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ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of a Fixed Combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg vs Betahistine Dihydrochloride 16 mg in Patients with Peripheral Vestibular Vertigo: A Prospective, Multinational, Multicenter, Double-Blind, Randomized, Non-inferiority Clinical Trial

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Abstract

Background and Objective Vertigo derived from peripheral vestibular disorders is quite frequently encountered in daily clinical practice and can be a severely disabling symptom associated with substantial impairment of health-related quality of life for the affected patients. Betahistine, a structural analogue of histamine and presumably the most widely prescribed anti-vertigo drug worldwide, has previously been shown to be an effective and safe treatment for these patients. The objective of the present study was to evaluate whether the fixed combination of cinnarizine and dimenhydrinate (Arlevert®) is non-inferior and thus a potentially useful alternative to betahistine dihydrochloride in the treatment of patients suffering from peripheral vestibular vertigo.

Methods In this prospective, multicenter, double-blind, randomized, non-inferiority clinical trial, outpatients from 8 ENT clinics in Austria, Bulgaria, the Czech Republic and Russia were randomly assigned to receive three times daily one tablet of either the fixed combination cinnarizine 20 mg/dimenhydrinate 40 mg or betahistine dihydrochloride 16 mg for 4 weeks. Primary endpoint was the reduction of the mean vertigo score (MVS), a validated 12-item composite score defined as the mean of 6 vertigo symptoms (dystasia and walking unsteadiness, staggering, rotary sensation, tendency to fall, lift sensation, blackout) and 6 trigger factors for vertigo (change of position, bowing, getting up, driving by car/train, head movements, eye movement), after 4 weeks of therapy, as judged by the patient on a 5-point visual analogue scale (VAS). The non-inferiority margin was set to 0.3. Secondary outcomes included the patient's and investigator's judgment of global efficacy, the patient's rating of impairment of daily activities, and safety/tolerability of the treatments.

Results Three hundred and six patients (mean age 53.5 years, approximately 60% female) were enrolled and randomized to the fixed combination cinnarizine/dimenhydrinate ($n = 152$) or betahistine ($n = 154$) groups; 297 patients completed the study and 294 (146 and 148, respectively) were valid for the per-protocol analysis, which was used for the non-inferiority analysis. Treatment with cinnarizine/dimenhydrinate led to a stronger reduction of the MVS [least squares mean (LSM)] after 4-week therapy (primary endpoint) in comparison to betahistine (0.395 vs 0.488; difference: −0.093, 95% CI −0.180; −0.007, $p = 0.035$); since the upper limit of the two-sided 95% confidence interval was not only below the non-inferiority margin of 0.3, but also entirely below 0, superiority of the fixed combination could be demonstrated. The combination preparation was also more effective after 1 week of therapy and received more favorable patient's ratings on overall efficacy and impairment of daily activities. Both treatments were very well tolerated. Only 12 patients (3.92%) reported 13 non-serious

Parts of this work have been presented as poster presentations at the 89th Congress of the German Society of Neurology (DGN) in Mannheim, Germany (2016) and at the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) Annual Meeting in Chicago, USA (2017).

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adverse events; 2 cinnarizine/dimenhydrinate-treated patients discontinued the study prematurely due to adverse events as compared to 5 betahistine-treated patients.

Conclusion The fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg was found to be not only non-inferior, but superior to betahistine 16 mg in the improvement of peripheral vestibular vertigo. Furthermore, taking into account a good and slightly favorable safety profile, the present study provides evidence that the fixed-combination preparation is a potent and even superior alternative to betahistine in the treatment of vertigo related to peripheral vestibular disorders.

Study Registration EudraCT No. 2011-004025-27.

Key Points

The fixed combination of cinnarizine 20 mg/dimenhydrinate 40 mg was found to be not only non-inferior, but superior to betahistine dihydrochloride 16 mg in reducing vertigo symptoms in adult patients with peripheral vestibular disorders.

Both treatments were well tolerated and also led to significant improvements of the patients' ability to cope with their daily activities as well as to an effective reduction of vegetative concomitant symptoms.

Overall, the results of the study provide evidence that the fixed combination cinnarizine/dimenhydrinate, compared to the widely used betahistine, is a potent and superior treatment option for patients suffering from vertigo of peripheral vestibular origin.

1 Introduction

Vertigo, an illusion of self-motion and/or perceived movement of one's surroundings, belongs to the symptoms most commonly reported in daily clinical practice [1, 2]. In a representative population survey conducted in Germany, lifetime prevalence of vertigo accounted for 7.4% of the general adult population, with a marked female preponderance and a significantly increased prevalence in the elderly [3–5].

The peripheral vestibular system comprises the three semicircular canals, the two otolith organs (saccule and utricle) and the vestibular nerve, located in the inner ear. Some of the most frequent vertigo syndromes are derived from a number of well-defined peripheral vestibular disorders, such as benign paroxysmal positioning vertigo (BPPV), vestibular neuritis, bilateral vestibulopathy or Menière's disease, for which specific medical or non-medical treatments are available [6, 7]. However, in general practice it often proves difficult or even impossible to establish clear-cut diagnoses and subsequent specific treatment options, due mainly to a large variety of reported symptoms, the complexity of underlying disorders or lack of suitable diagnostic equipment, especially in the primary care setting [8, 9]. Accordingly, in a multinational observational study involving 4294 patients with peripheral vestibular vertigo, vertigo complaints of the majority of patients could not be assigned to a specific disease (e.g. BPPV, Menière's disease), but were categorized rather unspecifically as suffering from peripheral vestibular vertigo of "other" or "unknown" origin [10].

Vertigo can lead to severe impairment of the affected patients, resulting in considerable limitations of daily activities and consequently lower health-related quality of life [3, 4]. Therefore, symptomatic treatment of vertigo is important to provide immediate relief to the patients, even if the underlying vestibular disorders have not yet been entirely clarified.

