Self-administered intranasal etripamil using a symptom-prompted, repeat-dose regimen for atrioventricular-nodal-dependent supraventricular tachycardia (RAPID): a multicentre, randomised trial

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Summary

Background Etripamil is a fast-acting, intranasally administered calcium-channel blocker in development for on-demand therapy outside a health-care setting for paroxysmal supraventricular tachycardia. We aimed to evaluate the efficacy and safety of etripamil 70 mg nasal spray using a symptom-prompted, repeat-dose regimen for acute conversion of atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia to sinus rhythm within 30 min.

Methods RAPID was a multicentre, randomised, placebo-controlled, event-driven trial, conducted at 160 sites in North America and Europe as part 2 of the NODE-301 study. Eligible patients were aged at least 18 years and had a history of paroxysmal supraventricular tachycardia with sustained, symptomatic episodes (≥20 min) as documented by electrocardiogram. Patients were administered two test doses of intranasal etripamil (each 70 mg, 10 min apart) during sinus rhythm; those who tolerated the test doses were randomly assigned (1:1) using an interactive response technology system to receive either etripamil or placebo. Prompted by symptoms of paroxysmal supraventricular tachycardia, patients self-administered a first dose of intranasal 70 mg etripamil or placebo and, if symptoms persisted beyond 10 min, a repeat dose. Continuously recorded electrocardiographic data were adjudicated, by individuals masked to patient assignment, for the primary endpoint of time to conversion of paroxysmal supraventricular tachycardia to sinus rhythm for at least 30 s within 30 min after the first dose, which was measured in all patients who administered blinded study drug for a confirmed atrioventricular-nodal-dependent event. Safety outcomes were assessed in all patients who self-administered blinded study drug for an episode of perceived paroxysmal supraventricular tachycardia. This trial is registered at ClinicalTrials.gov, NCT03464019, and is complete.

Findings Between Oct 13, 2020, and July 20, 2022, among 692 patients randomly assigned, 184 (99 from the etripamil group and 85 from the placebo group) self-administered study drug for atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia, with diagnosis and timing confirmed. Kaplan-Meier estimates of conversion rates by 30 min were 64% (63/99) with etripamil and 31% (26/85) with placebo (hazard ratio 2·62; 95% CI 1·66–4·15; p<0·0001). Median time to conversion was 17·2 min (95% CI 13·4–26·5) with the etripamil regimen versus 53·5 min (38·7–87·3) with placebo. Prespecified sensitivity analyses of the primary assessment were conducted to test robustness, yielding supporting results. Treatment-emergent adverse events occurred in 68 (50%) of 99 patients treated with etripamil and 12 (11%) of 85 patients in the placebo group, most of which were located at the administration site and were mild or moderate, and all of which were transient and resolved without intervention. Adverse events occurring in at least 5% of patients treated with etripamil were nasal discomfort (23%), nasal congestion (13%), and rhinorrhea (9%). No serious etripamil-related adverse events or deaths were reported.

Interpretation Using a symptom-prompted, self-administered, initial and optional-repeat-dosing regimen, intranasal etripamil was well tolerated, safe, and superior to placebo for the rapid conversion of atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia to sinus rhythm. This approach could empower patients to treat paroxysmal supraventricular tachycardia themselves outside of a health-care setting, and has the potential to reduce the need for additional medical interventions, such as intravenous medications given in an acute-care setting.

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Introduction

Paroxysmal supraventricular tachycardias are a substantial burden on both patients and health-care systems. In the USA, approximately 300 000 patients are newly diagnosed with paroxysmal supraventricular tachycardia each year, and 25% of patients who present to an

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See **Online** for appendix

Research in context

Evidence before this study

We searched the literature to identify evidence of acute, patient-administered treatments for paroxysmal supraventricular tachycardia, focusing on approaches for a non-medical setting and those that are not typically feasible outside of an acute-care setting—particularly the use of a so-called pill-in-pocket approach. We searched PubMed using the terms ("pill in pocket" OR "pill-in-pocket" OR "pill in the pocket" OR "pill-in-the-pocket" OR "rescue" OR "episodic treatment" OR "self-administer"' OR "short-acting" OR "fast-acting" OR "antiarrhythmic drug" OR "AAD" OR "calcium channel blocker" OR verapamil OR diltiazem OR "beta blocker" OR etripamil) AND ("PSVT" OR "paroxysmal supraventricular tachycardia" OR "SVT" OR supraventricular tachycardia OR "atrioventricular nodal reentrant tachycardia" OR "AVNRT" OR "atrioventricular reciprocating tachycardia" OR "AVRT" OR "Wolff Parkinson White" OR "reentrant tachycardia" OR "fractionated electrograms" OR "narrow complex tachycardia") for articles in any language published between Jan 1, 2000, and Dec 31, 2022. The search yielded 152 results, most of which were case series and case reports, and many of the treatment-related articles were not relevant because they focused on invasive, catheter-based, in-hospital, or chronic treatments. Two articles reported on clinical trials and were relevant to our search objective. One article, from 1985, reported a randomised, placebo-controlled, crossover study of a calcium-channel blocker (diltiazem) plus propranolol for termination of paroxysmal supraventricular tachycardia in 15 patients. A second article, from 2001, reported a randomised, placebo-controlled crossover study comparing a single dose of oral flecainide, diltiazem plus propranolol, and placebo for termination of paroxysmal supraventricular tachycardia in 33 patients. Although diltiazem plus propranolol was moderately effective at converting paroxysmal supraventricular tachycardia to sinus rhythm, the median time to conversion was 30–240 min and there was an increase in adverse events, including hypotension, syncope, second-degree atrioventricular block, and junctional rhythm with bradycardia.

NODE-301 was an event-driven study that evaluated single-dose etripamil, self-administered outside a health-care setting, for the treatment of symptomatic paroxysmal supraventricular tachycardia. Etripamil was safe and well tolerated, but superior efficacy of single-dose treatment with etripamil compared with placebo for the termination of paroxysmal supraventricular tachycardia at 5 h after drug administration was not shown. However, in a post hoc analysis, efficacy was observed at earlier time points (54% conversion with etripamil *vs* 35% with placebo at 30 min; hazard ratio 1·87 [95% CI 1·09–3·22; p=0·016]). This finding, together with safety and efficacy data from pharmacological and phase 2 studies of etripamil, provided the basis for the RAPID trial, which we report here as part 2 of the NODE-301 study. This trial evaluates a symptom-prompted, optional-repeat-dose approach—rather than increasing the dose in a one-time regimen—to augment both drug exposure and the efficacy of paroxysmal supraventricular tachycardia conversion.

