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Etripamil Nasal Spray for Rapid Conversion of Supraventricular Tachycardia to Sinus Rhythm

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ABSTRACT

BACKGROUND There is no nonparenteral medication for the rapid termination of paroxysmal supraventricular tachycardia.

OBJECTIVES The purpose of this study was to assess the efficacy and safety of etripamil nasal spray, a short-acting calcium-channel blocker, for the rapid termination of paroxysmal supraventricular tachycardia (SVT).

METHODS This phase 2 study was performed during electrophysiological testing in patients with previously documented SVT who were induced into SVT prior to undergoing a catheter ablation. Patients in sustained SVT for 5 min received either placebo or 1 of 4 doses of active compound. The primary endpoint was the SVT conversion rate within 15 min of study drug administration. Secondary endpoints included time to conversion and adverse events.

RESULTS One hundred four patients were dosed. Conversion rates from SVT to sinus rhythm were between 65% and 95% in the etripamil nasal spray groups and 35% in the placebo group; the differences were statistically significant (Pearson chi-square test) in the 3 highest active compound dose groups versus placebo. In patients who converted, the median time to conversion with etripamil was <3 min. Adverse events were mostly related to the intranasal route of administration or local irritation. Reductions in blood pressure occurred predominantly in the highest etripamil dose.

CONCLUSIONS Etripamil nasal spray rapidly terminated induced SVT with a high conversion rate. The safety and efficacy results of this study provide guidance for etripamil dose selection for future studies involving self-administration of this new intranasal calcium-channel blocker in a real-world setting for the termination of SVT. (Efficacy and Safety of Intranasal MSP-2017 [Etripamil] for the Conversion of PSVT to Sinus Rhythm [NODE-1]; NCT02296190) (J Am Coll Cardiol 2018;72:489–97)

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ABBREVIATIONS AND ACRONYMS

AVRT = atrioventricular reciprocating tachycardia

CI = confidence interval

IV = intravenous

OR = odds ratio

PSVT = paroxysmal supraventricular tachycardia

SBP = systolic blood pressure

SVT = supraventricular tachycardia

Currently, there is no short-acting, nonparenteral drug available for the acute termination of supraventricular tachycardia (SVT) that can be self-administered. Such a drug would provide individuals the ability to rapidly terminate SVT episodes without the need to visit a health care facility.

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Etripamil (Milestone Pharmaceuticals, Montreal St.-Laurent, Quebec, Canada) is a short-acting L-type calcium-channel blocker with a rapid onset of action designed for intranasal administration. It has been formulated as a nasal spray for self-administration by patients who experience SVT recurrences. It has a high potency and a short first half-life of about 20 min. Like other non-dihydropyridine calcium-channel blockers, etripamil slows atrioventricular nodal conduction and prolongs atrioventricular nodal refractory periods by inhibiting calcium ion influx through the calcium slow channels in the atrioventricular node cells. A phase 1 trial in healthy volunteers demonstrated that intranasal administration of etripamil was well tolerated and caused a dose-dependent PR interval prolongation indicative of the desired pharmacological effect on atrioventricular nodal conduction. There was no observed prolongation of QRS or Fredericia-corrected QT interval.

NODE-1 (Efficacy and Safety of Intranasal MSP-2017 [Etripamil] for the Conversion of PSVT to Sinus Rhythm) was a phase 2 study designed to demonstrate the superiority of etripamil over placebo for the acute termination of SVT in the electrophysiology laboratory, evaluate the safety of etripamil, and identify dose(s) to be tested in future phase 3 studies to be conducted outside the hospital environment.

METHODS

STUDY DESIGN AND PATIENTS. NODE-1 (NCT02296190) was a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study designed to evaluate the effects of etripamil nasal spray in male and female patients 18 years of age and older with documented histories of SVT who were scheduled to undergo electrophysiological studies prior to planned catheter ablation. The exclusion criteria were a history of adverse reaction to intravenous (IV) verapamil, a significant or chronic condition of the nasal cavity that would interfere with intranasal drug administration, systolic blood pressure (SBP) <100 mm Hg or diastolic blood pressure <50 mm Hg at screening or at the treatment visit, history or evidence of congestive heart failure (except New York Heart Association functional class I) or pulmonary edema, a prolonged Bazett-corrected QT interval (>455 ms), ventricular pre-excitation, second- or third-degree atrioventricular block, pregnancy, breastfeeding, failure to agree to use an acceptable form of contraception, concomitant use of certain medications (e.g., digoxin, class I to IV antiarrhythmic drug), and documentation of an arrhythmia other than SVT.

