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Double-Blind Placebo-Controlled Trial of Bepotastine Salicylate in Patients With Allergic Rhinitis

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Objectives/Hypothesis: To evaluate the efficacy and safety of a slow-release form of bepotastine salicylate (HL151, Belion CR) in patients with perennial allergic rhinitis (PAR).

Study Design: Double-blind, placebo-controlled multicenter comparative study.

Methods: Two hundred seventy-two PAR patients (aged 19–65 years) were studied to determine the efficacy and safety of HL151 (20 mg once daily administration) relative to those of a placebo in terms of improvements in total and nasal symptom scores. The subjects were randomized to the placebo (n = 138) or HL151 group (n = 134, 20 mg orally once daily for 4 weeks), and reflective and instantaneous total nasal symptom scores (TNSS) were measured daily in comparison with baseline. Among 272 subjects, 229 subjects (119 in the placebo group, 110 in the HL151 group) who completed the study were included for efficacy analysis.

Results: Instantaneous and reflective TNSS and nasal symptoms such as rhinorrhea, nasal itching, and sneezing at 2 and 4 weeks showed that HL151 was superior to the placebo (all $P < .05$). There were no significant differences in terms of adverse events and adverse drug reactions between the two groups. Regarding serious adverse events, there was only one case of acute hepatitis B, which was reported not to be associated with HL151.

Conclusions: This multicenter trial showed that once-daily use of HL151 is efficacious and safe in adult patients with PAR and could improve compliance due to its convenience.

Key Words: Allergy, rhinology, adult rhinology, immunology, allergic rhinitis.

Level of Evidence: 1b

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INTRODUCTION

Allergic rhinitis is the inflammation of the nasal mucosa and is characterized by the expression of more than one of the following four major symptoms: nasal obstruction, rhinorrhea, nasal itching, and sneezing. In allergic rhinitis, inflammation is accompanied by the infiltration of inflammatory cells such as eosinophils and mast cells. Several inflammatory mediators including histamines released by these inflammatory cells lead to inflammatory responses including vasodilatation and tissue edema of the nasal mucosa, causing nasal obstruction. These mediators also increase mucosal glandular secretion, nasal itching, and sneezing.

The most common treatment approach for allergic rhinitis is focused on the blockage of the release of inflammatory mediators by medications such as antihistamines or leukotriene receptor antagonists.[1] Antihistamines have been used as a first-line treatment choice in patients with allergic rhinitis for over 50 years.[2] Bepotastine besilate was first developed and approved in Japan in 2000.[3] It is a potent second-generation antihistamine and one of the most commonly used oral antihistamines in Asia.[3] It is known to be effective in conditions including allergic rhinitis, urticaria, and eczema.[3,4]

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Bepotastine besilate was introduced first and bepotastine salicylate was developed later.[5] Both forms of bepotastine are known to be effective in the treatment of perennial allergic rhinitis (PAR).[5] However, due to their short half-lives, both drugs need to be administered twice daily. Recently, a controlled-release form of bepotastine salicylate (HL151, Belion CR), which can be administered once daily, was developed to improve medication compliance with convenience. Hence, the aim of this study was to compare and evaluate the efficacy and adverse effects of HL151 (20 mg once daily) with those of a placebo in patients with PAR.

MATERIALS AND METHODS

Study Subjects

Patients who met the following criteria were included in the trial: patients aged 19 to 65 years, patients with a clinical diagnosis of PAR (symptoms of sneezing, itching, rhinorrhea, and/or nasal obstruction on most days) for at least 2 years, and patients with a documented positive (3+) skin prick test and/or immunoglobulin E test (≥class 2 of multiple allergen simultaneous test [MAST] or) for perennial allergens including *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae*. Before entering the double-blind phase of study treatment, the patients were required to show a minimal baseline reflective total nasal symptom score (rTNSS) of 5 at visit two. All patients provided written informed consent before the start of the trial.

The exclusion criteria were as follows: patients with non-allergic rhinitis, severe asthma, or nasal polyps or severe septal deviations; patients who had undergone nasal surgery within the previous 12 weeks; patients with acute or chronic rhinosinusitis within 4 weeks; patients who had undergone immunotherapy within 4 weeks; or patients who had used astemizole within 12 weeks, ketotifen within 2 weeks, depot corticosteroids within 8 weeks, or short-acting systemic or topical corticosteroids, sodium cromoglycate (4%), or nedocromil sodium within 1 week before the baseline. In addition, patients were excluded if they had an acute respiratory tract infection, if they were not allergic, or if they had a history of hypersensitivity to drugs such as ebastine or sodium cromoglycate.

