

Original Article

Efficacy of Epinephrine Nasal Spray in the Treatment of Urticaria

David I. Bernstein, MD^{a,b}, Neetu Talreja, MD^c, Thomas B. Casale, MD^d, H. Henry Li, MD, PhD^e, Michael A. Kaliner, MD^e, Richard Lowenthal, MS^f, and Sarina Tanimoto, MD, PhD^f Cincinnati, Ohio; Boise, Idaho; Tampa, Fla; Wheaton, Md; and San Diego, Calif

What is already known about this topic? Epinephrine has been used for the treatment of acute urticaria since 1939. Its use has declined since the introduction of oral or injectable antihistamines.

What does this article add to our knowledge? ARS-2 (epinephrine nasal spray) was able to relieve symptoms of urticaria exacerbations in patients with chronic spontaneous urticaria with minor adverse events. This demonstrates that on-demand nasal epinephrine has the potential to manage acute urticarial symptoms safely.

How does this study impact current management guidelines? ARS-2 (epinephrine nasal spray) may provide a safe, rapid, and effective option for current standard of care for the treatment of acute exacerbations of chronic spontaneous urticaria.

BACKGROUND: Although current treatment options for acute exacerbations of antihistamine refractory chronic spontaneous urticaria (CSU) are generally considered safe and effective, patients have breakthrough symptoms necessitating treatment. Epinephrine injections were once used for the treatment for acute urticaria or acute exacerbations of chronic urticaria or angioedema, but their use has declined. The development of an intranasal epinephrine spray (ARS-2) offers a needle-free alternative for the treatment of CSU exacerbations.

OBJECTIVE: To assess the efficacy and safety of ARS-2 for the treatment of exacerbations of CSU.

METHODS: This was a phase 2, single-dose, randomized, placebo-controlled crossover efficacy study in which adult

patients (n = 21) experiencing an acute flare or exacerbation of urticaria symptoms were treated with ARS-2 (1 or 2 mg) or placebo. Urticaria symptoms and severity were assessed based on both patient-reported and investigator-rated assessments. **RESULTS:** Relative to placebo, both 1- and 2-mg doses of ARS-2 resulted in lower patient-reported hive and pruritus scores ($P < .05$) and a lower investigator-reported extent of urticaria and erythema scores ($P < .05$). Additionally, a greater percentage of patients receiving ARS-2 were considered by investigators to have been effectively treated. Patient-reported satisfaction scores were also significantly higher for both doses of ARS-2 relative to placebo. Only minor adverse events were reported.

^aBernstein Clinical Research Center, Cincinnati, Ohio

^bDivision of Immunology, Allergy, and Rheumatology, College of Medicine, University of Cincinnati, Cincinnati, Ohio

^cThe Allergy Group and Treasure Valley Medical Research, Boise, Idaho

^dDivision of Allergy and Immunology, Morsani College of Medicine, University of South Florida, Tampa, Fla

^eInstitute for Asthma and Allergy, Wheaton, Md

^fARS Pharmaceuticals Operations, San Diego, Calif

This study was funded, initiated, administered, and sponsored by ARS Pharmaceuticals Operations, Inc.

Conflicts of interest: D. Bernstein has received grant support from ALK-Abelló, Amgen, AstraZeneca, Genentech, GlaxoSmithKline, Novartis, Regeneron, Sanofi, and Teva and served as an advisor for ALK America, Aquestive Therapeutics, Bryn, Gerson-Lehman, and Guidepoint Global. He reports serving as a consultant and/or advisor for ARS Pharmaceuticals. N. Talreja received research grants or compensation for participation in clinical trials sponsored by 9Meters, AbbVie, Allakos, Amgen, Anaptybio, Arcutis, Arena, ARS Pharma, AstraZeneca, Biohaven, Braintree Laboratories Inc, Castle Biosciences Inc, Celldex Therapeutics, Cindome Pharma, Inc, Eli Lilly and Company, Escient Pharmaceuticals, Inc, Evommune Inc, Gossamer, GlaxoSmithKline, Incyte Co, Jasper Therapeutics Inc, Knopp, Nerre, Novartis Pharmaceuticals, Pearl Therapeutics, Pfizer, Phathom, Regeneron Pharmaceuticals, Sanofi-Aventis Recherche & Development, Seres, Teva Branded Pharmaceutical Products R&D, Uniquity

