THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Stambler BS, Camm AJ, Alings M, et al. Self-administered intranasal etripamil using a symptom-prompted, repeat-dose regimen for atrioventricular-nodal-dependent supraventricular tachycardia (RAPID): a multicentre, randomised trial. *Lancet* 2023; published online June 15. https://doi.org/10.1016/S0140-6736(23)00776-6.

SUPPLEMENTARY APPENDIX

Section S1: Committee oversight and author roles.

Michael Chen (study biostatistician) takes primary responsibility for analyses and data handling. Drs. Ip, Alings, Stambler, Dorian, and Camm serve on the steering committee for Milestone Pharmaceuticals.

Data Safety Monitoring Committee:

Daniel Beyerbach, MD, Columbia University (Chair and physician); Sean Pokorney, MD, Duke Department of Medicine (Interim Physician); Benjamin Steinberg, MD, University of Utah (Physician); Hussein Al-Khalidi, PhD, Duke Clinical Research Institute (Biostatistician).

Blinded Electrocardiographic Data Adjudication Group:

Cardiovascular Research Foundation
1700 Broadway, 9th Floor
New York, NY 10019
646-434-4500

Adjudication Committee members:
José Dizon, MD, (Chair); Angelo Biviano, MD; Ioanna Kosmidou MD, PhD; John Morrow, MD; James Peacock, MD.

Section S1: Full list of inclusion and exclusion criteria.

Patients who met all of the following criteria were eligible to participate in the study:

1. Male or female patients at least 18 years of age.
2. Electrographically documented history of PSVT (e.g., ECG obtained during an episode of PSVT, Holter monitoring, loop recorder, etc.). If the patient had a prior ablation for PSVT, the patient must have had documented ECG evidence of PSVT post-ablation.
3. History of sustained episodes of PSVT (i.e., typically lasting approximately 20 minutes or longer).
4. Females of childbearing potential who were sexually active with a male partner who is not surgically sterile (i.e., vasectomy) must have agreed to use a highly effective form of contraception from the time of signed informed consent until 30 days after the last administration of the study drug. Females of childbearing potential should have had a negative serum pregnancy test result at the screening visit and at the final study visit and a negative urine pregnancy test at the test dose randomisation visit, and they must have used a highly effective form of contraception between the visits.
5. The following categories define females who were NOT considered to be of childbearing potential:
    a. Premenopausal females with 1 of the following:
        i. Documented hysterectomy,
        ii. Documented bilateral salpingectomy or tubal ligation, or
        iii. Documented bilateral oophorectomy, or
    b. Postmenopausal females, defined as having amenorrhea for at least 12 months without an alternative medical cause;
6. Male patients, except those who are surgically sterile, must have used a highly effective form of contraception during the 3 days after any study drug administration.
7. Signed written informed consent.

Patients who met any of the following criteria were excluded from participation in the study:

1. Systolic blood pressure <90 mmHg after a 5-minute rest in a sitting position at the screening visit or before the test dose. In patients treated with a chronic prophylactic drug for PSVT (e.g., beta-blockers, verapamil, and diltiazem), the drug could be stopped for at least the equivalent of 5 half-lives, patients could be rescreened once, and chronic use of the drug could not be restarted after randomisation.
2. History of severe symptoms of hypotension, especially syncope, during episodes of PSVT.
3. History of atrial arrhythmia that did not involve the AV node as part of the tachycardia circuit (e.g., atrial fibrillation, atrial flutter, intra-atrial tachycardia).
4. History of allergic reaction to verapamil.
5. Current therapy with digoxin or any Class I or III antiarrhythmic drug, except if these drugs were stopped at least the equivalent of 5 half-lives before the test dose randomisation visit.

6. Current chronic therapy with oral amiodarone or had taken oral amiodarone within 30 days prior to the test dose randomisation visit.
7. Evidence of ventricular pre-excitation (e.g., delta waves, short PR interval <100 ms, and/or Wolff–Parkinson–White syndrome) on the ECG performed at the screening visit or before the test dose administration.
8. Evidence of a second- or third-degree AV-block on the ECG performed at the screening visit or before the test dose administration.
9. History or evidence of severe ventricular arrhythmia (e.g., torsades de pointes, ventricular fibrillation, or ventricular tachycardia).
10. Current congestive heart failure defined by the New York Heart Association Class II to IV.
11. History of acute coronary syndrome or stroke within 6 months of screening.
12. Evidence of hepatic dysfunction defined as alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal or total bilirubin >2 times the upper limit of normal at the screening visit, unless due to Gilbert syndrome.
13. Evidence of end-stage renal disease as determined by an estimated glomerular filtration rate assessed at the screening visit of <15 mL/min/1·73 m^2 or requiring haemodialysis.
14. Females who were pregnant or lactating.
15. Evidence or history of any significant physical or psychiatric condition, including drug abuse, which, in the opinion of the investigator, could jeopardize the safety of patients or affect their participation in the study. Additionally, the investigator had the ability to exclude a patient if, for any reason, the investigator judged that the patient was not a good candidate for the study or would not be able to follow study procedures.
16. Participation in any investigational drug or device study or the use of any investigational drug or device within 30 days of the screening visit.
17. Previously enrolled in a clinical trial for etripamil and received the study drug during a perceived episode of PSVT.

