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ORIGINAL RESEARCH

A Clinical Study to Assess the Efficacy and Safety of MP-AzeFlu Nasal Spray in Comparison to Commercially Available Azelastine Hydrochloride and Fluticasone Propionate Nasal Sprays in Chinese Volunteers with Allergic Rhinitis

Bing Zhou · Lei Cheng · Jing Pan · Huizhong Wang · Yongde Jin · Changqing Zhao · Peng Lin · Guolin Tan · Hongyan Fang · Hua Zhang · Huifang Zhou · Yaowu Dong · Hans Christian Kuhl · Rajesh Kumar Ramalingam · Duc Tung Nguyen

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ABSTRACT

Introduction: The objective of the present study was to evaluate the efficacy and safety of MP-AzeFlu nasal spray in comparison to commercially available azelastine hydrochloride and fluticasone propionate sprays in Chinese patients with moderate-to-severe allergic rhinitis (AR).
Methods: We conducted a 14-day multicenter, randomized, double-blind, active controlled prospective clinical study in adult and adolescent patients with AR, who had moderate-to-severe symptoms. The primary efficacy endpoint was the change from baseline in combined 12-h reflective total nasal symptom score

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B. Zhou (✉)
Department of Otolaryngology Head and Neck Surgery, Beijing TongRen Hospital, Capital Medical University, Beijing 100051, China
e-mail: entzhou@263.net

L. Cheng
Department of Otorhinolaryngology & Clinical Allergy Center, The First Affiliated Hospital, Nanjing Medical University, Nanjing, 210029, China

J. Pan
Department of Otolaryngology Head and Neck Surgery, Tianjing Renmin Hospital, Nankai University, Tianjing, China

H. Wang
Department of Otolaryngology Head and Neck Surgery, Zibo Central Hospital, Zibo, China

Y. Jin
Department of Otolaryngology Head and Neck Surgery, Yanbian University Hospital, Yanji, China

C. Zhao
Departments of Otolaryngology Head and Neck Surgery, Second Affiliated Hospital, Shanxi Medical University, Taiyuan, China

P. Lin
Department of Otolaryngology Head Neck Surgery, Tianjin First Central Hospital, Tianjin Medical University, Tianjin, China

G. Tan
Department of Otolaryngology Head Neck Surgery, Third Xiangya Hospital, Central South University, Changsha, China

H. Fang
Department of Otolaryngology Head Neck Surgery, Chongqing General Hospital, Chongqing, China

H. Zhang
Department of Otolaryngology Head Neck Surgery, The first affiliated Hospital of Xinjiang Medical University, Wulumuqi, China

(rTNSS) (morning [AM] + afternoon [PM]). The safety profile of the study medications was assessed through the recording, reporting, and analysis of baseline medical conditions, adverse events (AEs), vital signs, and focused nasal examination. Three hundred patients per treatment group were randomized, which led to a total sample size estimation of 900 patients.
Results: MP-AzeFlu group showed significantly higher symptom reduction for the entire 2-week treatment period in rTNSS when compared with the AZE group (LS mean difference: − 1.96; 95% CI: − 2.53, − 1.39; $p < 0.0001$), or the FLU group (LS mean difference: − 0.98; 95% CI: − 1.55, − 0.41; $p = 0.0007$). The results of adult RQLQ showed improvement in QoL in all treatment groups. Except for dysgeusia (bitter taste) that was reported by more patients (13 [4.3%]) in the MP-AzeFlu group, the incidence of all other TEAEs in the MP-AzeFlu group was comparable or even lower than in other treatment groups.
Conclusions: MP-AzeFlu, when administered as one spray per nostril twice daily for 14 days, alleviated AR symptoms in Chinese patients with moderate-to-severe AR.
Trial Registration: Clinicaltrials.gov; NCT03599791, Registered June 29, 2018, retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT03599791.

H. Zhou
Department of Otolaryngology Head Neck Surgery, Tianjin Medical University General Hospital, Tianjin, China

Y. Dong
Department of Otolaryngology Head Neck Surgery, Tonghua Central Hospital, Tonghua, China

D. T. Nguyen
Global Clinical Sciences, MEDA Pharma GmbH & Co. KG (A Viatris Company), Bad Homburg, Germany

R. K. Ramalingam
Mylan Pharmaceuticals Private Limited (Now Viatris), Bengaluru, India

L. Cheng
International Centre for Allergy Research, Nanjing Medical University, Nanjing, 210029, China

H. C. Kuhl
Biometrics, MEDA Pharma GmbH & Co. KG (A Viatris Company), Bad Homburg, Germany

Keywords: Allergic rhinitis; Azelastine; Fluticasone; Fixed-dose combination; Seasonal allergic rhinitis

Key Summary Points

Why carry out the study?

There has been a progressive rise in allergic rhinitis cases in China with a growth rate of 6.5% between 2006 and 2011.

Azelastine HCl (AZE) nasal spray and fluticasone propionate (FLU) nasal spray are both marketed in China. However, the fixed-dose combination of AZE and FLU is not yet approved in China.

MP-AzeFlu Nasal Spray consists of azelastine HCl and fluticasone propionate, which are provided in a unique formulation.

The objectives of the study were to evaluate the efficacy and safety of MP-AzeFlu nasal spray in comparison to currently available first-line commercially available AR treatments azelastine (AZE) and fluticasone (FLU) nasal sprays in Chinese patients with moderate-to-severe allergic rhinitis/rhino conjunctivitis (AR).

What was learned from the study?

Results of this study confirmed the superior efficacy and the similar safety profile of MP-AzeFlu nasal spray compared to AZE or FLU in Chinese patients.

Sub-group analyses showed that MP-AzeFlu was effective in reducing nasal and ocular symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) and the effect was superior to that of FLU and AZE.

There was no increase in frequency of dysgeusia under MP-AzeFlu treatment in Chinese patients compared with previous clinical experiences outside of China.