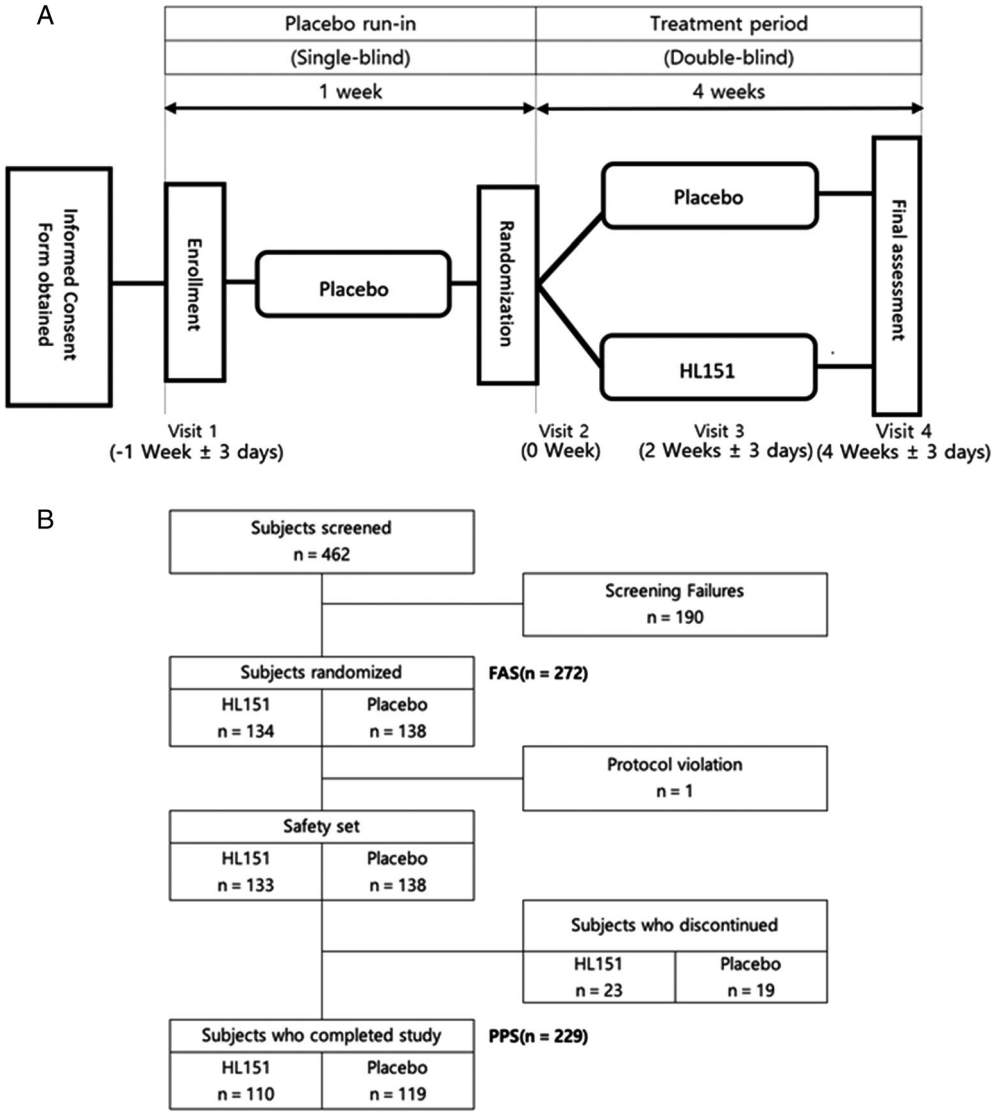

Fig. 1. Study flowchart (A) and study design (B) showing disposition of patients. FAS = full analysis set; PPS = per protocol set.

Patients who were using any other H1-receptor antagonists or medication, those with any clinically relevant disorder that might have interfered with the study, and those working night shifts (11 PM–8 AM) were also excluded. Pregnant or breastfeeding women were not admitted to the study, and those of child-bearing potential could participate only if protected by an effective means of contraception.

TABLE I.
Patient Demographic and Baseline Characteristics (Per Protocol Set).

	HL151 Group, n = 110	Placebo Group, n = 119	Total, N = 229	*P* Value
Sex, n (%)				
Male	46 (41.82)	51 (42.86)	97 (42.36)	.8737*
Female	64 (58.18)	68 (57.14)	132 (57.64)	
Age, yr, mean ± SD	34.15 ± 10.51	33.91 ± 10.94	34.03 ± 10.71	.7364†
Duration of PAR, ≤5 years, n (%)	29 (26.36)	35 (29.41)	64 (27.95)	.7392*
Body weight, kg, mean ± SD	64.47 ± 13.56	65.64 ± 13.52	65.08 ± 13.52	.4916†
rTNSS, mean ± SD	6.78 ± 1.43	6.74 ± 1.45	6.76 ± 1.44	.7425‡
rISS: rhinorrhea, mean ± SD	1.69 ± 0.57	1.73 ± 0.51	1.71 ± 0.54	.5300§
rISS: nasal obstruction, mean ± SD	1.93 ± 0.53	1.93 ± 0.54	1.93 ± 0.54	.9195‡
rISS: nasal pruritus, mean ± SD	1.66 ± 0.66	1.65 ± 0.67	1.66 ± 0.66	.8807§
rISS: sneezing, mean ± SD	1.51 ± 0.64	1.42 ± 0.53	1.46 ± 0.59	.3258‡
iTNSS, mean ± SD	6.69 ± 1.79	6.79 ± 2.00	6.74 ± 1.90	.5451‡
iISS: rhinorrhea, mean ± SD	1.70 ± 0.63	1.78 ± 0.67	1.74 ± 0.65	.2146‡
iISS: nasal obstruction, mean ± SD	1.95 ± 0.61	1.93 ± 0.64	1.94 ± 0.62	.9839‡
iISS: nasal pruritus, mean ± SD	1.63 ± 0.72	1.66 ± 0.76	1.64 ± 0.74	.7770‡
iISS: sneezing, mean ± SD	1.40 ± 0.72	1.41 ± 0.69	1.41 ± 0.70	.7142‡