This study was carried out in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and Good Clinical Practice guidelines. All sites obtained Institutional Review Board or ethics committee approval, and study-specific procedures were not conducted until after patient informed consent was obtained. A complete list of study sites and primary investigators is available in the Online Appendix.

RANDOMIZATION. During a pre-study visit patients were randomly assigned to 1 of the 5 following study groups in a 1:1:1:1:1 ratio using an interactive web response system: placebo or etripamil at 35, 70, 105, or 140 mg.

BASELINE ELECTROPHYSIOLOGICAL STUDY DATA COLLECTION. Before attempted induction of SVT, vital signs, consisting of blood pressure and heart rate, were recorded, and a continuous surface rhythm strip was obtained. Baseline vital signs were the averages of the measurements taken 10 and 20 min before SVT induction, and the time 0 vital signs were the averages of the measurements during SVT between 5 and 0 min before study drug administration. Sedation could be given during the study via single or multiple administrations using minimally necessary doses of benzodiazepines and/or narcotics at the investigator's discretion, but a continuous sedative or analgesic or inhaled anesthetic drug was not permitted until minute 30 after study drug administration.

SVT INDUCTION. Induction of SVT was attempted using standard pacing and programmed stimulation methods. If SVT could not be induced after a reasonable number of attempts, or could be induced but did not sustain for 5 min, IV isoproterenol was infused at a rate of 1 μg/min, and attempts to induce SVT were repeated. If SVT induction was unsuccessful with isoproterenol 1 μg/min, the infusion rate could be increased. If isoproterenol was used, a surface rhythm strip was collected once the heart rate had stabilized. If induction was successful with

isoproterenol, the infusion was continued at 1 μg/min for 5 min of sustained SVT and continuing for either 15 min after study drug administration or until termination of SVT, whichever occurred first.

STUDY DRUG ADMINISTRATION. After a minimum of 5 min in sustained SVT, electrophysiology laboratory personnel administered the study drug to the patient using 4 prefilled Aptar Pharma unit-dose spray devices via alternating nares over 30 s or less. Each device delivered 100 μl of placebo or 35 mg of etripamil. The appropriate combination of 4 devices containing active compound or placebo was used to deliver the assigned, randomized dose of etripamil (0, 35, 70, 105, or 140 mg). The devices were prefilled, packaged into drug kits, and administered in a specific order, with sprays of etripamil delivered before sprays containing placebo.

ASSESSMENTS AFTER STUDY DRUG ADMINISTRATION. Starting at time 0, vital signs were recorded every 2 min for 30 min, and the cardiac rhythm was continuously monitored. A successful conversion was defined as conversion of SVT to sinus rhythm lasting at least 30 s within 15 min after study drug administration. For patients who did not convert within 15 min after study drug administration, SVT was then terminated by standard intracardiac stimulation techniques. Surface rhythm strips were collected in all patients at the time of conversion and at 15 min after study drug administration. At any time beyond 30 min after study drug administration, the patient's scheduled ablation (outside the scope of this study) could be performed at the discretion of the treating physician.

FOLLOW-UP PROCEDURES. From 12 h to 5 days after the procedure, physical examination, assessment of vital signs, 12-lead electrocardiography, and clinical laboratory analysis were performed. Adverse events and concomitant medications were recorded.

STATISTICAL METHODS. Efficacy analyses were performed in randomized patients in whom SVT was induced and sustained for 5 min, had received study drug, and completed the assessment of conversion to sinus rhythm (i.e., evaluable population). Safety analyses were based on all randomized patients who were induced into SVT and received study drug.