INTRODUCTION

Allergic rhinitis is a major chronic respiratory disease due to its prevalence, impact on quality of life, impact on individual performance and productivity, economic burden, and links with asthma [1]. Allergic rhinitis (AR) affects 10–40% of the global population [1]. There has been a progressive rise in AR cases in China with a growth rate of 6.5% between 2006 and 2011. Recent studies demonstrated that there is a prevalence of 32.4% epidemiologic AR and 18.5% physician-diagnosed pollen-induced AR with urban areas having significantly higher patients with AR (23.1 vs. 14.0%, $P < 0.001$) compared to rural areas [2]. The projected healthcare costs for patients with AR in China is estimated to be almost $17.49 billion per year [3]. Assessment of quality of life (QoL) in allergic rhinitis patients in China have shown that there was a significant impairment in all QoL dimensions in patients with moderate-to-severe AR, especially in general health, mental-health, and social function dimensions [4]. Monotherapies using antihistamines or corticosteroids provide temporary relief but many patients still experience treatment failures or unsatisfactory results [5]. Combination therapies are an alternative option but patient adherence to the treatment is a problem. Patients co-medicate, but without success and reduced compliance. Uncontrolled AR is linked to worsening of comorbidities (e.g., asthma), emphasizing the medical need for a better treatment strategy.

Azelastine hydrochloride (HCl) nasal spray and fluticasone propionate nasal spray are widely prescribed rhinitis medications worldwide. A combination therapy with azelastine and fluticasone could provide a greater efficacy than therapy with each agent alone and has the potential to also increase adherence to therapy. MP-AzeFlu Nasal Spray consists of azelastine HCl and fluticasone propionate, which are provided in a unique formulation. The benefits of MP-AzeFlu nasal spray over mono-products (azelastine HCl and fluticasone propionate nasal sprays) were demonstrated in four efficacy pivotal clinical phase III studies in adults and adolescents in the US [6, 7]. Azelastine HCl nasal spray and fluticasone propionate nasal spray are both marketed in China. The objectives of the study were to evaluate the efficacy and safety of MP-AzeFlu nasal spray in comparison to currently available first-line commercially available AR treatments azelastine (AZE) and fluticasone (FLU) nasal sprays in Chinese patients with moderate-to-severe allergic rhinitis/rhino conjunctivitis (AR).

METHODS

Study Design

The study was a phase III clinical trial conducted between June 2018 and September 2019 in 28 study sites in China (NCT03599791). Patients were required to have at least a 2-year history of AR (seasonal and/or perennial) during the same time of year as the scheduled study time. This was a multicenter, randomized, double-blind, active controlled prospective clinical study in adult and adolescent patients with AR. The study consisted of a lead-in period for qualifying patients for the treatment period and obtaining baseline data. During the lead-in period, the patient self-administered the MP-AzeFlu vehicle without active ingredients (placebo). It was followed by a 14-day double-blind treatment period in which patients administered either MP-AzeFlu nasal spray or AZE nasal spray or FLU nasal spray (one spray per nostril twice daily) according to randomization (Fig. 1). Patients were requested to keep a patient diary of nasal and ocular symptoms throughout the study period. The patients were required to record their symptoms in a paper diary twice daily, right before using the nasal spray (similar to the four foreign clinical trials conducted earlier in the US). The symptom severity was scored on a four-point scale [0–3] where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms. For each patient, treatment duration was 17–23 days, including 3–7 days of placebo lead-in period and 14 (+ 2) days of treatment period. Patients were prohibited from using any investigational drug within 30 days prior to the screening visit. At least a 3-day lead-in period was required in

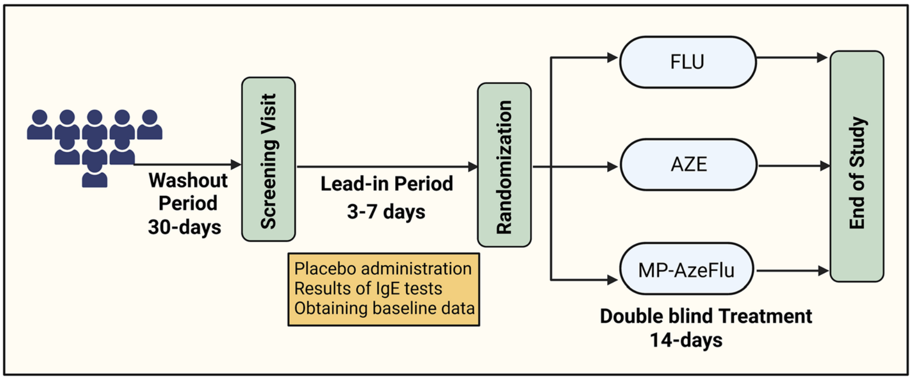

Fig. 1 Study design (created with Biorender.com)

this trial to obtain baseline for efficacy analyses. Furthermore, the lead-in period would provide study sites sufficient time to obtain data to confirm eligibility of the patients, e.g., to obtain results of specific IgE tests. The flexible duration of the lead-in period (from 3 to 7 days) would allow study sites to randomize a patient as soon as eligibility of the patient has been confirmed.

Ethics

The study was approved by the China National Medical Products Administration (NMPA) prior to enrollment of the first patient (Approval Number by China Food and Drug Administration [CFDA] 2017L01096). The ethical number for the leading site (Beijing Tongren Hospital, Capital Medical University) is TREC2018-13. This study was conducted in accordance with the Declaration of Helsinki 1964, International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) (ICH E6 (R2)), General Data Protection Regulation, local regulations as applicable and the Beijing Hospital Standard Operating Procedures. Prior to enrollment, written informed consent was obtained from each patient. A copy of the signed ICF was provided to each patient or legal representative (for pediatric patients) by the investigator, and the original was retained by the investigator.