Section S3: Criteria evaluated during test dose administration.

Before randomisation in the RAPID study, all patients received a test dose of an etripamil nasal spray dosing regimen (an initial dose of etripamil 70 mg followed by a second dose of etripamil 70 mg not earlier than 10 minutes and not later than 15 minutes after the first dose) to evaluate tolerability and train patients on the study procedures. Both doses of the etripamil dosing regimen had to be administered for the test dose to be considered evaluable. A failure of the test dose was considered if patients met any of the following criteria occurring after administration of either the first or second dose of etripamil nasal spray 70 mg:

1. Any symptoms consistent with clinically severe hypotension, such as pre-syncope, medically significant light-headedness, syncope, nausea, or vomiting.
2. For patients with a pre-test dose SBP >100 mmHg, decrease in SBP ≥40 mmHg after the test dose or post-test dose SBP <80 mmHg.
3. For patients with a pre-test dose SBP between 90 mmHg and 100 mmHg (inclusive), post-test dose SBP <75 mmHg.
4. Third-degree AV block, Mobitz II second-degree AV-block, or Wenckebach with bradycardia ≤40 bpm.
5. New, significant sinus bradycardia heart rate ≤40 bpm or sinus pauses (≥3 seconds) if considered by the investigator to put the patient's safety at risk if either were to occur while not under medical supervision.
6. Any new ventricular arrhythmia considered significant by the investigator.
7. Atrial fibrillation, atrial flutter, or atrial tachycardia (event lasting longer than 30 seconds).
8. Refusal of the second dose of the etripamil test dose regimen.

Patients who failed the test dose could proceed in the study as follows:

- If the investigator identified a possible reversible cause of the initial test dose failure (e.g., concomitant medication such as a beta-blocker), a re-challenge with a new test dose of the etripamil dosing regimen within a 14-day window from the initial test dose was possible after elimination of the reversible cause (e.g., withdrawal of concomitant therapy with the appropriate washout period). Patients could be randomised if they passed the second test dose, and the cause of the test dose failure was eliminated for the duration of the study.
- If the investigator could not identify a reversible cause of the initial test dose failure, or if the potential cause could not be modified (e.g., necessary antihypertensive drug to control blood pressure), patients were not randomised and completed a final study visit. Patients who failed the test dose comprised the test dose–only population.

Section S4: Summary of screened patients not proceeding to randomisation.

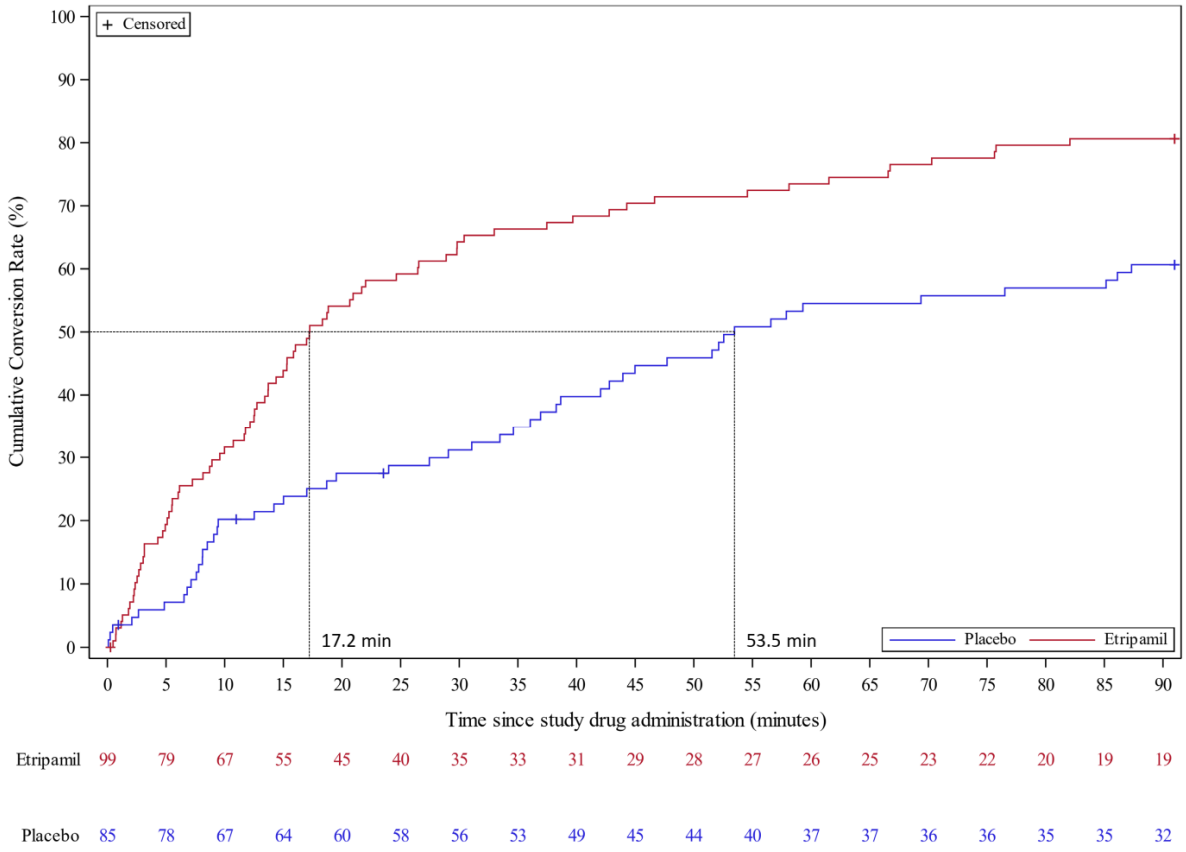
Of the 706 patients who underwent the test dose administration and associated monitoring, 4 passed the test dose but were not randomised due to adverse events of nasal site discomfort; 1 passed the test dose but was randomised after the event cut-off date (July 20, 2022). Nine patients did not pass due to the following: pre-defined hypotension (1 patient), blood pressure criteria (2 patients), ventricular arrhythmia (1 patient, though later determined to be 3 premature atrial beats with aberrant conduction), atrial tachycardia (1 patient), or refusal of second etripamil test dose (2 patients). Of the randomised patients not self-administering the blinded drug by the event cut-off date, 355 went into an extension phase of the RAPID study with blinds maintained.

