2 and 4 subjects, stratified by site generated by Castor EDC ® SLL certified
Allocation concealment mechanism	16b	**Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned** Participants will be randomised using Castor EDC ® SLL certified, which is an online data management program. This program will send the randomisation code for a specific trail

		participant to the pharmacy who is preparing the medication. In this way allocation concealment will be ensured to all concealed parties (physicians, research nurses, patients, data manager, statistician etc). Trial subjects, treating physicians and outcome assessors will be blinded throughout the entire study.
Implementation	16c	**Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions** All patients who give their consent and meet the inclusion criteria will be randomised. The ENT-surgeon or Research nurse in charge of recruitment will request randomization via mail, castorEDC, or phone to the coordinating investigator. Only the coordinating investigator can randomise patients. An automated email to the pharmacy with the randomization code will then be sent. On the day of allocation, the trial pharmacist will prepare the blinded trial medication (either methylprednisolone or placebo) and give it to the ENT surgeon for injection.
Blinding (masking)	17a	**Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how** Any individual involved in the trail, except for the pharmacy staff, will be blinded. This implies that all trial subjects, treatment physicians/nurses, outcome assessors and statisticians, will remain blinded until the trial's completion.
	17b	**If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial** Emergency unblinding may occur in the following situations: in case of a medical emergency where knowledge of the blinded treatment is necessary, for the treatment of (serious) adverse event, in the event of a SUSAR (Suspected Unexpected Serious Adverse Reaction) needing expedited reporting. The investigator must document the action taken and promptly notify the sponsor. Code breaks should only occur in exceptional circumstances as mentioned above and if it is absolutely essential for further management of the participant.
Methods: Data collection, management, and analysis		
Data collection methods	18a	**Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.** Primary/Secondary outcomes: After a written informed consent is retrieved, subjects will visit the study site for the treatment with methylprednisolone/placebo at day 1 and at day 15 (with a visit window of 5 days), during a follow-up visit at 6 months, and during the end of trial visit at 12 months after first study treatment. Telephone contacts will take place at 3 and 9 monthspost-study treatment to discuss DizzyQuest app compliance and the occurrence of adverse events and use of concomitant medication. Tables presented in *question 12* and *13* display the outcome measurements collected. Training + certification: Each individual involved in the trial must be in possession of a good

clinical practice (GCP) or BROK-certificate. In order to train all trail personnel, presentations at each trial site were held during the initiation visitation to discuss all study requirements and standard operating procedures.

18b **Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols.**

Patients will be closely monitored during the entire trial. Every Monday we will receive an output of patients' DizzyQuest usage, which will help us monitor compliance of patients. To avoid data loss, we will get in contact with patients who fail to report through the application and ask them to complete the questionnaires. Additionally, patients will have in-depth conversations and be questioned about their experiences during the trial at every follow-up visit, in which we can trace and solve potential obstacles.

Data management

19 **Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol**

The handling of personal data complies with the Dutch Personal Data Protection Act (in Dutch: De Wet Algemene Verordering Gegevensbescherming, AVG). All data collected for the trail, including but not limited to demographic data, audiological questionnaires, data from the DizzyQuest app will be entered in a ISO 9001 and ISO 27001:2005 certified Castor® EDC (electronic CRF). Personal and medical data that needs to be collected for the trail will be extracted from electronic medical records. We will use an unambiguous subject identification code that allows identification of all the data reported for each subject. The subject code will be documented on the subject identification list which will be filed in the ISF. There will be a subject identification list per participating site. The subject identification list, and any other data/documents containing personal identifiable information, of the participating site will remain at the site and will not be shared with the sponsor (LUMC) or any other participating site. Only members of the study team, who will be documented on the site signature and delegation log per site, will have access to the study data.

Analysed and processed data will be kept in a secured folder on the ENT department network drive of the LUMC, with restricted access to only the members of the study team. Every night backups are saved by the hospital IT automatically. The digital trial master file will be saved in PaNaMa RMS the research management system of the LUMC. Any hard copy documents will be stored in a locked cabinet at the ENT department of the LUMC. The (digital) investigator site files of the participating sites will be stored according to local procedures following the applicable regulations. The blinding is safeguarded by the pharmacies of all participating trial sites. If the study will not continue, all essential documents will be maintained for at least 2 years after formal discontinuation. All data will be stored for 25 years after the last subject has had the last study visit.

Statistical methods

20a **Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol**

Ordinal regression using mixed model analysis will be used to analyse the primary outcome

(i.e., class of vertigo). In addition, generalized estimating equation (GEE) analysis of the actual vertigo attacks recorded using the DizzyQuest app will be used to estimate the incidence rate ratio (IRR) for comparison between the methylprednisolone and placebo groups.

Mixed model analysis will be used to analyse differences in the questionnaire scores (DHI, TFI, FLS, eQ-5D/VAS, iMCQ, iPCQ) between the two groups. Logistic regression analysis will be used to analyse the remaining secondary outcomes (incidence of escape interventions, hearing loss, and adverse events).

In order to evaluate the average costs and outcomes between the methylprednisolone and placebo groups for the cost-effectiveness analysis, intention-to-treat and net-benefit analysis will be used. For all statistical analysis, multiple imputation to adjust for missing data will all be used. QALYs will be calculated using the Dutch tariff for the EuroQoL EQ-5D-5L and as sensitivity analysis the visual analogue scale valuing health, with power-transformation

20b **Methods for any additional analyses (eg, subgroup and adjusted analyses)**

Subgroup analyses will be performed with regard to sex, duration of the disease and the type of MD. Two sensitivity analyses will be carried out in addition to the intention to treat analysis: a per protocol analysis in which patients who received additional co-interventions to achieve vertigo control are excluded; and an as-treated analysis in which participants who received additional co-interventions are analysed.

20c **Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)**

Missing, unused and spurious data values will be coded as ‘888’; ambiguous values (e.g. if two or more boxes are ticked for a single dimension) will be treated as missing data. multiple imputations will be used to account for missing data.

Methods: Monitoring

Data monitoring 21a **Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol.**
Alternatively, an explanation of why a DMC is not needed

Since the intervention is categorized a low risk profile study no Data Safety Monitor Board (DSMB) or Data Monitoring Committee (DMC) is required and patient safety and treatment efficacy will we be performed by the independent expert.

21b **Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial.**

Interim analysis will be performed on the primary endpoint when 50% of the patients have been randomized and completed a follow-up of 6 months, where comparability of baseline characteristics will be assessed. In this analyses, differences in vertigo control between the two study arms should not be greater than 45%. In addition, if the difference

in vertigo control reveals to be clinically significant (i.e. >20%), but ≤ 20% of the participants in methylprednisolone reach vertigo control, the study will be terminated because of convincing effect of the treatment in the intervention arm.

Harms 22 **Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct**

Patients will be informed that Adverse Events (AE), Serious Adverse Events (SAE) and Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported as soon as possible to their ENT-surgeon or research nurse. Additional queries are made at 3, 6, 9, and 12 months to ensure that they did not fail to report occurrences. These events will be registered throughout the trial in Castor EDC.

Each SAE must be reported to the sponsor site within 24 hours after the physicians' knowledge. A SUSAR must be reported depending on the seriousness of the reaction and will be as follows:

- In the case of fatal or life-threatening SUSARs, not later than **7 days** after the sponsor became aware of the reaction
- In the case of non-fatal or non-life-threatening SUSARs, not later than **15 days** after the sponsor became aware of the reaction
- In the case of a SUSARs which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, not later than **7 days** after the sponsor became aware of the reaction being fatal or life-threatening

The sponsor site will report the SAEs or SUSAR through the web portal of CTIS that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse event.

Auditing 23 **Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor**

Monitoring in all sites in the Netherlands will be executed by one assigned monitor of the LUMC according to the monitor plan. The monitor will visit each centre yearly. The visitation frequency can be altered based on the amount of inclusions. During the visitation the monitor will verify:

- Source data verification
- In,- and exclusion criteria
- Informed consent
- Control of the Trial Master File
- SAE's/SUSARS
- Trial procedures
- Product accountability
- Visitation of the pharmacy

The principal investigator of a participating centre receives a summary of the findings after each monitoring visit. The monitor report includes: a summary of reviewed trial data; a general description of the quality; a summary of key findings / facts, deviations and deficiencies; an overview of measures and recommendations to ensure compliance with the protocol; an "overall" conclusion.

Ethics and dissemination

Research ethics approval	24	**Plans for seeking research ethics committee/institutional review board (REC/IRB) approval** The PREDMEN trial was submitted via the Clinical Trial Information System (CTIS), with CTIS number: *2023-503340-13-00*, reviewed by the Medical Review Research Ethics Committee Leiden The Hague Delft (MREC LDD), and authorized for execution in the Netherlands under the European Clinical Trial Regulation (ECTR), with ClinicalTrials.gov ID: *NCT05851508.* Additionally, the institutional research board of each participating centre individually reviewed and approved the study. The study is conducted in accordance with the principles outlined in the Declaration of Helsinki (October 2013), the Medical Research Involving Human Subjects Act (WMO, 26 February 1998), the International Conference on Harmonization Good Clinical Practice (ICH GCP, November 2016) guidelines, and any other applicable guidelines, regulations, and Acts.
Protocol amendments	25	**Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)** Any modifications to the protocol which may impact on the conduct of the study, affecting the patients, study procedures, or significant administrative aspects will require an official amendment to the protocol. This amendment must be approved in the clinical trials information system. Minor corrections to the protocol, which have no impact on the study, will be discussed with the sponsor's research team, and these minor corrections will be reported to the clinial trials information system if a major revision is submitted.
Consent or assent	26a	**Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)** Patients will be introduced to the trail and given a patient information letter by trained research nurses, ENT-surgeons, or the coordinating investigator. After a few days, research nurses or the coordinating investigator will have an informed consent conversation with patients and answer their questions. When the patient agrees to participate in the trial, the research nurse, involved ENT-surgeon or coordinating investigator will obtain a written informed consent.
	26b	**Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable** Not applicable
Confidentiality	27	**How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial.** Source documents for this study will include hospital records and procedure reports and

		data collection forms. These documents will be used to enter data on the (e)CRFs. Data reported on the (e)CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification code. Each study site has its own investigator site file, where study specific information is stored. This ISF will be secured with password-protected access systems, available to trial personnel only. All other participant information such as signed consent forms, will be stored in locked file cabinets in areas with limited access on the trial site. DizzyQuest app: All data handling will be documented in a processing agreement between the LUMC and the company that created the DizzyQuest App (Psymate). Until a reliable internet connection is established, the user's smartphone will store the DizzyQuest app's data. The smartphone stores data that is encrypted and inaccessible to outside parties. Data will be sent to the Smart eHealth servers in Belgium when the smartphone connects to the internet. All data will be automatically removed from the smartphone after the data transfer.
Declaration of interests	28	**Financial and other competing interests for principal investigators for the overall trial and each study site** None
Access to data	29	**Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators** Only the coordinating investigators and PI of the sponsor site will have access to the entire data set. Other principal investigators will have direct access to their own site's dataset and will have access to a cleaned data set of all sites on request. To ensure confidentiality, any identifying participant information will be removed from data distributed to project team members.
Ancillary and post-trial care	30	**Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation** The study has been classified as a low risk profile study. Therefore we do not anticipate any harm from trial participation. When the trial has completed after one year, the patient will be returned to the care of his personal ENT-surgeon. However, when any harm from trial participation occurs, the sponsor has an insurance that is in accordance with the legal requirements in the Netherlands (Article 7 WMO, under 1). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