Study Population

Male and female patients $\geq$ 12 years of age and having moderate-to-severe rhinitis or rhino conjunctivitis with a minimum 2-year perennial allergic rhinitis (PAR) history were eligible for the study. The patients needed to have 12-h reflective total nasal symptom score (rTNSS) of at least 8, a congestion score of 2 or 3, a sneezing or nasal itching score of 2 or 3 during screening visit. Similar criteria should be fulfilled by the patients before randomization. Patients who had moderate-to-severe rhinitis or rhino conjunctivitis, defined as rhinitis/rhino conjunctivitis with one or more of the following, presented [8]: (i) Sleep disturbance; (ii) Impairment of daily activities, leisure and/or sport; (iii) Impairment of learning or work; (iv) Troublesome symptoms. Patients who had moderate-to-severe rhinitis or rhino conjunctivitis and monotherapy with either intranasal antihistamine or glucocorticoid were not considered sufficient at the discretion of the investigator and/or designee. Additionally, they should have immunoglobulin E (IgE)-mediated hypersensitivity to one or more aeroallergens present in the study environment, confirmed by a positive response to an established standard diagnostic test at the site within the last year. The main exclusion criteria were: (i) presence of any hypersensitivity to drugs similar to azelastine hydrochloride (HCl), fluticasone propionate, or to any of the excipients; (ii) clinically significant arrhythmia (or unstable despite medical treatment) or symptomatic cardiac conditions; (iii) patients with a diagnosis of glaucoma, cataract, or central serous chorioretinopathy; (iv) presence of nasal disease(s) likely to affect deposition of intranasal medication, such as sinusitis, rhinitis medicamentosa, clinically significant polyposis, or nasal structural abnormalities (e.g., nasal septum deviation) or nasal surgery within the last year; (v) received specific immunotherapy within 6 months prior to the screening visit. If the patient received immunotherapy, a 6-month washout period was required following the last dose of immunotherapy.

Study Assessment and Endpoints

Efficacy Endpoint

Primary Efficacy The primary efficacy endpoint was the change from baseline in combined 12-h reflective total nasal symptom score (rTNSS) (morning [AM] + afternoon [PM]).

Secondary Efficacy Secondary efficacy endpoint were the changes in: (i) Combined 12 h reflective total ocular symptom score (rTOSS) (AM + PM); (ii) Combined reflective individual nasal symptoms (AM + PM); (iii) Combined reflective individual ocular symptoms (AM + PM); (iv) Combined reflective total 7 symptom score (rT7SS = rTNSS + rTOSS) (AM + PM).

Safety Endpoint

The safety profile of the study medications was assessed through the recording, reporting, and analysis of baseline medical conditions, adverse events (AEs), vital signs, and focused nasal examination. Assessment of AEs was performed from the time of giving informed consent to the end-of-study visit/examination. For this study, the AE follow-up period ended 14 days following the last administration of study medication. Any AEs, whether observed by the investigator or the patient, were reported.

Statistical Analysis

Sample Size Determination

Two hundred ninety-one patients were planned to be randomized in each treatment arm to demonstrate a treatment difference of at least 1.4 points with a standard deviation of 5.2 points assuming a two-sided type I error rate $\alpha = 5\%$ with a power of 90%. To account for potential dropouts, 300 patients per treatment group were randomized, which led to a total sample size estimation of 900 patients.

Statistical Methods

Efficacy Analysis The baseline score was the mean value obtained for the 3 days prior to randomization, including the morning of day 1 of treatment period. The significance level was (5%, two-sided) and confidence intervals (CIs) were 95% unless otherwise specified. For the primary efficacy analysis, baseline adjusted analysis of covariance (ANCOVA) with fixed effects treatment group, center and treatment day was used for analysis of changes from baseline for efficacy endpoints over the first week (day 2 to day 7) and over the entire 2-week treatment period (day 2 to day 14). The covariance matrix over treatment days was left unstructured. Degrees of freedom were determined by Satterthwaite approximation. Other treatment comparisons, e.g., per day were derived as contrast from the described overall model (day 2 to day 14). To maintain the overall type I error level for both time periods and both comparators, a hierarchical test procedure was implemented without further alpha adjustment as shown for the combined 12 h rTNSS (AM + PM): (i) rTNSS MP-AzeFlu vs. AZE until day 7; (ii) rTNSS MP-AzeFlu vs. FLU until day 7; (iii) rTNSS MP-AzeFlu vs. AZE until day 14; (iv) rTNSS MP-AzeFlu vs. FLU until day 14.

For secondary efficacy analysis, the same ANCOVA as implemented in the primary analysis was implemented for the key secondary efficacy endpoint rTOSS (AM + PM) as well as other secondary variables. The test sequence for the key secondary variable was continued as follows for Combined 12 h rTOSS (AM + PM): (i) rTOSS MP-AzeFlu vs. FLU until day 7; (ii) rTOSS MP-AzeFlu vs. FLU until day 14; (iii) rTOSS MP-AzeFlu vs. AZE until day 7 (iv) rTOSS MP-AzeFlu vs. AZE until day 14.

Quality of Life

The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was used to assess the improvement of QoL. The questionnaire was completed by adult patients only. The RQLQ questionnaire contained 28 items in seven domains (activities, sleep problems, non-nose/non-eye symptoms, practical problems, nose symptoms, eye symptoms and emotional function). Each physical item was scored from 0 (not troubled) to 6 (extremely troubled). The RQLQ was officially licensed version in Mandarin from EuroQoL Research Foundation und QOL Technologies Ltd for use in this trial.

Safety

All outputs for safety outcomes, including AEs, vital signs, and focused nasal examination were based on the safety population (SAF).

RESULTS

Study Population

Disposition and Population Analysis Sets

A total of 1666 patients were screened, and 900 patients were randomized out of which 898 patients received randomized study medication and were included in the safety population (SAF).

Population Analysis Sets

A total of 897 patients had at least one post-baseline assessment and therefore were included in the Modified Intention-to-Treat Population (ITT) for the efficacy analysis. The (modified) Intent-to-treat Population (ITT) included all randomized patients who have at least 1 dose of study medication and have at least one evaluation of efficacy after start of treatment with study medication. A total of 887 patients completed the treatment (Fig. 2).