Added value of this study

In the RAPID study, etripamil nasal spray—self-administered on-demand in a non-health-care setting, with a repeat-dosing regimen prompted by persistent symptoms—was superior to placebo for rapid conversion of atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia and was well tolerated in a representative population of patients with symptomatic, sustained paroxysmal supraventricular tachycardia. Efficacy was greater in the RAPID study than in the NODE-301 part 1 study by multiple measures, both by 30 min after drug exposure and at later times (up to 300 min). Favourable safety data were consistent with previous studies and are supportive of a potential treatment regimen involving the self-administration of etripamil outside of a health-care setting.

Implications of all the available evidence

Adjudicated by an expert committee, this event-driven study showed significant efficacy of self-administered etripamil in resolving symptomatic paroxysmal supraventricular tachycardia. The staged, repeat-dosing regimen has the potential to empower patients to treat symptomatic events themselves while avoiding additional medical interventions, such as intravenous medications. Moreover, this symptom-prompted treatment regimen was associated with significantly improved defined symptoms of paroxysmal supraventricular tachycardia. The potential for etripamil to decrease the health-care burden for this common tachyarrhythmia warrants further study.

emergency department with the condition are admitted to hospital.[1–4] When symptoms occur they can be severe, and include palpitations, chest discomfort, dyspnoea, light-headedness, syncope, and distress.[1–3] As the atrioventricular node is an obligatory component of the majority of paroxysmal supraventricular tachycardia circuits,[5] a drug that can transiently prolong atrioventricular-nodal refractoriness could represent a targeted strategy to terminate atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia and restore sinus rhythm. Although intravenous calcium-channel blockers or adenosine are effective,[5] they must be administered in a supervised setting. Oral agents (eg, calcium-channel blockers and β blockers) are used in some circumstances to treat paroxysmal supraventricular tachycardia; however, an acutely administered pill-in-pocket approach has low efficacy and acts slowly, and daily administration can be limited by inefficacy or side effects.[5–7] Catheter-based ablation is an important option for the treatment of types of paroxysmal supraventricular tachycardia, such as atrioventricular-nodal re-entrant tachycardia; however, fewer than half of the potential candidates undergo this procedure. In addition, the procedure might not be appropriate as first-line therapy for many patients.[8,9]

Etripamil is a fast-acting, intranasally administered, L-type calcium-channel blocker in development for medically unsupervised self-administration for acute conversion of atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia.[10–12] Etripamil is quickly absorbed by the nasal mucosa, with maximum concentration reached within 7 min after a 70 mg dose, and is rapidly metabolised. In a phase 2 study, etripamil doses of at least 70 mg were superior to placebo for the conversion of atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia in an electrophysiology laboratory.[11] A 70 mg dose was chosen for subsequent investigation owing to its favourable safety profile and because conversion rates were not considerably greater at higher doses.

NODE-301 was an event-driven study that evaluated single-dose etripamil, self-administered outside a healthcare setting, in patients for symptomatic paroxysmal supraventricular tachycardia.[11,12] Etripamil was safe and well tolerated, but superior efficacy of a single dose of 70 mg etripamil compared with placebo for termination of paroxysmal supraventricular tachycardia at 5 h after drug administration was not shown. In a post hoc analysis, evidence for the efficacy of etripamil at earlier time points was observed (54% conversion of paroxysmal supraventricular tachycardia with etripamil *vs* 35% with placebo at 30 min).[11] For the current study, an optional-repeat-dose approach—rather than increasing the dose in a one-time regimen—was chosen to augment both drug exposure and efficacy of conversion on the basis of findings from pharmacokinetic and phase 2 studies and the safety and efficacy results from the NODE-301 trial.[11,12] Moreover, clinical pharmacology data support that a repeated intranasal dose of 70 mg etripamil, administered 10 min after a first dose, yields the intended pharmacokinetic pattern with two separate peaks in drug concentration (unpublished). Therefore, on the basis of these observations and with an objective to improve the efficacy of etripamil while maintaining its favourable safety and tolerability profiles, the RAPID trial—as part 2 of the NODE-301 study—sought to evaluate a symptom-prompted, optional-repeat-dose etripamil regimen for on-demand, acute conversion of atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia to sinus rhythm within 30 min of the first dose.

Methods

Study design and participants

RAPID, as part 2 of the NODE-301 study, was a multicentre, randomised, double-blind, placebo-controlled, event-driven study, conducted at 160 sites in North America and Europe (appendix pp 7, 9–16). The study design has previously been summarised.[10]

The study population consisted of 658 newly enrolled patients and 34 patients whose masked data were carried forward from part 1 of the NODE-301 study and analysed in RAPID datasets.[10] As specified in the RAPID protocol and statistical analysis plan, these 34 were patients who did not have a paroxysmal supraventricular tachycardia episode by the cut-off date (Jan 15, 2020) of NODE-301 part 1. Eligible patients were at least 18 years old and had history of paroxysmal supraventricular tachycardia with sustained, symptomatic episodes (≥20 min) as documented by electrocardiogram (ECG). Sex was self-reported as male or female. Key exclusion criteria were any history of manifest pre-excitation on ECG, second-degree or third-degree atrioventricular block, ventricular arrhythmia, and atrial arrhythmia not involving the atrioventricular node. All inclusion and exclusion criteria are provided in the appendix (pp 3–4).

All patients provided written informed consent with signatures. The authors take responsibility for data accuracy and study-protocol compliance. Roles and oversight by committees are further described in the appendix (p 2). The study complied with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice Guidelines, and local regulatory requirements. Institutional Review Board approval was obtained from participating sites (appendix p 9). The study protocol is available in the appendix.

Randomisation and masking

Before randomisation, patients were administered two test doses of intranasal etripamil (each 70 mg, 10 min apart) during sinus rhythm.[10] Criteria evaluated during test dosing are provided in the appendix (p 5). Patients who tolerated the test doses were randomly assigned (1:1) using an interactive response technology (IRT) system to receive either etripamil or placebo; details of those who were not assigned are provided in the appendix (p 6). 48 patients who were previously enrolled in NODE-301 part 1 and who had not used study medication in that study were rescreened, tolerated test dosing, and were randomly assigned (1:1) to receive either etripamil or placebo in the RAPID trial. At the screening visit, a patient identification number was established for each patient using the randomisation system and was used in all documentation for that individual from the first to the last contact.

The sponsor, investigative sites, adjudication committee, and clinical research organisation involved were masked to treatment assignment, with the exceptions of the sponsor clinical study supplies coordinator and personnel directly involved in study-drug packaging, the data and safety monitoring committee (if unblinded safety data were requested), and IRT personnel, all of whom were appropriately isolated.