Dissemination policy	31a	**Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions .**

After completion of the trial, all patients who wish to know to which study arm they were allocated, will be informed.

Within one year from the end of a clinical trial in all Member States concerned, the sponsor will submit to the EU database CTIS a summary of the results of the clinical trial. The content of the summary of the results is set out in CTR Annex IV. It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of the summary is set out in CTR Annex V.

Furthermore, abstracts, papers and oral presentations will be submitted to several symposia and scientific papers. There will be two classes of reports of the PREDMEN trial:

A. Reports of the major outcomes of the PREDMEN trial.
B. Reports addressing in detail on aspect of the PREDMEN trial

Each paper, abstract, or oral presentation will be reviewed and approved by the sponsor's research team.

31b **Authorship eligibility guidelines and any intended use of professional writers**

Researchers who have been involved from the beginning and are certain to receive authorship will be listed as below:

Abstracts/papers/oral presentation: M.M.E. Boreel MD, B.F. van Esch, MD, PhD, B.M. Mol, MSc PhD, prof. P.P.G. van Benthem, MD, PhD, prof. T.D. Bruintjes, MD, PhD.

These arrangements for publication are based on the following merits: M.M.E. Boreel is the PhD student and is working full time on the research. B.F. van Esch is the principal investigator, B.M. Mol is head of research support, P.P.G. van Benthem is professor and the head of the Otorhinolaryngology Department and. T.D. Bruintjes is Professor Otorhinolaryngology, in particular Ménière's disease, and project leader. Other authors of participating centres will be added to the manuscript according to their participation and number of subjects they have included.

31c **Plans, if any, for granting public access to the full protocol, participant- level dataset, and statistical code**

In a period of no more than 2 years after the collection of the 1-year post randomization interviews and diaries, we will deliver a completely deidentified data set to an appropriate archive for sharing purposes. In due course, consultations will be held with the data protection officer regarding the preparation of this dataset. So that it complies with Dutch and local (LUMC) laws and regulations.

Appendices

Informed consent materials	32	**Model consent form and other related documentation given to participants and authorised surrogates** The patient information letter and informed consent form is included in the appendix.
Biological specimens	33	**Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable** Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

References:

1. Basura, G.J., et al., *Clinical Practice Guideline: Ménière's Disease.* Otolaryngol Head Neck Surg, 2020. **162**(2_suppl): p. S1-s55.
2. Hamid, M. and D. Trune, *Issues, indications, and controversies regarding intratympanic steroid perfusion.* Curr Opin Otolaryngol Head Neck Surg, 2008. **16**(5): p. 434-40.
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5. Webster, K.E., et al., *Intratympanic corticosteroids for Ménière's disease.* Cochrane Database Syst Rev, 2023. **2**(2): p. Cd015245.
6. Salt, A.N. and S.K. Plontke, *Pharmacokinetic principles in the inner ear: Influence of drug properties on intratympanic applications.* Hear Res, 2018. **368**: p. 28-40.
7. Parnes, L.S., A.H. Sun, and D.J. Freeman, *Corticosteroid pharmacokinetics in the inner ear fluids: an animal study followed by clinical application.* Laryngoscope, 1999. **109**(7 Pt 2): p. 1-17.
8. Cao, Z., et al., *Different medications for the treatment of Ménière's disease by intratympanic injection: A systematic review and network meta-analysis.* Clin Otolaryngol, 2019. **44**(4): p. 619-627.
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Reporting checklist for randomised trial.

Based on the CONSORT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the CONSORTreporting guidelines, and cite them as:

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

		Reporting Item	Page Number
Title and Abstract			
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	2
Introduction			
Background and objectives	#2a	Scientific background and explanation of rationale	4-5
Background and objectives	#2b	Specific objectives or hypothesis	5-6
Methods			
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	7

Trial design	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7
Participants	#4a	Eligibility criteria for participants	7-8
Participants	#4b	Settings and locations where the data were collected	7
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	10-11-12
Sample size	#7a	How sample size was determined.	8-9
Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	14-15
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	9
Randomization - Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size)	9
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	9-10
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	9

Blinding	#11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	12-13
Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12-13
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	10-11-12
Results			
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	21
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	21
Recruitment	#14a	Dates defining the periods of recruitment and follow-up	19
Recruitment	#14b	Why the trial ended or was stopped	N/A
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	21
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10-11-12
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	20
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	20
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	14
Discussion			

Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	3
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Registration	#23	Registration number and name of trial registry	14
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings	N/A
Other information			
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Registration	#23	Registration number and name of trial registry	14
Protocol	#24	Where the full trial protocol can be accessed, if available	N/A
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	16

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The effectiveness of intratympanic injections with methylPREDnisolon versus placebo in the treatment of vertigo attacks in MENière's disease (PREDMEN trial): a study protocol for a phase-3 multicentre, double-blinded, randomized, placebo-controlled trial

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The effectiveness of intratympanic injections with methylPREDnisolon versus placebo in the treatment of vertigo attacks in MENière's disease (PREDMEN trial): a study protocol for a phase-3 multicentre, double-blinded, randomized, placebo-controlled trial

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Abstract

Introduction: Intratympanic corticosteroids are commonly used in the treatment of Menière's disease (MD). However, few and small randomized controlled trials (RCT) on the effectiveness of intratympanic corticosteroids have been performed. A recent Cochrane review suggested that a well conducted placebo-controlled RCT with a large study population is required to evaluate the effectiveness of the use of intratympanic corticosteroids in MD. The following protocol describes a phase-3 multicentre, double-blinded, randomized, placebo-controlled trial to compare the effectiveness of methylprednisolone (62.5 mg/ml) to a placebo (sodium chloride 0.9%).

Methods and analysis: We aim to recruit 148 patients with unilateral MD from 6 hospitals in the Netherlands. Patients will be randomly assigned to either the methylprednisolone, or the placebo group. Two injections will be given, one at baseline and one after two weeks. Follow-up assessments will be done at 3, 6, 9 and 12 months. The primary outcome will be the frequency of vertigo attacks. Attacks will be evaluated daily with the DizzyQuest app. Secondary outcomes include hearing loss, tinnitus, health-related quality of life, use of co-interventions and escape medication, (serious) adverse events and cost-effectiveness. These will be evaluated with audiometry and multiple commonly used, validated questionnaires. For the primary and secondary outcomes mixed model analysis, estimating equation (GEE) analysis and logistic regression analysis will be used.

Ethics and Dissemination: This study was submitted via the Clinical Trials Information System, reviewed and approved by the Medical Research Ethics Committee Leiden The Hague Delft and the local institutional review board of each participating centre. All data will be presented ensuring the integrity and anonymity of patients. Results will be published in scientific journals and presented on (inter)national conferences.

Trial Registration: This study is registered at ClinicalTrials.gov Protocol Registration and Results System, with the registration ID: NCT05851508.

Strengths and limitations:

- In this randomized placebo-controlled study both participants and clinicians will remain blinded throughout the follow-up period, therefore minimizing the risk of bias.
- The prospective design with patients daily recording their vertigo attack directly in an app, lowers the risk of missing data and recall bias.
- This study includes a rather large patient population of 148 patients.
- VM and MD share multiple features in terms of clinical presentation and other symptomatology, distinguishing between the two could be challenging and therefore could form a possible limitation in this study.
- Subanalyses on clinical subgroups of MD (autoimmune, familial, and MD + migraine) will be difficult to conduct, because many patients cannot be classified in a subgroup or are part of multiple subgroups.

Introduction

Menière's disease (MD) is a clinical condition characterized by tinnitus and aural fullness, low- to mid-frequency sensorineural hearing loss, and spontaneous episodes of vertigo that can last 20 minutes to 12 hours [1]. Patients with MD experience a worse quality of life than healthy patients due to vertigo, tinnitus and hearing loss [2]. In addition, higher levels of anxiety and depression are seen in patients with MD [3].

Although its aetiology is unknown, endolymphatic hydrops (EH) is thought to be associated with MD. Almost all patients with MD have EH, but not all patients with EH have symptoms of MD. It is unknown if EH is a result of MD or a causal factor for MD [4, 5]. Until this day there is no agreement as to the ideal treatment of MD, due to the lack of evidence for the effect of various therapies. Current treatment consists of dietary and lifestyle modifications, oral diuretics, vestibular rehabilitation for chronic imbalance, intratympanic therapy, and/or ablative surgery [1]. With intratympanic gentamicin and corticosteroid injections the drug is directly delivered into the middle ear, from where it will be absorbed in the inner ear. Unlike gentamicin, corticosteroid therapy does not carry a risk of causing hearing loss. Therefore, it is currently the first step of standard care in the treatment of MD [1]. Although the mechanism of action of steroids on the inner ear remains speculative, it may improve cochlear blood flow and stabilize the vascular endothelium which enhances fluid homeostasis by upregulation of cochlear ion gene expression [6]. Recently, a Cochrane review was published evaluating the use of intratympanic corticosteroids in MD [7]. In this review, 10 randomized controlled trials (RCTs) and quasi-RCTs comparing intratympanic corticosteroids, all using dexamethasone, compared to either placebo or no treatment were included. The authors found that the evidence for the use of dexamethasone is uncertain. Intratympanic dexamethasone injection may marginally reduce the frequency of vertigo attacks. Regarding hearing and tinnitus, improvement was seen, but without statistical significance.