*χ^2 test.
†Wilcoxon rank sum test.
‡*t* test.
§Fisher exact test.
iISS = instantaneous individual symptom score; iTNSS = instantaneous total nasal symptom score; PAR = perennial allergic rhinitis; rISS = reflective individual symptom score; rTNSS = reflective total nasal symptom score; SD = standard deviation.

TABLE II.
Changes from Baseline in rTNSS and Individual Scores Determined Using the Analysis of Covariance Model (Per Protocol Set).

			HL151 Group, n = 110	Placebo Group, n = 119	Difference From Placebo
rTNSS	Week 2	LSMean ± SE	−1.987 ± 0.177	−0.929 ± 0.170	−1.057 ± 0.246
		95% CI	(−2.335, −1.639)	(−1.264, −0.595)	(−1.540, −0.575)
		P value			<.0001*
	Week 4	LSMean ± SE	−2.602 ± 0.200	−1.844 ± 0.192	−0.758 ± 0.279
		95% CI	(−2.995, −2.208)	(−2.222, −1.465)	(−1.304, −0.212)
		P value			.0067†
Rhinorrhea	Week 4	LSMean ± SE	−0.638 ± 0.057	−0.400 ± 0.055	−0.238 ± 0.079
		95% CI	(−0.750, −0.526)	(−0.508, −0.292)	(−0.393, −0.082)
		P value			.0029‡
Nasal obstruction	Week 4	LSMean ± SE	−0.615 ± 0.056	−0.517 ± 0.054	−0.099 ± 0.079
		95% CI	(−0.726, −0.504)	(−0.623, −0.410)	(−0.253, 0.055)
		P value			.2082
Nasal pruritus	Week 4	LSMean ± SE	−0.657 ± 0.060	−0.475 ± 0.058	−0.181 ± 0.084
		95% CI	(−0.775, −0.538)	(−0.589, −0.361)	(−0.345, −0.018)
		P value			.0302‡
Sneezing	Week 4	LSMean ± SE	−0.689 ± 0.056	−0.452 ± 0.054	−0.237 ± 0.079
		95% CI	(−0.800, −0.578)	(−0.559, −0.346)	(−0.391, −0.082)
		P value			.0028†

Estimation using the analysis of covariance model with the treatment group as a fixed factor and each baseline factor as a covariate.
*$P < .001$.
†$P < .01$.
‡$P < .05$.
CI = confidence interval; LSMean = least-squares mean; rTNSS = reflective total nasal symptom score; SE = standard error.

Study Design

This study was a multicenter, randomized, double-blind placebo-controlled study and was conducted at 13 university hospitals in South Korea from January 2017 to October 2017. The study consisted of a 1-week screening period and a 4-week treatment period. All subjects enrolled in this study satisfied the inclusion criteria and took a placebo orally during the screening period (1 week). Then, subjects who met the randomization criteria were randomized to the HL151 and placebo groups at a ratio of 1:1 using a block size of 4 or 6. Subjects received bepotastine salicylate or placebo orally once daily for 4 weeks. The color and form of placebo and HL 151 tablet was same. They were required to visit the clinics four times at 1- or 2-week intervals from enrollment until the final assessment. At visit 1, subjects received a medical examination and laboratory tests including allergy tests such as the skin prick test, immunoCAP, or MAST. At visit 2, 1 week after visit 1, patients were randomized to either the bepotastine or placebo group by using a block allocation method, and randomization code lists were retained by the investigational product manager until data entry was completed. This study was approved by institutional review board of each participating hospital before initiation, and the ClinicalTrials.gov Identifier is NCT03655210.

Allergy Diary

All subjects kept an allergy symptom diary. rTNSS were determined twice daily (morning and evening) and represented the sum of scores for nasal symptoms (itching, sneezing, rhinorrhea, and nasal obstruction) for a 12-hour duration. Instantaneous TNSS (iTNSS) were recorded once daily before the morning medication and represented the sum of nasal symptom scores just before the use of the medication. TNSS (possible score of 0–12) is the sum of four individual subject-assessed symptom scores for rhinorrhea, nasal congestion, nasal itching, and sneezing, each evaluated using a scale of 0 = none, 1 = mild, 2 = moderate, or 3 = severe. In addition, at the final visit, all the subjects rated their overall satisfaction on a scale of 0 (worse) to 4 (excellent).