Various anti-vertigo drugs are currently available for the symptomatic management of vestibular vertigo. Presumably the most frequently used anti-vertigo drug worldwide is betahistine, usually prescribed as betahistine dihydrochloride (Serc®, Betaserc®; Abbott Laboratories) at 16 mg three times daily. It is a histamine analogue, which acts as a weak H1 agonist and a potent H3 antagonist [11 for review], although its exact mechanism of action on the vestibular system still remains to be clarified. Betahistine is licensed and widely used for the treatment of Menière's disease and peripheral vestibular vertigo associated with Menière's disease-like symptom complexes, which may comprise the main symptoms vertigo (often associated with nausea and/or vomiting), tinnitus, and hearing loss. Primary care physicians frequently prescribe betahistine in case of rather unspecific symptomatology and etiology [10]. Numerous clinical trials have shown the good efficacy and tolerability of betahistine in the therapy of vertigo related to various vestibular disorders [12–14].

Moreover, a fixed-combination preparation composed of 20 mg cinnarizine and 40 mg dimenhydrinate (Arlevert®, Hennig Arzneimittel) has been successfully used in the treatment of vertigo of various origins for more than three decades. Its anti-vertiginous efficacy is based on a dual mechanism of action: cinnarizine, a specific calcium channel blocker, acts mainly on the peripheral vestibular system through inhibition of calcium influx into the vestibular hair cells and thus regulating hair-cell afferent vestibular transmission [15, 16]. The antihistamine dimenhydrinate exerts its anti-vertiginous and anti-emetic effects through inhibition of histamine- and cholinergic-receptor functions in the vestibular nuclei and vomiting center [17, 18]. Both active

components complement each other in a synergistic way [19]. The efficacy and safety of the fixed combination of cinnarizine and dimenhydrinate has been demonstrated in several randomized, placebo- and/or active-controlled clinical trials (RCTs) including patients suffering from various types of vertigo [19–28] as well as in a meta-analysis of five single RCTs [29].

In previously conducted randomized, controlled clinical trials, the efficacy and safety of the fixed combination cinnarizine/dimenhydrinate has been tested against betahistine (dimesylate salt) with respect to reducing vertigo associated with peripheral vestibular disorders. Whereas the fixed combination proved to be superior to betahistine in patients suffering from otogenic vertigo [21] or vestibular neuritis [26], it was shown to be non-inferior in patients suffering from Menière's disease [27, 28].

The present study was designed to further investigate the efficacy and safety of the fixed combination cinnarizine/dimenhydrinate in patients suffering from vertigo derived from peripheral vestibular disorders, a condition which is frequently encountered in daily clinical practice and often associated with substantial impairment of health-related quality of life for the affected patients. The objective of the study was to evaluate whether the fixed-combination preparation may be non-inferior and thus a potentially useful alternative to betahistine dihydrochloride (16 mg three times daily), which is currently the worldwide clinically accepted and frequently prescribed standard treatment for patients suffering from vertigo related to various peripheral vestibular disorders.

2 Patients and Methods

2.1 Patients

Male and female outpatients (aged ≥ 18 years) suffering from peripheral vestibular vertigo of various origins, including rather unspecific or unclear pathologies, were recruited. Patients with more strictly defined peripheral vestibular disorders, for which specific therapy options are available, such as confirmed Menière's disease or syndrome, BPPV, bilateral vestibulopathy and acute peripheral vestibular disorders requiring hospitalization, as well as patients with non-vestibular vertigo were excluded. Diagnoses of peripheral vestibular vertigo were made by the investigators (all experienced neurotologists), mainly based on patient history and supported in the vast majority of cases by clinical examinations, such as vestibulo-spinal movement patterns (e.g. posturography) and electronystagmography (ENG). In order to be eligible for enrollment, patients were required to rate the intensity of at least one of six single vertigo symptoms (dystasia and walking unsteadiness, staggering, rotary sensation, tendency to fall, lift sensation, blackout) as ≥ 2 ('medium') on a 5-point visual analogue scale (VAS; see efficacy assessments). Further exclusion criteria were derived from known contraindications of the two study medications, e.g. convulsions, suspected compressive intracranial processes, angle-closure glaucoma, prostate adenoma with residual urine, severe renal insufficiency, Parkinson's disease, pheochromocytoma, peptic ulcer, chronic liver disease, and pregnancy or lactation. Concomitant use of aminoglycosidic antibiotics, monoaminooxidase inhibitors, tricyclic antidepressants, parasympatholytics, glucocorticoids, or heparin was not allowed. Anti-vertiginous drugs had to be discontinued prior to start of treatment (1-week washout phase).

2.2 Study Design

This randomized, double-blind, active-controlled, multinational, multicenter, parallel-group, non-inferiority study was conducted between July 2013 and April 2015 at eight ENT clinics located in Austria, Czech Republic, Bulgaria and Russia. The study was registered in Europe under the EudraCT No. 2011-004025-27 and the protocol was approved by the Independent Ethics Committees of the participating study centers and the regulatory authorities of the respective countries. The study was performed in accordance with Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki in its current version. All patients gave their written informed consent prior to enrollment in the study.