Procedures

Patients were trained on study procedures for episodes of paroxysmal supraventricular tachycardia, including use of the ambulatory ECG cardiac monitoring system, performing a vagal manoeuvre, and self-administering

study drug in the event of symptoms. During routine daily activities, when patients recognised the onset of paroxysmal supraventricular tachycardia symptoms, they attached the ECG monitor, conducted the previously trained vagal manoeuvre and, if symptoms did not resolve, administered the masked study treatment. If symptoms persisted 10 min later, the patient administered a repeat dose of the same treatment through a second device. If symptoms did not resolve within 30 min of administration of the first dose, patients sought appropriate care. The ECG recording was continued for 5 h regardless of resolution of symptoms. A telephone coach was available for questions. Following the conclusion of the episode of paroxysmal supraventricular tachycardia, patients completed patient-reported-outcome questionnaires and were evaluated at study visits.

Routine follow-up visits were scheduled monthly, conducted at the site or by telephone, to assess adverse events and changes in concomitant medications, confirm ongoing eligibility, and retrain on study procedures. An additional follow-up visit was also required for patients who had symptoms of paroxysmal supraventricular tachycardia, who applied and activated the ECG cardiac monitoring system, and whose episodes terminated with a vagal manoeuvre. An open-label treatment period followed the randomised treatment follow-up visit.

A final visit occurred at the investigative site within 14 days if a patient self-administered study drug during the open-label treatment period or, in the case of not tolerating the test dose, self-administered blinded study drug without continued participation; started taking prohibited medication; or withdrew consent; or otherwise when the sponsor terminated the study. At this final visit, adverse events and concomitant medications were recorded, samples for laboratory analysis were obtained, a physical examination (including vital signs) was conducted, and a 12-lead ECG was recorded; completed patient questionnaires were collected and reviewed. A follow-up telephone call took place approximately 30 days later to assess for potential adverse events.

An independent committee of 4–6 cardiac electrophysiologists, masked to study assignments, examined all data from the 5 h ECG cardiac monitoring systems and adjudicated whether ECG tracings were consistent with an atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia; whether an event was terminated with vagal manoeuvre; whether the first dose of the drug was taken during an event (to exclude those that had already spontaneously terminated); whether paroxysmal supraventricular tachycardia, if converted to sinus rhythm, remained converted for at least 30 s; the time of any additional medical intervention; the time (in min, s) to conversion of atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia to sinus rhythm; and safety surveillance for bradyarrhythmias and tachyarrhythmias.

Outcomes

The primary efficacy endpoint was time to adjudicated conversion of confirmed atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia to sinus rhythm for at least 30 s within 30 min of drug administration. This outcome was centrally and independently assessed. Secondary efficacy endpoints were time to conversion at time points before and after 30 min; the percentage of patients requiring additional medical intervention in emergency departments to terminate an episode of paroxysmal supraventricular tachycardia; rating from the Treatment Satisfaction Questionnaire for Medication (TSQM-9);[15] changes in predefined symptoms of paroxysmal supraventricular tachycardia from a questionnaire based on the Patient Symptom Global Impressions of Improvement[13,14] (PGI-I); and sensitivity analyses to assess the robustness of the primary endpoint results. Key efficacy endpoints were assessed in defined subgroups of interest. Safety analyses were focused within 24 h of drug administration and were the assessment of adverse events, vital signs, laboratory samples, and arrhythmias and conduction disorders detected by ECG.

Statistical analysis

Sample size calculations used data from part 1 of the NODE-301 study (for an effect size, the Kaplan-Meier probabilities of conversion to sinus rhythm by 30 min were 54% for etripamil treatment and 35% for placebo[12]) and indicated that 180 patients, each with a paroxysmal supraventricular tachycardia event confirmed by adjudication, provided 90% power to detect a 19% relative-reduction treatment difference for the primary endpoint at a two-sided significance level of 0·05. We anticipated that at least 500 patients would be randomly assigned to accrue sufficient confirmed paroxysmal supraventricular tachycardia events.

The primary efficacy endpoint was analysed by Kaplan-Meier estimates of time to conversion by 30 min in etripamil versus placebo groups. Hazard ratios (HRs) were calculated with the Cox proportional method and p values with the Wilcoxon test. Conversions due to additional medical interventions were censored 1 min outside the observation window, events of ECG signal loss were censored at the time of occurrence, and methods were repeated for subgroups. Secondary analyses were hierarchically prespecified. The proportions of patients requiring additional medical interventions for a paroxysmal supraventricular tachycardia episode or emergency department visits (with or without arrhythmia-related intervention) were analysed by χ^2 tests. TSQM-9[15] measurements were analysed by ANOVA. Paroxysmal supraventricular tachycardia symptoms were assessed using a PGI-I–based questionnaire,[13,14] with severity scoring of each preintervention symptom on a scale of 0 (none) to 5 (severe) analysed by ANOVA. Changes relative to a patient's preintervention state were assessed

on a scale of 1 (very much worse) to 7 (very much improved). Responders were defined as patients citing a defined symptom as being present before the administration of study drug and scoring a 6 or 7 for improvement in that symptom on the PGI-I-based scale; comparisons were made by χ^2 testing. Safety data were summarised by group.

The efficacy population comprised all randomly assigned patients who self-administered study drug at the time of a confirmed episode of atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia (n=184); only one episode could be included for each patient. The efficacy population excluded patients who took study drug after paroxysmal supraventricular tachycardia conversion, patients who had an episode that was adjudicated as non-atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia (eg, atrial flutter or sinus tachycardia), or patients for whom substantial loss of ECG signal occurred (appendix p 17). Patients in whom conversion of a paroxysmal supraventricular tachycardia event to sinus rhythm occurred after a vagal manoeuvre and before receipt of study drug were also excluded, although this was infrequent: among the 199 instances of a manoeuvre being conducted, conversion to sinus rhythm occurred in seven (4%) patients.

Statistical analyses were conducted using SAS (version 9.4). This study is registered at ClinicalTrials.gov, NCT03464019.

Role of the funding source

All authors, including those employed by the funder, participated in the study design, data interpretation, or writing of the report.

Results

The RAPID study was conducted between Oct 13, 2020, and July 20, 2022, during which 842 patients were screened. 706 patients were enrolled, of whom 692 (98%) tolerated the test dose and were randomly assigned (figure 1); details of those who were not randomised are given in the appendix (p 6). Among the safety population—patients who self-administered blinded study drug for an episode of perceived paroxysmal supraventricular tachycardia—135 were randomised to the etripamil group and 120 were randomised to the placebo group. Among the efficacy population—patients who self-administered blinded study drug for an episode of perceived parox ysmal supraventricular tachycardia that was confirmed to be atrioventricular-nodal-dependent—99 patients self-administered the etripamil regimen and 85 patients self-administered the placebo regimen.

