A Phase II/III Trial on Rizatriptan for Vestibular Migraine

NCT02447991

June 22, 2018

SPECIFIC AIMS

Vestibular migraine (VM), also known as migrainous vertigo or migraine-associated vertigo, is characterized by recurrent vestibular attacks often accompanied by migraine headaches. It is a prevalent presenting complaint to physicians in primary care, otolaryngology, and neurology. Epidemiologic data suggest that VM may affect 1% of the general population and 10% of patients seeking treatment for recurrent attacks of vertigo. Yet, the clinical spectrum of VM and its underlying pathophysiological mechanisms remain unclear, with much debate about the causal relationship of vestibular symptoms and headache, no evidence-based guidelines for clinical management, limited characterization of its disease burden, and no information about its negative impact on health-related quality of life. Currently there is no proven therapy for VM. Vestibular suppressants such as meclizine and dimenhydrinate are often used for symptomatic relief, but they do not prevent attacks and may have sedating side effects. Uncontrolled case reports suggest that migraine abortive and prophylactic medications are effective for treating VM. Triptans, in particular, hold promise for aborting vestibular attacks in patients with VM based on the results of several uncontrolled studies and one underpowered controlled trial. However, substantial placebo response rates are well documented in controlled treatment trials for migraine, making it impossible to know if patients in these studies of VM responded to specific pharmacologic effects of study medications or non-specific elements of treatment.

The primary Specific Aim of this study is to conduct the first successful Phase II clinical trial of any medication for aborting vestibular attacks in subjects with VM, specifically to carry out a two-site, double blind, parallel arms, placebo controlled trial of rizatriptan. We hypothesize that rizatriptan will be superior to placebo in:

1a. Reducing the severity and duration of vestibular attacks in patients with VM,
1b. Reducing the severity of symptoms commonly associated with vestibular attacks in patients with VM (e.g., nausea, vomiting, motion sensitivity, gait disturbance, headache, photophobia, and phonophobia), and
1c. Improving treatment satisfaction and health-related quality of life in patients with VM, and that
1d. Rizatriptan will be well tolerated by patients with VM.

These efficacy and safety data will inform decisions about the feasibility of a Phase III clinical trial of rizatriptan for VM, but additional information will be needed to fully design such a trial. The sample size and duration of a Phase III trial will depend on the natural history of vestibular attacks in patients with VM. Subject selection criteria will depend on prevalence and confounding effects of comorbid conditions and use of co-existing therapies. Therefore, the secondary Specific Aim of this study is to collect data that will be crucial for preparing detailed Manuals of Operating Procedures for future Phase III trials. We hypothesize that needed data will include:

2a. The natural range of frequency and severity of vestibular attacks in treatment-seeking patients with VM,
2b. The type and severity of medical and psychiatric conditions that commonly coexist with VM, and
2c. The types, doses, and frequency of use of prescription and non-prescription medications for VM,

including data on the effects of these variables on the efficacy of rizatriptan for treating vertigo attacks in VM.

To accomplish these Specific Aims, we propose to enroll 240 patients diagnosed with VM from the busy tertiary neurotology practices at UCLA and Mayo Clinic into a 2-phase investigation consisting of an Observation Period of up to 12 months, followed by a Treatment Period of up to 3 treated episodes or end of study, whichever comes first. During the Observation Period we will prospectively characterize the frequency and severity of vestibular attacks and associated symptoms in VM, the prevalence and severity of comorbid conditions, and the use of abortive and prophylactic medications and non-prescription treatments in patients receiving usual clinical care. We will train patients to recognize vestibular spells appropriate for study treatment and stabilize potentially confounding comorbid conditions. We will measure subjects' satisfaction with usual care and their health-related quality of life. Approximately 120 persistently symptomatic subjects will be randomly assigned to treatment with either rizatriptan or placebo in a ratio of 2:1. We will measure the effects of study treatment on reducing or resolving vestibular and associated symptoms, reducing the need for additional symptomatic treatments, and improving treatment satisfaction and health related quality of life over the 48 hours that follow each treated attack. We will capture the incidence and severity of treatment-emergent adverse effects. The results will provide data to guide future Phase III study designs. They also may yield insights into pathophysiologic processes that cause VM and suggest directions for future mechanistic investigations.

RESEARCH STRATEGY

I. SIGNIFICANCE

A. What is vestibular migraine (VM)?

The observation that migraine and dizziness often occur together dates back to the nineteenth century when Livening noted their connection in his classic book *On Megrim: Sick Headaches and Some Allied Health Disorders*.[16] However, only in recent years have vestibular symptoms been recognized as part of the migraine syndrome. Vestibular migraine (VM), also known as migrainous vertigo and migraine-associated vertigo, affects about 1% of the general population and 10% of patients seen in dizziness and headache clinics.[17] Episodic vestibular symptoms occur in about 25% of unselected migraine patients.[18] Vestibular symptoms can occur during headaches, but often occur during headache-free intervals.[3-5,19,20] Only about one quarter of patients reliably experience headaches during vestibular attacks.[5,19] Vestibular attacks in patients with VM typically last from minutes to days.[3-5,21-23] If examined during an attack, patients with VM may show spontaneous or positional nystagmus that can have central or peripheral features, raising concerns about other neurotologic illnesses.[3,24-26] These factors have made it difficult to characterize the relationship between migraine and vestibular symptoms.[27] As a result, a causal relationship has not been proven. This problem has been used as an argument against the concept of VM, but it is no different than the situation with other transient symptoms that accompany migraine.[28] For example, scintillating scotomata are universally accepted as migrainous phenomena, yet their pathophysiologic link with headache is still unknown after hundreds of years of clinical observation. Conventional migraine and VM share numerous features. Both have a marked female preponderance (2-3:1).[5] Attacks of both can be precipitated by alcohol, lack of sleep, fasting, certain foods, and emotional stress.[21,23,28] Patients with VM have past or present histories of migraine and often have family histories of both migraine and vestibular symptoms.[29-30] Finally, case reports and case series suggest that migraine abortive and prophylactic agents, including triptans, may be effective for treating VM.[1-4]

Neurotologic conditions such as Meniere's disease and benign paroxysmal positional vertigo (BPPV) share some symptoms with VM.[6,31,32] Meniere's disease may start with recurrent vertigo without ear symptoms; however, with Meniere's disease, tinnitus and hearing loss invariably occur within a year of onset.[32,33] Vertigo attacks in BPPV are positional and last no more than 1-2 minutes. Vertigo attacks in VM may have a positional element, but symptoms persist even when patients are still and typically last longer than 2 minutes.[20] VM may coexist with Meniere's disease,[21] BPPV, chronic subjective dizziness (CSD),[34] anxiety, depression,[5] and other conditions that may alter its clinical presentation and morbidity. Recent advances in our understanding of the pathophysiologic mechanisms of migraine provide new hope for elucidating the link between periodic headaches and vestibular symptoms.[35] The proposed study may increase our knowledge of these factors, too.

The current (2nd) edition of International Classification of Headache Disorders (ICHD-II)[36] does not contain VM, but the recently published beta version of the 3rd edition does.[14] VM is defined the appendix of ICHD-3 (Table 1), which is the first step toward full recognition in the official nomenclaure.[14] These criteria define the types of vestibular symptoms; minimum number, severity, and duration of vestibular attacks; association of vestibular and migrainous symptoms; requirement for a migraine diagnosis; and absence of other causes of symptoms.

Table 1. Diagnostic criteria for vestibular migraine (as included in the appendix of ICHD-3, beta version)[14]

A	At least 5 episodes of fulfilling criteria C and D.
B	A current or past history of migraine without aura or migraine with aura.
C	Vestibular symptoms[a] of moderate or severe intensity,[b] lasting between 5 minutes and 72 hours.
D	At least 50% of episodes are associated with at least one of the following three migrainous features: 1. Headache with at least two of: a) unilateral location, b) pulsating quality, c) moderate or severe intensity, d) aggravation by routine physical activity 2. Photophobia and phonophobia 3. Visual aura

a. *Vestibular symptoms qualifying for a diagnosis of vestibular migraine include: 1) spontaneous vertigo – false sensation of self motion or that the visual surround is spinning or flowing; 2) positional vertigo – vertigo occurring after a change in head position; 3) visually-induced vertigo – vertigo triggered by a complex or large moving visual stimulus; 4) head-motion induced vertigo – vertigo occurring during head motion; 5) head motion-induced non-vertiginous dizziness with nausea, characterized by a sensation of disturbed spatial orientation.*

[b.] *Moderate, interferes with but does not prohibit daily activities; severe, prevents daily activities.*

B. What is the public health burden of VM?

Neuhauser et al.[20] found a 1% prevalence of VM in the general population of Germany and concluded that VM is underdiagnosed, causing considerable personal and health-care burden. At a rate of 10%, VM is the third most common diagnosis in specialty neurotology centers.[21] In our clinical practices, patients with VM have been symptomatic for an average of 4.5 years before referral and have seen 4-5 previous physicians for their symptoms.[34] Most have missed significant work, school, or home obligations.

C. How is VM treated? Why investigate an abortive versus a prophylactic therapy?

Currently there is no proven therapy for VM. Vestibular suppressants such as meclizine and dimenhydrinate are frequently used for symptomatic relief of vestibular symptoms, but these medications do not prevent vestibular attacks and often have sedating side effects.[3] Case reports[1-4] and one uncontrolled trial[7] suggest that commonly used migraine abortive and prophylactic drugs may be effective for treating vestibular attacks in patients with VM, but high placebo effects are well documented in controlled treatment trials for migraine headaches. A single placebo-controlled study suggested benefit for a triptan in VM, but the study failed to reach statistical significance for several important reasons (see "Prior Controlled Study" below).[8] Advantages of studying an abortive rather than a prophylactic drug in this first-ever phase II treatment trial of VM include: 1) adequate phase I data exist to design a triptan trial for VM, 2) the target symptoms (discrete attacks) and primary outcome measure (response vs. no response) are straightforward, 3) patients prefer taking medication just at the time that symptoms occur, rather than daily medication, 4) potential confounds can be managed more easily in an abortive study than in a prophylactic trail, and 5) we will learn more about the clinical course and pathophysiology of VM (secondary Specific Aim), whether or not the abortive agent is effective.