One, and Upstream Bio, Inc; and has served as an advisor for Novartis Pharmaceuticals and speaker for ARS Pharma. T.B. Casale reports on financial support from Thermo Fisher Scientific and serves as a consultant and/or advisor for ARS Pharmaceuticals. H.H. Li has received research grants or compensation for participation in clinical trials sponsored by ARS Pharma, AstraZeneca, BioCryl Pharmaceuticals, CSL Behring, Intellia, KalVista Pharmaceuticals, Pharming, and Shire/Takeda; and has served as an advisor and/or speaker for BioCryl Pharmaceuticals, CSL Behring, Pharming, and Shire/Takeda. M.A. Kaliner reports serving as a consultant and/or advisor for ARS Pharmaceuticals. R. Lowenthal and S. Tanimoto are employed by ARS Pharmaceuticals Operations, San Diego, Calif.

Received for publication May 20, 2025; revised January 30, 2026; accepted for publication February 9, 2026.

Available online ■ ■

Corresponding author: Sarina Tanimoto, MD, PhD, ARS Pharmaceuticals Operations, Inc, 11682 El Camino Real, Ste 120, San Diego, CA 92130. E-mail: sarinat@ars-pharma.com.

2213-2198

© 2026 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). <https://doi.org/10.1016/j.jaip.2026.02.010>

Abbreviations used

BSA- Body surface area

CSU- Chronic spontaneous urticaria

UAS- Urticaria Activity Score

VAS- Visual analog scale

CONCLUSION: ARS-2 may offer a safe and effective treatment option for urticaria exacerbations. © 2026 The Authors.

Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2026;■:■-■)

Key words: Urticaria; Antihistamine refractory urticaria; Epinephrine; Intranasal epinephrine; ARS-2

INTRODUCTION

Chronic spontaneous urticaria (CSU) is characterized by the occurrence of urticaria for 6 weeks or longer without identifiable specific triggers.^{1,2} The global prevalence of CSU ranges from 0.02% to 2.7%³ with considerable humanistic, societal, and economic burden.² Chronic spontaneous urticaria results from the activation of mast cells and the subsequent release of mediators. The mediators can be preformed (ie, histamine, tryptase, and cytokines) or *de novo* synthesized (leukotrienes, prostaglandin D₂, and platelet-activating factor) and are responsible for a range of responses including vasodilation, increased vascular permeability, and stimulation of sensory nerve endings.^{1,4}

The current algorithm for treating CSU recommends the use of a second-generation H₁-antihistamine as first-line treatment. If symptoms are not adequately controlled, the long-term addition of omalizumab, dupilumab, or remibrutinib should be considered, followed by the addition of cyclosporine as third-line treatment.¹ Additionally, although acute exacerbations of CSU can be treated with a short course of oral glucocorticoids,⁵ long-term or frequent acute use of systemic glucocorticoids is associated with a high rate of side effects.

The use of epinephrine for the treatment of acute urticaria dates back to epinephrine's initial approval in 1939. However, its use declined after the introduction of oral or injectable antihistamines (ie, diphenhydramine). ARS-2 (epinephrine nasal spray, ARS Pharmaceuticals Operations, Inc, San Diego, Calif) is a needle-free nasal epinephrine delivery system being developed to treat acute exacerbations of CSU without the risks associated with injection products. We conducted the current study to assess the efficacy and safety of ARS-2 for the treatment of exacerbations of CSU.

METHODS

Study design and participants

RELIEF-CSU1 was a phase 2, single-dose, randomized, open-label, placebo-controlled crossover efficacy study to assess the efficacy of ARS-2 for the treatment of acute exacerbations of chronic urticaria. We enrolled patients aged 18 to 65 years who had either acute urticaria with known etiology or acute exacerbations of CSU with unknown etiology at least two times a week while receiving

chronic daily antihistamine treatment. An acute exacerbation was defined as patient-rated pruritus and hive severity score of 2 or greater by Urticaria Activity Score (UAS) twice daily.⁶ Key exclusion criteria included use of β -blockers, prior nasal fractures, injuries or disorder, or abnormal cardiovascular examination including any prior history of myocardial infarction or clinically significant abnormal electrocardiogram (eg, second- or third-degree heart block, uncontrolled arrhythmia, QT interval corrected using Fridericia's formula greater than 450 ms for male subjects and greater than 470 ms for female subjects).