Eligible patients were randomly assigned in a 1:1 ratio to receive either the fixed combination of cinnarizine 20 mg/dimenhydrinate 40 mg (Arlevert®, Hennig Arzneimittel) or betahistine dihydrochloride 16 mg (Betavert® N, Hennig Arzneimittel) for 4 weeks (28 ± 2 days). In order to ensure double-blind conditions, a double-dummy technique was used owing to the different appearance of cinnarizine/dimenhydrinate and betahistine tablets. Therefore, placebo (dummy) tablets identical to the respective active cinnarizine/dimenhydrinate and betahistine tablets with respect to size, weight, shape, color and taste were manufactured. Patients in fact took 2 tablets three times daily: 1 tablet of active cinnarizine/dimenhydrinate plus 1 tablet of betahistine placebo (cinnarizine/dimenhydrinate group) or 1 tablet of active betahistine plus 1 tablet of cinnarizine/dimenhydrinate placebo (betahistine group) in the test and reference groups, respectively. Patients were instructed to simultaneously take two tablets each in the morning, at noon, and in the evening after the main meals, starting on the day after the entry examination. The intake of study medication, including any possible change in dosage, mode of administration or interruption of intake, was registered on occasion of the intermediate and final visits; compliance of medication intake was estimated by means of the number of tablets returned by the patients at the final visit.

The randomization sequence was computer generated with a block size of 4 and prospectively stratified according to the study center and the severity of vertigo symptoms at baseline, i.e. total score of 6 (unprovoked) vertigo symptoms <6 (Stratum 1) or ≥ 6 (Stratum 2), to optimize group comparability. Participants, care providers, and those assessing the outcomes were all blinded to treatment group assignment. Each individual patient's group assignment code was kept in a sealed envelope to be opened only in case of emergency; even in case of opening the envelope, no information on the group assignment of any other patient would have been revealed, since the batch number of the study medication was blinded as well.

2.3 Efficacy and Safety Assessments

The primary efficacy endpoint was the change in the mean vertigo score (MVS) of the fixed combination cinnarizine/dimenhydrinate and betahistine from baseline to the end of treatment (4 weeks; 28 ± 2 days). The MVS, a 12-item composite score to measure the severity of vertigo symptoms, is defined as the mean intensity of 6 (unprovoked) vertigo symptoms (dystasia and walking unsteadiness, staggering, rotary sensation, tendency to fall, lift sensation, blackout) and vertigo in consequence of 6 triggering factors [change of position (lying), bowing, getting up, driving by car/train, head movements (inclination, twist), eye movement]. The intensity of each of the 12 single symptoms was rated by the patients by means of a 5-point VAS ranging from 0, no symptom to 4, very strong symptom, i.e. the MVS ranges from 0–4. The validity of the MVS has been demonstrated previously by means of Cronbach's alpha calculations, which showed an overall good reliability and lack of any significant redundancies among the single items of the composite score [21, 25].

Secondary efficacy endpoints comprised the change in MVS from baseline to 2nd visit (1 week; 7 ± 2 days), the mean change of the two 6-item sub-scores (6 vertigo symptoms; vertigo in consequence of 6 trigger factors), the patient's ability to cope with daily activities assessed by means of a 3-point verbal rating scale (no, slight or strong impairment, respectively) as well as the patient's and investigator's ratings of overall efficacy by means of a 5-point verbal rating scale (very much improved, much improved, slightly improved, not improved, deteriorated). Furthermore, the change of a mean score composed of four vegetative concomitant symptoms (nausea, vomiting, sweating, and tachycardia) was determined, as well as other concomitant symptoms such as tinnitus, impaired hearing, impaired vision, aural fullness and headache. The intensity of each of these single concomitant symptoms was assessed by the patient on the same 5-point VAS as used in case of the vertigo symptoms; all assessments have been recorded on occasion of each of the three visits (at baseline, after 1 week, after 4 weeks of therapy).

Adverse events (AEs) were assessed throughout treatment and recorded in the case report forms on occasion of the intermediate (after 1 week) and final visit (after 4 weeks); for each AE, the investigator evaluated seriousness (serious, non-serious), severity (mild, moderate, severe) and possible relatedness to the study medication. Blood pressure was measured at each visit. Moreover, on occasion of the intermediate and final visits, both patients and investigators judged the tolerability of the treatment on a 4-point verbal rating scale (very good, good, moderate, poor).

2.4 Statistical Analysis

The primary efficacy endpoint (mean reduction in the MVS between baseline and Week 4) was primarily analyzed for the per-protocol (PP) population and repeated, for sensitivity reasons, for the intent-to-treat (ITT) population. For most efficacy endpoints, analysis of covariance (ANCOVA) was performed to calculate the two-sided 95% CIs for the difference between treatments, using baseline values as covariates. For the primary efficacy endpoint, non-inferiority of the fixed combination cinnarizine/dimenhydrinate to betahistine could be claimed if the 95% CI for the difference in the MVS after 4-week treatment, calculated in terms of baseline-adjusted means (least squares means, LSM), was entirely below the prespecified non-inferiority margin of 0.3. The margin refers to an earlier clinical trial comparing the fixed combination with betahistine dimesylate in patients suffering from Menière's disease [28], where the margin had been set to 0.5 with respect to a 12-week treatment. Due to the broader patient population and shorter treatment period (4 weeks), the non-inferiority margin for the present study was tightened to 0.3, a value which is slightly below an approximate minimal clinically important difference (MCID) calculated as 1/12 of the used vertigo intensity VAS range (0–4) [30–32]. Based on a previous study, which compared the fixed combination of cinnarizine and dimenhydrinate to betahistine dimesylate in patients with peripheral (otogenic) vertigo [21], and taking into account the selected non-inferiority margin, a sample size of 200 patients was estimated to achieve 90% power to detect non-inferiority between the two treatment groups. Assuming a dropout rate of 10%, 224 patients needed to be randomized.

In addition, differences between treatment groups in the changes from baseline were evaluated by the Kruskal-Wallis test, and changes from baseline within treatment groups by the Wilcoxon signed-rank test. Categorical variables were compared using Fisher's exact test. Comparability of

treatment groups at baseline was assessed non-parametrically using Kruskal-Wallis or Wilcoxon rank sum test in case of continuous variables, or Fisher's exact test in case of categorical variables. Statistical analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA).