The most commonly intratympanically administered corticosteroids are dexamethasone and methylprednisolone [1]. Phillips et al. [8] determined the efficacy of intratympanic OTO-104 (a

sustained-released dexamethasone hydrogel) for the treatment of MD, in three double blind, placebo-controlled RCTs, with a total of 165, 174 and 148 patients respectively. OTO-104 showed numerically larger decreases in definitive vertigo days compared with placebo across all three studies. However, in only one study this difference was statistically significant. Pharmacokinetic studies show that dexamethasone phosphate has molecular and pharmacokinetic characteristics that complicate its use as a topical therapy for hearing disorders, which may explain its questionable effectiveness. [9]. An animal study found that the concentrations of methylprednisolone are higher and have longer duration in perilymph and endolymph compared to dexamethasone and hydrocortisone, and therefore could be a more effective drug [10]. Typically soluble forms of methylprednisolone are administered and expected to be less permeable through the membranous boundaries compared to the less polar forms. However, there is no data whether these soluble forms are metabolized to the base form in the ear and if they are, at what rate [9]. Despite the fact that little is known about the pharmacokinetics of methylprednisolone, there are clinical indications of its effectiveness [11, 12]. Cao et al. [12] performed a literature review and demonstrated that methylprednisolone is more effective than dexamethasone in a clinical setting.

Although in the last decade, there is an increasing tendency and emerging evidence for the use of intratympanic steroids, no large RCT on the effectiveness of intratympanic methylprednisolone in MD has been conducted [13]. A meta-analysis published in 2021 included eight studies comparing intratympanic gentamicin to intratympanic corticosteroids, in which gentamicin appeared to be superior in terms of control of vertigo attacks [14]. However, gentamicin is known to be ototoxic and can induce hearing loss. Patel et al. [15] compared intratympanic gentamicin injections to methylprednisolone injections in a double-blind RCT with a 24-month post-treatment follow-up. Vertigo attacks decreased in both groups, indicating a treatment effect. However, no placebo group was involved and the sample size was relatively small (n=60).

In conclusion, there is a need of solid evidence on the effectiveness of intratympanic steroids in MD. Until now the effectiveness of methylprednisolone has not been investigated by means of a placebo

controlled RCT. Therefore a well conducted RCT with a large study population and a long follow-up period is now required to evaluate the effectiveness of intratympanic methylprednisolone in MD. In this protocol we present the methods of a phase-3 multicentre, double-blinded, randomized, placebo-controlled trial evaluating the effectiveness of intratympanic injections with methylprednisolone versus placebo in the treatment for MD patients.

Methods

Trial design

In this phase 3, multicentre, double-blind, placebo-controlled randomized trial the effect of two intratympanic methylprednisolone sodium succinate 62.5 mg/ml (Solu-Medrol in Act-O-Vial, Pfizer BV) injections 14 days apart is compared to two placebo (i.e., sodium-chloride 0.9%) injections with the same time interval on vertigo attacks in patients with MD. Parallel groups will be randomly assigned to one of both arms and outcomes will be measured during a one year follow-up period.

Study subjects

Patients with MD will be recruited by six participating sites in the Netherlands and will be approached by their own ENT specialist and informed about this trial. After a one week reflection period, informed consent forms can be signed. Baseline and outcome data will be extracted from participants' electronic medical records and collected in the cloud-based clinical data management platform Castor EDC (version v2023.1.0.1, LUMC).

In- and exclusion criteria

In order to be eligible for the study a study subject needs to have unilateral, definite MD according to the diagnostic criteria derived from the American Academy Otolaryngology Head and Neck Surgery, Classification Committee of the Bárány Society, European Academy of Otology and Neurotology and International Classification of Vestibular Disorders published in 2015 [16]. The criteria for definite MD are:

Two or more spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours,

AND

Audiometrically documented low- to medium-frequency sensorineural hearing loss in one ear,

defining the affected ear on at least one occasion before, during or after one of the episodes of vertigo,

AND

Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear (not better accounted for by another vestibular diagnosis).

Other inclusion criteria are:

- Age ≥ 18 years at the start of the trial.
- ≥ 4 vertigo attacks over the last 6 months.
- Willing to adhere to daily completion of study questionnaires using the DizzyQuest app and to the follow-up assessments.

Study subjects who meets any of the following criteria will be excluded:

- Bilateral MD.
- Severe disability (e.g. neurological, orthopedic, cardiovascular) or serious concurrent illness that might interfere with treatment or follow-up.
- Active additional neuro-otologic disorders that may mimic MD (e.g. vestibular migraine (VM) , recurrent vestibulopathy, phobic postural vertigo, vertebro-basilar TIAs, acoustic neuroma).
- Otitis media with effusion based on tympanogram results.
- History of intratympanic injections with corticosteroid less than 6 months ago.
- History of intratympanic injections with gentamicin or ear surgery for treating MD.
- Pregnant women or nursing women.

Sample size

A sample size calculation was performed based on recommendations as summarized in the Clinical Practice Guideline for Menière's disease [1]. An expected proportion of subjects achieving vertigo control of 87.5% was assumed for methylprednisolone treatment compared to an assumed 67.5% for placebo, i.e. a difference in treatment effect of 20%. With a statistical power (1-β) of 80% and a type 1 error (α) of 5%, 67 patients per group are required. With an estimated 10% loss-to-follow-up, 74 patients will be included in each arm, giving a total sample size of 148. In total, over the six

participating centres, 340 MD patients yearly visit the Otolaryngology department and will be screened for the trial. It is expected that 15% will meet the inclusion criteria and will be willing to participate. This will result in approximately 50 eligible patients for inclusion per year.

Randomization and blinding

Subjects will be randomly assigned to either methylprednisolone or placebo with a 1:1 allocation as per computer-generated random sequence, stratified by site generated by Castor EDC. Blinding will be maintained until all subjects have finished their treatment phases. All study participants, participating medical professionals, and outcome assessors will be blinded. The independent epidemiologist and pharmacy personnel will both be unblinded during randomization and therapy allocation.

Study procedure

After a one week reflection period and agreement with trial participation by means of signing the informed consent, a patient will be seen at the study site. Standard inquiries about the patient's demographics, family history, and medical history—particularly regarding any history of auto-immune disease and migraine—are made at the informed consent visit. Thereafter patients will receive an intratympanic injection with either methylprednisolone or placebo at day 1 and day 15 with a window of three days. The patient is lying down in supine position with their head rotated to the side and prior to the intratympanic injection the eardrum will be anesthetized. Thereafter, a myringotomy is being performed and a small spinal puncture needle is passed through the tympanic membrane to inject fluid into the middle ear cavity at the level of the round window. The patient is then required to remain on their side without swallowing for thirty minutes.

At baseline, results of Magnetic Resonance Imaging (MRI) must be available to make sure other causes of disease are ruled out [17]. To assess the vestibular function of the horizontal semicircular

canals, the caloric test and video Head Impulse test (vHIT) will be performed. To evaluate the anterior and posterior semi-circular canals, the vHIT will be conducted at baseline in order to assess the presence of vestibular hypofunction or areflexia.

During a follow-up period of one year, overall wellbeing and vertigo attacks are being assessed daily with the aid of the DizzyQuest app. Two telephone contacts will take place at 3 and 6 months to assess possible (serious) adverse events, DizzyQuest app compliance and the use of escape medication or co-interventions. A physical follow-up visit in the outpatient clinic will be scheduled at 6 and 12 months. During these outpatient clinic visits additional audiometry and multiple questionnaires concerning tinnitus, dizziness and quality of life will be filled-in. An overview of follow-up moments of the corresponding outcomes and a flowchart of the study procedure are presented in table 1 and figure 1, respectively.

Outcome measures

Vertigo: The primary outcome measure will be defined by the class of vertigo as defined by the AAO HNS 1995 guideline. The class of vertigo is defined by the average number of attacks per month during 6 and 12 months after treatment divided by the number of attacks 6 months before treatment times 100. As a result the following class of vertigo is defined:

- A: Complete control of vertigo = 0
- B: Substantial control of vertigo = 1-40
- C: Limited control of vertigo = 41- 80
- D: Insignificant control of vertigo = 81 – 120'
- E: Worse control of vertigo > 120

Moreover, the daily attack vertigo frequency will be monitored with the aid of the DizzyQuest app (Psymate 2)[18, 19]. The DizzyQuest app will be used to track the primary outcome measure, the frequency of dizziness attacks. Patients will answer daily questionnaires about their health and wellbeing and patients can report vertigo attacks at any time using the Dizzy quest app. Additionally,

the Dizziness Handicap Inventory (DHI) questionnaire will be administered at baseline, after six months, and after a year to assess how dizziness affects daily life [20]. The effect of the injections in the DHI will be reported as raw data, as well as change in handicap category (mild handicap, moderate handicap or severe handicap) related to improvement, unchanged or worsened.

The following secondary outcomes will be measured

Hearing: Pure tone audiometry will be performed at baseline, after six months, and after a year. In line with the guideline of AAO HNS 1995 guideline[17], we will use the average scores of four-tone audiometry at 0.5, 1, 2 and 3 kHz and we will assess the word recognition scores as the percent correct score at the presentation level in decibel. A decrease of ≥ 10 dB or a change in word recognition score of ≥ 15% points is considered clinically significant.

Tinnitus: The Tinnitus Functional Index (TFI) measures the impact of tinnitus on daily life [21]. This survey will be administered at baseline, after six months, and after a year. One point decrease of increase will be defined as improved or worsened tinnitus respectively [22].