The baseline characteristics of the etripamil and placebo groups were generally balanced in both the safety and efficacy populations (table 1). For the efficacy population, the mean age was 54 years (SD 12) and 131 (71%) of 184 patients were female,

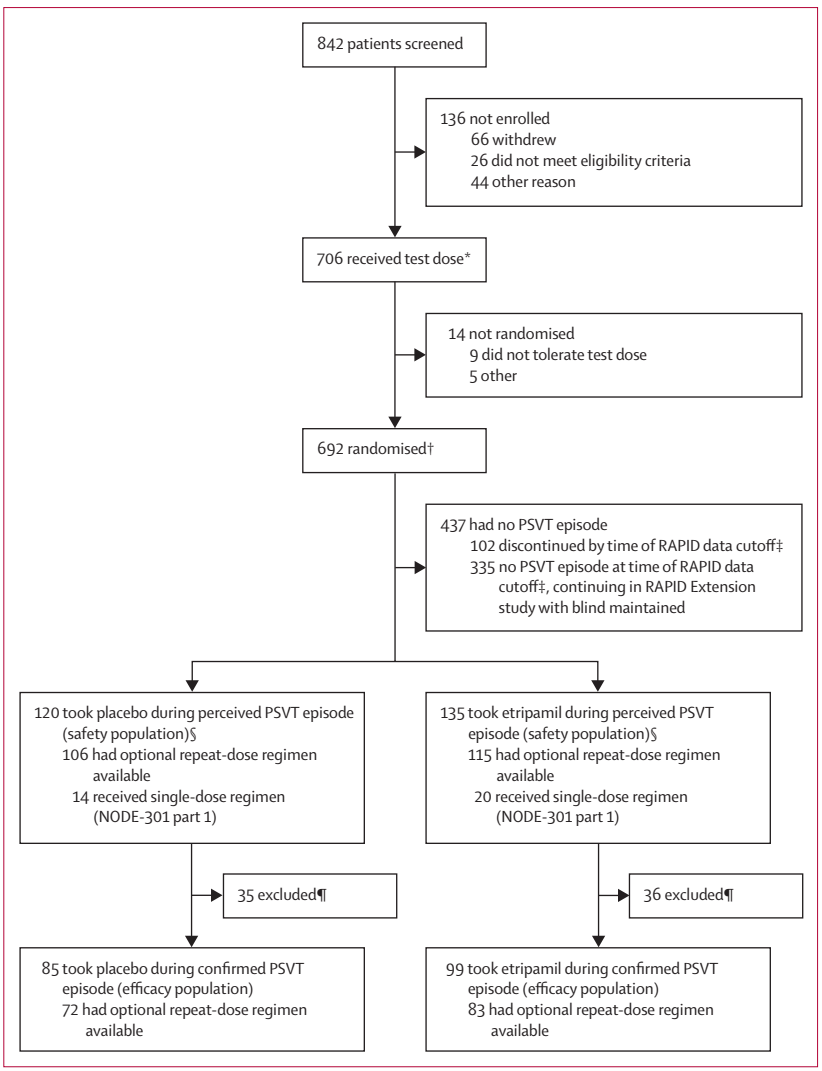

Figure 1: **Trial profile**
PSVT=paroxysmal supraventricular tachycardia. *Patients received two doses of 70 mg etripamil as a test dose. The 706 patients include 48 who were previously enrolled in NODE-301 part 1 and did not have a PSVT event or use study medication in that trial; these patients were re-randomised for the RAPID trial after tolerating the test dose. Also included are 34 patients from NODE-301 part 1 whose masked data were carried forward and analysed in RAPID datasets; these patients received one 70 mg dose of etripamil as a test dose during NODE-301 part 1 and did not have a paroxysmal supraventricular tachycardia episode by the cut-off date (Jan 15, 2020) of that study. †Includes 658 patients randomised to a placebo or an etripamil optional-repeat-dose regimen and 34 patients randomised to a placebo or etripamil single-dose regimen from the NODE-301 part 1 study. ‡July 20, 2022. §For patients on the optional-repeat-dose regimen, a second dose was administered if symptoms persisted after 10 min. ¶The efficacy population excluded patients who took the study drug after PSVT conversion or during an episode that was adjudicated as non-atrioventricular-nodal-dependent PSVT (eg, atrial flutter or sinus tachycardia), or if substantial electrocardiogram signal loss occurred.

reflecting that paroxysmal supraventricular tachycardia occurs more frequently in females than in males. The average number of paroxysmal supraventricular tachycardia episodes per year and concomitant use of medications acting on the atrioventricular node were similar between groups. The most common symptoms before drug administration were rapid pulse, palpitations, and feeling dizzy or light-headed, which were balanced between groups (table 2).

	Safety population		Efficacy population	
	Placebo (n=120)	Etripamil (n=135)	Placebo (n=85)	Etripamil (n=99)
Age at informed consent, years	56·2 (12·0)	52·4 (14·0)	56·7 (10·0)	50·8 (14·0)
Sex				
Female	88 (73%)	93 (69%)	62 (73%)	69 (70%)
Male	32 (27%)	42 (31%)	23 (27%)	30 (30%)
Race				
White	110 (92%)	126 (93%)	78 (92%)	93 (94%)
Black or African American	3 (3%)	4 (3%)	2 (2%)	3 (3%)
Asian	4 (3%)	2 (1%)	2 (2%)	0
American Indian or Alaska Native	0	1 (1%)	0	1 (1%)
Other	3 (3%)	2 (1%)	3 (4%)	2 (2%)
Age at confirmation of PSVT, years	55·1 (12·4)	50·7 (14·4)	55·4 (10·2)	48·5 (14·4)
Duration of PSVT, years	1·7 (3·8)	2·2 (5·3)	1·9 (4·2)	2·8 (6·1)
Number of PSVT episodes in past year	10·8 (22·9)	6·3 (13·9)	9·2 (14·0)	6·4 (15·7)
Lifetime number of emergency department visits for PSVT	3·9 (11·2)	4·6 (15·5)	4·6 (13·2)	5·2 (18·0)
Weight at screening, kg	83·9 (20·1)	81·9 (19·7)	84·4 (20·1)	82·8 (20·7)
Use of concomitant medications of interest*				
β blockers or calcium-channel blockers	80 (67%)	86 (64%)	53 (62%)	63 (64%)
β blockers	40 (33%)	45 (33%)	27 (32%)	33 (33%)
Calcium-channel blockers	29 (24%)	30 (22%)	18 (21%)	24 (24%)
β blockers and calcium-channel blockers	11 (9%)	11 (8%)	8 (9%)	6 (6%)

Data are mean (SD) or n (%). PSVT=paroxysmal supraventricular tachycardia. *Drugs acting on the atrioventricular node. A patient could be taking more than one medication.