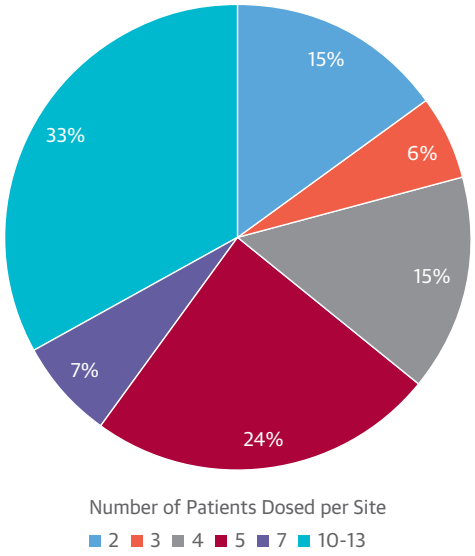
Sample size determination. It was expected that there would be a 50 percentage point difference in the SVT conversion rate between patients receiving placebo and any dose of etripamil within 15 min after study drug administration (i.e., 30% for placebo, 80% for etripamil). Accounting for a 2-sided test with a type I error rate of $\alpha = 0.05$, 20 patients per group provided 84% power when using the Fisher exact test. Therefore, a sample size of at least 100 evaluable patients (i.e., at least 20 evaluable patients per group) was considered appropriate to meet study objectives.

Statistical analyses. The primary efficacy endpoint was the rate of successful SVT conversion to sinus rhythm lasting at least 30 s within 15 min of study drug administration. The primary efficacy analysis was performed using the Fisher exact test to compare the conversion rate between each etripamil group and the placebo group. To control the type I error rate of $\alpha = 0.05$, a hierarchical procedure was used for hypothesis testing. The hierarchy first compared the conversion rate in the highest etripamil dose (140 mg) versus placebo; if that comparison resulted in a p value <0.05, the next highest etripamil dose (105 mg) was compared with placebo. These comparisons continued in a stepwise fashion until either all doses were tested or a comparison yielded a p value of ≥ 0.05, in which case all doses prior to that comparison were considered to have statistically significant conversion rates versus placebo. A 2-sided test with a significance level of 0.05 was used for each comparison. The odds ratio (OR), 95% confidence interval (CI), and p value for the OR were calculated and tabulated for each pairwise treatment comparison.

Conversion rates were analyzed using a Cochran-Mantel-Haenszel test and stratified by isoproterenol to test for an association between treatment and conversion rate. Secondary and exploratory efficacy analyses were performed as follows. 1) The Cochran-Armitage test for trend was used to assess the presence of an association between conversion rate and the etripamil dose groups. 2) The dose-response relationship (percentage conversion at time 15) was assessed using a generalized linear model with logit link and binomial distribution. 3) Time to conversion was summarized for patients whose SVT was successfully converted to sinus rhythm after study drug administration. The distribution of conversion times from initiation of treatment to SVT termination and conversion to sinus rhythm during a 15-min period of observation was estimated using the Kaplan-Meier method. Patients who did not convert within 15 min after study drug administration were censored at that time point. In a post hoc analysis, the hazard ratio and 95% CI were based on a Cox proportional hazards regression model with treatment as a factor. 4) The interaction test between etripamil and isoproterenol was carried out in an analysis-of-covariance model.

Continuous safety data are summarized with descriptive statistics. Discrete safety data are summarized with frequency counts.

FIGURE 1 Percentage of the Study Population Dosed by the Number of Patients Dosed per Site



3 sites dosed 10, 11, and 13 patients (i.e., 33% of the total number of dosed patients); 5 sites dosed 5 patients (i.e., 24% of the total number of dosed patients); 21 sites dosed 1 to 4 patients (i.e., 43% of the total number of dosed patients).

RESULTS

BASELINE PATIENT CHARACTERISTICS. A total of 199 patients were randomized into the double-blind study; 95 patients withdrew prior to dosing: 70 patients because of inability to induce (n = 42) or sustain (n = 28) SVT, 5 patients on the basis of physician discretion, 1 patient lost to follow-up, 1 because of withdrawal of consent, and 18 patients for other reasons. A total of 104 patients had SVT induced and sustained for ≥5 min and were dosed with study drug. The median age was 55.0 years (mean 52.2; range: 19 to 85 years), and the median body mass index was 28.57 kg/m^2 (mean 29.35 kg/m^2; range: 19.0 to 64.1 kg/m^2). Overall, there were more female than male patients (n = 59 [56.7%] vs. n = 45 [43.3%], respectively). The predominant races were white (80.8%) and black or African American (12.5%). There were no imbalances in baseline characteristics across the 5 treatment groups. Isoproterenol was given to 46.2% of patients. The mean heart rate in SVT at time 0 was 177 beats/min in the placebo group and 168, 173, 180, and 155 beats/min in the etripamil 35-, 70-, 105-, and 140-mg groups, respectively. The mechanism of induced SVT was atrioventricular nodal re-entrant tachycardia in 87% of patients. A total of 29 sites dosed patients. Twenty-six sites dosed between 1 and 5 patients, and 3 sites dosed between 10 and 13 patients (i.e., 33% of the study population). The percentage of patients dosed by number of patients per site is shown in Figure 1.