D. What is the scientific basis for treating VM with triptans?

The serotonin system has long been implicated in the pathogenesis of migraine.[37] Many common migraine drugs are thought to exert effects on serotonin receptors or serotonin uptake, including ergotamines, beta blockers, methysergide, and tricyclic antidepressants. The trigeminal vascular theory for migraine headaches[38] holds that trigeminal nerve fibers surrounding pial arteries on the ventral surface of the brain are activated, releasing substance P and calcitonin gene related protein, increasing vascular permeability, dilating cerebral vessels, and triggering a local inflammatory response that further activates pain fibers of the trigeminal vascular system. Triptans constrict pain-producing intracranial extracerebral blood vessels, reduce trigeminal sensory nerve activity, and inhibit vasoactive neuropeptide release,[39] possibly via their strong affinity for $5HT_{1B}$ and $5HT_{1D}$ receptors,[39,40] which are heavily expressed in the peripheral trigeminal system. These receptors are also present in vestibular ganglion cells and inner ear cells in rats and monkeys.[41] Parallel expression of $5HT_{1B}$ and $5HT_{1D}$ receptors in the peripheral vestibular and trigeminal systems suggests that similar mechanisms may be at work to produce vertigo and headaches. Triptans could, therefore, be effective for treating both vertigo and headaches.[41] Serotonin agonists decrease emesis in animal models of motion sickness.[42-44] In three small placebo controlled studies, rizatriptan protected patients with migraine/VM from developing motion sickness triggered by vestibular stimulation (N=10, N=25),[9,11] but not visual motion stimulation (N=10).[10] In controlled studies for non-vestibular migraine headaches, rizatriptan significantly decreased the severity of nausea.[45]

E. What are the risks of taking triptans?

Triptans are well tolerated with minimal side effects, the most common being somnolence.[46] Patients with ischemic or other heart disease, uncontrolled hypertension, and basilar migraine are typically excluded from treatment with triptans because of concerns about vasospasm. However, in vitro and in vivo data suggest minimal vasoconstrictor effects on coronary or peripheral arteries in normal human subjects.[47-49] In an uncontrolled case series of three women with VM, triptan treatment resolved vertigo attacks but induced or aggravated headaches.[2] This has not been reported in any other cases of VM patients treated with triptans, but it illustrates the importance of conducting a well controlled treatment trial measuring all VM symptoms.

F. What are the pharmacokinetics and costs of rizatriptan versus other triptans?

Rizatriptan is rapidly and near completely absorbed (~90%) from the gastrointestinal tract following administration of the oral tablet. Absolute bioavailability is 47% owing to moderate first-pass metabolism.[50] The mean time to maximum plasma concentration (t_{max}) following a single rizatriptan 10-mg tablet in healthy volunteers is about 1 hour,[50,51] which is shorter than that of other triptans.[46] Rizatriptan has a relatively short plasma half-life of approximately 2–2.5 hours.[50,51] Healthy males showed no unexpected accumulation of

rizatriptan following administration of multiple 10 mg doses.[52] Rizatriptan is also available in a wafer form that dissolves in the mouth but it is absorbed at a slower rate than the oral tablets (mean t_{max} 1.6–2.5 hours).

Rizatriptan is eliminated primarily via oxidative deamination catalyzed by monoamine oxidase A and renal elimination which together account for 76% of total plasma clearance.[50] Cytochrome P-450 inhibitors minimally affect rizatriptan pharmacokinetics,[53,54] reducing a major source of potential drug-drug interactions. Patients receiving propranolol may have an increase in plasma rizatriptan concentration, possibly reflecting competitive inhibition of monoamine oxidase A.[55] Rizatriptan crosses the blood-brain barrier better than other triptans.[56] Though other triptans can be administered intranasally or by or injection, rapidly absorbed oral rizatriptan is a logical, cost-effective choice for this first phase II study. Rizatriptan is now available in generic formulation, making it a cost-effective option for future clinical care. If oral rizatriptan is effective for treating vertigo attacks in VM, then other routes of administration can be assessed in later studies.

G. Summary of Significance

One percent of the general population and up to 10% of treatment-seeking patients with recurrent vestibular attacks suffers from VM. Little is known about its clinical course or the prevalence and severity of comorbid conditions, leading to diagnostic confusion and inadvertently misguided therapies. In the absence of proven treatments, current clinical practice relies on anecdote and uncontrolled studies, several of which suggest good response to triptans.[1-4] This investigation, if successful, will provide the first evidence base for any abortive or prophylactic therapy for VM (Specific Aim #1). It also will lay the foundation for a definitive Phase III trial of rizatriptan for treating vestibular attacks and associated symptoms in patients with VM. Data on the key clinical features of VM and its comorbid conditions will provide the detailed information needed to write Manuals of Operating Procedures for future trials including guidance on subject selection and methods of handling potential confounds (Specific Aim #2). More immediately, it will provide clinically useful information to improve diagnostic clarity of VM. It also may provide insights into the pathophysiology of the condition.

II. INNOVATION

A. Prior Controlled Study of Triptans for Vestibular Migraine

Neuhauser et al.[8] conducted a placebo-controlled trial of oral zolmitriptan for aborting VM attacks, but the study did not reach statistical significance due to inadequate power. Criteria for entry into that study included age between 18 and 65 years and a diagnosis of VM according to the investigators' original 2001 definition.[20] That definition differed from the recently published ICHD-3 diagnosis (Table 1)[14] in that it required a lifetime history of just two, not five, attacks of vestibular symptoms. Randomization to treatment required demonstration of active illness as defined by two or more moderate to severe vestibular attacks in the 12 months preceding study entry. Of 73 subjects initially enrolled, only 19 (26%) were randomized to crossover treatment. Most subjects (N=32 or 44% of initial sample) who were not randomized failed to meet requirements for frequency and severity of acute attacks. Another 14 subjects (19%) could not be randomized because they lived too far from the study location. Among those who were randomized, 10/19 (53%) subjects treated a total of 17 attacks (8 with zolmitriptan, 9 with placebo). The others had no attacks after randomization or dropped out of the study. Response rates were 3/8 (38%) for zolmitriptan and 2/9 (22%) for placebo, numbers too small to make any conclusions with regard to treatment response. Five lessons can be learned from this failed trial. First, investigators must enroll patients who have more frequent and severe attacks. The natural waxing and waning course of illness prevented nearly half of subjects in the zolmitriptan trial from being randomized. This problem is related to one of the fundamental questions about VM. How many attacks are needed to diagnose the condition with reasonable sensitivity and specificity? The new diagnostic criteria for VM, included in the appendix of ICHD-3, require five, rather than two, lifetime vestibular attacks in patients who meet other criteria for migraine headache.[14] Five has already been adopted as the number of attacks required to meet criteria for other types of migraine in the ICHD. The larger number was chosen to increase diagnostic specificity.[14] It also will likely identify individuals with more active illness. The second lesson from the failed zolmitriptan trial is that a prospective period of observation is needed to ensure that enrolled subjects continue to be symptomatic before they are assigned to treatment. This will reduce the randomization of subjects whose retrospectively reported history of vestibular attacks is not sustained when observed prospectively. The third lesson is that a greater chance of success may be achieved by focusing on patients with severe, long duration attacks, irrespective of other migraine features during attacks. This is likely to provide clearer direction to subjects about which attacks qualify for study treatment. The fourth lesson is that efforts should be made to treat more attacks per randomized subject. It is usually not desirable to treat many attacks in just a few subjects because

generalizability could suffer; however, it is reasonable to gather more data from each carefully enrolled subject than Neuhauser and colleagues did in their failed trial.[8] The fifth lesson is that a large number of potential subjects, recruited from more than one center, will be required to complete an adequate Phase II study. All five of these factors have been incorporated into the present proposal.

B. Preliminary Studies: Clinical and Research Experience with VM at UCLA and Mayo Clinic

Investigators at UCLA and Mayo Clinic have had extensive experience in research and clinical management of patients with VM.[5,6,19,21,22,24,27,28,31,34,35] We have published two of the largest cross-sectional diagnostic studies of migraine and vestibular symptoms reported to date.[5,19] The group at UCLA recently reviewed the clinical features of 208 patients who presented to the neurotology clinic over a two-year period with idiopathic recurrent spontaneous attacks of vestibular symptoms without associated auditory symptoms.[19] Of these 208 patients, 180 (87%) met ICHD-II criteria for migraine (112 with aura and 68 without aura). Among the patients with recurrent vertigo and ICHD-II migraine, 70% experienced headache, aura, photophobia, or phonophobia with some or all of their vestibular attacks, meeting the ICHD-3 criteria for VM.[14] The age of onset of migraine headaches preceded the onset of vestibular attacks by an average of 14 years, and aura preceded vestibular attacks by 8 years. The most frequent duration of vestibular attacks was between 1 hour and 1 day.

The Mayo Clinic group reviewed medical records of all patients that they evaluated for vestibular symptoms between April 2008 and July 2009,[5] identifying 228 patients with headache disorders, including 88 with VM. As in the UCLA study, the most common duration of vestibular attacks was between 1 hour and 1 day. More than half of the patients with VM has at least one comorbid condition such as Meniere's disease, BPPV, CSD, anxiety, or depression.[5,6] Comorbidity affected subjects' clinical presentations, but the characteristic features of VM could still be identified by careful diagnostic assessments.[6] The Mayo Clinic group is halfway through a double-blind, parallel group comparison trial of verapamil vs. sertraline for patients with co-existing VM/CSD. This pharmacologic dissection (not efficacy, hence no placebo) study was designed to identify which episodic and chronic vestibular symptoms are more likely to respond to a medication effective for migraine (verapamil) versus one useful for CSD (sertraline). The interim analysis identified several factors that strongly reinforced our decision to proceed with an abortive, not prophylactic, trial in this Phase II proposal. Fully two-thirds of potentially eligible subjects were excluded from the VM/CSD study because they had active medical conditions or were taking medications that would confound migraine prophylaxis. That problem would apply to any other prophylactic medication trial for VM. Until more data on the nature and prevalence of these confounds emerge from the VM/CSD trial and other studies, a Phase II trial of any prophylactic medication for VM will be impossible to design properly and doomed to failure if attempted. These confounds are much less likely to affect an abortive trial as they would cause far fewer problems with comorbidity and drug-drug interactions. The VM/CSD interim analysis also demonstrated that we have sufficient patient volumes to support the present proposal (>100 patients with VM annually) and great success enrolling subjects (75% of eligible individuals).

C. Considerations for Improved Subject Selection for the Current Proposal

In our clinical and research experience vestibular attacks can be reliably identified and should be the easiest of all VM symptoms to target for treatment. The most frequent duration of vestibular attacks with VM is hours to a few days. Focusing on patients with this duration of attacks is logical to maximize recruitment and ensure that enrolled subjects have attacks of sufficient duration to assess response to treatment. Therefore, our cohort of interest will be patients with a lifetime histories of five or more vestibular attacks lasting 2-72 hours with full interictal recovery and diagnoses of migraine. With regard to comorbidities, the requirement for at least five spontaneous episodes without hearing loss over more than a year will effectively exclude early cases of Meniere's syndrome. Patients with previously established Meniere's disease will be excluded from this study because their acute vertiginous symptoms overlap considerably with those of VM. Vertigo attacks caused by BPPV are of short duration (<2 minutes), making them easy to distinguish from the hours-long attacks of VM in our cohort of interest. CSD causes chronic non-vertiginous symptoms, not episodic symptoms. Therefore, patients with coexisting BPPV or CSD will not be excluded if they have vestibular attacks and meet all other inclusion and exclusion criteria. Coexisting anxiety or depressive disorders will be managed during the observation period and will not be exclusionary, if they can be stabilized within three months. These considerations balance the needs for successful subject recruitment, subject safety, and focus on the target symptoms of interest (i.e., recurrent, spontaneous vestibular attacks in patients with VM), while retaining generalizability to real world clinical settings and gathering critical information about potentially confounding variables for future Phase III trials, all informed by our preliminary data and previous clinical experience.