Table 1: **Baseline characteristics**

	Baseline*		Responders†		p value‡
	Placebo (n=85)	Etripamil (n=99)	Placebo (n=85)	Etripamil (n=99)	
Rapid pulse	69 (81%)	79 (80%)	20 (24%)	42 (42%)	0·0059
Palpitations	63 (74%)	71 (72%)	19 (22%)	40 (40%)	0·0092
Feeling dizzy or light-headed	32 (38%)	42 (42%)	9 (11%)	24 (24%)	0·0078
Shortness of breath	18 (21%)	25 (25%)	2 (2%)	14 (14%)	0·0037
Anxiety	27 (32%)	33 (33%)	6 (7%)	17 (17%)	0·039
Chest tightness, pain, or pressure	15 (18%)	23 (23%)	3 (4%)	9 (9%)	0·44
Passing out or fainting	0	0	0	0	NA

Data are n (%). NA=not applicable. *Baseline data represent symptoms after randomisation, within an episode of paroxysmal supraventricular tachycardia, and before study drug administration. †Responders were defined as patients who cited a defined symptom before administration of study drug and scored 6 (much improved) or 7 (very much improved) for the change from baseline in that symptom on the Patient Global Impressions of Improvement seven-point scale. ‡Obtained from χ^2 test.

Table 2: **Secondary efficacy analyses: symptomatic assessments**

The Kaplan-Meier plot of cumulative incidence of conversion by 30 min in the efficacy population is shown in figure 2A. The primary efficacy outcome, conversion from atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia to sinus rhythm up to 30 min and for at least 30 s, occurred in 63 (64%) of 99 patients in the etripamil group and 26 (31%) of 85 patients in the placebo group; the HR was 2·62 (95% CI 1·66–4·15; p<0·0001). Median time to conversion was 17·2 min (95% CI 13·4–26·5) with the etripamil regimen compared with 53·5 min (38·7–87·3) with placebo (appendix p 8).

Prespecified sensitivity analyses of the primary assessment were done to test robustness, yielding supporting results (appendix p 20).

Primary efficacy assessments in predefined subpopulations (based on demographic and other features) did not show substantial differences in HRs between groups, including between patients with a duration of 30 min or less versus more than 30 min between symptom onset and drug administration, or among subgroups based on age and the concomitant use of cardiac medications, including calcium-channel blockers and β blockers. Plots of point estimates of all HRs show benefit of etripamil across subgroups (figure 3).

Secondary outcomes were assessed hierarchically. The first assessment did not meet significance (measures of conversion of paroxysmal supraventricular tachycardia by 10 min showed a non-significant improvement for etripamil versus placebo [HR 1·74, 95% CI 0·96–3·14; p=0·052]), therefore the assessments that followed are reported as exploratory; p values should be considered as nominal. Treatment effects were observed with prespecified assessments of conversion to sinus rhythm as early as 5 min and maintained up to 5 h (figure 2, appendix p 18). The effect sizes, estimated by the absolute differences in Kaplan-Meier proportions, were 21% (95% CI 8–35) at 15 min, 33% (19–47) at 30 min, and 20% (5–33) at 60 min. There were lower percentages of patients seeking additional medical interventions (eg, intravenous adenosine) and emergency department visits in the etripamil group than in the placebo group, but significance was not shown (appendix p 22). Patients treated with etripamil showed symptomatic improvement compared with those on placebo as measured by the TSQM-9 Effectiveness scale (least-squares mean difference between groups of 17·80 [95% CI 8·43–27·18; p=0·0002]); however, no significant difference between groups was observed on the Overall Satisfaction scale (least-squares mean difference 7·75 [1·09–16·60; p=0·085]) and no difference was found on the Convenience scale. The secondary assessment of typical symptoms associated with paroxysmal supraventricular tachycardia—of which the presence before study treatment and changes after drug administration were recorded on the patient questionnaire—showed significantly greater proportions of responders among the etripamil group compared with the placebo group for rapid pulse (p=0·0059), palpitations (p=0·0092), anxiety (p=0·039), shortness of breath (p=0·0037), and feeling dizzy or light-headed (p=0·0078; table 2).

The ability of patients to accurately perceive symptomatic, atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia was measured by the rates of confirmation of events from ECG cardiac monitoring system data. 196 (80%) of 244 events with adequate ECG data were verified by adjudicators to be atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia (appendix p 17).

The numbers of patients to whom the repeat-dose regimen was available but who self-administered only one dose of blinded drug for a perceived paroxysmal supraventricular tachycardia episode were 34 (34%) of 99 in the etripamil group and 18 (21%) of 85 in the placebo group. 65 (66%) patients in the etripamil group and 67 (79%) in the placebo group administered a repeat dose for persisting symptoms.

Etripamil was well tolerated when administered in a non-health-care setting during a paroxysmal supraventricular tachycardia episode (table 3) or as a test dose during a clinic visit in sinus rhythm (appendix p 19). The most common treatment-emergent adverse events were localised to the nasal administration site and were mild and transient. Rates of nosebleeds were low; none were severe or required treatment. Rates of adverse events were similar whether patients received single or repeated doses of drug (during test dose or randomised drug administration). Patients who administered etripamil for perceived paroxysmal supraventricular tachycardia that was not confirmed to be atrioventricular-nodal-dependent did not have a safety profile different from those for whom this arrhythmia was confirmed. Masked expert adjudication of continuous ECG data (table 4) showed no second-degree or third-degree atrioventricular block or pauses associated with etripamil use. Occurrences of non-sustained, wide-complex tachycardia that was adjudicated as non-sustained ventricular tachycardia were more frequent in the placebo group than in the etripamil group. Although there were increased observations of non-sustained ventricular tachycardia in patients taking two doses of blinded study drug (18% in the etripamil group and 20% in the placebo group) compared with those taking one dose (10% in both groups), the similar occurrences in both groups indicate no drug effect (appendix p 21). Episodes of non-sustained ventricular tachycardia in each group were infrequent, brief (mean duration of 5·8 beats in the placebo group and 4·7 beats in the etripamil group), and asymptomatic, with 89% of instances occurring at the termination of paroxysmal supraventricular tachycardia. Recurrences of paroxysmal supraventricular tachycardia after conversion to sinus rhythm were low, observed in three (3%) of 99 patients in the etripamil group and three (4%) of 85 patients in the placebo group over the 5 h following study drug administration. No serious adverse events occurred within 24 h after etripamil administration.