Section S5: Efficacy Analysis of Primary Endpoint without Highest Enrolling Site

RAPID was conducted in 160 sites with 706 patients performing a test dose for an average of 4.4 patients enrolled per site.

In the RAPID study, the highest enrolling site contributed 21 of the 255 patients comprising the Safety Population dataset (8·2%), and a smaller percentage of the 706 patients in the Overall Safety Population (3·0%). To assess for potential site bias, a sensitivity analysis was performed, using the primary outcome assessment but excluding the patients from this site, and the results were consistent with the primary efficacy analysis (hazard ratio=2·675, 95% CI=1·644–4·352], p=0·0001), showing that the study's efficacy results were not driven or biased by this relatively highly enrolling site.

Figure S1: Kaplan–Meier plot illustrating median time-to-conversion (efficacy population, primary analysis, primary endpoint)



Median times-to-conversion: 17·2 minutes (95% CI= 13·4, 26·5) with the etripamil regimen *vs* 53·5 minutes (95% CI= 38·7, 87·3) with placebo.

Table S1: List of study investigators and sites which obtained ethics approval

In total, 168 sites obtained ethics approval, including 74 in North America and 94 in the European Union (6 of which were not activated following approval).

The full list of investigators and study sites is listed below.

Investigator	Site
James E. Ip, MD	New York-Presbyterian Hospital/Weill Cornell Medical Center New York, NY, USA
Alonzo Jones, Sr, MD	Columbus Regional Research Institute Columbus, GA, USA
Bruce S. Stambler, MD	Piedmont Heart Institute Atlanta, GA, USA Piedmont Heart Institute Fayetteville Fayetteville, GA, USA
David E. Schleinkofer, MD	Parkview Physicians Group–Cardiology (within Parkview Health) Fort Wayne, IN, USA
Stephen Winters, MD	Atlantic Health System–Morristown Medical Center Morristown, NJ, USA
Wilson Lam, MD	Baylor College of Medicine McNair Campus Houston, TX, USA
Robert Goldstein, MD	Great Lakes Medical Research, LLC Willoughby, OH, USA
Isaac Dor, MD	Comprehensive Cardiovascular Care, LLC/Clinical Investigation Specialists, Inc. Gurnee, IL, USA
Sandeep Talwar, MD	Alpine Research Organization, Inc. Bountiful, UT, USA
Padraig G. O'Neill, MD, FACC, FHRS	Mercy Medical Group–Cardiology (Dignity Health Medical Foundation) Sacramento, CA, USA
Michael J. Koren, MD	Jacksonville Center for Clinical Research Jacksonville, FL, USA
Sean C. Beinart, MD	Adventist Healthcare Shady Grove Medical Center Rockville, MD, USA
Srivani Ambati, MD	Peak Cardiology Apex, NC, USA
Sean P. Mazer, MD	New Mexico Heart Institute Albuquerque, NM, USA
Robert M. Kinn, MD	Franciscan Physician Network–Indiana Heart Physicians Indianapolis, IN, USA
Karine Roy, MD	Institut universitaire de cardiologie et de pneumonologie de Québec–Université Laval Québec, QC, Canada
Ramin Manshadi, MD	Manshadi Heart Institute, Inc. Stockton, CA, USA
Richard Kuk, MD	Centra Cardiovascular Group Lynchburg, VA, USA