TABLE 1 Summary of Conversion of Induced, Sustained Supraventricular Tachycardia to Sinus Rhythm Within 15 min After Study Drug Administration

	Placebo (n = 20)	Etripamil 35 mg (n = 20)	Etripamil 70 mg (n = 23)	Etripamil 105 mg (n = 20)	Etripamil 140 mg (n = 21)
Patients converted to sinus rhythm	7 (35)	13 (65)	20 (87)	15 (75)	20 (95)
p value (vs. placebo), Fisher exact test		0.1128	0.0006	0.0248	<0.0001

Values are n (%).

EFFICACY. Conversion rates from SVT to sinus rhythm. Of the 104 patients in the evaluable population, 20 received etripamil 35 mg, 23 received 70 mg, 20 received 105 mg, 21 received 140 mg, and 20 received placebo. The percentages of patients in whom SVT converted to sinus rhythm within 15 min after study drug administration and in whom sinus rhythm was maintained for at least 30 s (primary efficacy endpoint) were 35%, 65%, 87%, 75%, and 95% in the placebo and etripamil 35-, 70-, 105-, and 140-mg groups, respectively (Table 1). Applying the prespecified hierarchy for determining significance, the 3 highest etripamil doses of 140, 105, and 70 mg showed statistically significant higher conversion rates compared with placebo, with respective conversion rate differences from placebo of 60% (OR: 37.14; 95% CI: 3.84 to 1,654.17; p < 0.0001), 40% (OR: 5.57; 95% CI: 1.19 to 27.63; p = 0.0248), and 52% (OR: 12.38; 95% CI: 2.28 to 82.26; p = 0.0006). There was a statistically significant trend between treatment with etripamil and conversion to sinus rhythm (p < 0.0001, Cochran-Armitage test). A maximal-efficacy dose-response model best fit the dose-response relationship; the conversion rate increased with the dose with a steep slope until 70 mg and reached a plateau at higher doses (Figure 2).

Overall, no differences in conversion rates were observed on the basis of the administration or lack of administration of isoproterenol.

Time to conversion from SVT to sinus rhythm. For the 3 etripamil doses with statistically significant conversion rates compared with placebo (70, 105, and 140 mg), the time at which 50% of patients converted

was <3 min, with the shortest time in the etripamil 140-mg group (1.8 min). Because only 35% patients converted to sinus rhythm within 15 min in the placebo group, the time at which 50% of patients converted cannot be determined.

Distribution of time to conversion for each patient is reported as a Kaplan-Meier plot (Figure 3). Patients who did not convert within 15 min after study drug administration were censored at 15 min. On the basis of a Cox proportional hazards regression model with treatment as a factor, the 3 highest etripamil doses of 140, 105, and 70 mg showed statistically significant shorter time to conversion compared with placebo (Table 2).