D. Summary of Innovation

Two important improvements over previous work have been incorporated into this proposal. The first innovation is a practical one in terms of study design. We carefully considered shortcomings in the previously published zolmitriptan trial[8] and incorporated design elements into this proposal to overcome them, including enhanced subject selection criteria, a prospective observation period, and specific strategies for addressing the common problem of comorbidity in VM (essentially ignored in previous studies). If we are successful, then these elements will inform the design of future therapeutic investigations for patients with VM, including not only Phase III studies of rizatriptan, but also clinical trials of other abortive and prophylactic therapies.

The second innovation concerns the fundamental definition of VM. We will use the recently published ICHD-3 diagnostic criteria[14] as they represent the current consensus of international experts in the field, although they have not yet been formally validated. We will focus our intervention specifically on recurrent spontaneous vestibular attacks lasting at least 1 hour in the absence of auditory deficits. We will require that enrolled subjects have at least 2 qualifying vestibular attacks during the observational phase so that we can teach them when and how to treat attacks in a systematic and consistent manner before they enter the treatment phase. If we are successful, our results will support the concept of VM as defined by the new criteria.

III. APPROACH

We propose a two-center, randomized, double blind, placebo-controlled, parallel, three-episode, clinical trial of rizatriptan 10 mg oral tablets versus placebo for treating spontaneous vestibular attacks in patients with VM. Our primary Specific Aim is to test hypotheses 1a-1d that rizatriptan will be:

1a. Superior to placebo in reducing the severity and duration of vestibular attacks as measured by:

(1) Proportion of treated attacks in which subjects experience a reduction in severity rating from Grade 3/2 to Grade 1/0 at one hour after taking study medication (see below for rating description). This is the main outcome measure; 1a(2)-1d(2) are secondary outcome measures.

(2) Proportion of treated attacks in which subjects achieve sustained relief (i.e., vestibular symptom severity rating of Grade 1/0) for 24 hours after taking study medication, without use of non-study therapies.

(3) Proportion of treated attacks in which subjects experience freedom from vestibular symptoms (i.e., severity rating of Grade 0) at one hour after taking study medication.

(4) Use of fewer non-study therapies after each attack treated with study medication.

1b. Superior to placebo in reducing severity of symptoms associated with vestibular attacks as measured by:

(1) Proportion of treated attacks in which subjects experience relief (reduction to Grade 1/0) from VM-associated symptoms (e.g., nausea, vomiting, motion sensitivity, gait disturbance, headache, photophobia, and phonophobia) at one hour after taking study medication.

(2) Proportion of treated attacks in which subjects achieve sustained relief from VM-associated symptoms for 24 hours after taking study medication without use of non-study therapies.

1c. Superior to placebo on treatment satisfaction and health-related quality of life as measured by:

(1) Scores on the Treatment Satisfaction Questionnaire for Medication (TSQM)[57] at 48 hours after each attack treated with study medication

(2) Scores on the Short Form 12 (SF-12)[58] at 48 hours after each attack treated with study medication

1d. Tolerated as well as placebo by patients with VM as measured by:

(1) No greater rate of treatment-emergent serious adverse events reported on the NCI Common Toxicity Criteria Scale 4.0[59] obtained 48 hours after each attack treated with study medication.

(2) No greater rate of treatment discontinuation for adverse events of any type or severity.

Our secondary Specific Aim is to gather data that will be needed to establish rigorous inclusion and exclusion criteria, determine sample sizes, and prepare Manuals of Operating Procedures for future Phase III treatment trials of rizatriptan and other abortive and prophylactic medications for VM. We intend to gather the following specific information during the Observation Phase of this study, which will last up to 12 months:

2a. The natural range of frequency and severity of vestibular attacks in treatment-seeking patients with VM.

Our goal is to identify the mean, median, and range of naturally occurring vestibular attacks in patients with VM, allowing future investigators to accurately estimate the sample sizes and study durations needed for abortive and prophylactic medication trials.

2b. The type and severity of medical and psychiatric conditions that commonly coexist with VM.
Our goal is to identify the prevalence and severity of common comorbidities of VM, allowing future investigators to make informed decisions about the inherent compromise between excluding subjects with potential confounds versus including subjects with manageable comorbidities to maintain real world generalizability.

2c. The types, doses, and frequency of use of prescription and non-prescription medications for VM.
Our goal is to create a compendium of usual clinical care and self-treatment of VM, giving future investigators naturalistic data to (1) guide selection of allowable co-treatments in future studies of prophylactic and abortive medications for VM and (2) determine which usual care treatments may be worthy of future controlled trials.

We also intend to collect the data described in 2a-c through the treatment phase of the study. Our goal is to conduct exploratory analyses of the influence of these variables on the efficacy of rizatriptan for VM, further enhancing the design of future Phase III trials and providing possible insights into the pathophysiology of VM

A. Resources and Research Facilities
UCLA and Mayo Clinic are well-established tertiary neurotology centers with strong referral bases regionally and nationally. Both centers see large volumes of patients with VM annually and maintain large databases of patients previously diagnosed with VM. Members of the study teams at both sites have been involved in neurotology research and clinical practice for many years and have recently published investigations of VM as detailed in Preliminary Results. Facilities needed to carry out study procedures already exist at both sites. The Research Pharmacy at Mayo Clinic will support both sites.

B. Subject Selection and Recruitment
New patients referred to UCLA or Mayo Clinic for recurrent vestibular symptoms during the time of the study will undergo diagnostic evaluations per usual clinical practice at each site. Patients who meet the selection criteria below will be invited to participate in the study. Existing databases will be screened for potentially eligible subjects. Individuals who appear to meet selection criteria will be sent a postal invitation to contact the study centers. Those who are interested will be scheduled for clinical re-evaluation and to review the study procedures and verify eligibility. New patients and individuals identified through existing databases who agree to participate will be enrolled after giving written informed consent. Others will be offered usual clinical care.

C. Study Plan
The study will be conducted in accordance with the principles of Good Clinical Practice and will be approved by required institutional review boards and regulatory agencies. All subjects will give written informed consent before undergoing any study procedures. We have received a letter from the FDA indicating that our proposal meets the requirements for exemption from IND registration (appendix).

1. Inclusion Criteria
a) Age ≥18 years and ≤65 years (the FDA-approved age range for rizatriptan therapy in adults).
b) History that fulfills all criteria for VM as defined in Table 1, except that attacks must last at least 2 hours. (Shorter attacks will not last long enough to judge treatment response.)
c) Episodes must have a spontaneous onset and resolution without associated hearing loss or interictal neurotologic deficits. (Patients with uncomplicated presbycusis or fully compensated peripheral vestibular deficits from illnesses unrelated to current vestibular attacks may participate if they meet all other criteria.)
d) Other causes of vestibular symptoms ruled out by appropriate clinical investigations.
e) Current medication list compatible with Concomitant Medications below.
f) Able to maintain a Vestibular Symptom Diary and complete all other study procedures.

2. Exclusion Criteria
a) Ménière's disease by AAO-HNS criteria[60]
b) Migraine with brainstem aura (formerly basilar-type migraine) by ICHD-3 criteria.[14]

c) Ischemic heart disease, coronary artery vasospasm, uncontrolled hypertension. (Potential subjects with uncomplicated mild hypertension may be enrolled if they are willing to bring their blood pressure under control within the first three months of study participation and maintain treatment throughout.)
d) History of stroke or transient ischemic attack.
e) History of using rizatriptan specifically to treat vestibular attacks.
f) History of adverse response to triptans.
g) Women who are pregnant or breastfeeding. (Women of childbearing age must be willing to use medically acceptable methods of birth control throughout the study.)
h) Unable or unwilling to comply with study requirements for any reason.

D. Study Visits and Phases

1. Visit 1. Prior to study entry, potential subjects will be evaluated clinically, including neurotologic history, examination, and laboratory testing per usual practice at each site. These steps will be part of routine clinical care, not study procedures. Study personnel will identify potential subjects (i.e., those diagnosed with VM) by contacting treating clinicians and providing information pamphlets to patients at each site. Interested patients will be invited to Visit 1 where the study will be reviewed with them in detail. Those who elect to participate will provide written informed consent. Investigators will then abstract baseline data from their medical records including demographics, medical history, list of allergies and current medications, family history, and results of neurotologic examinations and testing. Subjects will be asked to provide detailed descriptions of all symptoms experienced during vestibular attacks, which will be recorded verbatim. If this information fulfills all inclusion and exclusion criteria, subjects will be instructed in procedures for the Observation Phase, including use of the Vestibular Symptom Diary. Subjects also will complete the symptom self-report measures listed in Table 2.

2. Observation Phase. Subjects will be followed for up to 12 months to prospectively characterize the frequency and severity of their vestibular attacks, associated symptoms, and comorbid conditions. Subjects will record data about all vestibular attacks that they experience during this period in their Vestibular Symptom Diaries (see description below). Subjects will be permitted to treat their symptoms according to usual clinical care. They will record all interventions in their Vestibular Symptom Diaries. Study personnel will review this information with subjects by telephone on a monthly basis and will inquire about interval changes in subjects' health and medications. This process will build rapport with subjects, ensure that they continue to meet inclusion/exclusion criteria, and identify comorbid conditions that could affect their safety or subsequent study treatment. Study personnel also will use these data to train subjects to reliably recognize attacks that will be appropriate for treatment with study medication when they enter the Treatment Phase of the investigation. Treatable comorbidities (e.g., mild hypertension, anxiety disorders) will be managed in coordination with subjects' primary care clinicians or relevant specialists. Patients whose comorbidities cannot be managed and patients who do not have two qualifying episodes after 12 months of observation will be disenrolled.

3. Visit 2. As soon as possible after subjects have their second qualifying attack, they will return to the study sites for re-evaluation. They will complete procedures in Table 2. Investigators will instruct subjects in the dosing of study medication, completion of treatment response and adverse event rating scales, and procedures for serious adverse events. Subjects will receive written information on adverse effects of rizatriptan. Women of child bearing years will have a pregnancy test to confirm they are not pregnant.

4. Treatment Phase. Subjects who qualify for randomization will enter the Treatment Phase. They will be randomly assigned to parallel study arms in a 2:1 ratio of rizatriptan 10 mg encapsulated tablets or look-alike placebo capsules. Subjects will treat three vestibular attacks that manifest with Grade 3/2 vestibular symptoms. Associated symptoms, including headache, need not be present and may be of lesser severity. Headaches without vestibular symptoms are not eligible for study treatment, but may be treated in the subjects' usual manner. Subjects will be instructed to ingest one study capsule as soon as possible after onset of Grade 3/2 vestibular symptoms. They will record treatment response in their Vestibular Symptom Diaries by rating the severity of vestibular and associated symptoms at the time they take study medication and at 0.5, 1, 2, 4, 24, and 48 hours post-dose. Subjects will record adverse effects in accordance with the Common Toxicity Criteria Scale 4.0, treatment satisfaction on the TSQM, and quality of life on the SF-12 at 48 hours post-dose. Then they will contact study personnel by phone to review the attack and treatment response.