Demographics and Baseline Characteristics

The mean (SD) age of the patients was 35.8 (11.83) years. There were slightly more male (51.9%) than female (48.1%) patients in the study (Table 1). Demographic characteristics were generally balanced between the treatment groups. The mean (SD) baseline combined rTNSS was 17.18 (3.35) and the mean (SD) baseline combined rTOSS was 7.90 (4.94). The baseline disease background of patients regarding symptom scores was generally considered similar among the three treatment groups. A total of 384 (42.8%) patients in the study were PAR-only patients, whereas 268 (29.8%) patients were judged with mixed seasonal allergic rhinitis (SAR)/PAR and 244 (27.2%) patients were judged to have SAR only. Thus, 652 patients had PAR and 512 patients had SAR.

Efficacy Analysis

Primary Efficacy Analysis

The mean (SD) rTNSS change from baseline was − 5.79 (5.17), − 3.35 (4.95) and − 4.82 (5.28) for MP-AzeFlu, AZE, and FLU group, respectively, over the first week. MP-AzeFlu treatment demonstrated a significant superiority when compared with the AZE group (LS mean difference: − 1.73; 95% confidence interval [CI] − 2.32, − 1.15; $p < 0.0001$) or compared with the FLU group (LS mean difference: − 1.17, 95% CI − 1.76, − 0.58; $p < 0.0001$) over the first week. The mean (SD) reduction in rTNSS score over the entire 2-week treatment period was − 7.59 (5.73), − 4.62 (5.65), and − 7.02 (6.08) for MP-AzeFlu, AZE, and FLU group, respectively. The MP-AzeFlu group showed significantly higher symptom reduction for the entire 2-week treatment period when compared with the AZE group (LS mean difference: − 1.96; 95% CI − 2.53, − 1.39; $p < 0.0001$), or the FLU group (LS mean difference: − 0.98; 95% CI − 1.55, − 0.41; $p = 0.0007$). The LS mean (standard error) change from baseline was − 3.50 (0.22), − 2.09 (0.22), and − 2.19 (0.22) for MP-AzeFlu, AZE, and FLU group, respectively, on the second day of treatment. The LS mean (standard error) change over the first week was − 5.68 (0.22), − 3.94 (0.22), and − 4.51 (0.22) for MP-AzeFlu, AZE, and FLU group, respectively. The overall LS mean(standard error) change in rTNSS score for the entire 2-week period was − 7.42 (0.22), − 5.46 (0.22), and − 6.44 (0.22) for MP-AzeFlu, AZE, and FLU

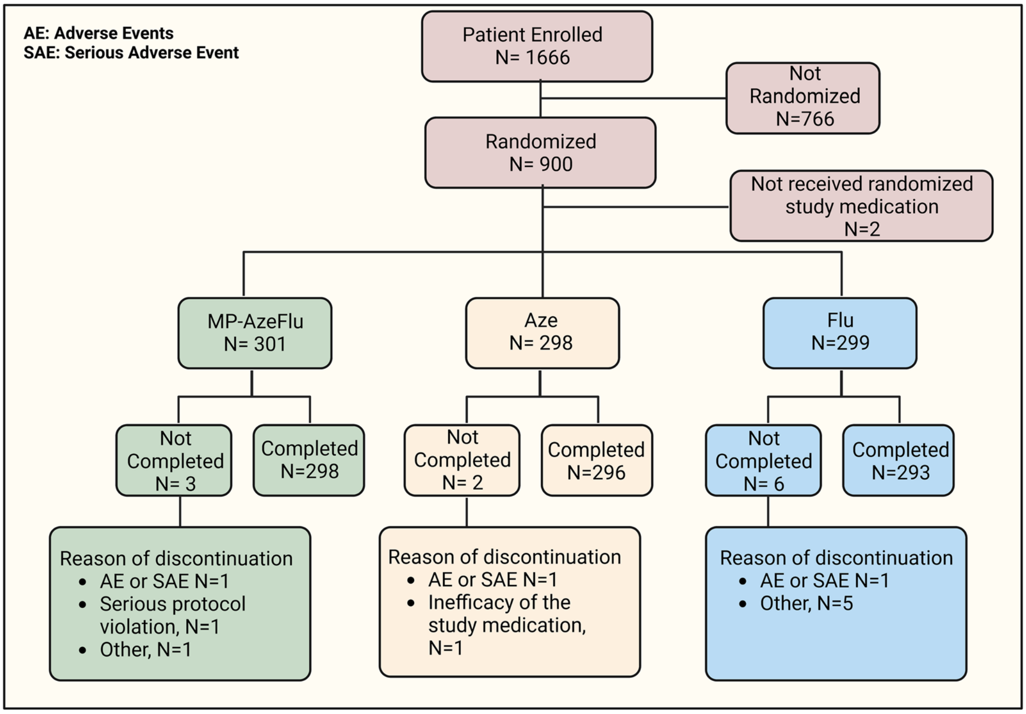

Fig. 2 CONSORT-flow diagram of patient disposition (created with Biorender.com)

group, respectively (Fig. 3). Similar results were found when the analysis was performed on the per-protocol population (PP).

Sensitivity analyses on patients with baseline combined 12-h rTNSS ≥ 12 were also performed. The results were similar to the primary analysis results for the ITT. In the ITT, in patients with a baseline combined rTNSS ≥ 12, the MP-AzeFlu group showed a statistically significant superiority in the change from baseline rTNSS over the first week when compared with the AZE group (LS mean difference: – 1.71; 95% CI – 2.31, – 1.11; $p < 0.0001$) or compared with the FLU group (LS mean difference: – 1.17; CI – 1.75, – 0.55; $p = 0.0002$; 95%). A statistically significant difference was also found over the entire 2-week treatment period when comparing the MP-AzeFlu group with the AZE group (LS mean difference: – 1.95; 95% CI – 2.54, – 1.37; $p < 0.0001$) and with the FLU group (LS mean difference: – 0.98; 95% CI – 1.56, – 0.40; $p = 0.001$). The MP-AzeFlu group showed a statistically significant superiority over the first week, and over the entire 2-week treatment period, when compared with the AZE group and with the FLU group.