Efficacy and Safety Assessment

Based upon previous articles,[6–8] primary and secondary end points were determined. A change in the rTNSS from baseline at visit 4 was used as the primary end point. The secondary end points were as follows: change in the rTNSS from baseline at visit 3, change in the iTNSS from baseline at visits 3 and 4, change in each reflective nasal symptom from baseline at visits 3 and 4, change in each instantaneous nasal symptom from baseline at visits 3 and 4, and overall satisfaction scores.

For safety assessment, the parameters used included an evaluation of adverse effects, laboratory tests, vital signs, physical examinations, and electrocardiograms.

Sample Size Estimation

The sample size estimation was based upon previous studies.[7–9] The mean changes in rTNSS associated with placebo and HL151 groups were −1.29 and −2.08, respectively, and the corresponding standard deviation values for placebo and HL151 groups were 2.34 and 1.78, respectively. The following conditions were assumed to calculate the sample size required to demonstrate the superiority of the HL151 group to placebo group: 1) level of significance: 0.050 (two-sided test), 2) power of the test: 0.80, and 3) allocation ratio: 1. A total of 109 patients or more were required in each group to provide 80% power, and a two-sided P value of <.050. Considering the potential number of dropouts and the safety assessment, the target sample size was 136 patients per group.

Statistical Analysis

For an efficacy assessment of the primary and secondary end points, analysis of covariance (ANCOVA) with the value before administration was performed using a per protocol set, and the least-squares means (LSMeans) of changes in each TNSS variation from baseline, adjusted for bias before administration, were determined for each administration group. Then, intergroup differences in LSMeans and 95% confidence intervals (CIs) during the observation period were calculated. For the primary and secondary end points, a pairwise test (between-group comparison) was performed using the above ANCOVA model and the PROC MIXED procedure in the Statistical Analysis System (SAS, version 9.2; SAS Institute, Cary, NC) to verify the superiority of bepotastine salicylate over placebo. Values of $P < .05$ (two-sided) were considered statistically significant.

Safety was analyzed in the safety analysis set, which consisted of subjects who had been randomized and had received medication at least once. The incidence of adverse events (AEs) or adverse drug reactions (ADRs) in the HL151 group was determined, and the Fisher exact test was used for analysis. Laboratory test results, vital signs, and results of physical examinations and echocardiography were also checked. The t test or Fisher exact test was used for statistical analysis.

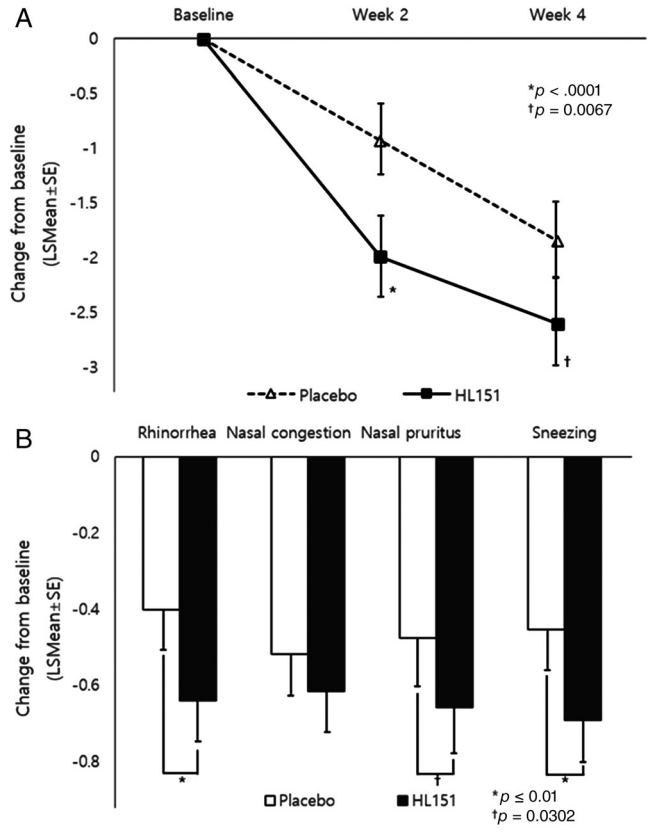

Fig. 2. Change from baseline analysis of covariance model (per protocol set). (A) Time course of reflective total nasal symptom score (LSMean) at each point and final assessment point. (B) Individual nasal symptom scores (LSMean) at week 4 of treatment. LSMean = least-squares mean; SE = standard error.