Subjects will treat one attack with study medication in a 48-hour period. Repeat dosing of study medication within 48 hours will not be permitted. Subjects must have a vertigo-free period of at least 48 hours before treating a subsequent vestibular attack with study medication. The relatively short plasma half-life of rizatriptan (2-2.5 hours) justifies the 48-hour wash out period. Subjects may use other medications to treat residual symptoms (see Concomitant Medications) but must wait at least 1 hour after taking the study medication. Additional treatments will be reported to study personnel together with other attack data. Subjects will remain in the Treatment Phase until they have treated three separate vestibular attacks, experience serious or intolerable adverse effects, withdraw for other reasons, or reach the end of the study. Study personnel will conduct telephone assessments on a monthly basis as they did during the Observation Phase. Extra visits to study clinics will be arranged as needed to re-evaluate subjects' health and treat problematic symptoms.

5. Visit 3. Subjects will return to their study center as soon as possible after treating their third attack with study medication, preferably within two weeks of their last treated attack. They will complete rating scales listed in Table 2 and review their Vestibular Symptom Diaries with study personnel. Arrangements will be made for follow-up clinical care, and subjects will be discharged from the study.

Table 2. Study Procedures and Rating Scales

Procedures	Visit 1 Enrollment	Observation Phase	Visit 2 Randomization	Treatment Phase	Visit 3 End Point
Obtain informed consent	X				
Abstract medical record data	X				
Verify enrollment criteria	X				
Characterize baseline symptoms	X				
Instruct re Vestibular Symptom Diary	X		X		
Assess & stabilize comorbidity		1st 3 months			
Review Vestibular Symptom Diary		Monthly	X	Monthly	X
Update health & medication list		Monthly	X	Monthly	X
Randomize for treatment			X		
Instruct re study treatment			X		
Dispense drug/placebo			X		
Treat 3 attacks				X	
Pregnancy Test			X		
Rating Scales					
Dizziness Handicap Inventory[61]	X		X		X
Anxiety Scale (GAD-7)[62]	X		X		X
Depression Scale (PHQ-9)[63]	X		X		X
Vestibular Symptom Diary		X		X	
Common Toxicity Criteria Scale 4.0[59]				X	
Treatment Satisfaction (TSQM)[57]				X	
Quality of Life Scale (SF-12)[58]	X		X	X	X
NEO-PI-3 Personality Inventory[78]	X				

E. Outcome and Safety Measures (#1-4 mirror measures used in Phase III registration trials of rizatriptan)[12,13]

1. **Vestibular Symptom Diary**. During Observation and Treatment Phases of the study, subjects will track the frequency of their headaches vestibular symptoms (unsteadiness/dizziness), and sensitivity to potential triggers of attacks (head/body motion, environmental stimuli, specific positions).
2. **Common Toxicity Criteria Scale 4.0** (National Cancer Institute).[59] A clinician-rated, comprehensive measure of toxicity from study medications in all body systems.
3. **Treatment Satisfaction Questionnaire for Medication** (TSQM).[57] A validated self-report measure of treatment satisfaction in four domains: effectiveness, side effects, convenience, and global satisfaction. Subjects will be asked whether they think they received rizatriptan or placebo after each dosing
4. **Short Form 12** (SF-12).[58] A 12-item self-report measure of health-related quality of life in six domains.
5. **Dizziness Handicap Inventory** (DHI).[61] A 25-item self-report of vertigo, dizziness, functional impairment, and emotional symptoms associated with vestibular symptoms.

6. **Generalized Anxiety Disorder Scale** (GAD-7).[62] A 7-item self-report rating scale for anxiety, a common comorbidity of VM. The GAD-7 has cut-offs for clinically significant levels of anxiety symptoms.
7. **Patient Health Questionnaire** (PHQ-9).[63] A 9 item self-report rating scale for depression, another common comorbidity of VM. The PHQ-9 has cut-offs for clinically significant levels of depressive symptoms.
8. **NEO-PI-3 Personality Inventory** (NEO-PI-3).[78] A 240-item questionnaire that assesses traits of the Five Factor Model of personality (neuroticism, extraversion, openness, agreeableness, conscientiousness).

F. Handling of Study Drug. The Mayo Clinic Research Pharmacy will support both study sites. The research pharmacists will purchase rizatriptan 10 mg tablets from a commercial supplier. Unaltered rizatriptan tablets will be encapsulated. Look-alike lactose-containing placebo capsules will be manufactured in the Mayo Clinic Pharmacy Production Laboratory following Good Manufacturing Practices. For patients who are allergic to lactose, carboxymethyl cellulose will be used instead of lactose. All capsules will be labeled with NDC numbers so that active drug and placebo can be identified. Randomization codes will be entered into the Research Pharmacy record. When prescriptions for study drug are received from physician investigators, drug or placebo will be placed into prescription bottles with required labeling. Prescriptions will be verified and cross-checked against the Research Pharmacy record for each subject. Then the prescription will be dispensed to subjects or mailed to their homes. Subjects will return used and unused bottles to verify medication accuracy and adherence. Should any questions arise after study drug is dispensed, the research pharmacists will be able to identify study drug for each subject by cross referencing the NDC numbers and randomization codes. Research pharmacists will maintain drug logs and all other applicable regulatory paperwork.

G. Concomitant Medications. Subjects may use medications for migraine prophylaxis and comorbid medical conditions, although medication doses must be stabilized during the Observation Phase and remain unchanged for the entire Treatment Phase. Those who take triptans for migraine headaches can continue to use them but not within 48 hours of taking study medication for vertigo attacks during the Treatment Phase. Subjects may use symptomatic medications for relief of vertigo attacks during the Observation Phase and for relief of symptoms that remain after taking study medication during the Treatment Phase (starting 1 hour after taking the study medication so that the primary outcome measure is not affected). Subjects must discontinue monoamine oxidase inhibitors at least 3 months before randomization. Use of other antidepressants is permitted. Theoretical concerns about serotonin syndrome arising from concomitant use of SSRI or SNRI antidepressants and triptans have not been observed in investigations of concomitant medication use.[64-67] These antidepressants will not be excluded, but subjects will be advised of potential adverse interactions.

H. Safety Procedures. Study personnel will be available during working hours and 24-hour emergency coverage will be provided at each site. Subjects who develop serious adverse events or medical conditions incompatible with safe use of rizatriptan will be withdrawn from the study. See Human Subjects for additional details.

I. Data Management. All data entry, data quality checking, data management, and statistical analyses will be conducted at the Data & Statistical Coordinating Center (DSCC) at UCLA under the direction of Dr. Honghu Liu, who has extensive experience running DSCCs for clinical trials. The PI, Co-PI, and co-investigators will work with Dr. Liu to program questionnaires and data input forms (paper and electronic) as needed for the study. All members of the study staff will be trained in data collection and entry techniques prior to the start of the study. Strict rules and regulations for patient security and confidentiality will be implemented by the DSCC. All data transferred from each of the sites will be carefully checked and maintained, and the DSCC will ensure that both sites follow the data security procedures. These procedures will be incorporated into data handling protocols, and auditing principles and periodically checking will be used to ensure compliance.

We will use a reliable and secure system for data transfer. All survey and abstraction data will be transferred from each data sources to the DSCC through secured mechanisms (e.g., secured website, FTP or password protected files). All data sets will be stored in password protected folders on network server or password protected computers designated for use by the DSCC. We will monitor the data through serial evaluation of the databases and analytic products throughout the process. Any discrepancy and/or inconsistency in the data will be evaluated and corrected in a timely manner.

An analytical ID generated through a scramble function will be created for each individual patient to protect patient confidentiality. Data analyses conducted at the DSCC will use analytical files that contain only the encrypted analytical IDs; no other patient identifying information will be available. Standard labels and format libraries will be created to facilitate analysis. A codebook that contains the information about the standard variable names and coding system will be created.

J. Statistical Methods

1. Power Analysis. The primary goal of this Phase II study is to demonstrate sufficient superiority of rizatriptan over placebo in the main outcome measure, 1a(1), to warrant a future Phase III trial. In the previous triptan study for VM[8] (see Prior Controlled Study of Triptans for VM), the response rate for active drug was 3/8 (38%) versus 2/9 (22%) for placebo. If the small sample from that failed trial reflected a true response, then the odds ratio favoring the triptan for VM would be 2.1. To improve our estimate, we examined the results of two large registration trials that used a simple randomization design similar to the present proposal to test rizatriptan for conventional migraine.[12,13] Those studies had response rates of 74% and 77% for rizatriptan versus 28% and 37% for placebo giving odds ratios of 7.4 and 5.7 favoring rizatriptan. The lower response rates in the VM trial most likely reflected the inadequate sample size, but could suggest that triptans are less effective for VM than conventional migraine. To account for this possibility, we took the limited results of Neuhauser, et al.[8] as a worst-case scenario for our sample size calculation. Focusing on the main outcome measure, 1a(1), in this double-blind, randomized trial, with PASS [68] simple randomization design[69] and using a type I error of 0.05, type II error of 0.2 (equivalent to power of 80%), two-sided tests, then treating 120 subjects (with 2:1 ratio for treatment and placebo) will allow us to detect an odds ratio as small as 3.2. Thus, the plan to enroll 200 subjects in the Observation Phase and select 120 for the Treatment Phase will be sufficient, even if the response of VM to rizatriptan proves to be only half that of conventional migraine. Phase II trials typically gather data on secondary outcomes (e.g., 1a(2)-1d(2)) and other variables (2a-c) to inform the design of Phase III trials, but sample sizes need not be planned to demonstrate significant differences in these variables.

2. Randomization. A randomization scheme will be developed to assign the 120 patients expected to be included in the Treatment Phase to parallel treatment arms in a 2:1 ratio of active drug:placebo.

3. Statistical Analysis and Modeling. We will use SAS and R[70] statistical software, creating ad hoc algorithms and macro procedures to solve analytical questions for which no marketed algorithms exist.

1. As a first step to understanding the nature of our data, we will conduct univariate analysis of demographics, primary and secondary outcome measures, illness-related variables (e.g., frequency, severity, and duration of vertigo attacks), associated symptoms, comorbid conditions, and self-report rating scales. The marginal distribution of each measure will be calculated at each time point and across time. The time trends of outcome measures will be evaluated by graphical analyses. For example, parallel plots for each of the outcome measures will be created to examine the patterns of change over time.

2. We will test the four hypotheses of Specific Aim #1 using bivariate methods and multivariate modeling. First, we will analyze differences between rizatriptan and placebo on all outcome measures at each time point using chi-squares to cross-tabulate categorical variables, and t-tests, analyses of variance (ANOVAs), or marginal regressions to compare continuous variables.