After we received written informed consent and screening, we instructed patients to return to the investigational sites if and when they experienced an acute flare or exacerbation of urticaria symptoms. Patients were also instructed not to take any other acute medications before returning to the site. The severity prompting return to the sites was not prespecified in the protocol. However, urticaria symptoms and severity were assessed based on both patient-reported and investigator-rated assessments. Each patient received a single treatment of ARS-2 1 mg, ARS-2 2 mg, or placebo nasal spray in a crossover manner. The study drugs were supplied with a label containing the treatment information. The study was conducted in accordance with international guidelines, including the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice. The protocol and informed consent forms were approved by institutional review boards at each site. This study was registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT05496465). The investigational product (ARS-2) was referred to as ARS-1 in the EPI U01 Protocol. When referring to its use for the treatment of urticaria, the code name has been updated to ARS-2.

Outcomes

We evaluated the efficacy assessments based on patient-reported and investigator-rated assessments before the dose, at 5, 10, 15, 30, 45, 60, and 120 minutes, and every 60 minutes after dosing until the symptoms resolved or returned to baseline for CSU. Patient-reported assessments included a patient-reported itch and hive severity score from 0 (none) to 3 (severe) using the UAS twice daily and a patient-reported pain score based on a self-reported visual analog scale (VAS). Investigator-rated assessments included the extent of urticaria defined as the percentage of body area with urticaria (grade 1 = urticarial lesions covering <10% the body surface area [BSA]; grade 2 = urticarial lesions covering 10% to 30% BSA; and grade 3 = urticarial lesions covering >30% BSA) and the erythema score (0 = none; 1 = almost clear [slight redness]; 2 = mild erythema [definite redness]; 3 = moderate erythema [marked redness]; and 4 = severe erythema [fiery redness]). Additional exploratory assessments included the investigator's assessment as being effectively treated and a patient satisfaction VAS score. Safety analysis was based on adverse events and vital signs.

Statistical analysis

Efficacy assessments are presented as means \pm SEMs at each time point. Each result was based on data from all patients who received at least two treatments being compared. Statistical comparisons were based on within-patient differences (eg, ARS-2 – placebo). We made comparisons using Wilcoxon signed rank test. All tests were two-sided.

The study was registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT05496465 - <https://clinicaltrials.gov/study/NCT05496465?term=NCT05496465&rank=1>) on August 11, 2022.

