Clinical trial results:
Multi-Centre, Randomized, Double-Blind, Placebo-Controlled, Efficacy, and Safety Study of Etripamil Nasal Spray for the Termination of Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia

The RAPID Study (NODE-301 Part 2) and RAPID Extension (NODE-301 Part 3)

Summary

EudraCT number	2018-000308-41
Trial protocol	NL BE PL FR DE
Global end of trial date	20 January 2023

Results information

Result version number	v1 (current)
This version publication date	28 March 2025
First version publication date	28 March 2025

Trial information

Trial identification

Sponsor protocol code	MSP-2017-1138

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03464019
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Milestone Pharmaceuticals Inc.
Sponsor organisation address	1111 Dr. Frederik-Philips Blvd, Suite 420, Montreal, Canada, H4M 2X6
Public contact	Guy Rousseau, Milestone Pharmaceuticals Inc., +1 514803-2668, grousseau@milestonepharma.com
Scientific contact	Guy Rousseau, Milestone Pharmaceuticals Inc., +1 514803-2668, grousseau@milestonepharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the RAPID study is to determine whether Etripamil nasal spray (NS) self-administered by patients is superior to placebo at terminating episodes of paroxysmal ventricular tachycardia (PSVT) in an at-home setting.

Protection of trial subjects:

The study protocol, all study protocol amendments, written study participant information, informed consent form (ICF), Investigator's Brochure (IB) and any other relevant documents were reviewed and approved by an independent ethics committee (IEC) or institutional review board (IRB) at each study center.

The study was conducted in accordance with the protocol, the ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation (ICH)/Good Clinical Practice (GCP) and other Guidelines, and applicable laws and regulations.

An ICF approved by each study center's IEC/IRB was signed by the participant or their legally authorized representative and the authorized person obtaining the ICF before the participant was entered in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 June 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 178
Country: Number of subjects enrolled	United States: 192
Country: Number of subjects enrolled	Spain: 114
Country: Number of subjects enrolled	Netherlands: 110
Country: Number of subjects enrolled	Poland: 112
Country: Number of subjects enrolled	Belgium: 22
Country: Number of subjects enrolled	France: 8

Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Hungary: 5
Worldwide total number of subjects	748
EEA total number of subjects	378

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	575
From 65 to 84 years	173
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were screened & recruited at sites in France, Spain, the Netherlands, Belgium, Poland, Germany, Hungary. The Efficacy Population included all modified Intent to Treat-mITT patients who took study drug to treat an episode of PSVT confirmed by the Adjudication Committee. The disposition described here is for the Efficacy Population.

Pre-assignment

Screening details:

At the end of the RAPID extension study, the disposition was:
Patients screened = 877;
Patients with screen failure = 130;
Patients who had a test dose = 748;
Patients randomized = 735.
Patients in Test Dose (TD) only population = 445
Patients in the mITT and Safety population = 303
Patients in the Efficacy population = 214

Period 1

Period 1 title	RAPID (Part 2) plus RAPID Ext (Part 3) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Randomization and double-blinding were used to minimize bias arising from the assignment of participants to treatment groups and the expectations of participants, investigators and individuals collecting data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Etripamil

Arm description:

Self-administration of etripamil for a perceived episode of PSVT during the randomized treatment period.

Arm type	Experimental
Investigational medicinal product name	Etripamil
Investigational medicinal product code	MSP-2017
Other name	
Pharmaceutical forms	Nasal/oromucosal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

The dose of etripamil to be evaluated in the RAPID study is 70 mg per nasal spray device. Each nasal spray device delivers a total of 200µL of etripamil.

Arm title	Placebo

Arm description:

Self-administration of placebo for a perceived episode of PSVT during the randomized treatment period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal/oromucosal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

Each nasal spray device delivers a total of 200 µL of placebo

Arm title	Test Dose Only

Arm description:

Single Test Dose of Etripamil in sinus rhythm before randomization

Arm type	Pre-Randomization
Investigational medicinal product name	Etripamil
Investigational medicinal product code	MSP-2017
Other name	
Pharmaceutical forms	Nasal/oromucosal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

The dose of etripamil to be evaluated in the RAPID study is 70 mg per nasal spray device. Each nasal spray device delivers a total of 200µL of etripamil.