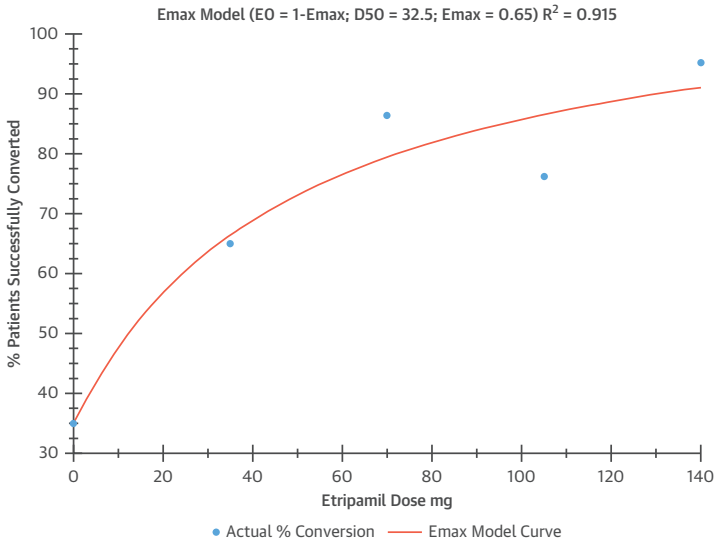
SAFETY. At least 1 adverse event, per patient, considered related to the study drug according to the investigators' assessment, was reported in 17 patients (85.0%) in the etripamil 35-mg group, 18 (78.3%) in the 70-mg group, 15 (75.0%) in the 105-mg group, 20 (95.2%) in the 140-mg group, and 4 (20.0%) in the placebo group. The incidence of adverse events was not dose dependent.

Most adverse events were mild (44.2%) or moderate (24.0%) across all treatment groups. A total of 3 severe adverse events were considered possibly related to etripamil. One patient who received 35 mg experienced facial flushing, shortness of breath, and chest discomfort; 1 patient who received 105 mg had nausea and vomiting; and 1 patient who received 105 mg had a serious adverse event of cough. There were no adverse events that led to study discontinuation or death.

Adverse events that occurred with an incidence of >10% in any etripamil group and ≥10% in the placebo group were nasal discomfort, nasal congestion, oropharyngeal pain, rhinorrhea, cough, dysgeusia, increased lacrimation, vomiting, and nausea. One patient had an episode of second-degree atrioventricular block with hypotension beginning 5 min after conversion to sinus rhythm immediately following administration of etripamil 140 mg, which resolved after 43 min, and ablation was subsequently performed.

Vital signs were recorded before induction into SVT and every 2 min for 30 min after study drug was given. The mean SBP decreased from the baseline measurements (20 and 10 min before SVT induction) to measurements done while in SVT before study drug administration (time 0). Compared with baseline prior to SVT induction, SBP measurements recorded from 2 to 16 min after study drug administration demonstrated no statistically significant decrease in mean SBP in the placebo, 35-mg, and 70-mg groups, and a maximum statistically significant decrease of 17 mm Hg 6 min post-dose when 65% of the patients were in sinus rhythm in the 105-mg group, and 20 mm Hg 6 min post-dose when 80% of the patients were in sinus rhythm in the 140-mg group. There was no decrease in mean SBP compared with baseline from 16 to 30 min after study drug administration when all the patients were in sinus rhythm (Figure 4).

FIGURE 2 Etripamil Dose Response Maximal Efficacy Model



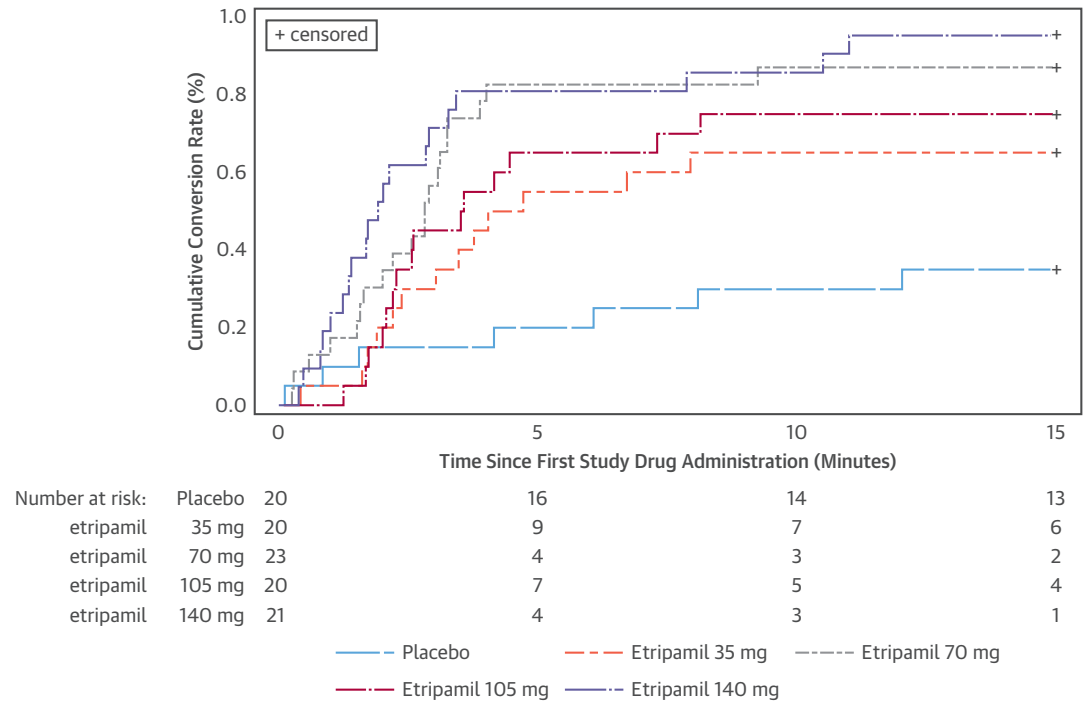
D50 = dose (milligrams) related to 50% of the maximal effect; E0 = placebo effect; Emax = maximal efficacy.