Secondary Efficacy Analysis

Change from Baseline in the Combined 12-h rTOSS (AM + PM), the Key Secondary Endpoint The MP-AzeFlu group showed a significant difference in the change from baseline in the combined rTOSS compared to AZE group (LS mean difference: – 0.51; 95% CI – 0.89, – 0.11; $p = 0.0121$), and FLU group (LS mean difference: – 0.67; 95% CI – 1.07, – 0.28; $p = 0.0008$) over the first week. The difference in the change from baseline over the entire 2-week treatment period was also statistically significant between the MP-AzeFlu group and the AZE group (LS mean difference: – 0.54; 95% CI – 0.92, – 0.16; $p = 0.0056$), and between the MP-AzeFlu group and the FLU group (LS mean difference: – 0.55; 95% CI – 0.93, – 0.17; $p = 0.0043$). The LS mean (standard error) change from baseline was – 1.32 (0.15), – 0.91 (0.15), and – 0.67 (0.15) for MP-AzeFlu, AZE, and FLU group, respectively, on the second day of treatment. The LS mean (standard error)

Table 1 Demographics and baseline characteristics of the safety population

	MP-AzeFlu *N* = 301	**AZE** *N* = 298	**FLU** *N* = 299
Demographics			
Age (years)			
Mean (SD)	37.1 (12.2)	34.8 (11.1)	35.6 (11.9)
Gender (*N*%)			
Male	151 (50.2)	156 (52.3)	159 (53.2)
Female	150 (49.8)	142 (47.7)	140 (46.8)
Height (cm)			
Mean (SD)	167.5 (9.0)	168.1 (8.0)	167.8 (7.9)
Weight (kg)			
Mean (SD)	66.4 (13.5)	66.6 (12.5)	66.2 (13.3)
BMI (kg/m^2)			
Mean (SD)	23.5 (3.4)	23.4 (3.4)	23.3 (3.4)
Baseline characteristics			
Baseline combined rTNSS (AM + PM)			
Mean (SD)	17.2 (3.2)	17.1 (3.3)	17.1 (3.4)
Baseline combined rTOSS (AM + PM)			
Mean (SD)	8.1 (4.9)	7.7 (4.9)	7.7 (4.9)
Baseline combined rT7SS (rTNSS + rTOSS)			
Mean (SD)	25.3 (6.9)	24.8 (7.0)	24.9 (7.3)

change over the first week was − 2.43 (0.14), − 1.93 (0.14), and − 1.75 (0.14) for MP-AzeFlu, AZE, and FLU group, respectively. The overall LS mean (standard error) change in rTOSS score for the entire 2-week period was − 3.25 (0.14), − 2.72 (0.14), and − 2.70 (0.14) for MP-AzeFlu, AZE, and FLU group, respectively (Fig. 4).

Morning and Afternoon Reflective Total Nasal Symptom Score The rTNSS calculated in the morning (AM) and in the afternoon (PM) were also analyzed separately (Supplementary Material Table 1). Significant differences ($p < 0.0001$) in LS mean in both rTNSS (AM) and rTNSS (PM) scores over the first week were found between the MP-AzeFlu and the AZE group ($p < 0.0001$) and also between the MP-AzeFlu and FLU group ($p = 0.0008$). The LS mean differences in rTNSS (AM) and rTNSS (PM) scores over the entire 2-week treatment period between the MP-AzeFlu and AZE group ($p < 0.0001$), and between the MP-AzeFlu and FLU ($p = 0.0006$) group, were also statistically significant.

Change from Baseline in the Combined Reflective Total 7 Symptom Scores The rT7SS is the sum of 7 symptom scores including all nasal and ocular symptoms. The MP-AzeFlu treatment group showed the largest reduction of rT7SS scores from baseline among the three treatment groups (Table 2). The LS-mean differences, over the first week and over the entire

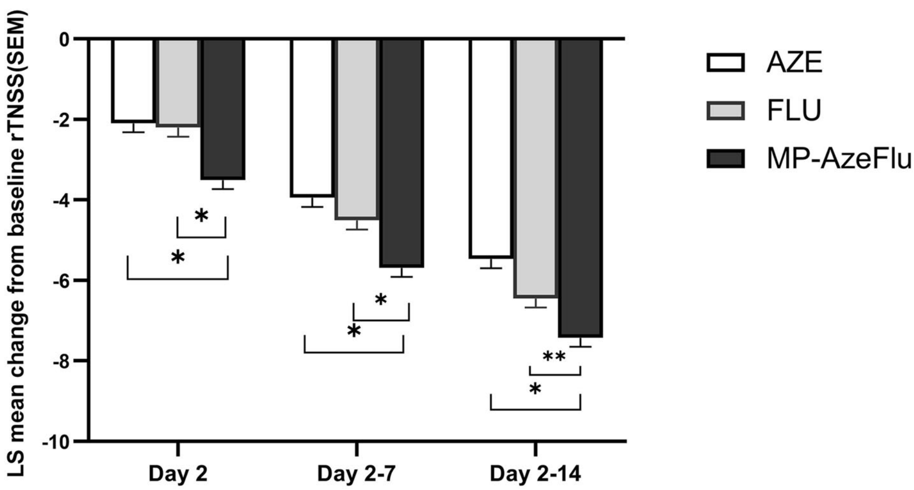

Fig. 3 LS mean change from baseline in rTNSS (AM + PM) scores during the second day, first week, and entire treatment period with MP-AzeFlu vs. AZE vs. Flu (*$p < 0.0001$, **$p = 0.0007$) (See also Supplementary Material Table 2)