3 Results

3.1 Study Population and Baseline Characteristics

A total of 306 patients were enrolled in the study and randomly assigned to treatment with either the fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg (n = 152) or betahistine dihydrochloride 16 mg (n = 154). Three patients (2.0%) in the cinnarizine/dimenhydrinate group and six patients (3.9%) in the betahistine group did not complete the 4-week treatment, corresponding to an overall dropout rate of 2.9% (Fig. 1). Due to the lack of post-randomization data, one patient in the cinnarizine/dimenhydrinate group and two patients in the betahistine group were excluded from the efficacy analysis. For the remaining six patients, who terminated the study prematurely after the second visit (1 week), the 'last observation carried forward' (LOCF) method was applied; thus, the ITT population comprised 303 patients.

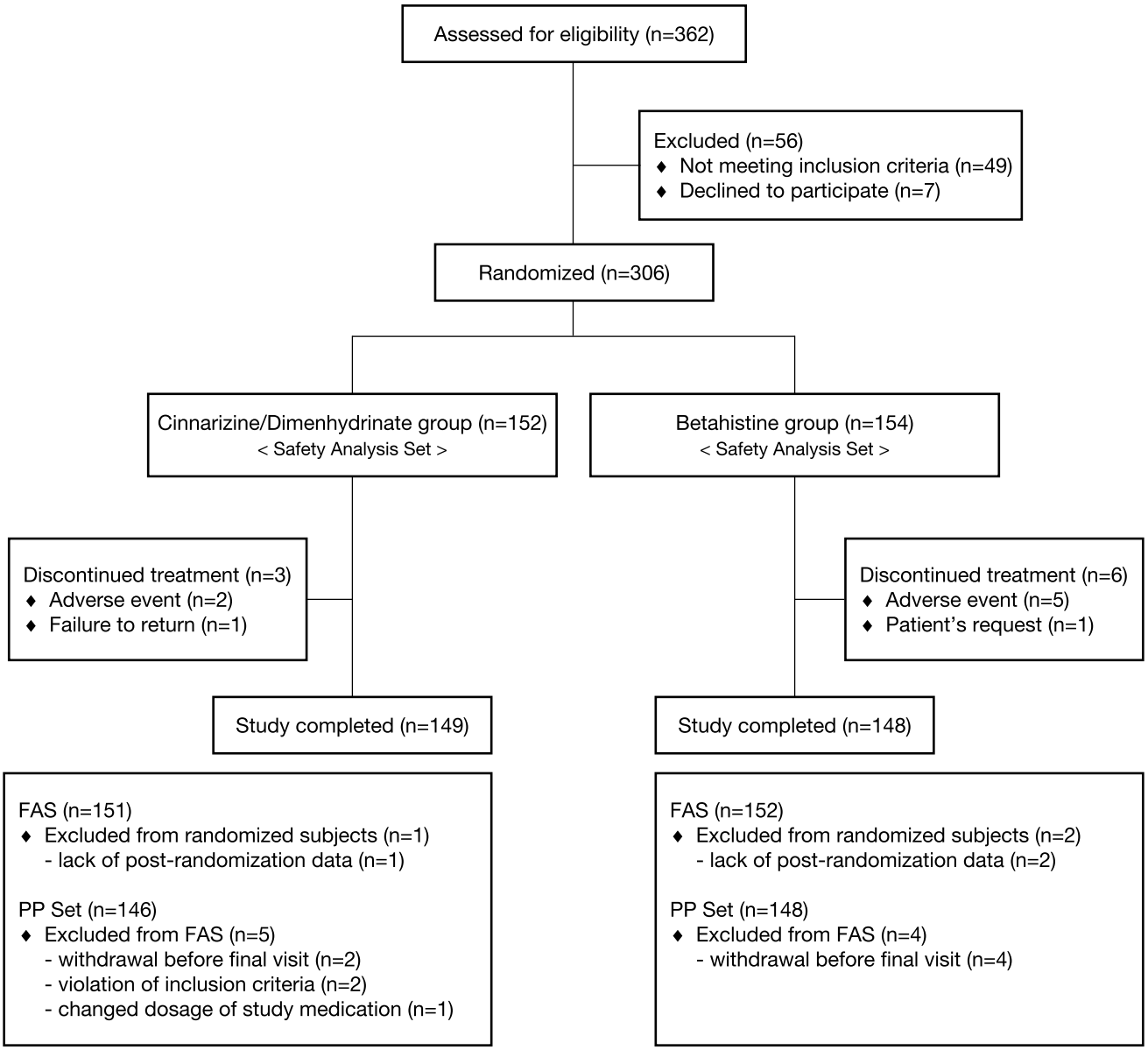

Fig. 1 Patient disposition. *Cinnarizine/dimenhydrinate* fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg, *betahistine* betahistine dihydrochloride 16 mg, *FAS* full analysis set, *PP* per-protocol

Taking into account 9 dropouts and 3 further patients in the cinnarizine/dimenhydrinate group with major protocol violations, the PP population comprised 294 patients. All randomized patients were included in the safety analysis.

The demographic and baseline clinical characteristics of all patients enrolled in the study are summarized in Table 1. The mean age of the study participants was 53.5 (SD ± 14.2, range 18–86) years and the majority were female ($n = 184$, 60.1%). The most common diagnosis was "Menière-like symptom complex", which is a rather unspecific, broadly defined condition including patients suffering from vestibular vertigo associated with various degrees of tinnitus and/or hearing loss, but not patients with confirmed Menière's disease or syndrome. Further diagnoses were "other peripheral vertigo", including peripheral vertigo not otherwise specified, as well as "labyrinthine dysfunction". With respect to the three diagnostic categorizations, there was a largely even distribution between both treatment groups (Table 1). About one-third of the patients suffered from concomitant diseases (mainly hypertension) and received respective concomitant medications. In the cinnarizine/dimenhydrinate group, six patients had been pretreated with anti-vertiginous drugs (two with betahistine, one each with cinnarizine/dimenhydrinate, piracetam, betahistine and cinnarizine/dimenhydrinate, betahistine and piracetam), as compared to two patients in the betahistine group (betahistine, vinpocetine). There were no significant differences (20% significance level) between the treatment groups regarding baseline demographic and clinical characteristics (Table 1).