Investigator	Site
Aditya Verma, MD	ClinScale Management Visalia, CA, USA
Timothy Phelan, MD	ProMedica Toledo Hospital Toledo, OH, USA
Alexandru A. Stoian, MD	St. Lawrence Health System: Canton Potsdam Hospital Potsdam, NY, USA
Kenneth Ellenbogen, MD	Virginia Commonwealth University Health System Richmond, VA, USA
J. Vijay Jayachandran, MD	Apex Trials Group Fort Worth, TX, USA
Terence P. Connelly, MD	Charlotte Heart and Vascular Institute Port Charlotte, FL, USA
Marcos Daccarett, MD	St. Luke's Idaho Cardiology Associates Boise, ID, USA
Gaurang Gandhi, MD	Hatton Institute for Research & Education, TriHealth, Inc.–Cardiology Cincinnati, OH, USA
Suneet Mittal, MD	The Valley Hospital Ridgewood, NJ, USA
Amir Abdel-Wahab, MD	Dalhousie University–Queen Elizabeth II–Health Sciences Centre Halifax, NS, Canada
Ralph Augostini, MD	The Ohio State University Wexner Medical Center Columbus, OH, USA
John H. Ip, MD, FACC	Sparrow Clinical Research Institute Lansing, MI, USA
Denise Sorrentino, MD	Mercy One Iowa Heart Center West Des Moines, IA, USA
Jean-Francois Roux, MD	CIUSSS de l'Estrie-CHUS-Hôpital Fleurimont Sherbrooke, QC, Canada
Ramandeep Brar, MD	Los Alamitos Cardiovascular Group Los Alamitos, CA, USA
Clarence Khoo, MD	University of Manitoba Winnipeg, MB, Canada
Matthew Bennett, MD	Vancouver Coastal Health Research Institute Vancouver, BC, Canada
Eric Lo, MD	Central Florida Medical Research, LLC New Smyrna Beach, FL, USA
Benoit Coutu, MD	Centre Hospitalier de l'Université de Montréal Montreal, QC, Canada
Laurence Sterns, MD	Victoria Cardiac Arrhythmia Trials Inc Victoria, BC, Canada
Gerald S. Greer, MD	Arkansas Cardiology, PA Little Rock, AR, USA
Pradeep Gujja, MD	Heart House Research Foundation, LLC Springfield, OH, USA
Robert A. Gianfagna, MD	Trinity Medical WNY, PC Cheektowaga, NY, USA
Vijendra Swarup, MD	Arizona Arrhythmia Research Center Phoenix, AZ, USA

Investigator	Site
Felix Sogade, MD	Georgia Arrhythmia Consultants and Research Institute, LLC Macon, GA, USA
Stephen Wilton, MD	Libin Cardiovascular Institute of Alberta–University of Calgary Calgary, AB, Canada
Christopher Ruisi, MD	Baptist Health Ambulatory Services DBA Baptist Health Research Institute Jacksonville, FL, USA
Saverio Barbera, MD	Monument Health Clinical Research, a department of Monument Health Rapid City Hospital, Inc. Rapid City, SD, USA
Javier E. Banchs, MD	Baylor Scott and White Research Institute–Round Rock Round Rock, TX, USA
Victoria Korley, MD	St. Michael's Hospital Toronto, ON, Canada
Christopher Schulze, DO	Cardiology Consultants of Philadelphia Yardley, PA, USA
Roger Damle, MD	South Denver Cardiology Associates, PC Littleton, CO, USA
Jeffrey Sean Healey, MD	Hamilton Health Sciences East Hamilton, ON, Canada
A. Shekhar Pandey, MD	Cambridge Cardiac Care Centre Cambridge, ON, Canada
Jeffrey L. Anderson, MD	IHC Health Services Inc. DBA Intermountain Medical Center Murray, UT, USA
K.L. Venkatachalam, MD	Mayo Clinic–Jacksonville Jacksonville, FL, USA
Peter Noseworthy, MD	Mayo Clinic–Rochester Rochester, MN, USA
Blandine Mondésert, MD	Montreal Heart Institute–Institut de Cardiologie de Montréal Montréal, QC, Canada
Atul Verma, MD	Partners in Advanced Cardiac Evaluation (PACE) Newmarket, ON, Canada
Douglas G. Friars, MD, FCFP	Dawson Road Family Medical Clinic Guelph, ON, Canada
Thomas R. Kambur, MD	The Presbyterian Hospital DBA Novant Health Heart and Vascular Institute Charlotte, NC, USA
Evan Lockwood, MD	Royal Alexandra Hospital Edmonton, AB, Canada
Glenn Meininger, MD, FACC	MedStar Health Research Institute–Chesapeake Cardiovascular Associates Baltimore, MD, USA
Greg Olsovsky, MD	Scott & White Memorial Hospital: Baylor Scott & White Research Institute Temple, TX, USA
Alonzo Jones, Sr, MD	IACT Health Columbus, GA, USA
Gerald Greer, MD, FACC, FHRS	Arkansas Cardiology Little Rock, AR, USA
Rohit Mehta, MD	Sanger Heart and Vascular Institute Charlotte, NC, USA