3. After testing bivariate differences, we will use repeated measures mixed effects models[71,72] to compare outcome measures between rizatriptan and placebo over time, and examine the effects of covariates on treatment response. As an example, for the special case of binary outcome vertigo severity (Grade 3/2 versus Grade 1/0) and the more general case of ordinal outcome vertigo severity (Grade 3, 2, 1, 0), we will use SAS PROC GLIMMIX[73] to model the logits of cumulative probabilities including vectors for study drug, illness related variables, associated symptoms, rating scales, random effects, and time. The estimates on the linear scale will represent log cumulative odds. The cumulative logits are formed as $\log \{\Pr(\Upsilon_i \leq j) / \Pr(\Upsilon_i > j)\} = X_i\alpha + Z_i\gamma_l + \varepsilon_l$ for i=1, …, n, where Υ_i is the n_i x 1 vector of the outcome measure for the i^{th} patient, j=0,1,2,3, n_i is the number of measurements for the i^{th} subject in the period, X_i is n_i x p known predictors (indicator signifying rizatriptan and placebo, and time variable.) The fixed effects parameter vector of α is p x 1. Z_i is n_i x k known predictors, which are associated with the random part of the model, including time-varying and time factors. γ_l is the k x 1 random effect parameter vector and $\gamma_l \sim N(0,D)$, ε_l is n_i x 1 and $\varepsilon_l \sim N(0,\sigma^2 I)$, which is independent of γ_l . Let

$\Sigma_i(\theta) = Z_i D Z_i^T + \sigma^2 I$ with θ being the parameter of covariance vector. Integrating out γ_i in the above random effect model, we can write $\Upsilon_i \sim N(X_i\alpha , \Sigma_i(\theta))$.

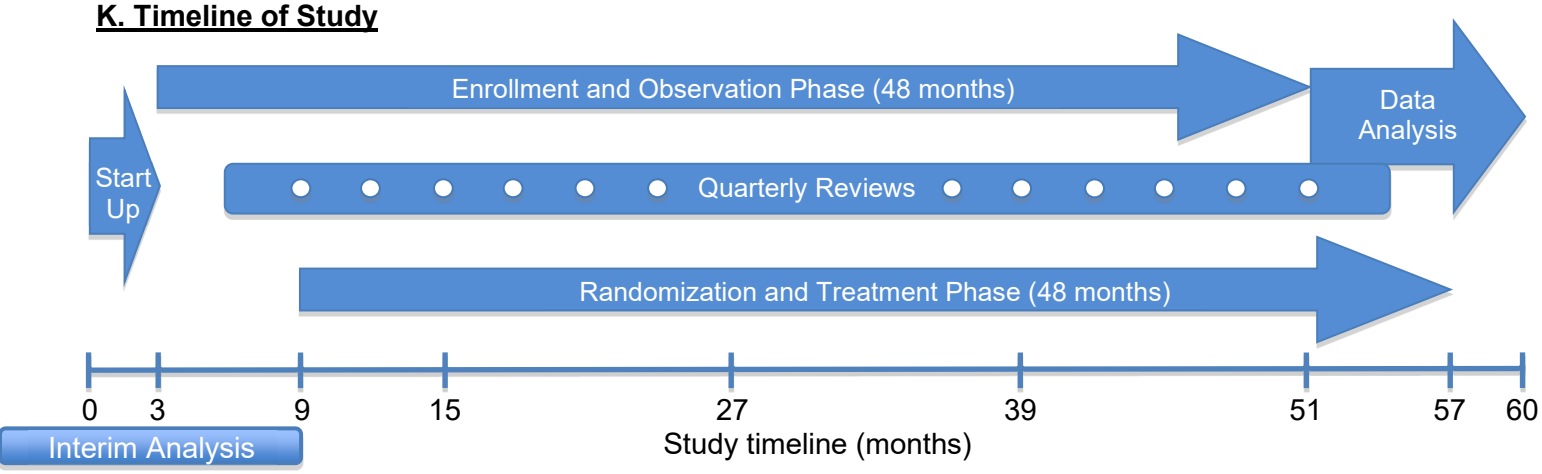
4. We will use this 3-step analysis procedure to test all outcome measures for hypotheses 1a-1d. However, the principal result of the study will be determined by the findings of bivariate analyses and multivariate modeling of the main outcome measure, 1.a.(1), plus favorable findings on tolerability measures, 1d(1)-1d(2). We will include all subjects who treat at least one vertigo attack with study drug (i.e., intent-to-treat analysis). A statistically significant result favoring rizatriptan over placebo on 1a(1) and absence of statistically significant differences on 1d(1)-1d(2) will support development of a Phase III clinical trial of rizatriptan for treating vestibular attacks in patients with VM. The design of future trials will also be informed by results of tests of secondary measures 1a(2)-1c(2). We did not hypothesize equal tolerability for rizatriptan and placebo, but rather an absence of significantly higher rates of serious adverse effects and drug-related treatment discontinuation, so our statistical analyses of measures 1d(1)-1d(2) will not include equivalence tests.

5. Analyses of Specific Aim #2 (a-c) will be descriptive and exploratory. As a Phase II trial, this proposed study is not powered for a thorough examination of covariates and confounds. We will start by reviewing univariate analyses of data collected during the Observation Phase of the study to identify results that will be critical for designing future Phase III trials. First, we will examine the distribution of VM attack frequency and severity (2a) to determine if these variables have normal, skewed, bimodal, or other distributions. This will allow future investigators to estimate recruitment patterns for Phase III studies. Second, we will establish a rank order of comorbid conditions (2b) by prevalence and likelihood of affecting the clinical course or treatment of VM. This will allow future Phase III investigators to understand trade-offs between strictness of subject selection criteria and generalizability of results. Third, we will establish a rank order of usual care and self-medication therapies for VM (2c). This will allow future investigators to establish criteria for allowable co-treatments in Phase III trials. Finally, we will repeat the multivariate modeling of step 3 above, including variables representing data 2a-c collected during the Treatment Phase of the study. Variables found to have significant or trend level effects on rizatriptan versus placebo treatment will mark design considerations for Phase III trials and potentially generate hypotheses for epidemiologic, mechanistic, or other lines of investigation of VM.

6. Missing Data: We do not anticipate a major problem with missing data from subjects who complete this study. Furthermore, repeated measures mixed effects models allow unbalanced data (e.g., missing follow-up data). Nevertheless, we will use the following approach to missing data. We will calculate the frequency and pattern of missingness of each measure as missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR).[74,75] Based on the nature of missingness, we will determine which imputation approach would be appropriate. For complex situations, we will use EM algorithm, fully Bayesian, maximum likelihood procedures, and parametric multiple imputation (MI) methods, which are appropriate under general MAR conditions. ML and MI tend to yield similar results when implemented in comparable ways. Nonrandom dropout may be a problem because subjects having the most severe attacks may object to taking placebo pills or seek alternative treatment. Subject demographics and illness characteristics can be used to test the MAR assumption. To reduce the possible impact of non-random dropout or MNAR missingness, subject characteristics variables will be used in the missing data model with MI/ML, which can reduce estimation bias due to MNAR missingness, and partially restore lost power due to missingness.[76,77] We will examine the distribution of the outcome of interest (treated attacks in which subjects experience a reduction in severity rating) and the auxiliary variable, and apply joint modeling and MI methods to utilize the auxiliary information (e.g., subject characteristics). We will apply MNAR methods (e.g., selection models, pattern mixture models, and shared parameter models) to perform sensitivity analysis to evaluate model robustness.[75]

7. Interim analysis: We will conduct an interim analysis at study midpoint without breaking the blind to assess (1) recruitment, (2) safety, and (3) efficacy. Plans for shortfalls in recruitment are noted below. We will terminate the study for insufficient safety if there is a statistically significant difference between arms in adverse events of greater than minor severity, or for lack of efficacy if response rates are <25% in both arms, i.e., no better than placebo rates in previous triptan trials. We will continue the study if the primary outcome, 1(a)1, is >25% in at least one arm, but not statistically different between arms. If the primary outcome is statistically different, then we will terminate the study because the primary aim will be met. We will break the blind and identify the results as positive (rizatriptan superior to placebo) or negative (rizatriptan inferior to placebo).

K. Timeline of Study



During the first three months of the study, we expect to finalize data entry methods and train study personnel. Then we will begin recruitment into the Observation Phase. Patients will remain in the Observational Phase until they have two qualifying attacks or for a maximum of 12 months. These phases will continue for a total of four years. Subjects who are active in the Treatment Phase at month 57 will be scheduled for a Final Visit (Visit 3) regardless of how many attacks they have treated. We will conduct reviews every 3 months to evaluate enrollment and the flow of subjects through all parts of the study to determine whether recruitment efforts have to be extended and to examine safety data with the DSMB. Analysis of data from the Observation Phase will begin as soon as that portion of the study is closed. Interim analysis will occur at month 33. Analysis of treatment outcome data will commence after the last subject has a Final Visit.

L. Feasibility and Limitations

The primary hindrance to successful completion of this study will be patient recruitment and retention. Rizatriptan has a proven track record of safety in thousands of patients over more than a decade of clinical use, so we do not expect significant problems with medication intolerance. The study of zolmitriptan by Neuhauser, et al.,[8] demonstrated the pitfalls of a triptan trial for patients with VM. Just 26% of enrolled subjects were randomized to treatment because they did not continue to have active verstibular attacks. We believe that we will substantially increase that randomization rate by enrolling only subjects with more active illness, as described in "Considerations for Improved Subject Selection for the Current Proposal." The previous investigators excluded 12% of subjects for coexisting medical problems. We expect to stabilize coexisting medical problems such as uncontrolled hypertension or anxiety disorders during our 12 month Observation Phase, allowing us to retain a higher percentage of enrolled subjects. Neuhauser, et al.,[8] also excluded 14% of subjects from randomization because they lived too far from the study center. Geographic barriers are much less of a problem for medical care in 2013 than they were in 2003. Both of our centers have expanded the reach of patient care through electronic communications and other secure technologies, eliminating the need for a geographic exclusion. These factors and the improvements in study design based on the five-point examination of shortcomings in the zolmitriptan trial (see "Prior Controlled Study of Triptans for Migraine-Associated Vertigo") should allow us to successfully randomize 50% of enrolled subjects into the Treatment Phase of this study. Keeping in mind that the sample size calculation reflected the worst-case scenario (100 subjects for the Treatment Phase), then we will have to recruit a maximum of 200 subjects into the Observation Phase. Our recently published studies[5,19] indicate that we see approximately 200 new patients with VM at our two centers annually. A record review suggests that half of those would likely meet study inclusion criteria. Therefore, we expect to examine 400 potential subjects during the 4 years of active enrollment. Study success would require us to recruit 50% of those patients. The Mayo Clinic team has enrolled 79.3% of eligible patients into a currently active trial of sertraline versus verapamil for patients with VM/CSD, which demonstrates our ability to achieve needed enrollment. Subjects entering the current Mayo study have almost no experience with triptans. Most have been prescribed vestibular suppressants (e.g., meclizine) for acute attacks, meaning that we will lose almost no subjects due to prior rizatriptan treatment. (N.B. – The current Mayo study will not compete with this proposal. Its inclusion criteria target chronic, not acute, symptoms).