Quality of life: Apart from the DHI and TFI, the EuroQol 5 dimension (EQ-5D) and EuroQol – Visual Analog Scale (EQ-VAS) questionnaires will be used to measure quality of life at baseline, after six and twelve months [23, 24]. These questionnaire are standardized tests of health status that are used in economic and clinical evaluations

Use of escape medication and co-interventions: In case participants remain suffering from intolerable vertigo attacks, regardless of which group they are allocated to, the use of metoclopramide and co-interventions such as intratympanic injections of gentamicin or methylprednisolone will be allowed and documented during the follow up period. This will be based on experience of participants vertigo

frequency and shared decision making. If patients receive additional treatment, they will not be unblinded.

Adverse events

Patients will be informed that Adverse Events, Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions must be reported as soon as possible to their ENT-surgeon or research nurse. Additional queries are made at 3, 6, 9, and 12 months to ensure that they did not fail to report occurrences. These events will be registered throughout the trial in Castor EDC. Each serious adverse event must be reported to the sponsor within 24 hours after the physicians' knowledge. In the event that patient safety is compromised, patients can be unblinded.

Cost-effectiveness

Cost-effectiveness will be assessed from both a healthcare and societal cost-utility perspective, where cost per avoided vertigo attack and cost per Quality Adjusted Life Year (QALY), respectively, will be used as the metrics. MD -related medical expenses, other healthcare expenses, and the cost of lost productivity will all be included in the estimated societal cost, which will be calculated using the iMTA Medical Consumption Questionnaire (iMCQ) and IMTA Productivity Cost Questionnaire (IPCQ).

Statistical analysis

Ordinal regression using mixed model analysis will be used to analyse the primary outcome (i.e., class of vertigo). In addition, generalized estimating equation (GEE) analysis of the actual vertigo attacks recorded using the DizzyQuest app will be used to estimate the incidence rate ratio (IRR) for comparison between the methylprednisolone and placebo groups. A decrease of 100% is considered total control of vertigo episodes, while a reduction of >40% is considered a substantial and thus clinically relevant reduction [17].

Mixed model analysis will be used to analyse differences in the questionnaire scores (DHI, TFI, FLS, eQ-5D/VAS, iMCQ, iPCQ) between the two groups. Logistic regression analysis will be used to analyse the remaining secondary outcomes (incidence of escape interventions, hearing loss, and adverse events). A reduction in hearing of 10 decibels or a 15% change in word recognition will be regarded as a clinically significant difference [17].

Subgroup analyses will be performed with regard to sex, duration of the disease and the type of MD (delayed MD, familial MD, and autoimmune MD). These subgroups will be defined as described in Frejo et al [25]. Two sensitivity analyses will be carried out in addition to the intention to treat analysis: a per protocol analysis in which patients who received additional co-interventions to achieve vertigo control are excluded; and an as-treated analysis in which participants who received additional co-interventions are analysed.

In order to evaluate the average costs and outcomes between the methylprednisolone and placebo groups for the cost-effectiveness analysis, intention-to-treat and net-benefit analysis will be used. For all statistical analysis, multiple imputation to adjust for missing data will all be used[26]. QALYs will be calculated using the Dutch tariff for the EuroQoL EQ-5D-5L [23] and as sensitivity analysis the visual analogue scale valuing health, with power-transformation [27]. All outcomes with corresponding statistical analysis methods are summarized in Table 2. A p-value < 0.05 will be considered as statistically significant for all analyses and will be performed using SPSS version 25 or higher (SPSS Chicago Illinois, USA).

Patient and public involvement

The PREDMEN trial is supported by the Dutch Association for the hard of hearing, and more specifically its Committee Dizziness and Balance (Commissie Duizeligheid en Evenwicht van Hoormij-NVVS) and the Dutch association for psychological health care and social services for patients with SNHL and tinnitus (GGMD). Both organizations are involved in the realization of the trial, the writing process and implementation of trial results. Moreover, they will serve as a sounding board for MD

patients participating in this trial and one patient representative will be a member of the steering committee. In line with their suggestions, patients will be involved in every stage of the research.

Ethics and Dissemination

Ethics

The PREDMEN trial was submitted via the Clinical Trial Information System (CTIS), with CTIS number: *2023-503340-13-00*, reviewed by the Medical Research Ethics Committee Leiden The Hague Delft (MREC LDD), and authorized for execution in the Netherlands under the European Clinical Trial Regulation (ECTR). Additionally, the institutional research board and the Board of Directors of each participating centre (Franciscus Gasthuis & Vlietland, Gelre ziekenhuizen, HagaZiekenhuis, Leiden University Medical Centre, Maastricht University Medical Centre, Medisch Spectrum Twente) individually reviewed and approved the study. The study is conducted in accordance with the principles outlined in the Declaration of Helsinki (October 2013), the Medical Research Involving Human Subjects Act (WMO, 26 February 1998), the International Conference on Harmonization Good Clinical Practice (ICH GCP, November 2016) guidelines, and any other applicable guidelines, regulations, and Acts.

Patient safety

Minor complications such as persistent membrane perforation (5.9%) and otitis media (7%) can occur [7, 28, 29] Safety risk will be comparable to normal clinical practice and it is not expected that significant adverse events will be seen in the intervention arm. ENT specialists are experienced with intratympanic injections due to its application in patients with sudden deafness. Since the intervention is characterized as a low risk profile study, no Data Safety Monitoring Board (DSMB) is required [30]. The sponsor will submit a report on the safety of each investigational medicinal product used in the clinical trial through CTIS. Interim analysis will be performed on the primary endpoint when 50% of the patients have been randomized and completed a follow-up of 6 months, where comparability of baseline characteristics will be assessed. In this analyses, differences in vertigo control between the two study arms should not be greater than 45%. In addition, if the difference in vertigo control

reveals to be clinically significant (i.e. >20%), but ≤ 20% of the participants in methylprednisolone reach vertigo control, the study will be terminated because of convincing effect of the treatment in the intervention arm.

Data safety

The handling of personal data complies with the Dutch Personal Data Protection Act (AVG). All data collected for the trial, including but not limited to demographic data, audiological questionnaires, and data from the DizzyQuest app will be entered in a ISO 9001 and ISO 27001:2005 certified Castor® EDC database (electronic CRF). Data will be protected with a unique subject identification code which is linked to a pass-word protected subject identification list. Only members of the study team, who will be documented on the site signature and delegation log per site, will have access to the study data. The sponsor and investigator will keep a clinical trial master file which will contain the essential documents relating to the clinical trial.

Dissemination

A summary of the results of this study will be submitted to CTIS within one year after termination of the trial. Results will also be published in scientific journals and presented on (inter)national conferences. All information that will be presented will be done so in a way that integrity and anonymity of patients is ensured. All data will be stored for 25 years after the last subject has had the last study visit.

Trial Registration

This study is registered at ClinicalTrials.gov Protocol Registration and Results System, with the registration ID: NCT05851508.

Contributors

The conception and design of the study were developed by BE, BM, PPvB, TB. The drafting of the original protocol was done by BE, BM, TB, TS. The coordination of the study was carried out by BE, BM, MB, TB. Patient recruitment and collection of data was performed by BE, MB, PPvB, TB. The statistical analysis plan was designed by TS. The present manuscript was drafted by MB. The funding was obtained by BE, BM, TB. All authors read and approved the final manuscript prior to submission for publication.

BE and TB acted as the guarantors of this study.

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Competing interests

No competing interest was declared.

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Tables

Table 1. Overview of follow-up moments of the corresponding outcomes

Moment in trial	*Type of follow up*	*Outcomes*
From moment of inclusion unit 1 year follow up		Daily questionnaire in Dizzy quest app
Baseline	First intratympanic injection	Baseline parameters MRI Otoscopy Audiometry: PTA and SDS Vestibular testing: vHIT, caloric testing Questionnaires: DHI, TFI, FLS, EQ-5D/VAS, iMCQ, iPCQ
2 weeks	Second intratympanic injection	Otoscopy Complications Use of co-interventions Use of escape medication (S)AE
3 months, 9 months	Telephone consult	Complications Use of co-interventions Use of escape medication (S)AE
6 months, 12 months	Consult in outpatient clinic	Otoscopy Complications Audiometry: PTA and SDS Questionnaires: DHI, TFI, FLS, EQ-5D/VAS, iMCQ, iPCQ Use of co-interventions Use of escape medication (S)AE

Abbreviations: DHI, Dizziness Handicap Index; EQ 5D, EuroQol 5D; FLS, Functional Level Scale; HIT, Head Impulse Test; iMCQ, iMTA Medical Consumption Questionnaire; iPCQ, iMTA Productivity Cost; Questionnaire; MRI, Magnetic Resonance Imaging; PTA, Pure Tone Average; SDS, speech discrimination score; (S)AE, (Serious) Adverse Event, TFI, Tinnitus Functional Index