Compliance rates were 97.3% in the cinnarizine/dimenhydrinate group (two noncompliant patients, one of whom was excluded from the PP analysis) and 98.6% (one noncompliant patient) in the betahistine group, excluding four and six dropouts, respectively. The calculation is based on approximately half of the patients (51.3% and 49.4%, respectively), who returned their unused study medication on occasion of the final visit.

3.2 Efficacy

3.2.1 Primary Efficacy Endpoint

As shown in Table 2 and Fig. 2, vertigo symptoms in both treatment groups significantly decreased in the course of the 4-week treatment ($p < 0.001$), starting from homogenous baseline values ($p = 0.736$). The LSM of the MVS after 4 weeks was 0.395 for the fixed combination and 0.488 for the betahistine group, and the difference between groups was − 0.093 (95% CI −0.180, −0.007). Thus, the 95% CI

Table 1 Baseline demographic and clinical characteristics of study participants ($n = 306$)

Characteristic	Cinnarizine 20 mg/dimenhydrinate 40 mg ($n = 152$)	Betahistine dihydrochloride 16 mg ($n = 154$)	*p* value
Male/female [*n* (%)]	58 (38.2)/94 (61.8)	64 (41.6)/90 (58.4)	0.561[a]
Age (years) [mean ± SD (range)]	53.0 ± 14.8 (18–84)	54.0 ± 13.6 (24–86)	0.643[b]
Weight (kg) [mean ± SD (range)]	76.9 ± 15.6 (46–130)	77.3 ± 16.1 (46–119)	0.836[b]
Height (cm) [mean ± SD (range)]	168.5 ± 11.9 (150–192)	168.6 ± 9.3 (148–194)	0.657[b]
BMI (kg/m^2) [mean ± SD (range)][d]	26.9 ± 5.0 (17–51)	27.0 ± 4.4 (17–41)	0.321[b]
Smokers [*n* (%)]	43 (28.3)	42 (27.3)	1.000[a]
Diagnoses			
Menière-like symptom complex [*n* (%)]	84 (55.3)	83 (53.9)	
Other peripheral vertigo [*n* (%)]	50 (32.9)	55 (35.7)	
Labyrinthine dysfunction [*n* (%)]	18 (11.8)	16 (10.4)	
Duration of vertigo (months) [mean ± SD (range)]	30.2 ± 69.6 (0–390)	19.5 ± 46.3 (0–310)	0.331[c]
Impaired hearing (5-point VAS; 0–4) [mean ± SD]	1.33 ± 1.33	1.50 ± 1.38	0.337[c]
Tinnitus (5-point VAS; 0–4) [mean ± SD]	1.79 ± 1.06	1.98 ± 1.15	0.104[c]
Patients with pretreatment for vertigo [*n* (%)]	6 (3.9)	2 (1.3)	0.172[a]
Patients with concomitant diseases [*n* (%)]	51 (33.5)	53 (34.8)	0.904[a]
Patients with concomitant medication [*n* (%)]	50 (32.8)	51 (33.1)	1.000[a]

BMI body mass index, *SD* standard deviation, *VAS* visual analogue scale

[a]Fisher's exact test

[b]Kruskal-Wallis test

[c]Wilcoxon rank sum test

[d]Body mass index = body weight/height^2

Table 2 Mean vertigo score (MVS) during the course of the study (per-protocol population; $n = 294$)

Time point/variable	Cinnarizine 20 mg/dimenhydrinate 40 mg ($n = 146$)	Betahistine dihydrochloride 16 mg ($n = 148$)	p value
Baseline (t_0)			
MVS (mean ± SD)	1.20 ± 0.45	1.21 ± 0.45	0.736[a]
After 1 week (t_{1w})			
MVS (mean ± SD)	0.78 ± 0.45[b]	0.89 ± 0.45[b]	
Change from baseline (mean ± SD)	−0.43 ± 0.41	−0.31 ± 0.3	0.009[a]
Change as percentage from baseline (%)	−35.8	−25.6	
MVS LSM (95% CI)	0.779 (0.725; 0.832)	0.892 (0.839; 0.944)	
Difference (fixed combination—betahistine) (95% CI)	−0.113 (−0.188; −0.037)[c]		0.003[d]
After 4 weeks (t_{4w})			
MVS (mean ± SD)	0.39 ± 0.42[b]	0.49 ± 0.42[b]	
Change from baseline (mean ± SD)	−0.81 ± 0.50	−0.72 ± 0.42	0.138[a]
Change as percentage from baseline (%)	−67.5	−59.5	
MVS LSM (95% CI)	0.395 (0.333; 0.456)	0.488 (0.472; 0.550)	
Difference (fixed combination—betahistine) (95% CI)	−0.093 (−0.180; −0.007)[c]		0.035[d]

CI confidence interval, *LSM* least squares mean, *MVS* mean vertigo score, *SD* standard deviation

[a]Kruskal-Wallis test

[b]$p < 0.001$ vs baseline; Wilcoxon signed rank test

[c]95% CI completely below non-inferiority (0.3) and superiority (0) margins

[d]ANCOVA, with baseline values as covariates

for the difference in MVS LSM between treatments was not only entirely below the non-inferiority margin of 0.3, but also below zero, providing evidence of superiority [33] of the fixed combination over betahistine after 4 weeks' treatment ($p = 0.035$, primary endpoint). Compared to the primary analysis of the PP population ($n = 294$), results for the ITT sensitivity analysis set ($n = 303$) were even slightly more in favor of the fixed combination, with a difference in MVS after 4 weeks' treatment of −0.117 (95% CI −0.210; −0.025; $p = 0.013$).