RESULTS

Study Population and Demographics

Subjects were recruited from 13 university hospitals in South Korea, and the disposition of the patients during the study is shown in Figure 1. A total of 462 subjects were enrolled in the clinical trial, but 190 subjects were excluded due to screening failure and did not receive any study treatment. Therefore, 272 subjects were randomized, and one of those who did not receive placebo medication was excluded from the safety set. The safety evaluation was performed using the safety set (n = 271). The full analysis set included the same 271 subjects from the safety set. Of the subjects from the full analysis set, 229 completed the clinical trial and were included in the per protocol set. At baseline, demographic data showed no differences in sex, age, duration of PAR, and body weight between the placebo (n = 119) and HL151 groups (n = 110). In addition, the severity of allergic symptoms in terms of rTNSS, iTNSS, and score for each nasal symptom did not differ between the two groups (Table I).

Efficacy

The primary end point of this study was a change (LSMeans ± standard error) in the rTNSS from baseline to visit 4, the values for which were −1.844 ± 0.192 and −2.602 ± 0.200 in the placebo and HL151 groups, respectively. The between-group difference ([HL151 group] − [placebo group]) was −0.758 (95% confidence interval: −1.304 to −0.212, $P < .001$), which validated the hypothesis that bepotastine was superior to placebo in terms of efficacy. Several secondary end points also showed that bepotastine was superior to placebo in terms of efficacy. Changes in the rTNSS from baseline at week 2 (visit 3) showed similar results ($P < .0001$, Table II, Fig. 2). Individual reflective nasal symptom scores, such as those for rhinorrhea, itching, and sneezing, also showed that bepotastine treatment was more efficacious in reducing reflective individual symptoms (Table II, Fig. 2). However, nasal congestion did not significantly improve compared to that in the placebo group ($P > .05$). In terms of iTNSS, HL151 was superior to the placebo at visits 3 and 4. Furthermore, the improvements in individual instantaneous nasal symptoms, such as rhinorrhea and sneezing, were better in the HL151 group than in the placebo group (Table III, Fig. 3). Subjective satisfaction regarding the medication was also evaluated between the two groups. The overall satisfaction was 73.51% in the HL151 group and 53.72% in the placebo group, indicating a higher satisfaction rate in the HL151 group ($P < .05$, Fig. 4).

Safety

The incidence of AEs during the trial was 12.32% (17/138) in the placebo group and 19.55% (26/133) in the HL151 group, and the intergroup difference was not significantly different ($P = .1034$). The incidence of ADRs was 6.52% (9/138) in the placebo group and 5.26% (7/133) in the HL151 group, and the intergroup difference was not statistically different ($P = .6603$). Somnolence, abnormal laboratory test results such as increased alanine aminotransferase (ALT) or ALT levels, and gastrointestinal disorders were common ADRs, which were managed

TABLE III.
Changes From Baseline in iTNSS and Individual Scores Determined Using the Analysis of Covariance Model (Per Protocol Set).

			HL151 Group, n = 110	Placebo Group, n = 119	Difference From Placebo
iTNSS	Week 2	LSMean ± SE	−1.548 ± 0.182	−0.593 ± 0.175	−0.955 ± 0.254
		95% CI	(−1.907, −1.188)	(−0.938, −0.248)	(−1.453, −0.456)
		P value			.0002*
	Week 4	LSMean ± SE	−2.065 ± 0.218	−1.425 ± 0.209	−0.640 ± 0.304
		95% CI	(−2.495, −1.636)	(−1.838, −1.013)	(−1.236, −0.045)
		P value			.0351†
Rhinorrhea	Week 4	LSMean ± SE	−0.525 ± 0.064	−0.316 ± 0.062	−0.209 ± 0.089
		95% CI	(−0.651, −0.399)	(−0.438, −0.195)	(−0.384, −0.033)
		P value			.0199†
Nasal congestion	Week 4	LSMean ± SE	−0.511 ± 0.062	−0.402 ± 0.059	−0.109 ± 0.086
		95% CI	(−0.633, −0.390)	(−0.519, −0.285)	(−0.278, 0.059)
		P value			.2025
Nasal pruritus	Week 4	LSMean ± SE	−0.502 ± 0.063	−0.389 ± 0.061	−0.114 ± 0.088
		95% CI	(−0.627, −0.378)	(−0.509, −0.268)	(−0.287, 0.059)
		P value			.1962
Sneezing	Week 4	LSMean ± SE	−0.528 ± 0.063	−0.301 ± 0.061	−0.227 ± 0.088
		95% CI	(−0.652, −0.403)	(−0.420, −0.181)	(−0.399, −0.055)
		P value			.0100‡

*$P < .001$.
†$P < .05$.
‡$P < .01$.
CI = confidence interval; iTNSS = instantaneous total nasal symptom score; LSMean = least-squares mean; SE = standard error.