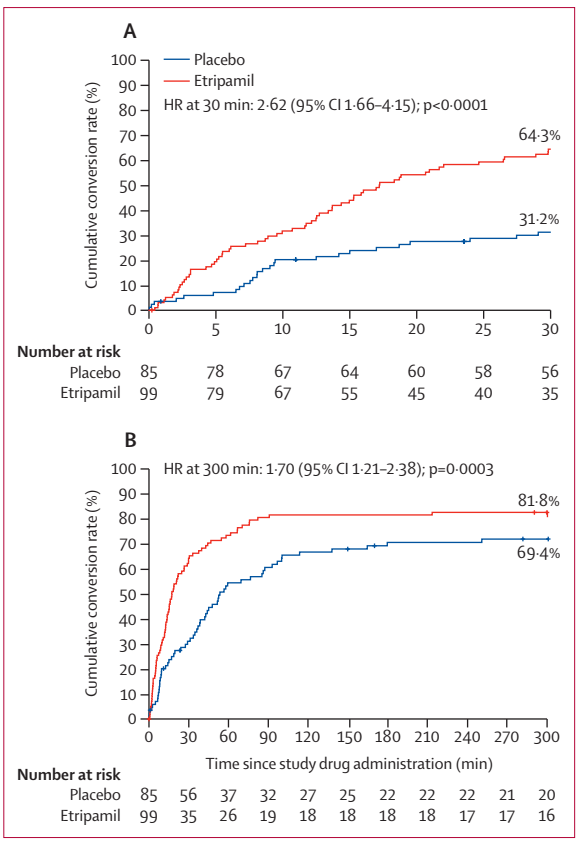

Figure 2: **Primary efficacy outcome**
Kaplan-Meier plots of conversion rates from paroxysmal supraventricular tachycardia to sinus rhythm within 30 min (A) and 300 min (B). HR=hazard ratio.

Discussion

In the RAPID trial, etripamil nasal spray—self-administered in a non-health-care setting with a repeat dose if symptoms persisted—was superior to placebo for the rapid conversion to sinus rhythm and was well tolerated in a population of patients with sustained paroxysmal supraventricular tachycardia. Efficacy was greater in RAPID than in part 1 of the NODE-301 study, as shown by the conversion to sinus rhythm by 30 min after etripamil administration (64% *vs* 54%) and the absolute effect size (33% *vs* 19%).[12] Moreover, greater rates of conversion were observed beyond 30 min in RAPID than in NODE-301 part 1: the efficacy of conversion by 300 min remained greater under the etripamil regimen than for placebo in RAPID, whereas in NODE-301 part 1 this was non-significant. The continued separation in event curves in RAPID, beyond the known duration of the pharmacological activity of etripamil, probably reflects maintenance of the early, quickly achieved efficacy gains. The most likely explanation for the greater efficacy and the shorter times to conversion in RAPID than in NODE-301 part 1 is the availability of the repeat-dose treatment-regimen, which most patients used, compared with only a single-dose etripamil regimen in NODE-301 part 1.[12] Conversions to

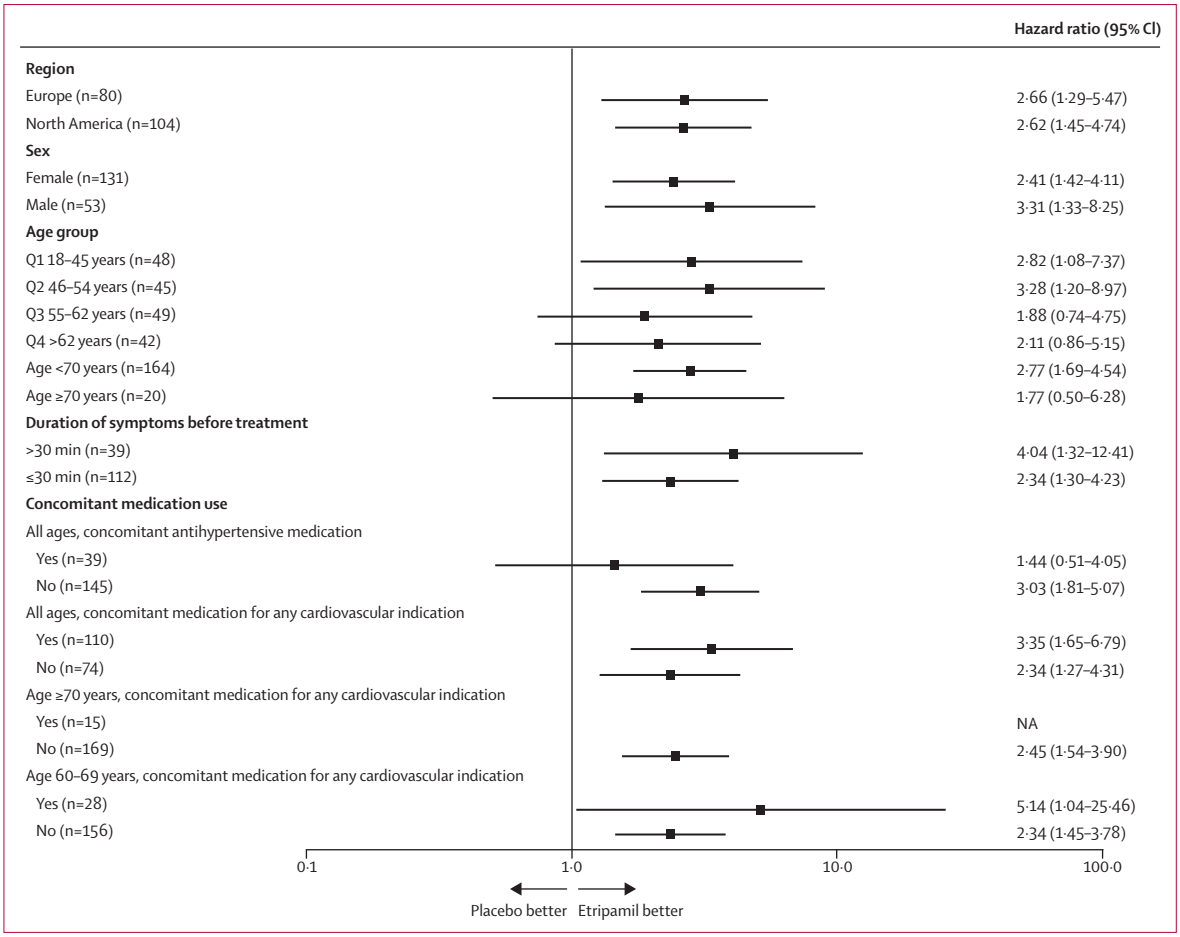

Figure 3: **Conversion of paroxysmal supraventricular tachycardia to sinus rhythm at 30 min by prespecified subgroup**
NA=not applicable.