Investigator	Site
Saleem Akbar, MD	North Texas Research Associates Allen, TX, USA
Malik Salman, MD	Cardiovascular Clinic of North Texas Denton, TX, USA
Bhola Rama, MD	Rama Research LLC Marion, OH, USA
Ramesh Arora, MD	Medvin Clinical Research Covina, CA, USA
Dhirenkumar Shah, MD, FACC	Cary Research Group, LLC Cary, NC, USA
Rakesh Shah, MD	Bay Area Heart Webster, TX, USA
Michael Cammarata, MD	FWD Clinical Research Boca Raton, FL, USA
Andrew Owens, MD	Revival Research Institute, LLC Denton, TX, USA
Katherine Ludington, MD	North Coast Cardiology Encinitas, CA, USA
Marcus Wharton, MD	Medical University of South Carolina (MUSC) Charleston, SC, USA
Michael Bagheri, MD	Respire Research La Mesa, CA, USA
Mohammed Khan, MD	AMITA Health Medical Group Heart & Vascular Elk Grove Village, IL, USA
Kenneth Warren Carr, MD	Titan Medical Research–Oceanside Oceanside, CA, USA
Sultan Siddique, MD	Prisma Health Midlands Columbia, SC, USA
Sunthosh Parvathaneni, MD	Mercy Research St. Louis, MO, USA
Subodh Devabhaktuni, MD	University of Arkansas for Medical Sciences Little Rock, AR, USA
Assad Mouhaffel, MD	Clinical Trials of America, LLC Monroe, LA, USA
George Mark, MD	Cardiovascular Associates of the Delaware Valley–Elmer Elmer, NJ, USA
Luigi Di Biase, MD	Montefiore Medical Center Bronx, NY, USA
Sunil Rangappa, MD	Amicis Research Center–Northridge Northridge, CA, USA
Jared Morton, MD	Idaho Catalyst Clinical Research, Idaho Falls, ID, USA
Hirad Yarmohammadi, MD	Columbia University New York, NY, USA
Amin Karim, MD	Angiocardiac Care of Texas Houston, TX, USA
Aldo Martinez Fleites, MD	United Health Research, LLC Miami, FL, USA
Thomas Nero, MD	Cardiology Associates of Fairfield Norwalk, CT, USA
Qaiser Shafiq, MD	Revival Research Institute, LLC Southgate, MI, USA
Benoit Coutu, MD	Centre Hospitalier de l Universite de Montréal (CHUM) Montréal, QC, Canada

Investigator	Site
Shekhar Pandey, MD	Cambridge Cardiac Care Centre Cambridge, ON, Canada
Yaariv Khaykin, MD	Partners in Advanced Cardiac Evaluation Newmarket, Ontario, Canada
Jacqueline Joza, MD	McGill University Health Center–Research Institute Montréal, QC, Canada
Gilbert Gosselin, MD	CSSS du Sud de Lanaudiere–Hospital Pierre Le Gardeur Terrebonne, QC, Canada
Allen Skanes, MD	London Health Sciences Centre London, ON, Canada
John Vyselaar, MD	Medical Arts Health Research Group–North Vancouver North Vancouver, BC, Canada
Daniel Savard, MD	CardioVasc HR St-Jean-sur-Richelieu, QC, Canada
Hein Heidbuchel, MD, PhD	Antwerp University Hospital (UZA) Edegem, Belgium
Olivier Xhaet, MD	CHU UCL Namur–Site Godinne Yvoir, Belgium
Emmanuel Catez, MD	UVC Brugmann University Hospital Brussels, Belgium
Johan Vijgen, MD	Jessa Ziekenhuis Hasselt, Belgium
Pascal Godart, MD	CHU Ambroise Pare Mons, Belgium
Ruben Casado, MD	Universite Libre de Bruxelles (ULB) - Hopital Erasme Bruxelles, Belgium
Georges Mairesse, MD	Clinique Du Sud–Luxembourg Arlon, Belgium
Tom Rossenbacker, MD	Imelda Hospital Bonheiden, Belgium
Peter Haemers, MD, PhD	University Hospital (UZ) Leuven Leuven, Belgium
Etienne Hoffer, MD	Regional Hospital Centre Citadelle Liège, Belgium
Pierre Hausman, MD	Grand Hopital de Charleroi (GHdC) - Site Saint-Joseph Gilly, Belgium
Andras Vertes, MD	Del-pesti Centrumkorhaz Budapest, Hungary
Gabor Duray, MD	Magyar Honvedseg Egeszsegugyi Kozpont Budapest, Hungary
Erzsebet Szolnoki, MD	Nehezlegzes Ambulancia Debrecen, Hungary
Zoltan Csanadi, MD	Debreceni Egyetem Klinikai Kozpont Debrecen, Hungary
Ferenc Lakatos, MD	Dr Lakatos Ferenc Belgyogyaszati-Kardiologiai Maganrendelo Bekescsaba, Hungary
Marco Alings, MD, PhD	Amphia Ziekenhuis–Locatie Breda Molengracht Breda, Netherlands
Reinhart Dorman, MD	Bravis ziekenhuis–Locatie Roosendaal Roosendaal, Netherlands
Y.S. Tuininga, MD, PhD	Deventer Ziekenhuis Deventer, Netherlands
W. Jansen, MD	Tergooiziekenhuizen Blaricum Blaricum, Netherlands