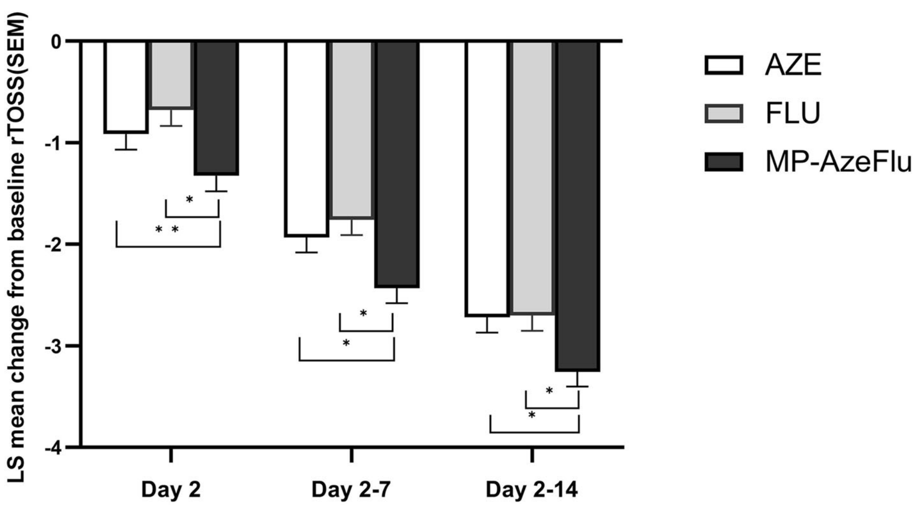

Fig. 4 LS mean change from baseline in rTOSS (AM + PM) scores during second day, first week, and entire treatment period with MP-AzeFlu vs. AZE vs. Flu (*$p < 0.05$, **$p = 0.05267$) (see also Supplementary Material Table 3)

2-week treatment period, between the MP-AzeFlu group and the AZE group, and between the MP-AzeFlu group and the FLU group, were all statistically significant (all $p < 0.0005$).

Additional analyses were performed for primary and key secondary endpoints in subgroups SAR and PAR. MP-AzeFlu proved to be significantly superior in terms of efficacy (combined 12-h reflective TNSS) compared to AZE alone, and FLU alone over the first week and the entire 2-week treatment in subgroup of patients with SAR and PAR (Table 3). Also, MP-AzeFlu proved to be significantly superior in relieving ocular symptoms (combined 12-h reflective TOSS) compared to AZE alone, and FLU alone over the first week and the entire 2-week treatment in subgroup of patients with SAR and PAR (Table 3).

Table 2 Analysis of combined rT7SS (AM + PM)—ITT population

Variable time point	Treatment	*N*	Mean (SD)	LSM	Source	*p* value	Treatment difference [95% (CI)]
Baseline	MP-AzeFlu	300	25.40 (6.96)	25.08	Treatment	0.6703	
	Aze	298	24.89 (7.07)	24.61			
	Flu	299	24.97 (7.33)	24.72			
Day 2 to day 7 change from baseline (AM + PM)	MP-AzeFlu	300	− 8.33 (7.64)	− 8.11			
	Aze	298	− 5.20 (7.58)	− 5.95	MP-AzeFlu vs. Aze	< 0.0001	− 1.73 (− 3.05, − 1.28)
	Flu	299	− 6.55(8.01)	− 6.24	MP-AzeFlu vs. Flu	< 0.0001	− 1.17 (− 2.76, − 0.99)
Day 2 to day 14 change from baseline (AM + PM)	MP-AzeFlu	300	− 11.00 (8.71)	− 10.69			
	Aze	298	− 7.17 (8.87)	-8.29	MP-AzeFlu vs. Aze	< 0.0001	− 1.96 (− 3.26, − 1.54)
	Flu	299	− 9.77 (9.31)	− 9.10	MP-AzeFlu vs. Flu	0.0003	− 0.98 (− 2.44, − 0.73)

Combined Reflective Individual Nasal Symptoms The LS mean differences of individual nasal symptom scores between the MP-AzeFlu and AZE treatment group and between the MP-AzeFlu and FLU group were statistically significant (all $p < 0.05$) except for the results of the nasal itching severity score over the entire 2-week period, where the difference between the MP-AzeFlu and FLU treatment group was close to statistical significance ($p = 0.0534$). All three treatment groups showed a reduction of the mean score for each of the four individual nasal symptoms over the first week and over the entire 2-week treatment period (Table 4).

Change from Baseline in the Combined Reflective Individual Ocular Symptom Scores (AM + PM) The LS mean differences over the entire 2-week treatment period between the MP-AzeFlu treatment group, and the other two treatment groups were statistically significant for itchy eye (all $p < 0.05$) and watery eye (all $p < 0.005$), but not for eye redness (Table 4).

Quality of Life

The results of adult RQLQ showed improvement of QoL in all treatment groups. The improvements in all domains already exceeded the minimum clinically significant difference of

Table 3 Treatment differences in changes from baseline in combined rTNSS and rTOSS, SAR, and PAR subgroups

Parameter	Comparison	First week		Entire 2-week treatment	
		SAR $N = 512$ Treatment difference (95% CI), p value	PAR $N = 652$ Treatment difference (95% CI), p value	SAR $N = 512$ Treatment difference (95% CI), p value	PAR $N = 652$ Treatment difference (95% CI), p value
rTNSS	MP-AzeFlu vs. Aze*	− 1.93 (− 2.72, − 1.15) **< 0.0001**	− 1.64 (− 2.33, − 0.95) **< 0.0001**	− 2.11 (− 2.87, − 1.36) **< 0.0001**	− 1.93 (− 2.60, − 1.27) **< 0.0001**
	MP-AzeFlu vs. Flu**	− 1.16 (− 1.95, − 0.37) **0.0043**	− 1.28 (− 1.97, − 0.60) **0.0003**	− 0.88 (− 1.64, − 0.12) **0.023**	− 1.17 (− 1.82, − 0.51) **0.0006**
rTOSS	MP-AzeFlu vs. Aze*	− 0.63 (− 1.16, − 0.11) **0.0177**	− 0.59 (− 1.04, − 0.14) **0.0108**	− 0.67 (− 1.18, − 0.16) **0.0101**	− 0.59 (− 1.02, − 0.16) **0.0076**
	MP-AzeFlu vs. Flu**	− 0.89 (− 1.42, − 0.36) **0.001**	− 0.78 (− 1.23, − 0.33) **0.0007**	− 0.75 (− 1.26, − 0.23) **0.0044**	− 0.67 (− 1.10, − 0.24) **0.0021**

Least square means, (95% confidence intervals for pairwise differences), and p value (bold indicates statistical significance)

− 0.50 at day 8 and then maintained until day 15 (study end). The improvement of QoL was less pronounced in the AZE group compared to MP-AzeFlu and FLU groups.