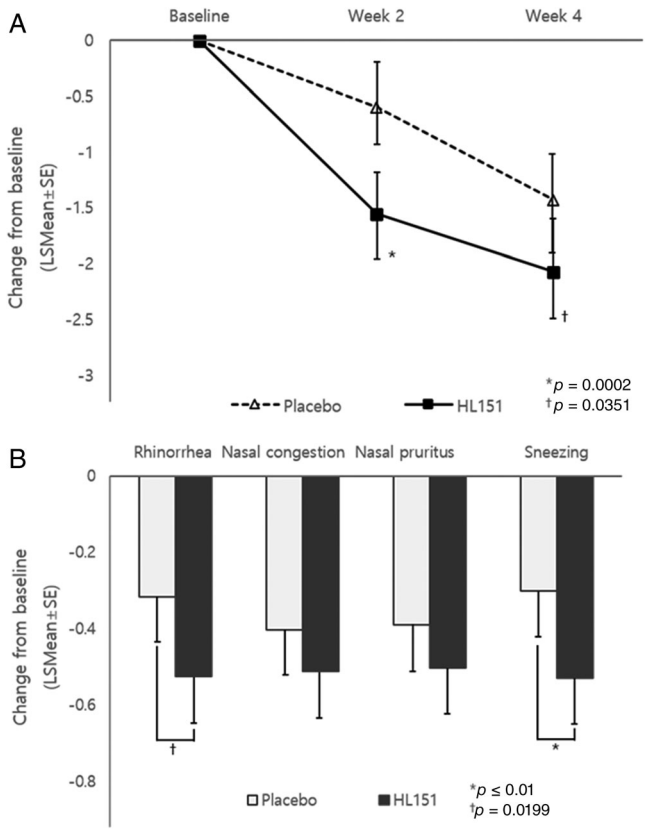

Fig. 3. Change from baseline analysis of covariance model (per protocol set). (A) Time course of instantaneous total nasal symptom score (LSMean) at each time point and final assessment point. (B) Individual nasal symptom scores (LSMean) at week 4 of treatment. LSMean = least-squares mean; SE = standard error.

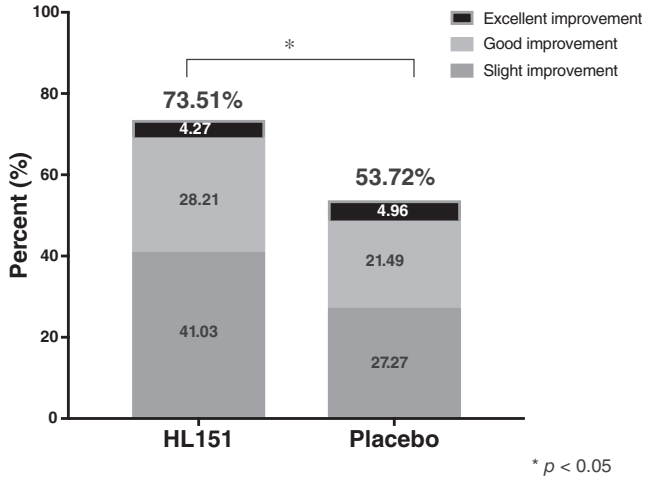

Fig. 4. Percentages of subjective satisfaction of symptoms.

easily without any problems. In the case of somnolence, three subjects in the HL151 group (2.26%) and two subjects in the placebo group (1.45%) complained of somnolence, but the incidence was not significantly different between two groups. With regard to serious AEs, one subject in the HL151 group was diagnosed with acute hepatitis A, which was considered to be unrelated to this clinical trial (Table IV).

TABLE IV.
Summary of Adverse Events (Safety Set).

Treatment Group	HL151 Group, N = 133	Placebo Group, n = 138
AEs, n (%)	26 (19.55)	17 (12.32)
ADR, n (%)	7 (5.26)	9 (6.52)
Somnolence	3 (2.26)	2 (1.45)
Abnormal laboratory test	2 (1.50)	3 (2.17)
Gastrointestinal disorders	1 (0.75)	2 (1.45)
Infections and infestations	0 (0.00)	2 (1.45)
Chest discomfort	0 (0.00)	1 (0.72)
Musculoskeletal disorders	1 (0.75)	0 (0.00)
Nasal dryness	1 (0.75)	0 (0.00)
SAEs, n (%)	1 (0.75)	0 (0.00)
Acute hepatitis A	1 (0.75)	0 (0.00)

ADR = adverse drug reaction; AEs = adverse events; SAEs = serious adverse events.

DISCUSSION

Bepotastine besilate was first approved in Japan in 2000 as a second-generation antihistamine, and a different salt form, bepotastine salicylate, was developed in 2013.[3,5] Both salt forms of bepotastine are administered twice daily by month due to their short half-lives. A bepotastine besilate tablet contains 10 mg of bepotastine besilate, and a bepotastine salicylate tablet contains 9.64 mg of bepotastine salicylate.[10] Both formulations contain the same 7.11-mg bepotastine base. A recent preclinical study using beagle dogs has shown that bepotastine salicylate is the bioequivalent to bepotastine besilate.[5] In addition, a pharmacokinetic study comparing two formulations showed that bepotastine salicylate has comparable pharmacokinetic characteristics with bepotastine besilate, and both formulations met the regulatory criteria and were well-tolerated in healthy subjects.[11] However, bepotastine salicylate has a disadvantage in that it undergoes slow racemization to less active R-enantiomer in high moisture conditions, such as 40.0°C and 75% relative humidity. Therefore, the more stable bepotastine salicylate was developed.[12]

The controlled-release form of bepotastine salicylate (HL151) was approved in South Korea in 2018, and this controlled-release form contains 19.28 mg of bepotastine salicylate and 14.22 mg of bepotastine base. A preclinical study showed that HL151 was the bioequivalent to bepotastine besilate, and two pharmacokinetic studies showed that HL151 has comparable pharmacokinetic characteristics with bepotastine besilate and was well-tolerated in healthy subjects (unpublished). In addition, because HL151 is a controlled-release form of bepotastine salicylate, it has the convenience of once-daily administration.