Investigator	Site
Sebastiaan Velthuis, MD, PhD	Meander Medisch Centrum–Locatie Amersfoort Amersfoort, Netherlands
B. van Bemmel, MD	Ropcke-Zweers Ziekenhuis Hardenberg, Netherlands
Gerhard Jan Willem Bech, MD	Reinier de Graaf Gasthuis Delft, Netherlands
Ron Pisters, MD	Ziekenhuis Rijnstate–Locatie Arnhem Arnhem, Netherlands
Suzanne Valk	Franciscus Gasthuis & Vlietland–Locatie Vlietland Schiedam, Netherlands
Tjeerd Romer, MD, PhD	Alrijne Ziekenhuis Leiderdorp, Netherlands
Justin Luermans, MD, PhD	Maastricht University Medical Center Maastricht, Netherlands
Driek Beelen, MD	IJsselland Ziekenhuis Capelle a/d Ijssel, Netherlands
Martijn van Eck, MD	Jeroen Bosch Ziekenhuis (JBZ) (Hieronymus Bosch Hospital)– Locatie Den Bosch Capelle a/d Ijssel, Netherlands
Jaco Houtgraaf, MD, PhD	Diakonessenhuis–Locatie Utrecht Utrecht, Netherlands
Thijs Vet, MD	Treant Zorggroep Hoogeveen, Netherlands
Dirk Shellings, MD, PhD	Slingeland Ziekenhuis Doetinchem, Netherlands
T. Oosterhof, MD	Ziekenhuis Gelderse Vallei Ede, Netherlands
Pawel Miekus, MD	NZOZ Pro Cordis Sopockie Centrum Badan Kardiologicznych Sopot, Poland
Waldemar Bebenek, MD	Osrodek Badan Klinicznych CLINSANTE S.C. Torun, Poland
Agata Bielecka-Dabrowa, MD, PhD	Instytut Centrum Zdrowia Matki Polki Lodz, Poland
Jacek Gniot, MD	SP ZOZ Szpital Specjalistyczny w Pulawach Pulawy, Poland
Witold Zmuda, MD	MEDICOME Sp. z o.o. Oswiecim, Poland
Michal Kasprzak, MD	Centrum Medyczne Kermed–Renata Bijata-Bronisz I Ewa Kowalinska Spolka Jawna Bydgoszcz, Poland
Wojciech Balak, MD	Nasz Lekarz Osrodek Badan Klinicznych Bydgoszcz, Poland
Pawel Ptaszynski, MD, PhD	Samodzielny Publiczny Zaklad Opieki Zdrowotnej Centralny Szpital Kliniczny, Uniwersytetu Medycznego w Lodzi Łodz, Poland
Jacek Nowak, MD, PhD	Prywatny Specjalistyczny Gabinet Internistyczny Libiaz, Poland
Janusz Prokopczuk, MD	American Heart of Poland S.A., IV Oddzial Kardiologii Inwazyjnej, Elektrostymulacji i Angiologii Kedzierzyn Kozle, Poland
Andrzej Przybylski, MD, PhD	Kliniczny Szpital Wojewódzki nr 2, Rzeszów Rzeszów, Poland
Iwona Wozniak-Skowerska, MD, PhD	Specjalistyczna Praktyka Lekarska Ruda Śląska, Poland

Investigator	Site
Pawel Derejko, MD	Kardiosystem Warszawa, Poland
Danuta Czarnecka, MD	Gabinety Daszmed Krakow, Poland
Adam Janas, MD	X Oddzial Kardiologii Inwazyjnej, Elektrofizjologii i Elektrostymulacji Tychy, Poland
Jose Luis Merino Llorens, MD, PhD	Hospital Universitario La Paz Madrid, Spain
Luis Tercedor, MD	Complejo Hospitalario Universitario de Granada–Hospital Universitario Virgen de las Nieves Granada, Spain
Andres Iniguez Romo, MD	Hospital Alvaro Cunqueiro Vigo (Pontevedra), Spain
Ricardo Ruiz Granell, MD, PhD	Hospital Clinico Universitario de Valencia Valencia, Spain
Jose Ramon Gonzalez Juanatey, MD	Hospital Clinico Universitario de Santiago Santiago de Compostela, A Coruña, Spain
Domingo Pascual-Figal, MD, PhD	Hospital Clinico Universitario Virgen de la Arrixaca Murcia, Spain
Manuel Martinez-Selles, MD, PhD	Hospital General Universitario Gregorio Maranon Madrid, Spain
Ignacio Anguera Camos, MD, PhD	Hospital Universitari de Bellvitge Barcelona, Spain
Alicia Ibanez Criado, MD	Generalitat Valenciana Conselleria De Sanitat Alicante, Spain
Javier Matrinez Basterra, MD	Complejo Hospitalario de Navarra Pamplona, Navarra, Spain
Alvaro Izquierdo, MD	Hospital Universitario Virgen Macarena Sevilla, Spain
Nuria Rivas Gandara, MD, PhD	Hospital Universitario Vall d'Hebron Barcelona, Spain
Josep M. Alegret Colome, MD	Hospital Universitari Sant Joan de Reus Reus, Tarragona, Spain
Diego Perez Diez, MD	Hospital Universitario Central de Asturias Oviedo, Austurias, Spain
Miguel Ángel Martínez Hervás, MD	Martínez Hervás Cardiólogos Granada, Spain
Maria Medina, MD	Hospital Universitario Virgen de la Victoria Malaga, Spain
Jose María Segura Saint-Gerons, MD, PhD	Hospital Universitario Reina Sofia Córdoba, Spain
Alonso Pedrote Leal, MD	Hospital Universitario Virgen del Rocio Sevilla, Spain
Ignacio Fernandez Lozano, MD	Hospital Universitario Puerta de Hierro Majadahonda, Spain
Aurelio Quesada, MD	Consorcio Hospital General Universitario de Valencia Valencia, Spain
Jose Guerra Ramos, MD	Hospital de la Santa Creu i Sant Pau Barcelona, Spain
Axel Sarrias, MD	Hospital Germans Trias i Pujol Badalona (Barcelona), Spain
Javier Ramos Maqueda, MD	Hospital Universitario Clínico Lozano Blesa Zaragoza, Spain