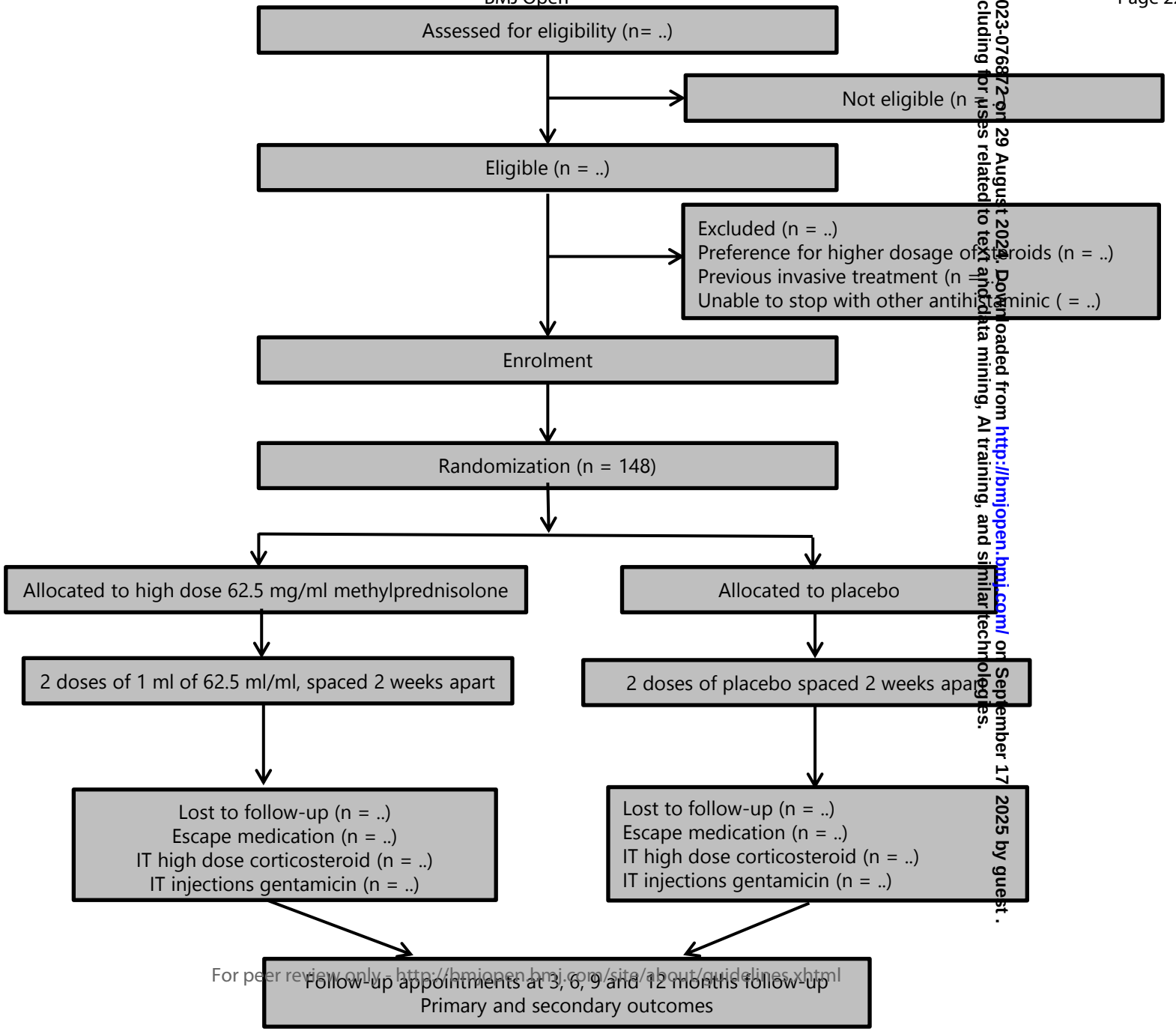
Table 2 Outcomes with corresponding statistical analysis method

	Outcome	*Type of data*	*Analysis*
Primary outcome	Number of spontaneous vertigo attacks, lasting more than 20 minutes	Count	Generalized estimating equation
	AAO HNS (1995) class of vertigo		Mixed model analysis
Secondary outcomes	Hearing (PTA; 0.5, 1, 2, 3 kHz and SDS)	Continuous	Logistic regression analysis
	Tinnitus (TFI)	Categorical	Mixed model analysis
	Quality of life (DHI, TFI, FLS, eQ-5D/VAS)	Categorical	Mixed model analysis
	Use of escape medication and co-interventions	Count	Logistic regression analysis
	(S)AE	Binary	Logistic regression analysis
	Cost effectiveness (iMCQ, iPCQ)	Categorical	Mixed model analysis

Abbreviations: DHI, Dizziness Handicap Index; EQ 5D, EuroQol 5D; FLS, Functional Level Scale; iMCQ, iMTA Medical Consumption Questionnaire; iPCQ, iMTA Productivity Cost; Questionnaire; PTA, Pure Tone Average; SDS, speech discrimination score; (S)AE, (Serious) Adverse Event, TFI, Tinnitus Functional Index

Figure 1.

Flowchart of the study procedure. IT, intratympanic.



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	**Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym** A phase-3 multicentre, double-blinded, randomised, placebo-controlled trial to compare the effectiveness of intratympanic injections with methylPREDnisolon versus placebo in the treatment of vertigo attacks in MENière's disease (PREDMEN trial).
Trial registration	2a	**Trial identifier and registry name. If not yet registered, name of intended registry** Clinical trial number: 2023-503340-13-00 Clinicaltrails.gov: ID: NCT05851508
	2b	**All items from the World Health Organization Trial Registration Data Set**

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT05851508
Date of registration in primary registry	3, oktober, 2023
Secondary identifying numbers	Identifiers: NCT05851508, Unique Protocol ID: PREDMEN, Secondary ID: 10140022110009
Source(s) of monetary or material support	Stichting ZonMW: *file number: 10140022110009*
Primary sponsor	Leiden University Medical Centre
Secondary sponsor(s)	Leiden University Medical Centre
Contact for public queries	M.M.E. Boreel, MD, Leiden University Medical Centre M.M.E.Boreel@lumc.nl
Contact for scientific queries	M.M.E. Boreel, MD, Leiden University Medical Centre M.M.E.Boreel@lumc.nl
Public title	The Effectiveness of Intratympanic Methylprednisolone Injections Compared to Placebo in the Treatment of Vertigo Attacks in Meniere's Disease (PREDME
Scientific title	A Multicenter, Double-blinded, Randomised, Placebo-controlled Trial to Compare the Effectiveness of Intratympanic Injections

	MethylPREDnisolone Versus Placebo in the Treatment of Vertigo Attacks in MENière's Disease (PREDMEN Trial).
Countries of recruitment	Netherlands
Health condition(s) or problem(s) studied	Meniere's Disease (MD)
Intervention(s)	Intratympanic injection with Methylprednisolone 62.5 mg/ ml
	Placebo comparator: Intratympanic injection with saline, (sodiumchloride 0.9%)
Key inclusion and exclusion criteria	Inclusion criteria: - Unilateral, definite MD according to the diagnostic criteria derived from the American Academy Otolaryngology Head and Neck Surgery, Classification-Page 4 of 6 Committee of the Bárány Society, European Academy of Otology and Neurotology and International Classification of Vestibular Disorders - adult patients (≥ 18 years), patient hospitalized - ≥ 4 vertigo attacks over the last 6 months. - Willing to adhere to daily Dizzy quest app questionnaires and the follow-up assessments
	Exclusion criteria: - Bilateral MD - Severe disability (e.g. neurological, orthopaedic, cardiovascular) or serious concurrent illness that might interfere with treatment or follow-up. - Active additional neuro-otologic disorders that may mimic MD (e.g. vestibular migraine, recurrent vestibulopathy, phobic postural vertigo, vertebro-basilar TIAs, acoustic neuroma). - Otitis media with effusion based on tympanogram results. - History of intratympanic injections with corticosteroid less than 6 months ago. - History of intratympanic injections with gentamicin or ear surgery for treating MD. - Pregnant women and nursing women.
Study type	Interventional
	Allocation: randomised intervention model. Masking: double blind (subject, caregiver, investigator, outcomes assessor)
	Primary purpose: treatment
	Phase III
Date of first enrolment	Oktober 2023
Target sample size	148
Recruitment status	Recruiting
Primary outcome(s)	Vertigo attacks
Key secondary outcomes	Hearing loss, tinnitus, health-related quality of life, use of escape medication, adverse events, cost-effectiveness, co-interventions, overall function, impact of dizziness.

Protocol version 3 **Date and version identifier**

- Issue date: 02-05-2023
- Version 4.0

Funding	4	**Sources and types of financial, material, and other support** This project will be funded by ZonMW *file number: 10140022110009*
Roles and responsibilities	5a	**Names, affiliations, and roles of protocol contributors** Coordinating investigators: • T.D. Bruintjes, MD, PhD, prof, ENT-surgeon, department of Otorhinolaryngology Head and Neck surgery. • M.M.E. Boreel, MD, physician-researcher, department of Otorhinolaryngology Head and Neck surgery. Head of research support Leiden University Medical Centre: • B.M. Mol, PhD, Head of research support Leiden University Medical Centre Principal investigators: • B.F. van Esch, MD, PhD, ENT surgeon, Department Otorhinolaryngology and Head and Neck Surgery, Leiden University Medical Centre, The Netherlands • S.M. Winters, MD, PhD , ENT-surgeon Apeldoorn Dizziness Centre, Gelre Ziekenhuizen • W.P.A. Kelders, MD, PhD , ENT-surgeon , Rotterdam Dizziness Centre, Franciscus Gasthuis & Vlietland • R. van den Berg, MD, PhD, ENT-surgeon Department of Otorhinolaryngology, Maastricht UMC+ • H.M. Blom, MD, PhD, Professor, ENT-surgeon Department of Otorhinolaryngology, Haga Hospital • D.A. van Zuylen, MD, ENT-surgeon, Department of Otorhinolaryngology, Medisch Spectrum Twente Epidemiologist: • T. Schermer, PhD, Apeldoorn Dizziness Centre, Gelre Hospital, Apeldoorn, The Netherlands
	5b	**Name and contact information for the trial sponsor** Legal Representative of Sponsor: mw. K.G. Freriks-Bauritius Title: Management director division 3. Leiden University Medical Centre, Albinusdreef 2, 2333 ZA Leiden secretariaatbbd3enzorg@lumc.nl.
	5c	**Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities** The funding source does not have any role in this study during its execution, analysis, interpretation of the data or decision to submit results.

5d **Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)**

Coordinating investigator:

- Study planning
- Randomisation
- Responsible for trial master file
- Planning of monitor visits
- Identification Study subjects, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol and investigators brochure
- Reporting of AE/SAE/SUSAR
- Processing and analysing raw data

Coordinating investigator/PI sponsor site/head of research support LUMC:

- Design and Conduct of the PREDMEN trial
- Preparation, writing and revisions of research protocol, agreement on final protocol
- Write and review all required documents (Patient information folder, Informed Consent, Standard operating procedures etc.)
- Organisation of approval medical ethical committee
- Preparation of Investigators brochure and CRF
- Publication study reports
- Reviewing progress of study and if necessary, making changes to the protocol or other necessary documents
- Management of the budget and problems with individual centrecontracts
- Provide annual risk report

Principal investigators/Research nurse Study sites:

- Identification Study subjects, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol and investigators brochure

Epidemiologist:

- Performing interim analysis
- Processing and analysing raw data

Introduction

Background and rationale

6a **Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention**

Menière's disease (MD) is a clinical condition characterized by tinnitus and aural fullness, low- to mid-frequency sensorineural hearing loss, and spontaneous episodes of vertigo that can last 20 minutes to 12 hours [1]. Although its aetiology is unknown, endolymphatic hydrops (EH) is thought to be associated with MD and treatment is often focussed on the regulation of EH.