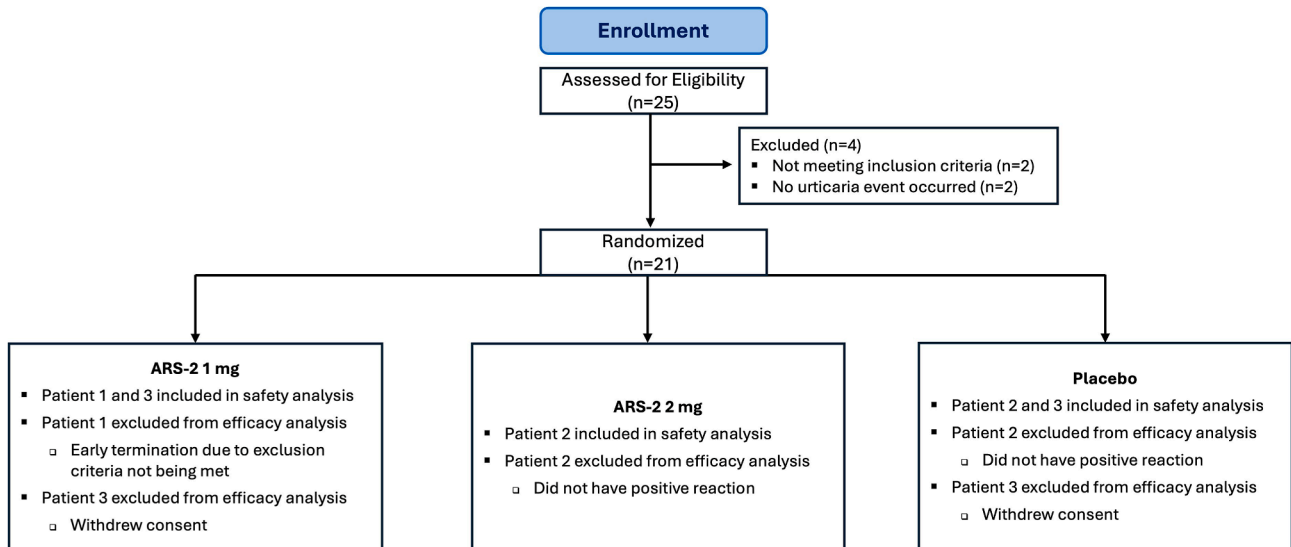


FIGURE 1. Consolidated Standards of Reporting Trials diagram showing the flow of patients in the study.

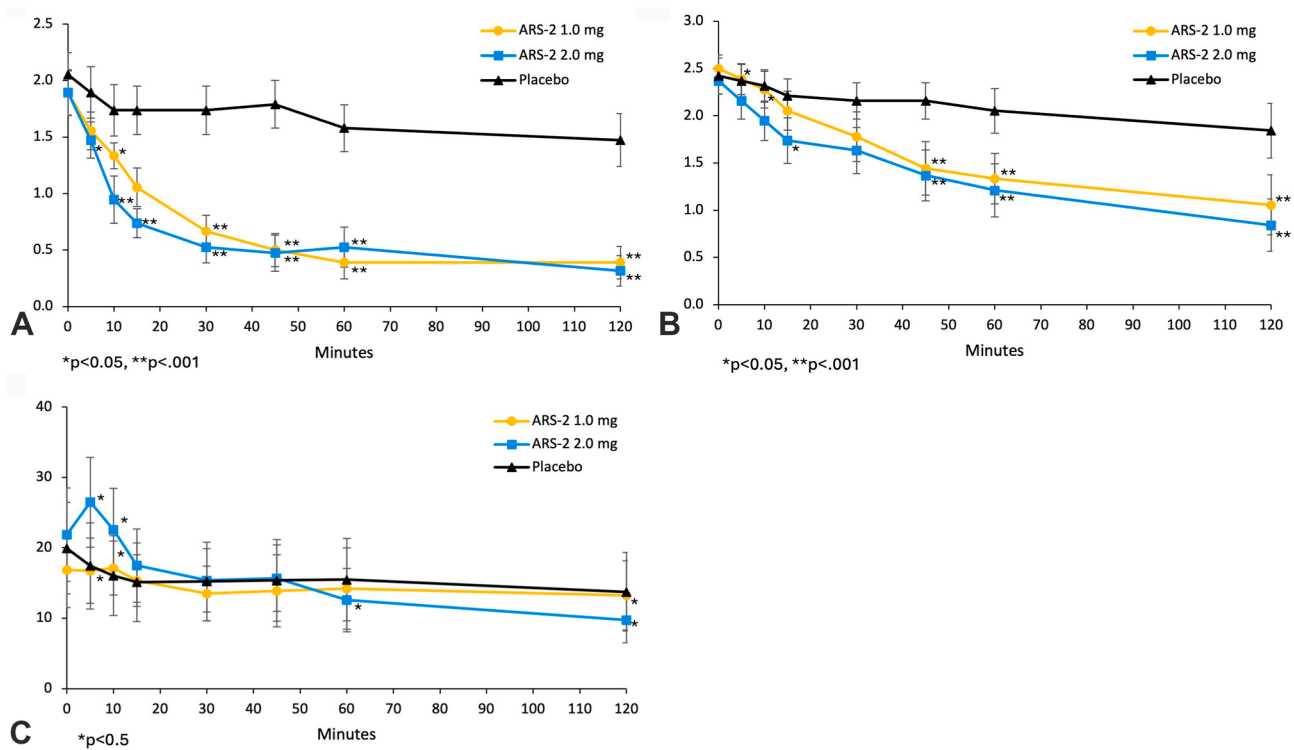


FIGURE 2. Mean patient-reported severity scores, by treatment and time point: (A) patient-report itch severity, (B) patient-report hives severity, and (C) patient-report pain severity (visual analog scale).