	Placebo (n=120)	Etripamil (n=135)
Adverse events affecting ≥5% of patients		
Nasal discomfort	6 (5%)	31 (23%)
Nasal congestion	1 (1%)	17 (13%)
Rhinorrhoea	3 (3%)	12 (9%)
Epistaxis	2 (2%)	8 (6%)
Other adverse events		
Syncope	0	0
Loss of consciousness	0	0
Presyncope	0	0
Dizziness	0	1 (1%)
Serious adverse events	1 (1%)	0
Serious adverse events related to study drug	0	0
Adverse events leading to death	0	0

Data are n (%). Treatment-emergent adverse events are defined as those that occurred within 24 h after the date of the randomised dose. Patients who had multiple occurrences of the same adverse event were counted only once for that event.

Table 3: **Adverse events in the safety population**

sinus rhythm were durable, as shown by the low rate of recurrence of paroxysmal supraventricular tachycardia.

Favourable safety data were consistent with previous studies[11,12] and are supportive of potential self-administration of etripamil outside of a health-care setting. No instances of presyncope or syncope were reported, and adjudicated ECG monitoring revealed no high-grade atrioventricular block or pauses at the termination of tachycardia. Safety results were similar for patients receiving single or repeat doses of study drug, which aligns with the finding that rates and types of adverse event were similar to those in the previous trial in which only a single-dose regimen was used.[11,12] Safety findings were similar for patients self-administering study drug for a paroxysmal supraventricular tachycardia episode that was confirmed by adjudication to be atrioventricular-nodal-dependent and for the minority of patients who self-administered study drug for episodes that were not confirmed as such (ie, adjudicated to be atrial fibrillation, atrial flutter, atrial tachycardia, sinus tachycardia, or sinus rhythm). Given the high rate (98%) of patients tolerating the test dose and proceeding to randomisation, a test dose might not be

	Placebo* (n=116)	Etripamil* (n=128)
Non-sustained wide-complex tachycardia†	19 (16%)	18 (14%)
Sustained wide-complex tachycardia (≥30 s)	1 (1%)‡	0
PSVT recurrence	5 (4%)	4 (3%)
Atrial fibrillation ≥30 s	4 (4%)	1 (1%)
Atrial tachycardia ≥30 s	1 (1%)	2 (2%)
Prolonged PR interval (≥30 s)	1 (1%)	2 (2%)
Pause ≥3 s§	1 (1%)	1 (1%)
Atrial flutter ≥30 s	1 (1%)	0
Sinus bradycardia ≤40 beats per min	1 (1%)	0
More than six premature ventricular contractions within 45 s	0	0
Second-degree atrioventricular block—Mobitz type I	0	0
Second-degree atrioventricular block—Mobitz type II	0	0
Third-degree atrioventricular block	0	0

Data are n (%). ECG=electrocardiogram. PSVT=paroxysmal supraventricular tachycardia. *Includes patients in the safety population with fully diagnostic 5 h ECG recordings available for examination. †Determined as non-sustained by adjudication committee. Mean duration: placebo 5·8 beats; etripamil 4·7 beats. No symptoms were concurrently reported. ‡The ECG was indeterminate between supraventricular tachycardia with a wide QRS complex and ventricular tachycardia, so for caution was adjudicated as ventricular tachycardia. This tachycardia was present before administration of the drug (placebo). §Pauses were observed only after a rescue treatment with intravenous adenosine in an emergency department.

Table 4: **ECG readings in the safety population**

required in the real-world setting for all patients; this hypothesis is being further assessed in an open-label study that does not contain prerequisite test dosing before at-home, self-administration of etripamil (ClinicalTrials.gov, NCT04072835).

Results of the RAPID study can be viewed in the context of evidence regarding acute, self-administered pill-in-pocket treatment for paroxysmal supraventricular tachycardia. Although this oral pill approach is used in practice, it is associated with low effectiveness, potential side effects, and slow times to resolution.[1,2,5] Only two randomised, placebo-controlled studies have examined a pill-in-pocket approach for acute termination of paroxysmal supraventricular tachycardia episodes. Yeh and colleagues[7] conducted a crossover study of a calcium-channel blocker plus propranolol in 15 patients. Alboni and colleagues[6] reported a comparison of oral flecainide, diltiazem plus propranolol, or placebo in 33 patients. Although diltiazem plus propranolol was moderately effective at converting paroxysmal supraventricular tachycardia to sinus rhythm, the median times to conversion were 30–240 min and there was an increase in adverse events, including syncope, second degree atrioventricular block, and junctional rhythm. Chronic orally administered atrioventricular-nodal agents have low effectiveness for the suppression of acute paroxysmal supraventricular tachycardia and can cause undesired effects at higher doses.[5–7] Vagal manoeuvres, although used,[1,2] have low rates of efficacy for acute conversion; despite protocol-directed training in this technique, the observed efficacy was only 6% in the NODE-301 part 1 study[16] and 4% in the current study.

Although patients with atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia might benefit from treatment with catheter ablation, this invasive approach is often not recommended as first-line therapy or for patients with infrequent episodes and might not be readily available to all patients.[8,17]

A symptom-prompted, fast-acting, and portable medication that can be acutely self-administered by patients could lead to improved management of paroxysmal supraventricular tachycardia. To this end, patients in RAPID were instructed to be attuned to particular symptoms before initiating the regimen and to complete patient-reporting outcome questionnaires following episodes;[10,13,14] improvement was observed in patient-defined symptoms following etripamil administration. Moreover, patients were able to accurately perceive atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia rather than a tachycardia that is less amenable to treatment with etripamil (appendix p 17). We conducted a prespecified analysis to assess robustness of the primary endpoint including all patients who self-administered study drug for any perceived paroxysmal supraventricular tachycardia (ie, the safety population) and found a treatment effect (appendix p 20), similar to the significant hazard ratio from the primary endpoint including patients for whom atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia was confirmed by adjudication (ie, the efficacy population). Risk reductions observed in RAPID indicate that the number needed to treat with etripamil to convert an episode of paroxysmal supraventricular tachycardia within 30 min of drug administration is 3·0, which is within the range for effectiveness of a treatment for a symptomatic condition.[18]

RAPID was not powered to detect significantly different rates between treatment groups regarding additional medical interventions and emergency department visits (appendix p 22); future studies will therefore be needed to confirm the potential of etripamil to decrease health-care burdens and costs.