Current treatment of MD consists of dietary and lifestyle modifications, oral diuretics, vestibular rehabilitation for chronic imbalance, intratympanic therapy, and/or ablative surgery [1]. With intratympanic gentamicin and intratympanic corticosteroid injections the drug is directly delivered into the middle ear, from where it will be absorbed in the inner ear. Although the mechanism of action

of steroids on the inner ear remains speculative it may improve cochlear blood flow and stabilize the vascular endothelium which enhances fluid homeostasis by upregulation of cochlear ion gene expression [2]. Unlike gentamicin, corticosteroid therapy does not carry a risk of causing hearing loss. Therefore, it is currently the first step of standard care in the treatment of MD [1].

Although in the last decade, there has been an increasing tendency and emerging evidence for the use of intratympanic steroids, no large RCT on the effectiveness of intratympanic methylprednisolone in MD has been conducted. A meta-analysis published in 2021 included eight studies comparing intratympanic gentamicin to intratympanic corticosteroids, in which gentamicin appeared to be superior in terms of control of vertigo attacks [3]. However, gentamicin is known to be ototoxic and can induce hearing loss. Patel et al. compared intratympanic gentamicin injections to methylprednisolone injections in a double-blind RCT with a 24-month post-treatment follow-up [4]. Vertigo attacks decreased in both groups, indicating a treatment effect. However, no placebo group was involved and the sample size was relatively small (n=60). Recently, a Cochrane review was published evaluating the use of intratympanic corticosteroids in MD. In this review, 10 randomised controlled trials (RCTs) and quasi-RCTs comparing intratympanic corticosteroids, all using dexamethasone, compared to either placebo or no treatment were included [5]. The authors found that the evidence for the use of dexamethasone is uncertain. Intratympanic dexamethasone injection may marginally reduce the frequency of vertigo attacks. Regarding hearing and tinnitus improvement was seen, but without statistical significance.

In conclusion, there is a need of solid evidence on the effectiveness of intratympanic steroids in MD. Until now the effectiveness of methylprednisolone has not been investigated by means of a placebo controlled RCT. Therefore a well-conducted RCT with a large study population and a long follow-up period is now required to evaluate the effectiveness of intratympanic methylprednisolone in MD.

	6b	**Explanation for choice of comparators**
		Pharmacokinetic studies show that dexamethasone phosphate has molecular and pharmacokinetic characteristics that complicate its use as a topical therapy for hearing disorders, which may explain its questionable effectiveness [6]. An animal study found that the concentrations of methylprednisolone are higher and have longer duration in perilymph and endolymph compared to dexamethasone and hydrocortisone, and therefore could be a more effective drug [7]. Typically soluble forms of methylprednisolone are administered and expected to be less permeable through the membranous boundaries compared to the less polar forms. However, there is no data whether these soluble forms are metabolized to the base form in the ear and if they are, at what rate. Despite the fact that little is known about the pharmacokinetics of methylprednisolone, there are clinical indications of its effectiveness [8, 9]. Cao et al. performed a literature review and demonstrated that methylprednisolone is more effective than dexamethasone in a clinical setting [8]. Therefore we choose to compare methylprednisolone to placebo.
Objectives	7	**Specific objectives or hypotheses**
		Primary objective: To determine whether methylprednisolone (62.5 mg/ml) is superior to placebo in controlling vertigo attacks in patients with MD.
		Secondary objective: To determine whether methylprednisolone (62.5 mg/ml) is superior to placebo in controlling tinnitus, hearing, quality of life, use of escape medication, adverse events and cost-effectiveness.
Trial design	8	**Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)**

The PREDMEN study is a phase-3 multicentre, double-blinded, randomized, parallel group trial with patients suffering from MD with a total follow-up period of 12 months.

Methods: Participants, interventions, and outcomes

Study setting	9	**Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained** Six medical centres from across the Netherlands are participating in the study in order to enrol a sufficient number of patients in three years. In these centres, an ENT-surgeon, specialized in dizziness, is involved and principal investigator for the trial. The following centres are participating in the PREDMEN study: - Leiden Universitair Medisch Centrum, Leiden (sponsor site) - Apeldoorns Duizeligheidscentrum, Gelre Ziekenhuizen, Apeldoorn - Maastrichts Universitair Medisch Centrum, Maastricht - Haga-ziekenhuis, Den Haag - Medisch Spectrum Twente, Enschede - Rotterdam Duizeligheids Centrum, Rotterdam
Eligibility criteria	10	**Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)** **Inclusion criteria:** - Unilateral, definite MD according to the diagnostic criteria derived from the American Academy Otolaryngology Head and Neck Surgery, Classification- Page 4 of 6 Committee of the Bárány Society, European Academy of Otology and Neurotology and International Classification of Vestibular Disorders - Adult patient (≥ 18 years), patient hospitalized - ≥ 4 vertigo attacks over the last 6 months. - Willing to adhere to daily Dizzy quest app questionnaires and the follow-up assessments.. **Exclusion criteria**: - Bilateral MD - Severe disability (e.g. neurological, orthopaedic, cardiovascular) or serious concurrent illness that might interfere with treatment or follow-up. - Active additional neuro-otologic disorders that may mimic MD (e.g. vestibular migraine, recurrent vestibulopathy, phobic postural vertigo, vertebro-basilar TIAs, acoustic neuroma). - Otitis media with effusion based on tympanogram results. - History of intratympanic injections with corticosteroid less than 6 months ago. - History of intratympanic injections with gentamicin or ear surgery for treating MD. - Pregnant women and nursing women
Interventions	11a	**Interventions for each group with sufficient detail to allow replication, including how and when they will be administered**

Eligible patients will be randomised in equal proportion between the Methylprednisolone (62.5 mg/ml) and the Placebo (sodium chloride 0.9%). group. Intratympanic injections will be administered two times at timepoint 0 and after two weeks.

Name and description of investigational product(s):

*M*ethylprednisolone sodium succinate 62.5 mg/ml (Solu-Medrol in Act-O-Vial).

Generic name methylprednisolone sodium succinate. *Manufacture a.o.:* Pfizer B.V.; Rivium Westlaan 142 2909 LD Capelle a/d Ijssel, The Netherlands

Name and description of Placebo:

Placebo: Saline, Sodiumchloride (NaCl) 0,9% saline for injection

11b **Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)**

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw subjects from the study for urgent medical reasons. We do not anticipate any major events arising from the study intervention because the trail medicine is already widely used and the study is classified as a low risk profile study.

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

Patients cannot fail to take the medication because the intervention is an injection administered by the physician at timepoint zero and after two weeks. However, patients are obliged to complete short questionnaires on the DizzyQuest app on a daily basis. We will obtain a weekly output of the patients compliance to the app, which will aid in patient monitoring. To avoid data loss, we will contact patients who fail to report through the application and ask them to complete the questionnaires. We expect no problems assessing the other outcomes because they will be monitored throughout clinical or telephonic appointments.

11d **Relevant concomitant care and interventions that are permitted or prohibited during the trial**

Prohibited medication:

- The administration of antihistaminic drugs including betahistine is prohibited due to the risk of drug competition. The true effect of methylprednisolone could therefore be over- or underestimated

Specific permitted medication:

- In case subjects continue to suffer from vertigo attacks in a high frequency, co-interventions can be offered, in either in the placebo,- or the intervention group. Co interventions include: intratympanic injections of gentamicin, dexamethasone, methylprednisolone or triamcinolone.

- Subjects are allowed to use metoclopramide in the acute phase of vertigo

Outcomes 12 **Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended**

Primary objective(s)	**Endpoint for the primary objective(s)**	**Analysis metric primary endpoint**	**Timepoints for primary objectives:**
To determine whether intratympanic injection with 62.5 mg/ml methylprednisolone is superior to placebo in reducing the frequency of vertigo attacks in patients diagnosed with unilateral MD during one year of follow-up.	Complete or substantial control of vertigo	Measured daily with the DizzyQuest app. Categorized in class of vertigo (A-D)	Daily
Secondary objective(s), if applicable	**Endpoint(s) for secondary objective(s), if**	**Analysis metric** **Secondary endpoint**	**Timepoints for secondary objectives:**
Use of co-interventions	Use of intratympanic injections with either gentamicin, methylprednisolone dexamethasone or triamcinolone	Frequency co-intervention used	Asked at 3, 6, 9 and 12 months
Use of Escape medication	Use of metoclopramide	Frequency escape medication used	Asked at 3, 6, 9 and 12 months
Hearing	Pure tone audiometry, word recognition score.	A decrease of ≥ 10 dB or a change in word recognition score of ≥ 15% points is considered clinically significant.	Measured at baseline, after 6 and 12 months
Change in quality of life on dizziness related quality of life	Questionnaires: Dizziness handicap inventory (DHI), Functional level scale (FLS)	DHI: handicap levels: Mild handicap = 16-34 Points; Moderate handicap = 36-52 Points and Severe handicap = 54+ Points. Improved, unchanged of worsened of level. FLS: Improvement (≥ 1 point decrease), unchanged or worsened (≤ 1 point increase)	Measured at baseline, after 6 and 12 months
Change in quality of life on tinnitus	Tinnitus handicap inventory (TFI)	Improvement (≥ 1 point decrease), unchanged or worsened (≤ 1 point increase)	Measured at baseline, after 6 and 12 months
Change in quality of life in general	EQ-5D and EQ-VAS scores	Mean value, standard deviation or, if the data is skewed, the median values and the 25th and 75th percentiles.	Measured at baseline, after 6 and 12 months
Adverse events	SAE, SUSARs	Frequency SAE/SUSAR	Reported when it occurs
Incremental cost differences	Cost-effectiveness and cost-utility analysis. Medical Consumption Questionnaire (iMCQ) and IMTA productivity Cost Questionnaire (iPCQ)	Cost-effectiveness analysis (costs per prevented vertigo attack), and a cost-utility analysis (costs per QALY, calculated from the EQ-5D and EQ-VAS	Measured at baseline, after 6 and 12 months