RESULTS

Study participants

A total of 21 of 25 screened patients were randomized and received at least one treatment (Figure 1). All randomized patients met the diagnostic criteria for CSU. Two patients were excluded from the efficacy analysis because they received only one treatment: one patient did not experience hives after the first dose, and one patient withdrew consent. One additional patient

was terminated from the study early when it was determined that one of the exclusion criteria (abnormal cardiovascular finding at screening or history) was not met; however, this patient received two treatments (ARS-1 2 mg and placebo) and was therefore included in the efficacy analysis.

Patients ranged in age from 18 to 65 years. Four patients (19%) were male and 17 (81.0%) were female. Patients had a mean (SD) height of 167.0 cm (10.0 cm), a mean (SD) weight

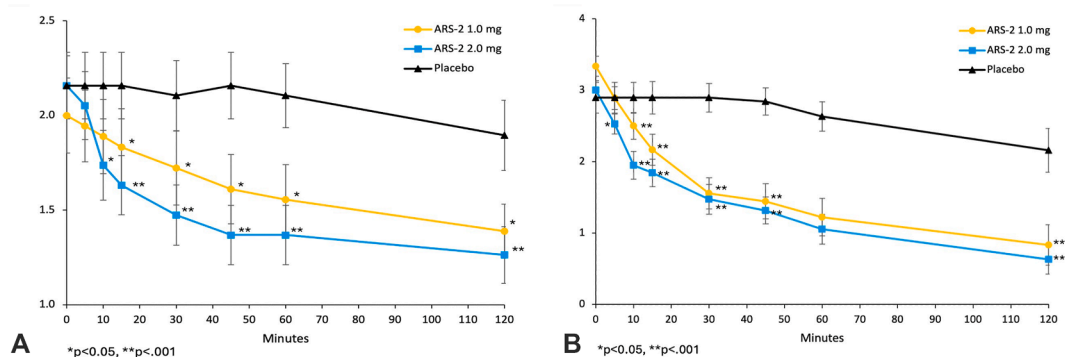


FIGURE 3. Mean investigator-reported scores, by treatment and time point: **(A)** investigator-reported extent of urticaria, and **(B)** investigator-rated erythema score.

of 81.0 kg (19.1 kg), and a mean (SD) body mass index of 29.1 kg/m² (6.8 kg/m²). Of the 19 patients included in the efficacy analysis, 18 were taking antihistamines and one was taking omalizumab without an antihistamine. Of 18 patients receiving antihistamine, 13 patients were taking a second-generation antihistamine alone (as needed, 10 patients; once daily, three times daily, and four times daily, 1 patient each). Five patients were receiving combinations of treatment: two patients took first- and second-generation antihistamine as needed, one patient took two second-generation antihistamines twice a day, one patient took first- and second-generation antihistamines and gabapentin, and one patient took second generation antihistamine three times a day, and two second-generation antihistamines as needed (prednisone and montelukast).

Patient-reported assessment

Mean baseline hive scores were 2.5 (SD, 0.6; range, 1-3), 2.4 (SD, 0.6; range, 1-3), and 2.4 (SD, 0.8; range, 1-3) and mean baseline itch scores were 1.9 (SD, 0.8; range, 0-3), 1.9 (SD, 0.9; range, 0-3), and 2.1 (SD, 0.8; range, 0-3) for ARS-2 1 mg, ARS-2 2 mg, and placebo, respectively.

Figure 2, A and B, respectively show the by-treatment and by-time point figures of patient-reported itch and hive severity. Relative to placebo, both 1- and 2-mg doses of ARS-2 resulted in rapid decreases in patient-reported itch and hive severity scores. We observed statistically significant differences in itch severity starting at 5 minutes after the dose for ARS-2 2 mg and 15 minutes after the dose for ARS-2 1 mg, and statistically significant differences in hive severity at 15 minutes after the dose for ARS-2 2 mg and 30 minutes after the dose for ARS-2 1 mg. These significant differences were observed through 120 minutes after the dose for both itch severity and hive severity ($P < .001$) (Figure 2, A and B). There were no significant differences between ARS-2 1 and 2 mg except for 10 minutes after the dose for itch ($P < .05$).

We observed no significant differences in patient-reported pain scores (VAS) between placebo and either dose of ARS-2 or between ARS-2 1 mg and ARS-2 2 mg (Figure 2, C).