M. Plans to Address Limitations
The patient flow just reviewed suggests that we will be able to meet study recruitment and retention targets. However, we intend to examine rates of enrollment into the Observation Phase and randomization into the Treatment Phase every quarter. If we fall short of targets for enrollment or randomization at any point, we will take three steps, as needed. (1) Contact patients with VM who were previously examined at our institutions. Both centers maintain databases of patients who participated in previous diagnostic studies (N>400), many of whom expressed interest in treatment trials. (2) The Mayo Clinic site will expand recruitment to the Mayo Clinic Health System of hospitals and clinics across a three-state area of the upper Midwest, and UCLA will expand recruitment to affiliated hospitals and clinics across Southern California. (3) Both sites will advertise selectively to regional and local professional organizations, patient advocacy groups, and the general public.

A negative treatment result (i.e., finding that rizatriptan is not superior to placebo) will not be a study failure. Rather, it will be evidence that rizatriptan lacks the efficacy needed to pursue a Phase III trial in patients with VM. A negative result will prompt a search for other abortive and prophylactic therapies for VM and might nudge researchers to re-evaluate the concept of VM as a migrainous phenomenon. Data collected for Specific Aim #2 should be helpful in considering alternative medications and different potential pathophysiologic processes for VM regardless of the efficacy of rizatriptan.

IV. HUMAN SUBJECTS

The proposed study will take place at UCLA and Mayo Clinic. In accordance with NIH policy, both sites have implemented mandatory educational programs for all study personnel on the protection of subjects in human research. Procedures are in place at both institutions to track the compliance of investigators with these programs. All key personnel will maintain current training certificates throughout the duration of this study. Certificates of training completion will be kept on file at both sites.

The study protocol will be submitted to the Institutional Review Boards (IRB) at each site for full review. This study is a randomized clinical trial that meets the federal definition of moderate risk. Subject enrollment will not begin until IRB approval is obtained. Written consent will be obtained from all subjects using IRB approved consent forms. All patient recruitment materials and announcements will be approved by the IRBs.

A. Involvement of human subjects

1. Number of subjects - We plan to recruit 240 subjects during the 5-year grant period, equally divided between the two study sites.

2. Inclusion/exclusion criteria.
Patients who meet all inclusion and exclusion criteria listed in the “Study Plan” and agree to take part in the study will be enrolled after providing written informed consent. Adults >65 years of age will be excluded from the study because FDA registration trials for rizatriptan did not include adults in this age group. Children <18 years of age will be excluded because the safety and efficacy of rizatriptan for VM has not been established and VM is a condition affecting adults more than children. Subjects must be mentally and physically capable of participating in all aspects of the study. Based on our prior experience and the known demographics of vestibular migraine (VM), we expect to enroll more women than men. The majority of subjects will be non-Hispanic white, but we will actively recruit patients from diverse racial/ethnic backgrounds.

Determination of eligibility. The PIs and Co-investigators will make final determinations of potential subject eligibility after reviewing clinical history, physical examination and test results, and final clinical diagnoses.

Special inclusion or exclusion criteria. None.

3. Vulnerable subjects.
We will exclude children (<18 years of age) from this study. We also will exclude older adults (>65 years of age) from this study (See IV.A.2). No members of other vulnerable groups will be targeted for recruitment.

B. Procedures

Study procedures are summarized Table 2 of the study protocol. The study involves three visits to the study sites, an Observation Phase and a Treatment Phase. At the Enrollment Visit, investigators will verify eligibility, obtain written informed consent, and gather initial data. Subjects will complete the self-report measures listed in Table 2. This visit is expected to last 2-3 hours. After the Enrollment Visit, subjects will enter up to a 12 month Observation Phase during which they will record descriptive data and ratings for each vertigo attack that they suffer, along with associated symptoms and treatments. The research coordinator will contact subjects on a monthly basis to review these data. Phone interviews are expected to last less than 30 minutes. During the Observation Phase, investigators will prospectively evaluate patients for comorbid medical and psychiatric conditions. Investigators will treat these conditions themselves or enlist the care of relevant medical specialists as indicated. Subjects may return to the study centers for ad hoc visits, if needed for additional evaluations. Subjects will continue in the observation period until they have two vestibular attacks that meet the inclusion criteria or until the 12 months are up.

Once they have experienced two qualifying vestibular attacks or at the end of the Observation Phase, subjects will return to their study center for a second visit. Investigators will collect interval history and subjects will complete the self-report measures listed in Table 2. This visit is expected to last 2 hours. Subjects who experience at least two vestibular attacks of moderate or greater severity during the Observation Phase and demonstrate acceptable adherence with data gathering and reporting procedures will be randomized to treat three subsequent vestibular attacks with either rizatriptan or placebo (ratio 2:1) in randomized and double-blind fashion. Subjects will rate treatment response and adverse effects. They will contact study personnel to review these data at 48 hours after each vestibular attack treated with study medications. The research coordinator will contact subjects on a monthly basis by phone to review progress, assess adherence, and gather data on any interval change that might affect treatment response or safety. The Treatment Phase may last as short as 6 days for subjects who have three vertigo attacks in quick succession after randomization to as long as 4 years for subjects who enroll at the start of the study and do not have 3 treatable attacks before the end of the study. Subjects will return to the study site for an End Point Visit (visit 3) as soon as possible after treating three attacks or sooner if they will be withdrawn from the study for any reason. The End Point Visit is expected to last 2 hours.

C. Recruitment and consent

Patients diagnosed with VM after completing clinical evaluations for episodic vertigo at UCLA or Mayo Clinic will be invited to participate in the study. Investigators will recruit patients that they see personally in their practices and patients seen by clinical colleagues at the study sites. Investigators will explain the study to potential subjects, answer questions, and provide subjects ample opportunity to read an IRB-approved written consent form describing the study. Subject who consent will be enrolled and begin study procedures. No study procedures will be performed before written informed consent is obtained. Potential subjects who decline to participate will be offered routine clinical care.

D. Potential Risks

1. Adverse Effects of Medication: The primary risk to subjects will be the potential for adverse effects of study medication. There is a wealth of data documenting the safety and efficacy of rizatriptan in treating patients with migraine. In this randomized trial, we will use a dose of rizatriptan that is generally well tolerated by patients with migraine (10 mg). Common adverse events include: drowsiness (4-10%), dizziness (4-10%), nausea (4-8%), fatigue (1-7%), tingling or numb feeling (4%), dry mouth (3%), muscle pain or cramps (2%), and tightness in the neck or jaw (2%), tremors, chills, and flushing (feeling of warmth). Serious adverse events include chest pain (3%), hypertension, coronary artery spasm, myocardial infarction, peripheral ischemia, ventricular arrhythmia, ischemic colitis, anaphylaxis, angioedema, analgesic overuse headache, cerebrovascular accident, and serotonin syndrome.

2. Loss of Confidentiality: There is also a risk of loss of confidentiality if identifying information and data from medical records or study forms are inadvertently released.

3. Time Demands: This study places demands on subjects' time for completion of the Vertigo Symptom Diary and self-report instruments as well as monthly telephone appointments with investigators or research coordinators. The Vertigo Symptom Diary will have to be completed during and after each attack. Subjects will

track vertigo, headache, and associated symptoms in their diaries. They will rate each symptom using a single number from 0-3 at 0.5, 1, 2, 4, 12, 24, and 48 hours after the onset of each vertigo attack, which is expected to take 10-20 seconds at each time point or less than 3 minutes total per attack. Over the course of the study, subjects also will be required to complete 20 rating scales ranging in length from 7 to 36 questions. Each of these will take 1-5 minutes to complete for a total of about 80 minutes over the entire study. Telephone appointments are expected to be less than 30 minutes long on a monthly basis. During study Visit 1 only, subjects will complete a personality questionnaire that will take 30-40 minutes.

4. Special circumstances involving studies assessing depression: This investigation is not designed specifically to treat depression, but depression is more common in patients with vestibular disorders than in the general population. For that reason, all patients at Mayo Clinic in Rochester are screened for depression as part of clinical testing in the Vestibular Laboratory. Those who screen positive are examined by a Mayo Clinic psychiatrist or psychologist familiar with mood symptoms in patients with vestibular disorders. This has been part of routine clinical practice for 6 years. The presence of depression, per se, will not disqualify potential participants from study entry. Only those whose depression is judged unlikely to be brought under control within 3 months of study entry (e.g., treatment resistant depression, depression with suicidality or psychosis) will be ineligible to enroll. For others, treatment of depression will be part of the overall plan to manage common VM comorbidities during the Observation Phase, as described above (Section III.D.2).

Depression may affect the clinical course and treatment of VM. Therefore, depressive symptoms will be measured in all subjects at Visits 1, 2, and 3 using the PHQ-9 to gather data to control for this confound. Any subject whose PHQ-9 scores suggest clinically significant depression (PHQ-9 >9) or suicidal thoughts (PHQ-9 question 9 >0) will be examined by a study physician at the time of the visit to ensure that treatment for depression is initiated or updated and that the level of depressive symptoms is compatible with continued study participation. Patients judged ineligible will be disenrolled and provided or referred for appropriate treatment.

E. Risk Minimization

1. Adverse Effects of Medication: Subjects with ischemic heart disease, uncontrolled hypertension, or coronary artery vasospasm will be excluded from the study because of the known cardiac complications of triptans. Those who are allergic or unable to tolerate triptans in the past will also be excluded from the study. (See “Exclusion Criteria”).

Subjects will be closely monitored. The research coordinator will inquire about adverse events and changes in health status during monthly telephone interviews. Subjects will be instructed to contact a member of the research staff regarding adverse events at any time during the study. They will be instructed to report cardiac symptoms or allergic reactions immediately. Subjects who develop treatment-related serious adverse events or new onset exclusionary medical conditions will be withdrawn immediately from the study.

2. Loss of Confidentiality: Confidentiality will maintained to the extent legally permissible by the appropriate handling of patient records and study data. Data obtained from source documents, interviews and questionnaires will be captured on research forms, entered online, and stored at DSCC. The information will be kept confidential in a secure electronic database with restricted and monitored access. A unique subject ID number will be used for each subject’s research case report forms and all communications, in accordance with the Health Insurance Portability and Accountability Act. No identifying information will be entered into the database.

3. Time Demands: The Clinical Trials Subcommittee of the International Headache Society published guidelines for data collection during clinical trials of migraine treatments.[15] The data collection instruments selected for this proposed study – a symptom diary and validated measures of functional impairment and quality of life – follow those recommendations. The specific diary method for rating symptoms during and after attacks was adopted from two major registration trials for rizatriptan,[12,13] which included several hundred subjects each. The self-reports of dizziness handicap, quality of life, depression and anxiety have been used by thousands of patients in clinical and research settings around the world for many years. Specific scales were chosen to achieve the goals of the study, while keeping demands on subjects’ time to a minimum.