Investigator	Site
Jacques Mansourati, MD, PhD	CHU de Brest–Hôpital de la Cavale Blanche Brest, France
Pascal Defaye, MD	CHU Grenoble-Alpes–Hôpital Michallon La Tronche, France
Laurence Guedon-Moreau, MD	CHU de Lille - Institut Cœur Poumon Lille Cedex, France
Antoine Milhem, MD	Hopital Saint-Louis de La Rochelle La Rochelle, France
Maxime De Guillebon, MD	Centre Hospitalier de Pau Pau, France
Philippe Chevalier, MD, PhD	Hôpital Louis Pradel–HCL Bron, France
Marc Badoz, MD	CHRU Besancon - Hopital Jean Minjoz Besançon, France
Charalampos Kriatselis, MD	Vivantes Klinikum Neukoelln Berlin, Germany
Gregor Simonis, MD	FAZ Dresden-Neustadt GbR Dresden, Germany
Thorsten Lewalter, MD	Peter Osypka Herzzentrum Munchen Munchen, Germany
Markus Zarse, MD	Maerkische Gesundheitsholding GmbH - Klinikum Luedenscheid Ludenscheid, Germany
Andreas Wilke, MD	Kardiologische Gemeinschaftspraxis Papenburg Papenburg, Germany
Fabian Kraemer, MD	Zentrum fuer Praevention und Rehabilitation Siegen, Germany
Ayham Al-Zoebi, MD	Kardiologische Praxis Dresden, Germany

Table S2: Adjudicated rhythm at time of application of ECG CMS and at time of blinded study drug administration

Verified cardiac rhythm	At time of application of ECG CMS N=255	At time of blinded study drug administration N=255
PSVT	196 (77%)	184 (72%)
Non-PSVT	48 (19%)	60 (24%)
No ECG	11 (4%)	11 (4%)
Accuracy of perceiving PSVT: verified PSVT (n) among patients with adequate ECG data (N')	196/244 (80%)	184/244 (75%)

Data are n (n/N as %) or n (n/N' as %).
CMS=cardiac monitoring system, ECG=electrocardiographic, PSVT=paroxysmal supraventricular tachycardia.

Table S3: Prespecified, secondary measures of efficacy

Prespecified, secondary measures of conversion of PSVT to sinus rhythm after randomised treatment administration*†	Hazard ratio (95% CI), p value*	Relative risk ratio (95% CI), p value†
Treatment group comparison, 5 minutes	‡	**2·719 (1·138–6·495), 0·0166**
Treatment group comparison, 10 minutes	**1·737 (0·961–3.139), 0·0522**	**1·566 (0·935–2·622), 0·0815**
Treatment group comparison, 15 minutes	**2·214 (1·290–3·800), 0·0038**	**1·943 (1·232–3·064), 0·0026**
Treatment group comparison, 45 minutes	**2·150 (1·439–3·212), 0·0001**	**1·601 (1·216–2·107), <0·001**
Treatment group comparison, 60 minutes	**1·889 (1·299–2·747), 0·0003**	**1·374 (1·087–1·736), 0·0054**
Treatment group comparison, 90 minutes	**1·927 (1·349–2·752), 0·0001**	**1·357 (1·107–1.663), 0·0019**
Treatment group comparison, 120 minutes	**1·798 (1·272–2·540), 0·0002**	**1·249 (1·039–1·501), 0·0138**
Treatment group comparison, 180 minutes	**1·708 (1·215–2·400), 0·0003**	**1·184 (0·995–1·409), 0·0496**
Treatment group comparison, 240 minutes	**1·729 (1·232–2·428), 0·0003**	**1·199 (1·009–1·424), 0·0326**
Treatment group comparison, 300 minutes	**1·700 (1·213–2·383), 0·0003**	**0·124 (0·000–0·248), 0·0492**

* The hazard ratio and 95% CI were calculated using the Cox proportional hazards model. The p value was obtained from the Wilcoxon test.