The RAPID trial has several limitations. The required screening procedures and training with the ECG cardiac monitoring system could have dissuaded some patients from participating; however, less than 2% of patients who received the test dose did not proceed to randomisation, suggesting that instructions on procedures and test-dose exposures of drug were not problematic. Confirmation of the mechanism of paroxysmal supraventricular tachycardia episodes could have been limited by the single-channel

ECG recordings examined. However, the adjudication committee comprising expert cardiac electrophysiologists undoubtedly contributed to the accuracy of ECG reading. Insufficient ECG quality was observed in only a minority of cases, and there is no evidence that limitations in ECG examinations affected the conclusions of this study—efficacy and safety were shown both in patients with paroxysmal supraventricular tachycardia confirmed by adjudication and in all patients taking etripamil. Some heterogeneity in baseline paroxysmal supraventricular tachycardia between patients was probably present, but would have been reduced by the study inclusion criteria requiring a history of documented, sustained paroxysmal supraventricular tachycardia episodes and by excluding patients with known non-atrioventricular-nodal-dependent tachycardia. The absence of a prescribed time between onset of a perceived paroxysmal supraventricular tachycardia episode and drug administration could have influenced measures of conversion; however, analysis of subgroups organised by time from symptom onset to drug administration suggests that this was not a factor. The RAPID study was designed to assess the efficacy and safety of a treatment regimen that included an optional repeat dose of etripamil to be administered 10 min after the first dose if paroxysmal supraventricular tachycardia symptoms persisted; the study was not designed to characterise the difference in efficacy between a single 70 mg dose and the second 70 mg dose. Use of the repeat-dose regimen potentially provides additional efficacy relative to that of a single-dose regimen, as shown by the comparison of RAPID efficacy data with NODE-301 part 1 efficacy data (eg, comparing percentage conversions by 30 min after drug administration).[12] The safety profile of etripamil shown in this study was predicated, in part, on the trial's inclusion and exclusion criteria. The real-world safety of etripamil would depend on applying these criteria when selecting patients for treatment.

This event-driven study of patients with symptomatic, sustained atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia showed that etripamil can be self-administered on demand in a non-health-care setting, with a staged, repeat-dose for persisting symptoms, to convert this tachycardia safely and effectively to sinus rhythm significantly more often and faster than with placebo. Post-conversion recurrence rates of paroxysmal supraventricular tachycardia were low. This symptom-prompted etripamil treatment regimen was associated with improved defined symptoms of paroxysmal supraventricular tachycardia. Findings of a reduced need for medical interventions and emergency visits are hypothesis-generating regarding the potential of etripamil treatment to decrease the burden on patients and health-care systems of this common tachyarrhythmia and warrant further investigation.

Contributors

BSS, AJC, PTS, and FP made substantial contributions to study conception and design. DBB, FP, SS, and MC analysed and interpreted the data. MC conducted the statistical analysis. All other authors contributed to the implementation and data collection. All authors were involved in the data interpretation and discussion of the results. All authors critically revised the manuscript and approved the final version for submission. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication. AJC, BSS, JEI, DBB, and MC accessed and verified the data.

Declaration of interests

BSS, PTS, BM, MC, PRK, JPP, SDP, and AJC are consultants for Milestone Pharmaceuticals. AJC has received grants and personal fees from Boehringer Ingelheim, Bayer, Pfizer, Bristol-Myers Squibb, and Daiichi Sankyo; personal fees from Medtronic, Boston Scientific, Menarini, and Biotronik; and support from Anthos, Sanofi, Abbott, GlaxoSmithKline, and Johnson & Johnson. PRK has received personal fees from Acesion Pharma, Allergan, Astellas Pharma, AstraZeneca, AtriCure, Boehringer Ingelheim, Bristol-Myers Squibb, Chattem, Correvio, Daiichi Sankyo, GlaxoSmithKline, InCarda Therapeutics, Johnson & Johnson, Medtronic, Merck, Novartis, Pfizer, Roche, and Sanofi-Aventis; serves on a data safety monitoring board for Eli Lilly; and has equity in CardioNet. SDP has received personal fees from Medtronic, Boston Scientific, Pfizer, Bristol-Myers Squibb, Janssen Pharmaceuticals, Philips, Zoll, and Sanofi-Aventis and research grants from Boston Scientific, Gilead Sciences, Pfizer, Bristol-Myers Squibb, the US Food and Drug Administration, Janssen Pharmaceuticals, Philips, Medtronic, and Sanofi-Aventis. HH has received lecture and consultancy fees from Abbott, Biotronik, Daiichi Sankyo, Pfizer-BMS, Medscape, and Springer Healthcare and unconditional research grants through the University of Antwerp and/or the University of Hasselt from Abbott, Bayer, Biotronik, Biosense Webster, Boston Scientific, Boehringer Ingelheim, Daiichi Sankyo, Fibricheck/Qompium, Medtronic, and Pfizer-BMS, all outside of the scope of this work. JLM has received grants and personal fees from Medtronic, Microport, and Sanofi. JPP has received grants for clinical research from Abbott, the American Heart Association, the Association for the Advancement of Medical Instrumentation, Bayer, Boston Scientific, iRhythm, and Philips and serves as a consultant to Abbott, AbbVie, ARCA biopharma, Bayer, Boston Scientific, Bristol Myers Squibb (Myokardia), Element Science, Itamar Medical, LivaNova, Medtronic, ElectroPhysiology Frontiers, ReCor, Sanofi, Philips, and UpToDate. AV has received personal fees from MedLumics and Adagio Medical and research grants from Bayer, Biosense Webster, and Medtronic. JMW has received personal fees from Sanofi-Aventis, Bristol-Myers Squibb, and Janssen Pharmaceuticals and a research grant from Milestone Pharmaceuticals. PTS has equity in Milestone Pharmaceuticals. DBB, FP, and SS are employees of Milestone Pharmaceuticals. JEI, MA, BSS, PD, and AJC serve on the steering committee for Milestone Pharmaceuticals. JH declares no competing interests.

Data sharing

Data sharing requests for studies with products/uses approved may be submitted 12 months after marketing authorisation in all planned regions. Qualified researchers from an appropriate institution may request access to individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices). Upon approval of a data sharing request, information necessary to address the research question will be provided under the terms of a signed data sharing agreement. Requests should be submitted to datasharing@milestonepharma.com.

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