In the placebo group and the combined active substance groups, the minimum mean heart rates (84.7 and 82.4 beats/min, respectively) were similar. The minimum heart rate in any individual patient occurring within 30 min after study drug administration was 58 beats/min in the placebo group and 70, 55, 71, and 47 beats/min in the etripamil 35-, 70-, 105-, and 140-mg groups, respectively. There was no statistically significant change between baseline and 15 min post-dose in mean Bazett-corrected QT intervals.

DISCUSSION

In this study, the 3 highest doses of etripamil tested demonstrated the ability to terminate SVT with very high and statistically significant conversion rates compared with placebo (Central Illustration). The median time to conversion for each of the etripamil doses was <3 min. From an efficacy standpoint, this makes this intranasal calcium-channel blocker an

FIGURE 3 Kaplan-Meier Plot of Conversion 15 min After Study Drug Administration



Patients who did not convert within 15 min after study drug administration were censored at 15 min.

excellent drug candidate to fill the existing gap in therapy for the rapid termination of SVT outside of the health care setting. Judicious selection of etripamil doses in future studies may be able to mitigate decreases in SBP, which occurred most often and for the longest duration in the etripamil 140-mg group.

During the course of the study it was recognized that the discomfort and cough possibly related to the presence of the drug in the throat could be dramatically reduced by elevating the head of the bed to 30°, keeping the chin close to the chest, and trying to avoid inhaling or swallowing the drug. It is conceivable that providing patients with this information could reduce or eliminate these adverse events in the future.

TABLE 2 Survival Analysis of Patients Converted to Sinus Rhythm at 15 min After Study Drug Administration

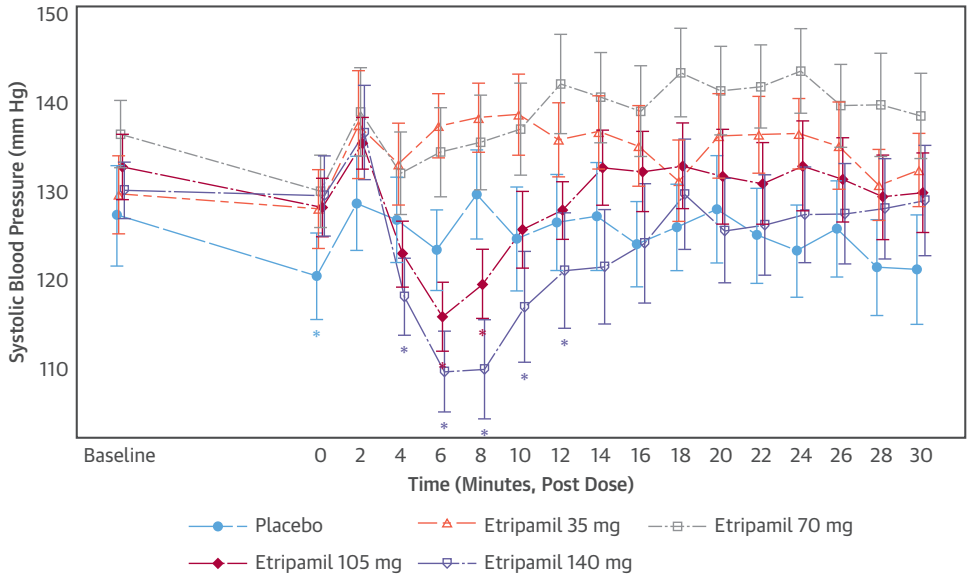
	Placebo (n = 20)	Etripamil 35 mg (n = 20)	Etripamil 70 mg (n = 23)	Etripamil 105 mg (n = 20)	Etripamil 140 mg (n = 21)
Patients converted	7 (35.0)	13 (65.0)	20 (87.0)	15 (75.0)	20 (95.2)
Patients censored*	13 (65.0)	7 (35.0)	3 (13.0)	5 (25.0)	1 (4.8)
Kaplan-Meier estimate, min					
Q1	7.08	2.28	1.57	2.13	1.23
Median	NC	4.38	2.82	3.54	1.92
95% CI	6.07-NC	2.20-NC	1.63-3.25	2.07-8.13	1.23-2.90
Q3	NC	NC	3.88	NC	3.27
Treatment comparison (vs. placebo)†					
Hazard ratio		2.43	4.99	3.13	6.67
95% CI for hazard ratio		0.97-6.11	2.09-11.93	1.27-7.71	2.79-15.94
p value		0.0587	0.0003	0.0131	<0.0001