Investigator-rated assessment

The by-treatment and by-time point figures of the investigator-rated extent of urticaria (percentage of body area with urticaria) and erythema score are provided in Figure 3, A and B. Relative to placebo, both doses of ARS-2 resulted in

TABLE I. Investigator's assessment of being effectively treated and patient satisfaction scores

Assessments	ARS-2 1 mg (n = 18), n (%)	ARS-2 2 mg (n = 19), n (%)	Placebo (n = 19), n (%)
Investigator's assessment that patient was effectively treated			
Yes	14 (77.8)	16 (84.2)	7 (36.8)
No	4 (22.2)	3 (15.8)	12 (63.2)
Patient satisfaction score (mean [SD]) visual analog scale	68.2 (30.4)	74.1 (30.5)	32.5 (38.0)

rapid improvements (decreases) in investigator-rated assessments of urticaria and erythema. Statistically significant improvements in investigator-reported extent of urticaria were observed starting at 10 minutes after the dose for ARS-2 2 mg and 15 minutes after the dose for ARS-2 1 mg. We observed statistically significant improvements in investigator-reported erythema scores starting at 5 minutes after the dose for ARS-2 2 mg and 10 minutes after the dose for ARS-2 1 mg. Significant differences were observed through 120 minutes after the dose ($P = .005$ for 1 mg or $<.001$ for 2 mg). With the exception of the period between 15 and 60 minutes after the dose for the extent of urticaria, there were no significant differences between the doses of ARS-2.

Additional exploratory assessments

Relative to placebo, both doses of ARS-2 resulted in significantly higher rates of being effectively treated according to investigator assessments ($P < .05$). There were no significant differences between ARS-2 1 mg and ARS-2 2 mg (Table I).

Relative to placebo, both doses of ARS-2 resulted in significantly higher patient satisfaction scores as measured by patient satisfaction by VAS and mean patient satisfaction scores ($P < .05$) (Table I). There were no significant differences between ARS-2 1 mg and ARS-2 2 mg for either measure.

The patient taking omalizumab without an antihistamine was terminated from the study after receiving ARS-2 2 mg and placebo (ARS-2 1 mg was not administered). This patient demonstrated a rapid response beginning at 5 minutes after the dose and persisting through 120 minutes. The patient had a VAS score of 100 after ARS-2 2 mg (versus a score of 55 after placebo).