F. Risk/Benefit Analysis: A potential benefit to subjects who participate in this study will be the possibility of a

reduction in vestibular attack duration and/or severity and interference with daily activities as well as possibly improved quality of life. It is also possible that there would be no benefit to the study participants. A benefit to society may be greater understanding of treatment options for vestibular attacks in patients with VM.

G. Gender/minority recruitment: Men and women of all racial and ethnic backgrounds will have an opportunity to participate in this study. White women have been heavily over-represented in large pre-registration and post-marketing trials of rizatriptan, with most studies including about 90% white patients and 90% women. Our published research in VM included a 2:1 female:male ratio, in keeping with the known sex distribution of VM. We anticipate a similar sex ratio for subjects in this study. We project that 20% of our sample will be from minority groups.

V. STUDY OVERSIGHT

The PI and Co-PI will have primary responsibility for the conduct of this clinical trial. A Data Safety Monitoring Board (DSMB) with oversight responsibility will be appointed by NIDCD. The DSMB will review subject accrual, frequencies and patterns of all adverse events, and protocol compliance on a quarterly basis and will make recommendations to the NIH regarding the continuation status of the protocol. Co-Investigator Dr. Liu will compile clinical data to prepare the reports for DSMB reviews.

The Principal Investigator, Co-PI and their research teams (co-investigators, research nurses, research coordinators, and others) will be responsible for identifying adverse events. Aggregate reports detailed by severity, attribution (expected or unexpected), and relationship to the study drug/study procedures will be made available by the DSCC for site review. A separate report detailing protocol compliance will also be available from the DSCC for site review monthly. The research team will review these reports monthly and determine whether the protocol or informed consent document requires revision based on the reports.

A. Definitions/Standards

An adverse event is defined as an unfavorable and unintended sign, symptom or disease associated with a participant's participation in the current study.

Serious adverse events include those events that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, create persistent or significant disability/incapacity, or cause a congenital anomaly or birth defects.

An unexpected adverse event is defined as any adverse experience, the specificity or severity of which is not consistent with the risks or information described in the protocol. Expected adverse events are those that are identified in the research protocol as having been previously associated with or having the potential to arise as a consequence of participation in the study.

All reported adverse events will be classified using the Common Terminology Criteria for Adverse Events (CTCAE), version 4, developed and maintained by CTEP at National Cancer Institute.

B. Study Intervention and Procedures: Definition of Expected Adverse Events

Treatment Study Drug – Rizatriptan (10mg within a 48-hour period). Common adverse events include drowsiness (410%), dizziness (4-10%), nausea (4-8%), fatigue (1-7%), tingling or numb feeling (4%), dry mouth (3%), muscle pain or cramps (2%), tightness in the neck or jaw (2%), tremors, chills, and flushing (feeling of warmth). Allergic reactions include rash or redness, swelling, or itching of the eyelids, face, or lips. Serious adverse events include chest pain (3%), hypertension, coronary artery spasm, myocardial infarction, peripheral ischemia, ventricular arrhythmia, ischemic colitis, anaphylaxis, angioedema, analgesic overuse headache, cerebrovascular accident, and serotonin syndrome.

C. Reporting Timeline

Local institutional reporting requirements to IRBs and DSMB remain the responsibility of the treating physician

and the PI and Co-PI.

1. Investigators must report any Serious Adverse Event (SAE) that is considered life-threatening/disabling or results in death of subject or is unexpected or unanticipated, within **24 hours** of learning of an event.
2. Investigators must report all other SAEs within **5 working days** of learning of the event.
3. Investigators must report all other suspected AEs within **20 working days** of the notification of the event or of becoming aware of the event.
4. All serious adverse events (SAEs) must be reported to the FDA.

a) Fatal or life-threatening AEs, regardless of causal relationship to study medication, must be reported to FDA on a MedWatch Form within 7 days of the event.
b) Serious, but not fatal or life threatening events, which are related and unexpected, must be reported to FDA on a MedWatch Form within 15 days of the event.
c) Other suspected AEs will be reported to FDA every quarter after the start of the study.

D. Adverse Event Data Management System (AEDAMS)

Upon entry of a serious or unexpected adverse event, the DSCC created Adverse Event Data Management System (AEDAMS) will immediately notify the PI and Co-PI and any additional agencies of any reported adverse events per study protocol.

Serious adverse events: Causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event will be determined by a thorough review. A determination of the causal relationship of all AEs will be made based upon the package insert (Sections 6.1 and 6.2)[22]. The Adverse Event Data Management System (AEDAMS) maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study.

Non-serious expected adverse events: Except those listed above as immediately reportable, non-serious expected adverse events that are reported to or observed by the investigator or a member of his research team will be submitted to the DSCC in a timely fashion (within 20 working days). Local site investigators are also required to fulfill all reporting requirements of their local institutions.

E. Study Discontinuation

NIH and local IRBs have the authority to stop or suspend this trial at any time. This study may be suspended or closed if:

- Accrual has been met
- The study objectives have been met
- The PI or Co-PI believe it is not safe for the study to continue
- The DSMB recommends to the NIDCD and it suspends or closes the trial
- The FDA suspends or closes the trial

F. Subject Discontinuation

An intent to treat approach will be used. All data acquired prior to termination for the reasons outlined below will be included in the primary analysis unless the subject withdraws consent. Every effort will be made to conduct a final study visit with subject upon withdrawal and subjects will be followed clinically until, if applicable, all adverse events resolve. The following events will result in subject discontinuation:

- Withdrawal of consent
- Withdrawal by the participant
- Withdrawal by the investigator Intercurrent illness or event that precludes further visits to the study site or ability to evaluate disease

G. Clinical Trials.gov

Dr. Baloh will register the trial on ClinicalTrials.gov as soon as IRB approvals are obtained.

REFERENCES

1. Bikhazi P, Jackson C, Ruckenstein MJ. Efficacy of antimigrainous therapy in the treatment of migraine-associated dizziness. Am J Otol 1997;18:350-354
2. Prakash S, Chavda BV, Mandalia H, Dhawan R, Padmanabhan D. Headaches related to triptans therapy in patients of migrainous vertigo. J Headache Pain 2008;9:185-188
3. Dieterich M, Brandt T. Episodic vertigo related to migraine (90 cases): vestibular migraine? J Neurol 1999;246:883-892
4. Evans RW, Baloh RW. Episodic vertigo and migraine. Headache 2001;41:604-605
5. Eggers SD, Staab JP, Neff BA, Goulson AM, Carlson ML, Shepard NT. Investigation of the coherence of definite and probable vestibular migraine as distinct clinical entities. Otol Neurotol 2011;32:1144-1151
6. Neff BA, Staab JP, Eggers SD, Carlson ML, Schmitt WR, Van Abel KM, Worthington DK, Beatty CW, Driscoll CL, Shepard NT. Auditory and vestibular symptoms and chronic subjective dizziness in patients with Ménière's disease, vestibular migraine, and Ménière's disease with concomitant vestibular migraine. Otol Neurotol. 2012 Sep;33(7):1235-44.
7. Gode S, Celebisoy N, Kirazli T, Akyuz A, Bilgen C, Karapolat H, Sirin H, Gokcay F. Clinical assessment of topiramate therapy in patients with migrainous vertigo. Headache. 2010;50(1):77-84.
8. Neuhauser H, Radtke A, von Brevern M, Lempert T. Zolmitriptan for treatment of migrainous vertigo: a pilot randomized placebo-controlled trial. Neurology 2003;60:882-883
9. Furman JM, Marcus DA, Balaban CD. Rizatriptan reduces vestibular-induced motion sickness in migraineurs. J Headache Pain 2011;12:81-88
10. Furman JM, Marcus DA. A pilot study of rizatriptan and visually-induced motion sickness in migraineurs. Int. J. Med. Sci. 2009;6:212-7.
11. Marcus DA, Furman JM. Prevention of motion sickness with rizatriptan: a double-blind, placebo-controlled pilot study. Med Sci Monit 2006;12:PI1-7
12. Ahrens SP, Farmer MV, Williams DL, Willoughby E, Jiang K, Block GA, Visser WH. Efficacy and safety of rizatriptan wafer for the acute treatment of migraine. Rizatriptan Wafer Protocol 049 Study Group. Cephalalgia 1999;19:525-530
13. Kramer MS, Matzura-Wolfe D, Polis A, Getson A, Amaraneni PG, Solbach MP, McHugh W, Feighner J, Silberstein S, Reines SA. A placebo-controlled crossover study of rizatriptan in the treatment of multiple migraine attacks. Rizatriptan Multiple Attack Study Group. Neurology 1998;51:773-781
14. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalgia 2013;33(9):629-808.
15. Tfelt-Hansen P., et al. International Headache Society Clinical Trials Subcommittee Guidelines for controlled trials of drugs in migraine: second edition. Cephalalgia. 2000 Nov;20(9):765-786.
16. Livening E. On Megrim, Sick Headache, and Some Allied Disorders: A Contribution to the Pathology of Nerve Storms. London, J & A Churchill, 1873
17. Lempert T, Neuhauser H. Epidemiology of vertigo, migraine and vestibular migraine. J Neurol 2009;256:333-338
18. Kayan A, Hood JD. Neuro-otological manifestations of migraine. Brain 1984;107 (Pt 4):1123-1142
19. Cha YH, Lee H, Santell LS, Baloh RW. Association of benign recurrent vertigo and migraine in 208 patients. Cephalalgia 2009;29:550-555
20. Neuhauser H, Leopold M, von Brevern M, Arnold G, Lempert T. The interrelations of migraine, vertigo, and migrainous vertigo. Neurology 2001;56:436-441
21. Brantberg K, Trees N, Baloh RW. Migraine-associated vertigo. Acta Otolaryngol 2005;125:276-279
22. Cha YH, Baloh RW. Migraine associated vertigo. J Clin Neurol 2007;3:121-126
23. Neuhauser H, Lempert T. Vestibular migraine. Neurol Clin 2009;27:379-391
24. Eggers SD. Migraine-related vertigo: diagnosis and treatment. Curr Pain Headache Rep 2007;11:217-226
25. Oh SY, Seo MW, Kim YH, Choi KD, Kim DS, Shin BS. Gaze-evoked and rebound nystagmus in a case of migrainous vertigo. J Neuroophthalmol 2009;29:26-28
26. von Brevern M, Zeise D, Neuhauser H, Clarke AH, Lempert T. Acute migrainous vertigo: clinical and oculographic findings. Brain 2005;128:365-374
27. Staab JP. Clinical clues to a dizzying headache. J Vest Res 2011;21(6):331-40.
28. von Brevern M, Baloh RW, Bisdorff A, Brandt T, Bronstein AM, Furman JM, Goadsby PJ, Neuhauser H, Radtke A, Versino M. Response to: Migraine and vertigo: a marriage of convenience? Headache 2011;51:308-309
29. Moretti G, Manzoni GC, Caffarra P, Parma M. "Benign recurrent vertigo" and its connection with migraine. Headache 1980;20:344-346
30. Oh AK, Lee H, Jen JC, Corona S, Jacobson KM, Baloh RW. Familial benign recurrent vertigo. Am J Med Genet 2001;100:287-291
31. Brantberg K, Baloh RW. Similarity of vertigo attacks due to Meniere's disease and benign recurrent vertigo, both with and without migraine. Acta Otolaryngol 2011;131:722-727
32. Rassekh CH, Harker LA. The prevalence of migraine in Meniere's disease. Laryngoscope 1992;102:135-138
33. Wladislavosky-Waserman P, Facer GW, Mokri B, Kurland LT. Meniere's disease: a 30-year epidemiologic and clinical study in Rochester, Mn, 1951-1980. Laryngoscope 1984;94:1098-1102