3.2.2 Secondary Efficacy Endpoints

Similarly to the calculations for the primary endpoint, there is evidence for superiority of the fixed combination cinnarizine/dimenhydrinate over betahistine in reducing the MVS (LSM) already after one week of treatment (Table 2, Fig. 2), with a calculated difference of −0.113 (95% CI −0.188, −0.037; $p = 0.003$). The same was true for the composite score of just the 6 (unprovoked) vertigo symptoms (i.e. without trigger factors), both after 1 week (LSM difference: −0.146, 95% CI −0.232, −0.059; $p = 0.001$) and after 4 weeks (LSM difference: −0.111, 95% CI −0.199, −0.023; $p = 0.013$), but not for the improvement of vertigo in consequence of the 6 trigger factors (LSM difference: −0.081, 95% CI −0.164, 0.003; $p = 0.057$ after 1 week, and −0.076, 95% CI −0.178, 0.026; $p = 0.146$ after 4 weeks of treatment).

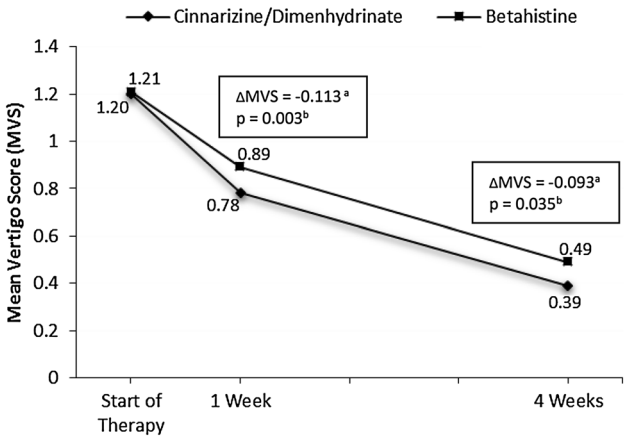

Fig. 2 Reduction of the mean vertigo score (MVS) during 4-week treatment with the fixed combination cinnarizine 20 mg/dimenhydrinate 40 mg ($n = 146$) or betahistine dihydrochloride 16 mg ($n = 148$) given three times daily. [a]ΔMVS = difference of MVS LSM (fixed combination−betahistine). [b]Analysis of covariance (ANCOVA) with baseline values as covariates. For more details see Table 2

A number of further secondary endpoints were analyzed for both the 1-week and 4-week treatment periods.

The results of the patients' judgment of impairment of daily activities are depicted in Fig. 3. The percentage of

patients experiencing 'strong impairment' (Fig. 3a) before start of treatment significantly decreased and the percentage of patients with 'no impairment' (Fig. 3b) before start of treatment significantly increased in the course of the 4-week therapy. Starting from homogenous baseline values, the fixed combination led to generally better improvements concerning both parameters, with a statistically significant superiority over betahistine (Fisher's exact test) regarding the patients' rating 'strong impairment' after 1 week ($p = 0.0013$) and 'no impairment' after 4 weeks ($p = 0.0035$), respectively.

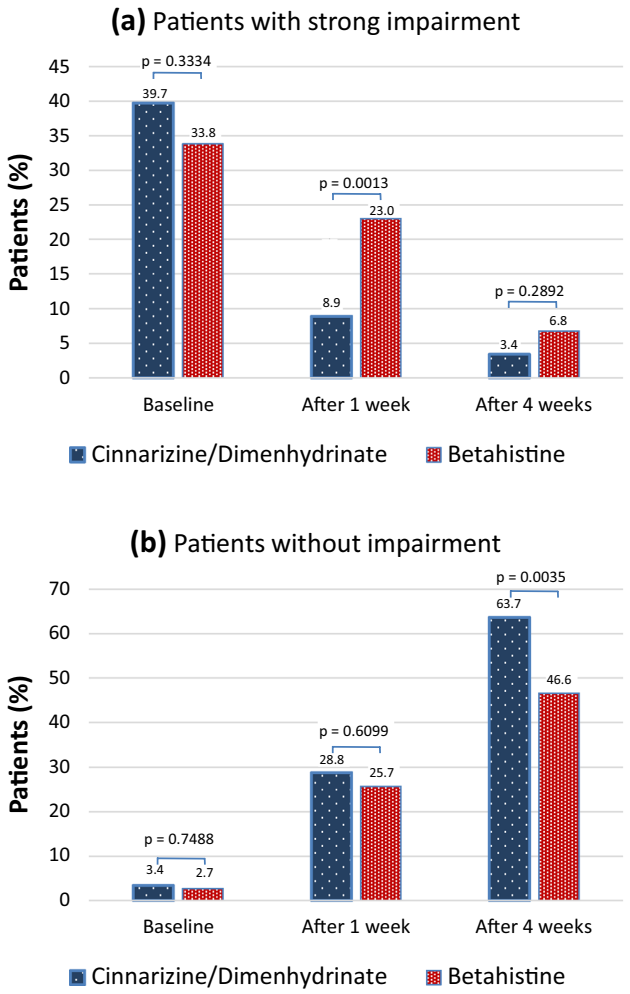

Fig. 3 Patients' impairment of daily activities at baseline, after 1 week and after 4 weeks of treatment with the fixed combination cinnarizine 20 mg/dimenhydrinate 40 mg or betahistine dihydrochloride 16 mg given three times daily. Baseline values were homogenously distributed between treatment groups. **a** Decreasing percentage of patients with strong impairment during the course of the study. The fixed combination cinnarizine/dimenhydrinate was significantly superior to betahistine after 1 week ($p = 0.0013$, Fisher's exact test). **b** Increasing percentage of patients with no impairment during the course of the study. The fixed combination cinnarizine/dimenhydrinate was significantly superior to betahistine after 4 weeks ($p = 0.0035$, Fisher's exact test)

Furthermore, a mean score composed of four vegetative concomitant symptoms (nausea, vomiting, sweating and tachycardia) has been analyzed in a similar way as the vertigo scores. In both treatment groups, the mean vegetative symptoms score highly significantly decreased within the 4-week period ($p < 0.001$), with the fixed combination leading to only slightly better results than betahistine (improvements by 81.1% and 79.1%, respectively). Improvements of other concomitant symptoms, such as tinnitus or headache, were distinctly less pronounced.