Values are n (%) unless otherwise indicated. *Patients who did not convert within 15 min after study drug administration are censored at 15 min after study drug administration. †The hazard ratio and 95% CI are based on a Cox proportional hazards regression model with treatment as a factor.

CI = confidence interval; Median = time to conversion of 50% of the patients; NC = not calculated; Q1 = 25th percentile; Q3 = 75th percentile.

ETRIPAMIL PHARMACOLOGY AND CHARACTERISTICS. Etripamil is a short-acting, phenylalkylamine class L-type calcium-channel blocker. It follows a 2-compartment pharmacokinetic model with a time to maximum plasma concentration of approximately 8 min and a mean first half-life of about 20 min across all doses tested when administered intranasally. The drug is metabolized by ubiquitous serum esterases, and the major metabolite is an inactive carboxylic acid. Dose-dependent side effects (nasal congestion, oropharyngeal pain) are most likely related to the intranasal route of administration. Neither animal nor human studies demonstrated prolongation of the QRS duration or corrected QT interval. The shelf life of etripamil is >1 year.

FIGURE 4 Mean ± SE Systolic Blood Pressure Over Time



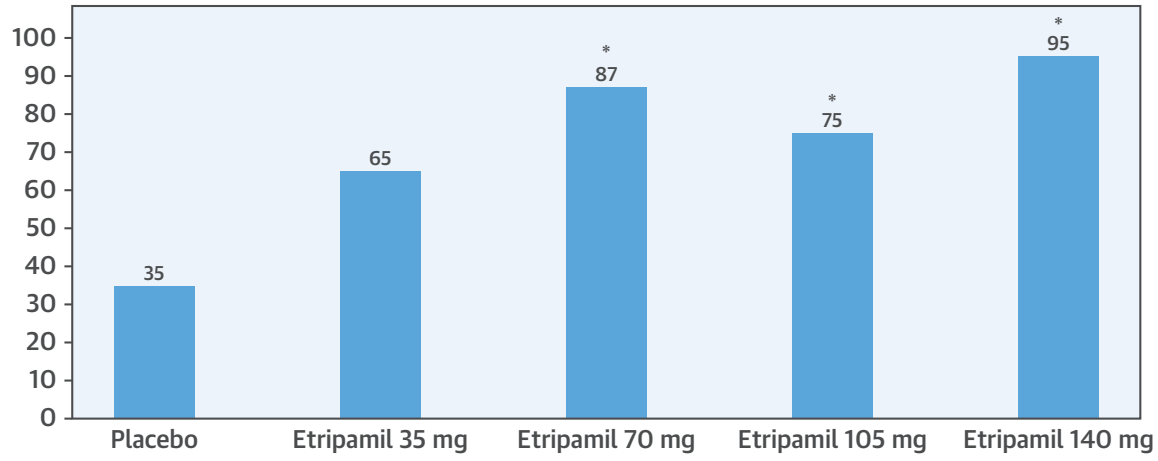
Baseline is defined as the average of the 20-min and 10-min pre-dose measurements. Time 0 is defined as the average of the measurements during supraventricular tachycardia between 5 and 0 min before study drug administration. *$p < 0.05$ versus baseline.