34. Staab JP, Ruckenstein MJ. Expanding the differential diagnosis of chronic dizziness. Arch Otolaryngol Head Neck Surg 2007;133:170-176
35. Baloh RW, Jen JC. Genetics of familial episodic vertigo and ataxia. Ann N Y Acad Sci 2002;956:338-345
36. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24 Suppl 1:9-160
37. Moskowitz MA, Bolay H, Dalkara T. Deciphering migraine mechanisms: clues from familial hemiplegic migraine genotypes. Ann Neurol 2004;55:276-280
38. Goadsby PJ, Lipton RB, Ferrari MD. Migraine--current understanding and treatment. N Engl J Med 2002;346:257-270
39. Napier C, Stewart M, Melrose H, Hopkins B, McHarg A, Wallis R. Characterisation of the 5-HT receptor binding profile of eletriptan and kinetics of [3H]eletriptan binding at human 5-HT1B and 5-HT1D receptors. Eur J Pharmacol 1999;368:259-268
40. Tfelt-Hansen P, De Vries P, Saxena PR. Triptans in migraine: a comparative review of pharmacology, pharmacokinetics and efficacy. Drugs 2000;60:1259-1287
41. Ahn SK, Balaban CD. Distribution of 5-HT1B and 5-HT1D receptors in the inner ear. Brain Res 2010;1346:92-101
42. de Waele C, Muhlethaler M, Vidal PP. Neurochemistry of the central vestibular pathways. Brain Res Brain Res Rev 1995;20:24-46
43. Javid FA, Naylor RJ. The effect of serotonin and serotonin receptor antagonists on motion sickness in Suncus murinus. Pharmacol Biochem Behav 2002;73:979-989
44. Licata F, Li Volsi G, Maugeri G, Ciranna L, Santangelo F. Serotonin-evoked modifications of the neuronal firing rate in the superior vestibular nucleus: a microiontophoretic study in the rat. Neuroscience 1993;52:941-949
45. Lipton RB, Pascual J, Goadsby PJ, Massiou H, McCarroll KA, Vandormael K, Jiang K, Lines CR. Effect of rizatriptan and other triptans on the nausea symptom of migraine: a post hoc analysis. Headache 2001;41:754-763
46. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalalgia 2002;22:633-658
47. Longmore J, Hargreaves RJ, Boulanger CM, Brown MJ, Desta B, Ferro A, Schofield WN, Taylor AA, Hill RG. Comparison of the vasoconstrictor properties of the 5-HT1D-receptor agonists rizatriptan (MK-462) and sumatriptan in human isolated coronary artery: outcome of two independent studies using different experimental protocols. Funct Neurol 1997;12:3-9
48. MaassenVanDenBrink A, Reekers M, Bax WA, Ferrari MD, Saxena PR. Coronary side-effect potential of current and prospective antimigraine drugs. Circulation 1998;98:25-30
49. Tfelt-Hansen P, Seidelin K, Stepanavage M, Lines C. The effect of rizatriptan, ergotamine, and their combination on human peripheral arteries: a double-blind, placebo-controlled, crossover study in normal subjects. Br J Clin Pharmacol 2002;54:38-44
50. Vyas KP, Halpin RA, Geer LA, Ellis JD, Liu L, Cheng H, Chavez-Eng C, Matuszewski BK, Varga SL, Guiblin AR, Rogers JD. Disposition and pharmacokinetics of the antimigraine drug, rizatriptan, in humans. Drug Metab Dispos 2000;28:89-95
51. Sciberras DG, Polvino WJ, Gertz BJ, Cheng H, Stepanavage M, Wittreich J, Olah T, Edwards M, Mant T. Initial human experience with MK-462 (rizatriptan): a novel 5-HT1D agonist. Br J Clin Pharmacol 1997;43:49-54
52. Goldberg MR, Lee Y, Vyas KP, Slaughter DE, Panebianco D, Ermlich SJ, Shadle CR, Brucker MJ, McLoughlin DA, Olah TV. Rizatriptan, a novel 5-HT1B/1D agonist for migraine: single- and multiple-dose tolerability and pharmacokinetics in healthy subjects. J Clin Pharmacol 2000;40:74-83
53. Seeburger JL, Cady RK, Winner P, Macgregor A, Valade D, Ge Y, Zhang Y, Hustad CM, Strickler N, Schaefer E, Connor KM, Ho TW. Rizatriptan for treatment of acute migraine in patients taking topiramate for migraine prophylaxis. Headache 2011 Epub ahead of print.
54. Merck & Co Inc. Maxalt® (rizatriptan benzoate tablets) and Maxalt-MLT® (rizatriptan benzoate orally disintegrating tablets): United States prescribing information. New Jersey, USA: 2003
55. Goldberg MR, Sciberras D, De Smet M, Lowry R, Tomasko L, Lee Y, Olah TV, Zhao J, Vyas KP, Halpin R, Kari PH, James I. Influence of beta-adrenoceptor antagonists on the pharmacokinetics of rizatriptan, a 5-HT1B/1D agonist: differential effects of propranolol, nadolol and metoprolol. Br J Clin Pharmacol 2001;52:69-76
56. Cumberbatch MJ, Hill RG, Hargreaves RJ. Rizatriptan has central antinociceptive effects against durally evoked responses. Eur J Pharmacol 1997;328:37-40
57. Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, Rowland CR. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes 2004;2:12
58. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-483
59. U.S. Department of Health and Human Services. National Institutes of Health, National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. 2010. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html
60. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. American Academy of Otolaryngology-Head and Neck Foundation, Inc. Otolaryngol Head Neck Surg 1995;113:181-185

61. Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. Arch Otolaryngol Head Neck Surg 1990;116:424-427
62. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092-1097
63. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA 1999;282:1737-1744
64. Goldberg MR, Lowry RC, Musson DG, Birk KL, Fisher A, De Puy ME, Shadle CR. Lack of pharmacokinetic and pharmacodynamic interaction between rizatriptan and paroxetine. J Clin Pharmacol 1999;39:192-199
65. Smith DA, Cleary EW, Watkins S, Huffman CS, Polvino WJ. Zolmitriptan (311C90) does not interact with fluoxetine in healthy volunteers. Int J Clin Pharmacol Ther 1998;36:301-305
66. Mathew NT, Hettiarachchi J, Alderman J. Tolerability and safety of eletriptan in the treatment of migraine: a comprehensive review. Headache 2003;43:962-974
67. Putnam GP, O'Quinn S, Bolden-Watson CP, Davis RL, Gutterman DL, Fox AW. Migraine polypharmacy and the tolerability of sumatriptan: a large-scale, prospective study. Cephalalgia 1999;19:668-675
68. Hintze J. Power Analysis and Sample Size (PASS) 11; Statistical Analysis and Graphics (NCSS), LLC. Kaysville, UT: 2011. Available at: www.ncss.com
69. Dupont WD. Power calculations for matched case-control studies. Biometrics 1988;44:1157-1168
70. Everitt BS, Hothorn T. A Handbook of Statistical Analyses Using R. Boca Raton, FL, Chapman & Hall/CRC, 2006
71. McCulloch CE, Searle SR. Generalized, Linear, and Mixed Models: Wiley Series in Probability and Statistics. New York, NY, John Wiley & Sons, Inc., 2001
72. McCullagh P, Nelder JA. Generalized Linear Models, Second Edition. New York, NY, Chapman & Hall, 1989
73. Schabenberger O. Introducing the GLIMMIX procedure for generalized linear mixed models. *SUGI 30 Proceedings*. 2005:196-30.
74. Little RJA, Rubin DB. Statistical analysis with missing data. Wiley-Interscience; 2002.
75. Schafer JL, Graham JW. Missing data: Our view of the state of the art. Psychological methods. 2002;7(2):147-177.
76. Collins LM, Schafer JL, Kam CM. A comparison of inclusive and restrictive strategies in modern missing data procedures. Psychological Methods, 2001;6(4):330–51.
77. Newgard CD, Haukoos JS. Advanced statistics: missing data in clinical research—part 2: multiple imputation. Academic Emergency Medicine, 2007;14(7):669–78.
78. McCrae RR, Costa Jr PT, Martin TA. The NEO-PI-3: a more readable revised NEO Personality Inventory. J Pers Assess. 2005 Jun;84(3):261-70.

BACKGROUND

Vestibular migraine (VM) was defined by the International Headache Society and Bárány Society as a disorder producing recurrent episodes of vertigo or dizziness accompanied at least 50% of the time by migrainous features in patients with histories of migraine. This randomized controlled trial tested the efficacy of rizatriptan as an abortive treatment for attacks of VM.

METHODS

Patients with VM (N=225) were observed prospectively to confirm the diagnosis. Those who experienced two verified VM attacks within 12 months (N=114) were randomized 2:1 to treat up to three subsequent attacks with rizatriptan 10 mg or placebo orally. The primary outcome was the proportion of attacks with vestibular symptoms (vertigo or unsteadiness/dizziness) reduced from moderate/severe to none/mild at 1 hour after administration of study drug. Secondary outcomes were: (1) proportion of attacks with symptoms resolved at 1 hour, (2) proportion of attacks with symptoms reduced from moderate/severe to none/mild at 24 hours, (3) treatment satisfaction at 48 hours, (4) quality of life at 48 hours, and (5) rates of adverse effects.

RESULTS

Of 308 treated attacks, 245(79.5%) with moderate/severe vestibular symptoms were used to test study outcomes. On the primary outcome, rizatriptan did not differ from placebo in reducing vertigo [73/153(47.7%) vs. 53/92(57.6%) attacks, $p<0.28$] or unsteadiness/dizziness [29/153 (18.9%) vs. 11/92 (12%) attacks, $p<0.24$]. On secondary outcomes, rizatriptan was superior to placebo in reducing unsteadiness/dizziness [120/149 (80.5%) vs. 52/88 (59.1%) attacks, $p<0.008$] at 24 hours and in treatment satisfaction [regression estimate 11.92, 95% CI (2.33, 21.62), $p<0.016$] and physical well-being [regression estimate 4.55, 95% CI (1.14, 7.97), $p<0.009$] at 48 hours. Rizatriptan caused more mild/moderate fatigue and drowsiness than placebo but otherwise did not differ in side effect burden.

CONCLUSIONS

Rizatriptan was tolerated well but provided limited benefits for attacks of VM. (Funded by National Institute of Deafness and Other Communication Disorders, DC13256.)