Safety Analysis

The most frequent TEAEs (Supplementary Material Table 4) in ≥ 1% of patients in MP-AzeFlu group were: dysgeusia (4.3%), epistaxis (1.3%), nasal dryness (1.0%), and headache (1.0%). Except for dysgeusia (bitter taste) that was reported by more patients (13 [4.3%]) in the MP-AzeFlu group, the incidence of all other TEAEs in MP-AzeFlu group was comparable or even lower than in other treatment groups. The incidence of fatigue was comparable to FLU treatment group and lower than AZE treatment group. Somnolence was lower than AZE treatment group but slightly higher compared to FLU treatment group. Most patients in all three treatment groups had no severe findings on the focused nasal examination at the study end. Mucosal edema and nasal discharge were generally improved over time across all treatment groups. No study treatment-related severe (Grade 3) TEAE was reported in this study.

DISCUSSION

The prevalence of AR in China has increased from 11.1 to 17.6% over 6 years (2005–2011) [9]. AR significantly affects the patients quality of life (QoL) and work productivity and performance. In addition, AR is often accompanied by co-morbidities such as asthma and atopic dermatitis [10]. Patients who are not susceptible or not willing for immunotherapy need effective pharmacotherapy. The recent Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines recommend the use of an INCS and intranasal antihistamine combination for the treatment of AR [11]. Combination therapies for AR are often

Table 4 Combined reflective individual nasal symptom scores and combined reflective individual ocular symptom scores from day 2 to day 14 (AM + PM)

Parameter	Treatment	*N*	Mean (SD)	Source	*p* value	Treatment difference [95% (CI)]
Combined reflective individual nasal symptom scores (AM + PM)	Change from baseline of nasal congestion severity score (AM + PM)					
	MP-AzeFlu	300	− 1.77 (1.620)			
	AZE	298	− 0.97 (1.647)	MP. vs. A	< 0.0001	− 0.56 (− 0.73, − 0.39)
	FLU	299	− 1.74 (1.742)	MP. vs. F	0.0108	− 0.22 (− 0.39, − 0.05)
	Change from baseline of runny nose severity score (AM + PM)					
	MP-AzeFlu	300	− 2.04 (1.734)			
	AZE	298	− 1.20 (1.665)	MP. vs. A	< 0.0001	− 0.65 (− 0.82, − 0.48)
	FLU	299	− 1.88 (1.819)	MP vs. F	0.005	− 0.24 (− 0.41, − 0.07)
	Change from baseline of sneezing severity score (AM + PM)					
	MP-AzeFlu	300	− 2.08 (1.695)			
	AZE	298	− 1.37 (1.709)	MP vs. A	< 0.0001	− 0.57 (− 0.74, − 0.40)
	FLU	299	− 1.85 (1.767)	MP vs. F	0.0022	− 0.27 (− 0.44, − 0.10)
	Change from baseline of nasal itching severity score (AM + PM)					
	MP-AzeFlu	300	− 1.69 (1.651)			
	AZE	298	− 1.07 (1.577)	MP vs. A	< 0.0001	− 0.36(− 0.52, − 0.19)
	FLU	299	− 1.55 (1.652)	MP vs. F	0.0534	− 0.16(− 0.32, 0.00)

Table 4 continued

Parameter	Treatment	*N*	Mean (SD)	Source	*p* value	Treatment difference [95% (CI)]
Combined reflective individual ocular symptom scores (AM + PM)	Change from baseline of itchy eye severity score (AM + PM)					
	MP-AzeFlu	300	− 1.17 (1.576)			
	AZE	298	− 0.92 (1.543)	MP. vs. A	0.0298	− 0.17 (− 0.32, − 0.02)
	FLU	299	− 0.94 (1.587)	MP vs. F	0.006	− 0.21 (− 0.37, − 0.06)
	Change from baseline of watery eye severity score (AM + PM)					
	MP-AzeFlu	300	− 1.24 (1.512)			
	AZE	298	− 0.86 (1.508)	MP. vs. A	0.0006	− 0.25 (− 0.40, − 0.11)
	FLU	299	− 0.95 (1.551)	MP vs. F	0.0021	− 0.23 (− 0.37, − 0.08)
	Change from baseline of eye redness severity score (AM + PM)					
	MP-AzeFlu	300	− 1.00 (1.467)			
	AZE	298	− 0.78 (1.490)	MP. vs. A	0.0621	− 0.13 (− 0.28, 0.01)
	FLU	299	− 0.86 (1.528)	MP vs. F	0.2792	− 0.08 (− 0.22, 0.06)

done by administering oral antihistamine and intranasal corticosteroid. However, there is little evidence to support this clinically [12]. ARIA guidelines recommend MP-AzeFlu for all patients with AR, independent of disease type or severity [11]. Although the study was not designed to investigate the onset of action, efficacy results revealed that MP-AzeFlu showed rapid onset of symptom relief in Chinese patients with AR, with effect observed 1 day after administration.

Efficacy

The reduction of each symptom score (rTNSS, rTOSS, and rT7SS) each day was mostly greater in the MP-AzeFlu group than the other two treatment groups. This is similar to the results from previous global studies, as the combination of azelastine HCl and fluticasone propionate showed greater and quicker effects than the individual components [6]. For the primary efficacy endpoint, the MP-AzeFlu group consistently showed the greatest reduction of combined 12-h rTNSS from baseline. The LS mean change from baseline was statistically significantly larger in the MP-AzeFlu group than in the other two treatment groups. In a randomized multicenter study done in 149 patients with SAR in Russia, MP-AzeFlu significantly ($p < 0.001$) reduced the rTNSS (– 2.47), rTOSS (– 1.62), and rT7SS (– 4.34) values [13]. The reduction in 12-h rTNSS was greater (7.59 points) among Chinese patients compared to a previous study (MP4001) done with US patients (5.3 points) [14]. The benefit of MP-AzeFlu over AZE and FLU on ocular symptoms was more pronounced in Chinese patients. The differences in change from baseline of combined rTOSS were consistently statistically significant between the MP-AzeFlu group and the other two treatment groups (all $p < 0.05$) whether over the first week or over the entire 2-week treatment period.