Finally, the generally good efficacy of both treatments, as demonstrated with respect to the primary endpoint, was largely reflected in the patients' and investigators' ratings of overall (global) efficacy. Already after 1 week of therapy, 49.3% of the patients in the cinnarizine/dimenhydrinate group rated the overall efficacy as either 'very much improved' or 'much improved', as compared to 21.6% of patients in the betahistine group; at the end of the 4-week therapy, these values increased to 71.2% and 62.8%, respectively (Fig. 4), but without statistically significant difference between treatments ($p = 0.138$; Fisher's exact test).

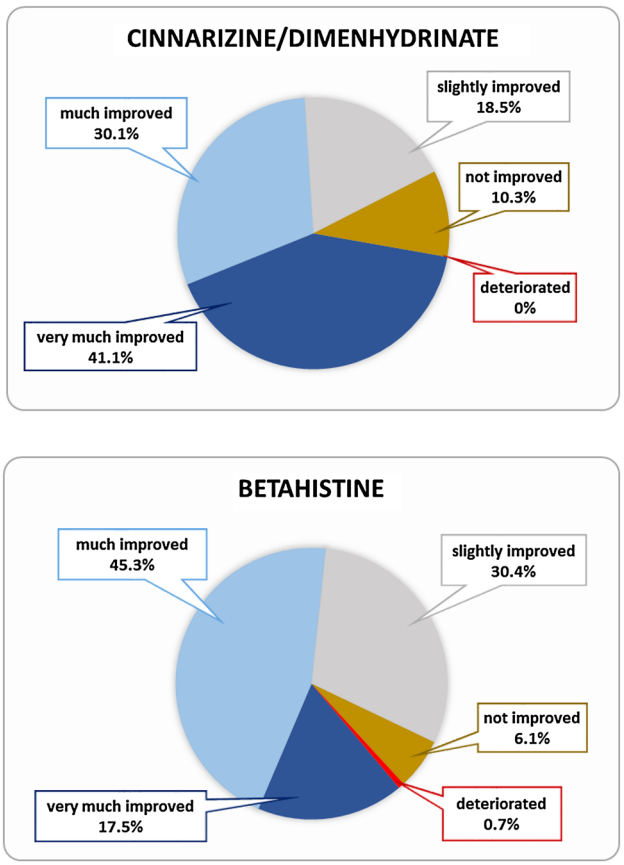

Fig. 4 Patient's rating (5-point verbal rating scale) of global efficacy after 4 weeks of treatment with the fixed combination cinnarizine 20 mg/dimenhydrinate 40 mg or betahistine dihydrochloride 16 mg three times daily (Per Protocol population; $n = 146$ and $n = 148$, respectively)

3.3 Safety

Only 12 (3.9%) of the 306 randomized patients, 4 in the cinnarizine/dimenhydrinate group (2.6%) and 8 (5.2%) in the betahistine group reported a total of 13 non-serious AEs, 7 of which were judged by the investigator as 'possibly' or 'probably' treatment related. No serious AEs or deaths were reported in the study. The most common AEs were vertigo attack (four patients in the betahistine group), dry mouth and allergic reaction (both reported by one patient in each group); other AEs were fatigue, stomach pain/pressure, increased blood pressure, dysuria, and worsening of seborrheic dermatitis. A total of 7 patients discontinued the study prematurely because of AEs, 2 in the cinnarizine/dimenhydrinate group and 5 in the betahistine group. Neither the fixed combination nor betahistine exerted any statistically significant or clinically relevant effect on blood pressure.

The low incidence of adverse events is also reflected in the patients' tolerability ratings. At the end of the study, 61.1% of patients in the cinnarizine/dimenhydrinate group rated the tolerability as 'very good', as compared to 49.3% in the betahistine group. All except three of the remaining patients in each treatment group judged the tolerability as 'good' (36.9% and 48.6%, respectively). The investigators' tolerability assessments of both treatments were virtually identical to the patients' ratings.

4 Discussion

Patients with peripheral vestibular disorders are suffering from vestibular, mostly episodic (recurrent) vertigo, often associated with vegetative symptoms such as nausea or vomiting, hearing loss, and/or tinnitus. This rather unspecific, broadly defined condition is quite frequently encountered in daily clinical practice, particularly in the primary care setting. Although the underlying disorder often cannot be categorized more specifically and a more clearly defined diagnosis often cannot be established, the patients are severely impaired and need immediate relief. Betahistine is one of the most widely used anti-vertigo drugs worldwide, and its efficacy and safety has been demonstrated in a number of placebo-controlled clinical trials in patients suffering from various vestibular disorders [12, 13, 34, 35]; it is largely considered as a first-line pharmaceutic agent for symptomatic treatment of vertigo associated with peripheral vestibular disorders.