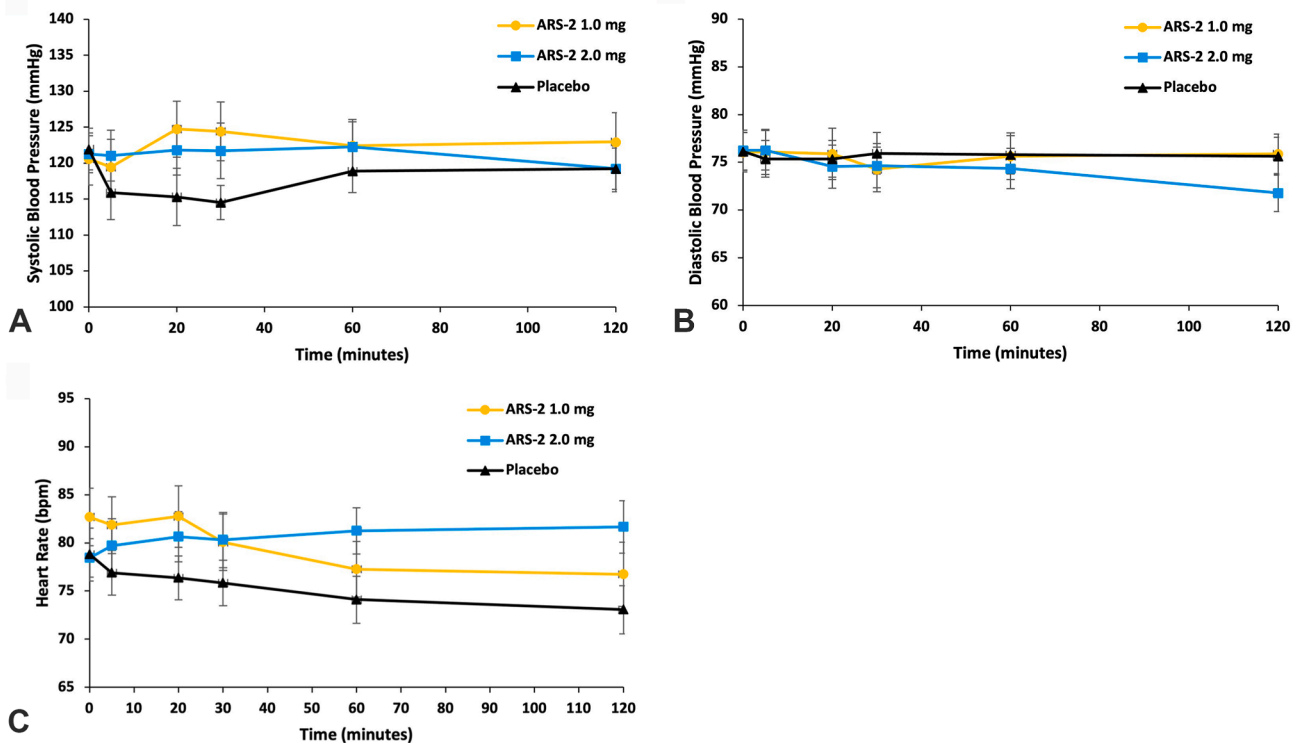


FIGURE 4. Mean vital signs versus time: (A) systolic blood pressure, (B) diastolic blood pressure, and (C) heart rate.

Safety and tolerability

Vital signs. Figure 4 shows mean vital signs versus time. No significant or consistent changes in vital signs were observed.

Adverse events. Six patients reported adverse events (31.6%) after receiving ARS-2 1 mg, and seven patients (35.0%) after receiving ARS-2 2 mg. No patients reported an adverse event after placebo. Adverse events reported by more than one patient in the 1-mg dose group included nasal discomfort (four patients; 21.1%). Adverse events reported by more than one patient in the 2-mg dose group included nasal discomfort (three patients; 15.0%) and headache (two patients; 10.0%).

DISCUSSION

Epinephrine has long been recognized as a treatment for urticaria,^{7,8} but its use had diminished owing to reliance on antihistamines⁹ and concerns regarding the risks of epinephrine injections to treat a non-life-threatening condition.¹⁰ This study demonstrates that ARS-2 offers a rapidly acting, needle-free alternative for managing acute exacerbations of CSU.

In this randomized, placebo-controlled crossover study, ARS-2 resulted in significant improvements in both patient- and investigator-reported measures of itch, hives, extent of urticaria, and erythema. Therapeutic effects were observed as soon as 5 minutes after the dose and persisted for a minimum of 120 minutes; no changes were observed after placebo. No meaningful differences in efficacy were noted between the 1- and 2-mg doses, suggesting that lower doses may warrant further

investigation. The rapid improvements noted after administration of ARS-2 contrast with currently used systemic glucocorticoids, which typically take several hours to be effective and carry a risk of cumulative toxicity.

Treatment with ARS-2 was well-tolerated, with only minor adverse events, primarily nasal discomfort and headache. Small, transient changes in blood pressure and heart rate were noted, although they never exceeded normal physiologic ranges. This finding may reflect the counterbalancing vasodilation associated with increased levels of histamine in CSU.¹¹

Epinephrine's therapeutic mechanism of action in urticaria is attributable to its adrenergic agonism, particularly high-affinity β_2 -receptor activation, which rapidly inhibits plasma exudation by preventing the separation of endothelial cells in post-capillary venules.^{12,13} β_2 -Agonism also inhibits the further release of histamine, tryptase, and other allergic mediators of inflammation from mast cells and basophils by activating membrane-bound adenylate cyclase and elevating cyclic adenosine monophosphate.¹⁴⁻¹⁶ These mechanisms provide a biologically plausible explanation for the rapid symptom relief associated with ARS-2 administration.

Investigators were more likely to consider patients effectively treated after either dose of ARS-2 than placebo, with correspondingly higher patient satisfaction scores. These comparable findings from both patients and investigators demonstrate that the improvements seen in symptom scores reflect real and noticeable relief for patients.