The current study indicated that study medications provided full-day sustained effects on patients when administered twice daily. In addition, a greater symptom relief in MP-AzeFlu group compared to AZE and FLU groups were demonstrated for both AM and PM rTNSS. In general, the benefit of MP-AzeFlu on individual nasal and ocular symptoms was also more pronounced in Chinese patients when compared with data from previous studies. The previous double-blind studies done with MP-AzeFlu did not test its efficacy in PAR (perennial allergic rhinitis). Nasal and ocular symptoms (nasal congestion, nasal itching, watery eyes, itchy eyes) are some of the most bothersome symptoms of AR. However, subgroup analysis done for AR types in the present study showed that MP-AzeFlu was effective in reducing nasal and ocular symptoms of SAR and PAR and the effect was superior to that of FLU and AZE. Previous studies have shown that use of intranasal corticosteroids inhibits nasal ocular reflex, resulting in effective symptom relief from nasal and ocular symptoms [15, 16].

FLU is an anti-inflammatory corticosteroid with highly specific glucocorticoid receptor activity. AZE is a second-generation INAH approved for use in SAR. AZE is a non-sedating H1-antagonist with antihistaminic, anti-inflammatory, and mast cell stabilizing properties [17]. It affects eosinophil function and also downregulates intercellular adhesion molecule-1 (ICAM-1) expression [18]. MP-AzeFlu has a synergistic action in inhibition of inflammatory cell recruitment and desensitization of sensory neurons [19]. A recent in vitro study has shown that MP-AzeFlu downregulates the production of the inflammation markers IL-6, IL-8, and GM-CSF in cultured fibroblasts isolated from nasal mucosa (NM) and nasal polyp (NP) [20]. Recent studies with MP-AzeFlu have shown its effectiveness in providing complete symptom control of AR than first-line therapies [6, 14, 21]. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines recommend MP-AzeFlu for all patients with AR, independent of disease type or severity [11]. Use of MP-AzeFlu might improve adherence of the patients towards taking medication.

Quality of Life

AR significantly affects the patient's quality of life (QoL) and work productivity and performance. In addition, AR is often accompanied by co-morbidities such as asthma and atopic dermatitis [10]. Studies done in Chinese patients have shown that AR substantially reduces their QoL (e.g., sleep disturbances, emotional problems, impairment in activities of daily life or social functioning) [4, 22]. Improvements of QoL were seen in all treatment groups and in line with previous clinical experiences. In general, the improvement of QoL was less pronounced in the AZE group compared to the MP-AzeFlu and FLU groups. The improvements in all RQLQ domains exceeded the minimum clinically significant difference of - 0.50 in all treatment groups. In a recent multicenter, prospective, non-interventional, real-life study, MP-AzeFlu improved patient-reported QoL regardless of the AR type [23].

Safety

Overall, compliance with the study treatments was high in all three treatment groups (average overall compliance > 99.7% in each treatment group). In the current study, the incidence of TEAEs was similar in all three groups, although for some events the incidence was found to be higher in the AZE group than other treatment groups (Supplementary Material Table 4). There was no increase in frequency of dysgeusia under MP-AzeFlu treatment in Chinese patients compared with previous clinical experiences outside of China. In this study, it is notable that MP-AzeFlu did not inherit all the TEAEs commonly reported by AZE or FLU treatment. TEAEs was not always reported in a higher frequency in MP-AzeFlu-treated patients. Instead, frequency of common TEAEs reported by MP-AzeFlu was mostly lower than (or equal to) those in the other two treatment groups except dysgeusia. This indicated that MP-AzeFlu is generally safe and tolerable to Chinese patients. Somnolence and fatigue are two of the most associated side effects of antihistamine usage. The current study showed lesser incidence of somnolence and fatigue for MP-AzeFlu.

CONCLUSIONS

Results of this study confirmed the superior efficacy and the similar safety profile of MP-AzeFlu nasal spray compared to AZE or FLU in Chinese patients. MP-AzeFlu, when administered as 1 spray per nostril twice daily for 14 days, alleviated AR symptoms in Chinese patients with moderate-to-severe AR. MP-AzeFlu showed superior efficacy in reduction of nasal or ocular symptom scores, when compared to AZE or FLU. Sub-group analyses showed that MP-AzeFlu was effective in reducing nasal and ocular symptoms of SAR and PAR and the effect was superior to that of Flu and Aze. MP-AzeFlu was safe and well tolerated by Chinese patients and had a similar safety profile to AZE and FLU. The most frequent treatment related TEAEs were dysgeusia and epistaxis. No new safety finding was observed for MP-AzeFlu in Chinese patients. The results confirm the findings from other phase III trials and therefore supports its positioning as first-line option in international guidelines as a drug of choice for the management of allergic rhinitis.

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Compliance with Ethics Guidelines. The study was approved by the China National Medical Products Administration (NMPA) prior to enrollment of the first patient (Approval Number by China Food and Drug Administration [CFDA] 2017L01096). The ethical number for the leading site (Beijing Tongren Hospital, Capital Medical University) is TREC2018-13. This study was conducted in accordance with the Declaration of Helsinki 1964, International Conference on Harmonization (ICH) guideline on Good Clinical Practice (GCP) (ICH E6 (R2)),

General Data Protection Regulation, local regulations as applicable and the Beijing Hospital Standard Operating Procedures. Prior to enrollment, written informed consent was obtained from each patient. A copy of the signed ICF was provided to each patient or legal representative (for pediatric patients) by the investigator, and the original was retained by the investigator.

Data Availability Statement. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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