CURRENT TREATMENTS FOR SVT. All medications currently approved for the acute termination of SVT must be administered in the presence of a trained health care professional and require the establishment of IV access along with real-time rhythm monitoring. IV beta-blockers and calcium-channel blockers are effective for acute treatment in patients with hemodynamically stable SVT. Oral beta-blockers and calcium-channel blockers alone or in combination may be self-administered ("pill-in-the-pocket") for acute treatment of well-tolerated SVT, with mean times to conversion of approximately 30 min or longer, but the overall efficacy and safety of the self-administration of these medications remains unclear because of the lack of scientific evidence and potential risk for hypotension and/or syncope (1,2). Antiarrhythmic drugs such as flecainide, which are not approved for this indication, have been used as a "pill-in-pocket" strategy (3), but with small studies showing variable conversion rates of about 50%, often approximating the placebo conversion rate. Mean conversion times were 1 h or longer, although by 2 h up to 80% of patients may spontaneously convert. Additionally, multiple factors limit the ability to prescribe these and other antiarrhythmic drugs: known or suspected coronary artery disease, left ventricular dysfunction, borderline or prolonged QT interval, and unfavorable or unknown metabolizer status.

FUTURE EVALUATION. Etripamil will need to be evaluated in future studies that are performed outside of the electrophysiology laboratory in nonsupine, nonsedated patients to confirm its efficacy in a real-world environment and to demonstrate an appropriate safety profile for self-administration without medical supervision. The observed balance between efficacy and safety in the 70-mg group makes this dose a good candidate for future studies.

STUDY LIMITATIONS. This study was carried out during an electrophysiology study prior to a planned ablation in a carefully monitored and controlled hospital environment, which introduced elements that differ from the real-world setting in which etripamil nasal spray might ultimately be used. The use of conscious sedation in the electrophysiology laboratory reduces circulating catecholamines (4,5), which could alter the time to spontaneous conversion along with the etripamil-related conversion rate due to effects on atrioventricular node conduction properties. Sedation may also predispose patients to hypotension, which may not be seen in a non-procedural setting. The possibility of catheter

CENTRAL ILLUSTRATION **Conversion Rate (%) of Induced Paroxysmal Supraventricular Tachycardia Within 15 min of Study Drug Administration**



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*$p < 0.05$ versus placebo.

movement causing SVT termination exists, which could affect efficacy results. It is conceivable that at least some of the adverse events associated with drug administration (i.e., supine position) could be eliminated or minimized if patients are allowed to self-administer the drug in a more optimal position outside of the electrophysiology laboratory environment. Because all patients were converted, per protocol, by overdrive pacing after 15 min in SVT, the time to spontaneous conversion for the 13 remaining patients who received placebo is unknown. Analysis of the time to conversion, for patients who were inducible into sustained SVT, was limited to 15 min in this proof-of-concept study, which could be considered too short to evaluate the spontaneous time to conversion in the placebo group. Almost 90% of patients had atrioventricular nodal re-entrant tachycardia, and thus the efficacy and safety in AVRT was less well established in this study.

CONCLUSIONS

Etripamil, an intranasally administered, L-type calcium-channel blocker, demonstrated high efficacy for rapid SVT termination and conversion to sinus rhythm and was generally well tolerated. The results of this study are promising and support the ongoing development of this new intranasal calcium-channel blocker for the acute termination of SVT, with a goal of providing this therapy for patient self-administration in the "real world" outside a health care setting. This has the potential to change the treatment paradigm for the acute management of SVT.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Etripamil, a short-acting calcium-channel blocker, when administered as a nasal spray, is more effective than placebo in terminating induced SVT, though a high dose was associated with lowering of blood pressure.

TRANSLATIONAL OUTLOOK: Larger clinical studies are needed to confirm the safety and efficacy of etripamil nasal spray for termination of spontaneously occurring episodes of SVT.

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APPENDIX For a complete list of study sites and primary investigators, please see the online version of this paper.