Number of subjects in period 1	Etripamil	Placebo	Test Dose Only
Started	160	143	445
Participants randomized	160	143	0
Participants in Efficacy Population	114	100	0
Completed	81	76	0
Not completed	79	67	445
Consent withdrawn by subject	1	5	32
Physician decision	-	-	2
Ablation	11	8	46
Adverse event, non-fatal	3	1	14
Other	1	5	-
Pregnancy	-	-	1
Study terminated by sponsor	61	46	314
Reason not provided by participant	-	-	15
Test Dose Failure	-	-	8
Lost to follow-up	-	1	7
Protocol deviation	1	-	2
Prohibited Medication	1	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Etripamil
Reporting group description:	
Self-administration of etripamil for a perceived episode of PSVT during the randomized treatment period.	

Reporting group title	Placebo
Reporting group description:	
Self-administration of placebo for a perceived episode of PSVT during the randomized treatment period.	
Reporting group title	Test Dose Only
Reporting group description:	
Single Test Dose of Etripamil in sinus rhythm before randomization	

Reporting group values	Etripamil	Placebo	Test Dose Only
Number of subjects	160	143	445
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	129	109	337
From 65-84 years	31	34	108
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	52.2	55.9	53.9
standard deviation	± 13.9	± 12.5	± 14.6
Gender categorical Units: Subjects			
Female	112	100	268
Male	48	43	177

Reporting group values	Total		
Number of subjects	748		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		

Adults (18-64 years)	575		
From 65-84 years	173		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	480		
Male	268		

Subject analysis sets

Subject analysis set title	Efficacy Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The data presented here summarizes demographic and patient-history characteristics for patients who were included in the Efficacy Population.

Reporting group values	Efficacy Population		
Number of subjects	214		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	175		
From 65-84 years	39		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	53.0		
standard deviation	± 13.0		
Gender categorical			
Units: Subjects			
Female	155		
Male	59		

End points

End points reporting groups

Reporting group title	Etripamil

Reporting group description:

Self-administration of etripamil for a perceived episode of PSVT during the randomized treatment period.

Reporting group title	Placebo

Reporting group description:

Self-administration of placebo for a perceived episode of PSVT during the randomized treatment period.

Reporting group title	Test Dose Only

Reporting group description:

Single Test Dose of Etripamil in sinus rhythm before randomization

Subject analysis set title	Efficacy Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The data presented here summarizes demographic and patient-history characteristics for patients who were included in the Efficacy Population.

Primary: Primary endpoint: The time to conversion of an episode of PSVT to sinus rhythm (SR) after study drug administration. (Kaplan Meier Analysis)

End point title	Primary endpoint: The time to conversion of an episode of PSVT to sinus rhythm (SR) after study drug administration. (Kaplan Meier Analysis)[1]

End point description:

The primary efficacy endpoint is defined as an adjudicated termination of a positively adjudicated episode of PSVT (atrioventricular (AV) nodal reentrant tachycardia or atrioventricular (AV) reentrant tachycardia determination if possible) and conversion to sinus rhythm (SR) for at least 30 seconds within 30 minutes of start of study drug dosing.