† The relative risk ratio and 95% CI were taken from a Landmark Analysis; the p value was obtained from a chi-square test using subjects converted and subjects censored by each time point.

‡ Hazard ratio not assessed, 5 minutes.

CI=confidence interval, PSVT=paroxysmal supraventricular tachycardia.

Table S4: Test dose–emergent adverse events occurring in ≥5% of patients overall

Category	Overall (N=706)
Nasal discomfort	226 (32%)
Nasal congestion	97 (14%)
Rhinorrhoea	123 (17%)
Throat irritation	96 (14%)
Lacrimation increased	121 (17%)
Sneezing	61 (9%)
Nasal pruritis	39 (6%)
Headache	40 (6%)

Data are n (n/N as %).

*Test dose–emergent adverse events were defined as those that occurred within 24 hours after the test dose date.

Table S5: Prespecified sensitivity (robustness) analyses on primary endpoint analysis—analysis of time-to-conversion of paroxysmal supraventricular tachycardia to sinus rhythm by 30 minutes after blinded study drug

Treatment group comparison in safety population (all patients with any perceived episode of PSVT), placebo (n=120) *vs* etripamil (n=135), conversion of perceived PSVT to SR after randomised treatment administration by 30 minutes	
Hazard ratio (95% CI) *	2·590 (1·639–4·093)
p value†	<0·0001
Treatment group comparison in efficacy population, placebo (n=85) vs etripamil (n=99), conversion of confirmed PSVT to SR after randomised treatment administration by 30 minutes‡	
Hazard ratio (95% CI) *	2·606 (1·648–4·120)
p value†	<0·0001

* The hazard ratio and 95% CI are calculated using the Cox proportional hazards model.

† p value is obtained from the Wilcoxon test.

‡ patients with PSVT conversion due to additional medical interventions censored at 31 minutes

CI=confidence interval, PSVT=paroxysmal supraventricular tachycardia, SR=sinus rhythm.

Table S6: Safety findings from ECG CMS Data During the randomised period (1 vs 2 doses)

Category, n (%)	Placebo 1 x dose N=42	Placebo 2 x dose N=78	Etripamil 1 x 70 mg N=63	Etripamil 2 x 70 mg N=72
Patients with treatment administered and interpretable ECG CMS data	39 (92.9)	77 (98.7)	61 (96.8)	67 (93.1)
Tachyarrhythmias[a]				
Non-sustained ventricular tachycardia (≥3 consecutive beats)	4 (10.3)	15 (19.5)	6 (9.8)	12 (17.9)
PSVT reoccurrence	3 (7.7)	2 (2.6)	1 (1.6)	3 (4.5)
Atrial tachycardia > 30 seconds	0	1 (1.3)	1 (1.6)	1 (1.5)
Atrial fibrillation > 30 seconds	2 (5.1)	2 (2.6)	1 (1.6)	0
Atrial flutter > 30 seconds	1 (2.6)	0	0	0
Ventricular tachycardia (≥ 30 seconds)	0	1 (1.3)[b]	0	0
Bradyarrhythmias[Error! Reference source not found.]				
PR interval prolongation (coded as atrioventricular block, first degree) lasting > 30 seconds	1 (2.6)	0	1 (1.6)	0
Sinus pause ≥ 3 seconds[a]	0	1 (1.3)	0	1 (1.5)
Sinus bradycardia ≤ 40 bpm during more than 30 seconds	0	1 (1.3)	0	0
Atrioventricular block second degree – Mobitz I	0	0	0	0
Atrioventricular block second degree – Mobitz II	0	0	0	0
Atrioventricular block complete	0	0	0	0

Data are n (n/N as %)

ECG CMS = electrocardiographic cardiac monitoring system; PSVT = paroxysmal supraventricular tachycardia.

Error! Reference source not found. Percentage calculated as patients receiving randomized study drug and with ECG CMS recordings evaluable as denominator.

Error! Reference source not found. This case received evaluations that were non-definitive between supraventricular tachycardia with aberrant conduction vs. ventricular tachycardia; for conservatism, it was rated as the latter. Of note, this tachycardia episode was present prior to administration of study drug (placebo).

Error! Reference source not found. Coded to the preferred term sinus arrest. Both cases occurred only after rescue administration of intravenous adenosine administration in patients who had sought emergency department care.

Table S7: Secondary efficacy analyses: additional medical interventions and emergency department visits

	Placebo (N=85)	**Etripamil (N=99)**
Patients obtaining additional medical interventions after randomised treatment		
n (%)	21 (25%)	15 (15%)
p value†	..	0·103
Emergency department visits after randomised treatment		
n (%)	18 (21%)	14 (14%)
p value†	..	0·209

Data are n (n/N as %)

† p value obtained from chi-square testing.