In this trial, we evaluated the efficacy and safety of the controlled-release form of bepotastine salicylate,

which has the longer half-life. This double-blind, placebo-controlled phase III clinical trial showed that once-daily administration of 20 mg of bepotastine salicylate (HL151, Belion CR) improved nasal symptoms and was safe in patients with PAR.

Bepotastine is known to have many antiallergic effects spanning both the early- and late-phase allergic mechanisms,[13] including antihistamine activity, inhibition of scratching induced by substance *P*, suppression of LTB4 and LTD4 activities, inhibition of eosinophil infiltration (possibly related to bepotastine interference with interleukin (IL)-5 production), and reduction of cytokines. Another study showed that bepotastine significantly suppressed antigen-induced IL-5 production in a concentration-dependent manner.[14] Other antihistamines, such as ketotifen and cetirizine, also inhibited IL-5 production; however, the effective doses of these drugs were significantly higher than that of bepotastine.[14]

A study using an animal model of allergic conjunctivitis showed that bepotastine was more potent than olopatadine and ketotifen in reducing vascular hyperpermeability.[15] Bepotastine also inhibited mast cell function and eosinophil chemotaxis, suggesting that it acts as an inhibitor of allergic response through multiple mechanisms: histamine H1 receptor antagonism, mast cell stabilization, and inhibition of eosinophil recruitment. Consistent with the above-mentioned mechanisms of action of bepotastine, a controlled-release tablet of bepotastine salicylate showed significant clinical improvement in both rTNSS, iTNSS, and in each nasal symptom including rhinorrhea, pruritis, and sneezing at weeks 2 and 4 of this phase III clinical trial.

Usually, antihistamines have few beneficial effects on nasal airway obstruction compared to those on other symptoms such as rhinorrhea, itching, and sneezing.[16] However, it has been reported that bepotastine had an inhibitory effect on nasal airway resistance in an experimental allergic rhinitis model.[17] Bepotastine decreased nasal airway resistance in a dose-dependent manner, and its effect was higher than those of other antihistamines such as cetirizine, terfenadine, and ketotifen. In accordance with this animal study, our clinical trial also showed similar results, in that the drug significantly decreased nasal obstruction at week 2 of this clinical trial. However, although bepotastine also decreased nasal obstruction at week 4, the decrease was not statistically significant, suggesting a slightly less beneficial effect on nasal obstruction.

In this clinical trial, the safety of HL151 was also investigated. There was no statistically significant difference in AEs and ADRs between the HL151 and placebo groups, and there was only one drug-unrelated serious AE in the HL151 group, proving the safety of HL151. One of the major ADRs of HL151 was somnolence, and there was no significant difference in the incidence of somnolence between the two groups (three subjects in the HL151 group [2.26%] and two subjects in the placebo group [1.45%]), indicating the safety of HL151. An interesting study showed that bepotastine has the least sedative effects among antihistamines.[18] In a study that compared the sedative effects of bepotastine and other antihistamines including fexofenadine, olopatadine, and cetirizine, bepotastine was observed to be associated with the least visual analog scale score for sedation and had similar psychomotor activity as that associated with placebo, indicating its low sedative effects. In accordance with this finding, a study investigating the penetration of bepotastine through the blood–brain barrier (BBB) revealed that it hardly penetrated the BBB and that it had similar H1 receptor occupancy as did the placebo.[19]

In our trial, the satisfaction rate of placebo group was very high (53.7%) and the difference between control and treatment group was relatively small (about 20%), although it was significantly different ($P < .05$). Many studies supported the placebo effect in allergic rhinitis treatment.[20,21] Because the outcome variable depends on subjective questionnaire rather than objective parameter, the treatment effect could be more susceptible to be influenced by the placebo effect.

This study was well designed and performed. However, the limitation of this clinical trial is that the subject was restricted only to adult patients with perennial allergic rhinitis. Patients with seasonal allergic rhinitis or patients younger than 18 years were not included in this trial and can be extended in the future.

CONCLUSION

This study demonstrated that the once-daily administration of the controlled-release form of bepotastine salicylate (HL151, Belion CR) was efficacious and safe in adult patients with PAR. Further studies are needed to compare the efficacy of HL151 with other once-daily antihistamines such as fexofenadine or levocetirizine, and with twice-daily administration of bepotastine to validate its efficacy in the future.