13 **Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure**

Participant timeline

Assessments	Screening Eligibility Clinic (-8 days till day -1)	Treatment visit 1 Clinic Baseline (± 5 days)	Treatment visit 1 Clinic 2 weeks (± 5 days)	Follow-up phase Telephone 3 months (± 2 weeks)	Follow-up phase Clinic 6 months (± 2 weeks)	Follow-up phase Telephone 9 months (± 2 weeks)	End of trial Clinic 12 months (± 2 weeks)
Explanation study participation to subject	X						
Screening procedure	X						
Sign Informed Consent	X						
Inclusion/exclusion criteria	X						
Medical History	X						
Baseline parameters (sex, age, onset age of MD etc.)	X						
Concomitant medication	X			X	X	X	X
Pure Tone (PTA) and Speech Discrimination Score (SDS)	X[1,3]				X		X
Vestibular tests (caloric testing and vHIT)	X[3]						
MRI – petrous bone	X[3]						
Functional Level Scale (FLS)	X				X[2]		X
Dizziness Handicap Inventory (DHI)	X				X[2]		X
Tinnitus Functional Index (TFI)	X				X[2]		X
Generic quality of life questionnaires (EQ-5D, EQ-VAS)	X				X[2]		X
IMTA Medical Consumption Questionnaire (iMCQ) and IMTA productivity Cost Questionnaire (iPCQ)	X				X[2]		X
Randomisation	X						
Methylprednisolone or placebo		x	x				X
(S)AEs		x	x	X	X	X	X
Co intervention: injection with either methylprednisolone, dexamethasone, triamcinolone or gentamicine				Daily			
Dizzy quest app	Daily						

	14	**Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size**
Sample size calculations		The sample size calculation is based on recommendations as summarized in the Clinical Practice Guideline by Bassura et al [1]. The absolute effect on vertigo control class is expected to be 87.5% in the methylprednisolone group versus 67.5% in the placebo group. In previous studies similar high percentages of control of vertigo were seen when placebo or sham surgery was compared to an intervention. Sample size calculation was executed with the software available from DSS Research Tools (https://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/statisticalpowercalculators.aspx analyses performed with the expected 20% difference in absolute effect on vertigo and two-tailed testing). With a statistical power of 80% and a Type 1 error of 5% 67 patients per group are required. With an estimated 10% loss-to-follow-up, we aim to include 74 patients in each group.
Recruitment	15	**Strategies for achieving adequate participant enrolment to reach target sample size.** To achieve an adequate sample size, six centres in the Netherlands, with a specific department specialized in vertigo, are participating. In these centres, there is one ENT-surgeon who is in charge of the trial and recruits patients from their outpatient clinic. Presentations to inform medical professionals and to promote the study are held in these centres. When a patient is eligible, the coordinating investigator or research nurse will arrange for all of the study's requirements in order to keep the burden for the ENT-surgeons on the trial sites as low as possible. The coordinating investigator will be full-time involved in the PREDMEN-trial. Additionally, the trial will be promoted in hospitals throughout the Netherlands, national congresses, informative websites on MD, and online patient communities.
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	**Method of generating the allocation sequence (eg, computer- generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign Interventions** Subjects will be randomly assigned to either methylprednisolone or placebo with a 1:1 allocation as per computer-generated random sequence of block sizes of 2 and 4 subjects, stratified by site generated by Castor EDC ® SLL certified
Allocation concealment mechanism	16b	**Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned** Participants will be randomised using Castor EDC ® SLL certified, which is an online data management program. This program will send the randomisation code for a specific trail

		participant to the pharmacy who is preparing the medication. In this way allocation concealment will be ensured to all concealed parties (physicians, research nurses, patients, data manager, statistician etc). Trial subjects, treating physicians and outcome assessors will be blinded throughout the entire study.
Implementation	16c	**Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions** All patients who give their consent and meet the inclusion criteria will be randomised. The ENT-surgeon or Research nurse in charge of recruitment will request randomization via mail, castorEDC, or phone to the coordinating investigator. Only the coordinating investigator can randomise patients. An automated email to the pharmacy with the randomization code will then be sent. On the day of allocation, the trial pharmacist will prepare the blinded trial medication (either methylprednisolone or placebo) and give it to the ENT surgeon for injection.
Blinding (masking)	17a	**Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how** Any individual involved in the trail, except for the pharmacy staff, will be blinded. This implies that all trial subjects, treatment physicians/nurses, outcome assessors and statisticians, will remain blinded until the trial's completion.
	17b	**If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial** Emergency unblinding may occur in the following situations: in case of a medical emergency where knowledge of the blinded treatment is necessary, for the treatment of (serious) adverse event, in the event of a SUSAR (Suspected Unexpected Serious Adverse Reaction) needing expedited reporting. The investigator must document the action taken and promptly notify the sponsor. Code breaks should only occur in exceptional circumstances as mentioned above and if it is absolutely essential for further management of the participant.
Methods: Data collection, management, and analysis		
Data collection methods	18a	**Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.** Primary/Secondary outcomes: After a written informed consent is retrieved, subjects will visit the study site for the treatment with methylprednisolone/placebo at day 1 and at day 15 (with a visit window of 5 days), during a follow-up visit at 6 months, and during the end of trial visit at 12 months after first study treatment. Telephone contacts will take place at 3 and 9 monthspost-study treatment to discuss DizzyQuest app compliance and the occurrence of adverse events and use of concomitant medication. Tables presented in *question 12* and *13* display the outcome measurements collected. Training + certification: Each individual involved in the trial must be in possession of a good

clinical practice (GCP) or BROK-certificate. In order to train all trail personnel, presentations at each trial site were held during the initiation visitation to discuss all study requirements and standard operating procedures.

18b **Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols.**

Patients will be closely monitored during the entire trial. Every Monday we will receive an output of patients' DizzyQuest usage, which will help us monitor compliance of patients. To avoid data loss, we will get in contact with patients who fail to report through the application and ask them to complete the questionnaires. Additionally, patients will have in-depth conversations and be questioned about their experiences during the trial at every follow-up visit, in which we can trace and solve potential obstacles.

Data management

19 **Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol**

The handling of personal data complies with the Dutch Personal Data Protection Act (in Dutch: De Wet Algemene Verordering Gegevensbescherming, AVG). All data collected for the trail, including but not limited to demographic data, audiological questionnaires, data from the DizzyQuest app will be entered in a ISO 9001 and ISO 27001:2005 certified Castor® EDC (electronic CRF). Personal and medical data that needs to be collected for the trail will be extracted from electronic medical records. We will use an unambiguous subject identification code that allows identification of all the data reported for each subject. The subject code will be documented on the subject identification list which will be filed in the ISF. There will be a subject identification list per participating site. The subject identification list, and any other data/documents containing personal identifiable information, of the participating site will remain at the site and will not be shared with the sponsor (LUMC) or any other participating site. Only members of the study team, who will be documented on the site signature and delegation log per site, will have access to the study data.

Analysed and processed data will be kept in a secured folder on the ENT department network drive of the LUMC, with restricted access to only the members of the study team. Every night backups are saved by the hospital IT automatically. The digital trial master file will be saved in PaNaMa RMS the research management system of the LUMC. Any hard copy documents will be stored in a locked cabinet at the ENT department of the LUMC. The (digital) investigator site files of the participating sites will be stored according to local procedures following the applicable regulations. The blinding is safeguarded by the pharmacies of all participating trial sites. If the study will not continue, all essential documents will be maintained for at least 2 years after formal discontinuation. All data will be stored for 25 years after the last subject has had the last study visit.

Statistical methods

20a **Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol**

Ordinal regression using mixed model analysis will be used to analyse the primary outcome

(i.e., class of vertigo). In addition, generalized estimating equation (GEE) analysis of the actual vertigo attacks recorded using the DizzyQuest app will be used to estimate the incidence rate ratio (IRR) for comparison between the methylprednisolone and placebo groups.

Mixed model analysis will be used to analyse differences in the questionnaire scores (DHI, TFI, FLS, eQ-5D/VAS, iMCQ, iPCQ) between the two groups. Logistic regression analysis will be used to analyse the remaining secondary outcomes (incidence of escape interventions, hearing loss, and adverse events).

In order to evaluate the average costs and outcomes between the methylprednisolone and placebo groups for the cost-effectiveness analysis, intention-to-treat and net-benefit analysis will be used. For all statistical analysis, multiple imputation to adjust for missing data will all be used. QALYs will be calculated using the Dutch tariff for the EuroQoL EQ-5D-5L and as sensitivity analysis the visual analogue scale valuing health, with power-transformation

20b **Methods for any additional analyses (eg, subgroup and adjusted analyses)**

Subgroup analyses will be performed with regard to sex, duration of the disease and the type of MD. Two sensitivity analyses will be carried out in addition to the intention to treat analysis: a per protocol analysis in which patients who received additional co-interventions to achieve vertigo control are excluded; and an as-treated analysis in which participants who received additional co-interventions are analysed.

20c **Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)**

Missing, unused and spurious data values will be coded as '888'; ambiguous values (e.g. if two or more boxes are ticked for a single dimension) will be treated as missing data. multiple imputations will be used to account for missing data.

Methods: Monitoring

Data monitoring

21a **Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol.**
Alternatively, an explanation of why a DMC is not needed

Since the intervention is categorized a low risk profile study no Data Safety Monitor Board (DSMB) or Data Monitoring Committee (DMC) is required and patient safety and treatment efficacy will we be performed by the independent expert.

21b **Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial.**

Interim analysis will be performed on the primary endpoint when 50% of the patients have been randomized and completed a follow-up of 6 months, where comparability of baseline characteristics will be assessed. In this analyses, differences in vertigo control between the two study arms should not be greater than 45%. In addition, if the difference

in vertigo control reveals to be clinically significant (i.e. >20%), but ≤ 20% of the participants in methylprednisolone reach vertigo control, the study will be terminated because of convincing effect of the treatment in the intervention arm.