Although these results are promising, the study has several important limitations, including the inclusion of subjective assessment measures in an open-label study. In addition, several other methodological constraints warrant consideration. The

UAS, although standard for urticaria studies, has not been validated for short-interval assessments such as the 120-minute time frame used here; likewise, the VAS is not a validated tool in this context. We conducted no formal power analysis; the sample size was based on practical considerations. Generalizability is also constrained by the enrolled population. Most patients had relatively mild disease that was controlled by daily antihistamines, and the presenting findings may not extend to patients with more severe or refractory CSR. Additionally, because the study excluded patients with a history of cardiovascular conditions, the overall tolerability of ARS-2 cannot be generalized to this population. Finally, because inclusion was restricted to patients between aged 18 and 65 years, the responses to ARS-2 cannot be extended to patients aged under 18 or over 65 years. Additional studies, including larger double-blind, reasonably powered studies, are needed to confirm and strengthen the current findings. The inclusion of a repeat dosing arm may also be valuable to demonstrate real-world applicability for treating urticaria.

Despite these limitations, the results indicate that ARS-2 may offer a safe, rapid, and effective treatment option for acute exacerbations of CSU, with fewer side effects than systemic corticosteroids. Further study is warranted to explore the efficacy of lower doses.

Acknowledgments

Medical writing was provided by Tricia Bliven-Chasinoff, MS, of Pacific Link Consulting and was funded by ARS Pharmaceuticals Operations, Inc.

REFERENCES

- Zuberbier T, Bernstein JA, Maurer M. Chronic spontaneous urticaria guidelines: what is new? *J Allergy Clin Immunol* 2022;150:1249-55.
- Mauer M, Abuzakouk M, Bérard F, Canonica W, Oude Elberink H, Giménez-Armau A, et al. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. *Allergy* 2017;72:2005-16.
- Kolkhir P, Giménez-Armau AM, Kulthanan K, Peter J, Metz M, Maurer M. Urticaria. *Nat Rev* 2022;8:1-22.
- Puxeddu I, Pistone F, Pisani F, Levi-Schaffer F. Mast cell signaling and its role in urticaria. *Ann Allergy Asthma Immunol* 2024;133:374-9.
- Agache I, Akdis C, Akdis M, Brockow K, Chivato T, del Giacco S, et al. EAACI Biologicals Guidelines – omalizumab for the treatment of chronic spontaneous urticaria in children and adults. *Allergy* 2022;77:17-38.
- Hollis K, Proctor C, McBride D, Balp MM, McLeod L, Hunter S, et al. Comparison of urticaria activity score over 7 days (UAS7) values obtained from once-daily and twice-daily versions: results from the ASSURE-CSU study. *Am J Clin Dermatol* 2018;19:267-74.
- National Institutes of Health. FDA approvals (urticaria): Adrenalin (epinephrine injection, USP) 1 mg/mL 1:1000 vial. Accessed June 12, 2024. <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=7663c49d-1b1d-755d-e053-2991aa0a4ee3&>
- Center for Drug Evaluation and Research. Summary review for adrenalin (epinephrine injection) 1 mg/ml. Accessed June 12, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/204200Orig1Orig2s000SumR.pdf
- Champion RH. Diseases of the skin: drug therapy of urticaria. *Br Med J* 1973;4:730-2.
- Pier J, Bingermann TA. Urticaria, angioedema, and anaphylaxis. *Pediatr Rev* 2020;41:283-92.
- Son JH, Chung BY, Kim HO, Park CW. A histamine-free diet is helpful for treatment of adult patients with chronic spontaneous urticaria. *Ann Dermatol* 2018;30:164-72.
- Baluk P, McDonald DM. The beta 2-adrenergic receptor agonist formoterol reduces microvascular leakage by inhibiting endothelial gap formation. *Am J Physiol* 1994;266(4 part 1):L461-8.
- Barnes PJ. Effect of β -agonists on inflammatory cells. *J Allergy Clin Immunol Pract* 1999;104:10-7.
- Kaliner M, Austen KF. Cyclic AMP, ATP, and reversed anaphylactic histamine release from rat mast cells. *J Immunol* 1974;112:664-74.
- Orange RP, Kaliner M, Laria PJ, Austen KF. Immunological release of histamine and slow reacting substance of anaphylaxis from human lung: Influence of cellular levels of cyclic AMP. *Fed Proc* 1971;30:1725-9.
- Brown JC, Simons E, Rudders SA. Epinephrine in the management of anaphylaxis. *J Allergy Clin Immunol Pract* 2020;8:1186-95.