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BIBLIOGRAPHY

1. Sur DK, Plesa ML. Treatment of allergic rhinitis. *Am Fam Physician* 2015; 92:985–992.
2. Kuna P, Jurkiewicz D, Czarnecka-Operacz MM, et al. The role and choice criteria of antihistamines in allergy management—expert opinion. *Postepy Dermatol Alergol* 2016;33:397–410.
3. Carrillo-Martin I, Gonzalez-Estrada A, Dimov V. Bepotastine besilate for the treatment of perennial allergic rhinitis. *Expert Opin Pharmacother* 2018;19:1727–1730.
4. Hashiguchi K, Tang H, Fujita T, Suematsu K, Gotoh M, Okubo K. Bepotastine besilate OD tablets suppress nasal symptoms caused by Japanese cedar pollen exposure in an artificial exposure chamber (OHIO chamber). *Expert Opin Pharmacother* 2009;10:523–529.
5. Cho KH, Choi HG. Development of novel bepotastine salicylate salt bioequivalent to the commercial bepotastine besilate in beagle dogs. *Drug Dev Ind Pharm* 2013;39:901–908.
6. Okubo K, Ichimura M, Koyama T, Susuta Y, Izaki H. Double-blind placebo-controlled study of bepotastine besilate in pediatric patients with perennial allergic rhinitis. *Expert Opin Pharmacother* 2015;16:2395–2408.
7. Davies RJ, European Multicentre Study Group. Efficacy and tolerability comparison of ebastine 10 and 20mg with loratadine 10mg. *Clin Drug Investig* 1998;16:413–420.
8. Marmouz F, Giralt J, Izquierdo I. Morning and evening efficacy evaluation of rupatadine (10 and 20 mg), compared with cetirizine 10 mg in perennial allergic rhinitis: a randomized, double-blind, placebo-controlled trial. *J Asthma Allergy* 2011;4:27.

9. Li H, Gu J-Q ZL, Cheng L, G-H L, Yin J. Bepotastine besilate versus loratatine in the treatment of allergic rhinitis: a multicenter randomized double-blind comparison clinical trial. *Chin J Allergy Clin Immunol* 2013;1.
10. Ha D, Choi Y, Kim DU, Chung KH, Lee EK. A comparative analysis of the impact of a positive list system on new chemical entity drugs and incrementally modified drugs in South Korea. *Clin Ther* 2011;33:926–932.
11. Kim KA, Park JY. Pharmacokinetic comparisons of bepotastine besilate and bepotastine salicylate in healthy subjects. *Clin Drug Investig* 2013;33: 913–919.
12. Lim DS, Youn YS, Kwack SJ, et al. Comparative efficacy and bioequivalence of novel h1-antihistamine bepotastine salts (nicotinate and salicylate). *J Toxicol Environ Health A* 2014;77:1451–1466.
13. Williams JI, Gow JA, Klier SM, McCue SL, Salapatek AM, McNamara TR. Non-clinical pharmacology, pharmacokinetics, and safety findings for the antihistamine bepotastine besilate. *Curr Med Res Opin* 2010;26: 2329–2338.
14. Kaminuma O, Ogawa K, Kikkawa H, Kikuchi M, Naito K, Ikezawa K. A novel anti-allergic drug, betotastine besilate, suppresses interleukin-5 production by human peripheral blood mononuclear cells. *Biol Pharm Bull* 1998;21:411–413.
15. Kida T, Fujii A, Sakai O, et al. Bepotastine besilate, a highly selective histamine H(1) receptor antagonist, suppresses vascular hyperpermeability and eosinophil recruitment in in vitro and in vivo experimental allergic conjunctivitis models. *Exp Eye Res* 2010;91:85–91.
16. Scadding GK, Kariyawasam HH, Scadding G, et al. BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (revised edition 2017; first edition 2007). *Clin Exp Allergy* 2017;47:856–889.
17. Murata T, Matsumoto Y, Suzuki T, Naito K, Takata I, Tsuzurahara K. Effect of betotastine besilate (TAU-284), a novel anti-allergic agent, on experimental allergic rhinitis [in Japanese]. *Arerugi* 1997;46:576–584.
18. Takahashi H, Ishida-Yamamoto A, Iizuka H. Effects of bepotastine, cetirizine, fexofenadine, and olopatadine on histamine-induced wheal-and flare-response, sedation, and psychomotor performance. *Clin Exp Dermatol* 2004;29:526–532.
19. Tashiro M, Duan X, Kato M, et al. Brain histamine H1 receptor occupancy of orally administered antihistamines, bepotastine and diphenhydramine, measured by PET with 11C-doxepin. *Br J Clin Pharmacol* 2008;65: 811–821.
20. del Cuvillo A, Sastre J, Bartra J, et al. Placebo effect in clinical trials involving patients with allergic rhinitis. *J Investig Allergol Clin Immunol* 2011; 21(40–45.
21. Schaefer M, Sahin T, Berstecher B. Why do open-label placebos work? A randomized controlled trial of an open-label placebo induction with and without extended information about the placebo effect in allergic rhinitis. *PLoS One* 2018;13:e0192758.