Harms 22 **Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct**

Patients will be informed that Adverse Events (AE), Serious Adverse Events (SAE) and Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported as soon as possible to their ENT-surgeon or research nurse. Additional queries are made at 3, 6, 9, and 12 months to ensure that they did not fail to report occurrences. These events will be registered throughout the trial in Castor EDC.

Each SAE must be reported to the sponsor site within 24 hours after the physicians' knowledge. A SUSAR must be reported depending on the seriousness of the reaction and will be as follows:

- In the case of fatal or life-threatening SUSARs, not later than **7 days** after the sponsor became aware of the reaction
- In the case of non-fatal or non-life-threatening SUSARs, not later than **15 days** after the sponsor became aware of the reaction
- In the case of a SUSARs which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, not later than **7 days** after the sponsor became aware of the reaction being fatal or life-threatening

The sponsor site will report the SAEs or SUSAR through the web portal of CTIS that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse event.

Auditing 23 **Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor**

Monitoring in all sites in the Netherlands will be executed by one assigned monitor of the LUMC according to the monitor plan. The monitor will visit each centre yearly. The visitation frequency can be altered based on the amount of inclusions. During the visitation the monitor will verify:

- Source data verification
- In,- and exclusion criteria
- Informed consent
- Control of the Trial Master File
- SAE's/SUSARS
- Trial procedures
- Product accountability
- Visitation of the pharmacy

The principal investigator of a participating centre receives a summary of the findings after each monitoring visit. The monitor report includes: a summary of reviewed trial data; a general description of the quality; a summary of key findings / facts, deviations and deficiencies; an overview of measures and recommendations to ensure compliance with the protocol; an "overall" conclusion.

Ethics and dissemination

Research ethics approval	24	**Plans for seeking research ethics committee/institutional review board (REC/IRB) approval** The PREDMEN trial was submitted via the Clinical Trial Information System (CTIS), with CTIS number: *2023-503340-13-00*, reviewed by the Medical Review Research Ethics Committee Leiden The Hague Delft (MREC LDD), and authorized for execution in the Netherlands under the European Clinical Trial Regulation (ECTR), with ClinicalTrials.gov ID: *NCT05851508.* Additionally, the institutional research board of each participating centre individually reviewed and approved the study. The study is conducted in accordance with the principles outlined in the Declaration of Helsinki (October 2013), the Medical Research Involving Human Subjects Act (WMO, 26 February 1998), the International Conference on Harmonization Good Clinical Practice (ICH GCP, November 2016) guidelines, and any other applicable guidelines, regulations, and Acts.
Protocol amendments	25	**Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)** Any modifications to the protocol which may impact on the conduct of the study, affecting the patients, study procedures, or significant administrative aspects will require an official amendment to the protocol. This amendment must be approved in the clinical trials information system. Minor corrections to the protocol, which have no impact on the study, will be discussed with the sponsor's research team, and these minor corrections will be reported to the clinial trials information system if a major revision is submitted.
Consent or assent	26a	**Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)** Patients will be introduced to the trail and given a patient information letter by trained research nurses, ENT-surgeons, or the coordinating investigator. After a few days, research nurses or the coordinating investigator will have an informed consent conversation with patients and answer their questions. When the patient agrees to participate in the trial, the research nurse, involved ENT-surgeon or coordinating investigator will obtain a written informed consent.
	26b	**Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable** Not applicable
Confidentiality	27	**How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial.** Source documents for this study will include hospital records and procedure reports and

		data collection forms. These documents will be used to enter data on the (e)CRFs. Data reported on the (e)CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification code. Each study site has its own investigator site file, where study specific information is stored. This ISF will be secured with password-protected access systems, available to trial personnel only. All other participant information such as signed consent forms, will be stored in locked file cabinets in areas with limited access on the trial site. DizzyQuest app: All data handling will be documented in a processing agreement between the LUMC and the company that created the DizzyQuest App (Psymate). Until a reliable internet connection is established, the user's smartphone will store the DizzyQuest app's data. The smartphone stores data that is encrypted and inaccessible to outside parties. Data will be sent to the Smart eHealth servers in Belgium when the smartphone connects to the internet. All data will be automatically removed from the smartphone after the data transfer.
Declaration of interests	28	**Financial and other competing interests for principal investigators for the overall trial and each study site** None
Access to data	29	**Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators** Only the coordinating investigators and PI of the sponsor site will have access to the entire data set. Other principal investigators will have direct access to their own site's dataset and will have access to a cleaned data set of all sites on request. To ensure confidentiality, any identifying participant information will be removed from data distributed to project team members.
Ancillary and post-trial care	30	**Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation** The study has been classified as a low risk profile study. Therefore we do not anticipate any harm from trial participation. When the trial has completed after one year, the patient will be returned to the care of his personal ENT-surgeon. However, when any harm from trial participation occurs, the sponsor has an insurance that is in accordance with the legal requirements in the Netherlands (Article 7 WMO, under 1). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

Dissemination policy	31a	**Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions .**

After completion of the trial, all patients who wish to know to which study arm they were allocated, will be informed.

Within one year from the end of a clinical trial in all Member States concerned, the sponsor will submit to the EU database CTIS a summary of the results of the clinical trial. The content of the summary of the results is set out in CTR Annex IV. It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of the summary is set out in CTR Annex V.

Furthermore, abstracts, papers and oral presentations will be submitted to several symposia and scientific papers. There will be two classes of reports of the PREDMEN trial:

A. Reports of the major outcomes of the PREDMEN trial.
B. Reports addressing in detail on aspect of the PREDMEN trial

Each paper, abstract, or oral presentation will be reviewed and approved by the sponsor's research team.

31b **Authorship eligibility guidelines and any intended use of professional writers**

Researchers who have been involved from the beginning and are certain to receive authorship will be listed as below:

Abstracts/papers/oral presentation: M.M.E. Boreel MD, B.F. van Esch, MD, PhD, B.M. Mol, MSc PhD, prof. P.P.G. van Benthem, MD, PhD, prof. T.D. Bruintjes, MD, PhD.

These arrangements for publication are based on the following merits: M.M.E. Boreel is the PhD student and is working full time on the research. B.F. van Esch is the principal investigator, B.M. Mol is head of research support, P.P.G. van Benthem is professor and the head of the Otorhinolaryngology Department and. T.D. Bruintjes is Professor Otorhinolaryngology, in particular Ménière's disease, and project leader. Other authors of participating centres will be added to the manuscript according to their participation and number of subjects they have included.

31c **Plans, if any, for granting public access to the full protocol, participant- level dataset, and statistical code**

In a period of no more than 2 years after the collection of the 1-year post randomization interviews and diaries, we will deliver a completely deidentified data set to an appropriate archive for sharing purposes. In due course, consultations will be held with the data protection officer regarding the preparation of this dataset. So that it complies with Dutch and local (LUMC) laws and regulations.

Appendices

Informed consent materials	32	**Model consent form and other related documentation given to participants and authorised surrogates** The patient information letter and informed consent form is included in the appendix.
Biological specimens	33	**Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable** Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

References:

1. Basura, G.J., et al., *Clinical Practice Guideline: Ménière's Disease.* Otolaryngol Head Neck Surg, 2020. **162**(2_suppl): p. S1-s55.
2. Hamid, M. and D. Trune, *Issues, indications, and controversies regarding intratympanic steroid perfusion.* Curr Opin Otolaryngol Head Neck Surg, 2008. **16**(5): p. 434-40.
3. Jiang, M., Z. Zhang, and C. Zhao, *What is the efficacy of gentamicin on the incidence of vertigo attacks and hearing in patients with Meniere's disease compared with steroids? A meta-analysis.* Journal of Neurology, 2021. **268**(10): p. 3717-3727.
4. Patel, M., et al., *Intratympanic methylprednisolone versus gentamicin in patients with unilateral Ménière's disease: a randomised, double-blind, comparative effectiveness trial.* Lancet, 2016. **388**(10061): p. 2753-2762.
5. Webster, K.E., et al., *Intratympanic corticosteroids for Ménière's disease.* Cochrane Database Syst Rev, 2023. **2**(2): p. Cd015245.
6. Salt, A.N. and S.K. Plontke, *Pharmacokinetic principles in the inner ear: Influence of drug properties on intratympanic applications.* Hear Res, 2018. **368**: p. 28-40.
7. Parnes, L.S., A.H. Sun, and D.J. Freeman, *Corticosteroid pharmacokinetics in the inner ear fluids: an animal study followed by clinical application.* Laryngoscope, 1999. **109**(7 Pt 2): p. 1-17.
8. Cao, Z., et al., *Different medications for the treatment of Ménière's disease by intratympanic injection: A systematic review and network meta-analysis.* Clin Otolaryngol, 2019. **44**(4): p. 619-627.
9. Salt, A.N. and S.K. Plontke, *Principles of local drug delivery to the inner ear.* Audiol Neurootol, 2009. **14**(6): p. 350-60.

Reporting checklist for randomised trial.

Based on the CONSORT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the CONSORTreporting guidelines, and cite them as:

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

		Reporting Item	Page Number
Title and Abstract			
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	2
Introduction			
Background and objectives	#2a	Scientific background and explanation of rationale	4-5
Background and objectives	#2b	Specific objectives or hypothesis	5-6
Methods			
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	7

Trial design	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7
Participants	#4a	Eligibility criteria for participants	7-8
Participants	#4b	Settings and locations where the data were collected	7
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	10-11-12
Sample size	#7a	How sample size was determined.	8-9
Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	14-15
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	9
Randomization - Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size)	9
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	9-10
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	9

Blinding	#11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	12-13
Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12-13
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	10-11-12
Results			
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	21
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	21
Recruitment	#14a	Dates defining the periods of recruitment and follow-up	19
Recruitment	#14b	Why the trial ended or was stopped	N/A
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	21
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10-11-12
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	20
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	20
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	14
Discussion			

Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	3
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Registration	#23	Registration number and name of trial registry	14
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings	N/A
Other information			
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Registration	#23	Registration number and name of trial registry	14
Protocol	#24	Where the full trial protocol can be accessed, if available	N/A
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	16