The present study investigated the use of the fixed combination cinnarizine 20 mg/dimenhydrinate 40 mg as an alternative treatment option to betahistine. Although the primary objective of the study was to show non-inferiority to betahistine 16 mg, the results of the study provide evidence of superiority of the fixed combination over betahistine with respect to the reduction of vertigo symptoms, as measured by the MVS, after both the 4-week therapy (primary efficacy endpoint) and 1-week therapy. Taking further into account a good and slightly favorable safety profile, there is evidence that the fixed combination of cinnarizine/dimenhydrinate is a potent and even superior alternative to betahistine in the treatment of vertigo related to peripheral vestibular disorders.

The overall superior efficacy of the fixed combination cinnarizine/dimenhydrinate as compared to betahistine may be explained by its broader spectrum of activity, based on the fact that cinnarizine and dimenhydrinate are acting at different sites of the vestibular system and complement each other in a synergistic way. Whereas cinnarizine acts mainly on the peripheral vestibular system, dimenhydrinate acts predominantly on the central vestibular system. Due to this dual mechanism of action, the fixed combination of cinnarizine and dimenhydrinate effectively relieves vertigo originating from various vestibular disorders. Betahistine, a structural analogue of histamine available as betahistine dihydrochloride (maximum daily dose 48 mg) and betahistine dimesylate (maximum daily dose 36 mg), is believed to act predominantly on the peripheral vestibular system, although the exact mode of action still remains to be clarified.

The findings of the present study are largely in line with results from previously conducted randomized, double-blind controlled clinical trials, where the fixed-combination preparation has been shown to be significantly more effective than betahistine (dimesylate) in patients with otogenic vertigo [21], vertigo due to vertebrobasilar insufficiency [23], acute vestibular disorders [24], or vestibular neuritis [26], and non-inferior in patients with Menière's disease [27, 28], respectively.

All demographic and clinical baseline characteristics of the study participants (age, gender, etc.) were homogenously distributed between both treatment groups. The majority of patients were female, and the mean age of all study participants was 53.5 years, which is in line with published demographic data from various studies in patients suffering from vertigo [8, 10]. Overall, the patients included in the present study constituted a representative sample of patients with peripheral vestibular vertigo in clinical practice.

Generally, the observed substantial improvement of vertigo symptoms, expressed by a mean reduction of the MVS by approximately 60–70% after 4-week treatment ($p < 0.001$ vs baseline), first of all indicates without doubt a clinically meaningful effect of *both* medications, although no placebo group has been included, which leaves the actual contribution of spontaneous resolution of vertigo symptoms unknown. Furthermore, both medications led to highly significant improvements of vegetative and other concomitant symptoms in the course of therapy ($p < 0.001$ vs baseline),

which probably contributed to the overall therapeutic success.

Comparing the effectiveness of both treatments, the fixed combination cinnarizine/dimenhydrinate proved to be superior to betahistine with respect to the reduction of the MVS both after 4 weeks ($p = 0.035$; primary efficacy endpoint) and after 1 week of treatment ($p = 0.003$). The overall better efficacy of the fixed combination is corroborated by secondary efficacy parameters such as the patient's rating of 'global efficacy' ('very much improved': 41.1% of patients in the fixed combination group vs 17.5% in the betahistine group) and 'impairment of daily activities' after 4 weeks ('no impairment': 63.7% vs 46.6%). Vegetative concomitant symptoms were also distinctly reduced by both treatments, but no statistically significant difference was found.

There are several limitations of the study that need to be addressed. Diagnoses of peripheral vestibular vertigo were basically made at the discretion of the investigators; although thoroughly carried out by experienced neurotologists and relying on medical history as well as clinical examinations, diagnostic criteria for inclusion of patients in the present study have not been strictly predefined. This means that the patient population was certainly more heterogeneous than in other studies including patients with more strictly defined vestibular disorders. Furthermore, the involvement of eight study centers located in four different countries, with different languages as well as varying cultural and healthcare backgrounds, has probably further increased heterogeneity of the collected data, which make interpretation of the findings more difficult. On the other hand, the broadly defined patient population may better reflect the real-world clinical care setting, which might contribute to a better generalization of the study results. A further limitation concerns the relatively short duration of treatment (4 weeks), which could have been insufficient, especially for some of the patients with Menière-like symptomatology, although the average improvement of vertigo after 4-week treatment within both treatment groups was actually found to be highly significant and can be considered as clinically meaningful. Taking into account the limitations discussed above, the findings of the present study should be interpreted with caution and further studies are necessary to confirm the results.

Both therapies proved to be safe and very well tolerated, with the fixed combination showing a slightly better safety profile than betahistine, expressed by fewer AEs, fewer dropouts due to AEs, and better tolerability ratings of the patients. The excellent tolerability of both medications found in the present study, which is also reflected in the patient's and investigator's tolerability ratings, is in line with what is known from numerous clinical studies and extensive experience in daily clinical practice.

5 Conclusions

The fixed combination of 20 mg cinnarizine and 40 mg dimenhydrinate was found to be not only non-inferior, but superior to betahistine 16 mg in the treatment of peripheral vestibular vertigo associated with various pathologies. Taking further into account a good and slightly favorable safety profile, the present study provides evidence that the fixed-combination preparation is a potent and even superior alternative to betahistine in the treatment of vertigo related to peripheral vestibular disorders.

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Compliance with Ethical Standards

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Conflict of interest Arne W. Scholtz, Ales Hahn, Bohdana Stefflova, Daniela Mezhidieva, Sergey V. Ryazantsev, Alexander Paschinin and Natalia Kunelskaya have no conflicts of interest that are directly relevant to the content of this article. Kai Schumacher is an employee of Berlin-Chemie AG/Menarini and Gerhard Weisshaar is an employee of Hennig Arzneimittel.

Ethics approval The study was conducted in accordance with the ICH guidelines for Good Clinical Practice (GCP) and the Declaration of Helsinki in its current version following approvals by the Ethics Committees of all institutions involved.

Informed consent Informed consent was obtained from all individual study participants prior to enrollment in the study.

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