End point type	Primary

End point timeframe:

Within 30 minutes of start of study drug dosing.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: minute				
median (confidence interval 95%)	17.0 (12.8 to 21.7)	51.6 (36.9 to 86.1)		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analyses - 30min
Comparison groups	Etripamil v Placebo

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Time to conversion of PSVT at 10 minutes

End point title	Time to conversion of PSVT at 10 minutes[2]

End point description:

Time to Conversion Analyses by Additional Specified Time Point

End point type	Secondary

End point timeframe:

Within 10 minutes of start of study drug dosing

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: Kaplan Meier Estimate (%)				
number (not applicable)	34.5	20.2		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analyses - 10min
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0119
Method	Wilcoxon (Mann-Whitney)

Secondary: Use of Study Drug Among Patients in Repeat-Dose Regimen Groups

End point title	Use of Study Drug Among Patients in Repeat-Dose Regimen Groups[3]

End point description:

The RAPID study was designed to assess the efficacy and safety of a treatment regimen of a repeat dose of etripamil to be administered 10 minutes after a first dose if PSVT symptoms persisted, by comparing this etripamil regimen to a placebo one.

End point type	Secondary

End point timeframe:

After the first dose administration

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	87		
Units: patients				
number (not applicable)	64	68		

Statistical analyses

Statistical analysis title	patients chose to take a repeat dose of study drug
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0536
Method	Chi-squared

Secondary: The percentage of patients that required additional medical intervention in an emergency department to terminate an episode of PSVT.

End point title	The percentage of patients that required additional medical intervention in an emergency department to terminate an episode of PSVT.[4]

End point description:

The percentage of patients requiring additional medical intervention in an emergency department to terminate an episode of PSVT.

End point type	Secondary

End point timeframe:

After an episode of PSVT

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: patient number	16	25		

Statistical analyses

Statistical analysis title	Analysis of Additional Medical Intervention
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042
Method	Chi-squared

Secondary: Relief of specific symptom: rapid pulse potentially associated with an episode of PSVT.

End point title	Relief of specific symptom: rapid pulse potentially associated with an episode of PSVT.[5]

End point description:

Impact of Study Drug on Patient-Reported Symptom: rapid pulse during Double-Blind Treated PSVT Episodes

End point type	Secondary

End point timeframe:

During double blind study drug administration

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: patients				
number (not applicable)	53	26		

Statistical analyses

Statistical analysis title	Relief of rapid pulse
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Chi-squared

Secondary: Rating of Treatment Satisfaction Questionnaire for Medication®-9 (TSQM-9) Global Satisfaction

End point title	Rating of Treatment Satisfaction Questionnaire for Medication®-9 (TSQM-9) Global Satisfaction[6]

End point description:

Treatment satisfaction was analyzed by comparing the TSQM-9 score for the Global Satisfaction domain

in the 2 treatment groups

End point type	Secondary

End point timeframe:

Completed as soon as possible after termination of the treated PSVT episode

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: point				
arithmetic mean (standard deviation)	59.4 (± 29.0)	52.7 (± 31.3)		

Statistical analyses

Statistical analysis title	Analysis of Treatment Satisfaction Questionnaire
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.109
Method	ANOVA

Secondary: Relief of specific symptom: palpitations during Double-Blind Treated PSVT Episodes

End point title	Relief of specific symptom: palpitations during Double-Blind Treated PSVT Episodes[7]

End point description:

End point type	Secondary

End point timeframe:

During double blind study drug administration

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: Patients				
number (not applicable)	50	25		

Statistical analyses

Statistical analysis title	Relief of palpitations
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Chi-squared

Secondary: Relief of feeling dizzy or lightheaded

End point title	Relief of feeling dizzy or lightheaded[8]

End point description:

End point type	Secondary

End point timeframe:

During double blind study drug administration

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: patients				
number (not applicable)	28	11		

Statistical analyses

Statistical analysis title	Relief of feeling dizzy or lightheaded
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Chi-squared

Secondary: Relief of shortness of breath

End point title	Relief of shortness of breath[9]

End point description:

End point type	Secondary

End point timeframe:

During double-blind study drug administration

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: patients				
number (not applicable)	19	4		

Statistical analyses

Statistical analysis title	Relief of shortness of breath
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Chi-squared

Secondary: Relief of anxiety potentially associated with an episode of PSVT

End point title	Relief of anxiety potentially associated with an episode of

End point description:

End point type	Secondary

End point timeframe:

During double blind study drug administration

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: patients				
number (not applicable)	20	9		

Statistical analyses

Statistical analysis title	Relief of anxiety
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048
Method	Chi-squared

Secondary: Relief of Chest tightness, pain or pressure

End point title	Relief of Chest tightness, pain or pressure[11]

End point description:

End point type	Secondary

End point timeframe:

During double blind study drug administration

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: Patients				
number (not applicable)	13	7		

Statistical analyses

Statistical analysis title	Relief of chest tightness, pain or pressure
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89
Method	Chi-squared

Secondary: Time to conversion of PSVT at 15 minutes

End point title	Time to conversion of PSVT at 15 minutes[12]

End point description:

End point type	Secondary

End point timeframe:

at 15 minutes

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: Kaplan Meier Estimate (%)				
number (not applicable)	45.1	22.2		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analyses - 15 min
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0038
Method	Wilcoxon (Mann-Whitney)

Secondary: Time to conversion of PSVT at 45 minutes

End point title	Time to conversion of PSVT at 45 minutes[13]

End point description:

End point type	Secondary

End point timeframe:

At 45 minutes

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: Kaplan-Meier Estimate (%)				
number (not applicable)	71.7	47.1		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analyses - 45min
Comparison groups	Etripamil v Placebo

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Time to conversion of PSVT at 60 minutes

End point title	Time to conversion of PSVT at 60 minutes[14]

End point description:

End point type	Secondary

End point timeframe:

At 60 minutes

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: Kaplan-Meier Estimate (%)				
number (not applicable)	74.3	56.4		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analyses - 60 minutes
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Time to conversion of PSVT at 90 minutes

End point title	Time to conversion of PSVT at 90 minutes[15]

End point description:

End point type	Secondary

End point timeframe:

At 90 minutes

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: Kaplan-Meier Estimate (%)				
number (not applicable)	80.5	61.6		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analyses - 90 minutes
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Time to conversion of PSVT at 120 minutes

End point title	Time to conversion of PSVT at 120 minutes[16]

End point description:

End point type	Secondary

End point timeframe:

At 120 minutes

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: Kaplan-Meier Estimate (%)				
number (not applicable)	81.4	66.8		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analyses - 120 minutes
Comparison groups	Etripamil v Placebo

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Time to conversion of PSVT at 180 minutes

End point title	Time to conversion of PSVT at 180 minutes[17]

End point description:

End point type	Secondary

End point timeframe:

At 180 minutes

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: Kaplan-Meier Estimate (%)				
number (not applicable)	81.4	70.0		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analyses - 180 minutes
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Time to conversion of PSVT at 240 minutes

End point title	Time to conversion of PSVT at 240 minutes[18]

End point description:

End point type	Secondary

End point timeframe:

At 240 minutes

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: Kaplan-Meier Estimate (%)				
number (not applicable)	82.3	70.0		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analyses - 240 minutes
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Time to conversion of PSVT at 300 minutes

End point title	Time to conversion of PSVT at 300 minutes[19]

End point description:

End point type	Secondary

End point timeframe:

At 300 minutes

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: Kaplan-Meier Estimate (%)				
number (not applicable)	83.2	72.3		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analyses - 300 minutes
Comparison groups	Etripamil v Placebo

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Rating of Treatment Satisfaction Questionnaire for Medication®-9 (TSQM-9): Effectiveness

End point title	Rating of Treatment Satisfaction Questionnaire for Medication®-9 (TSQM-9): Effectiveness[20]

End point description:

End point type	Secondary

End point timeframe:

Completed as soon as possible after termination of the treated PSVT episode

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: point				
arithmetic mean (standard deviation)	62.3 (± 29.9)	44.9 (± 33.6)		

Statistical analyses

Statistical analysis title	Analysis of Treatment Satisfaction Questionnaire
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA

Secondary: Rating of Treatment Satisfaction Questionnaire for Medication®-9 (TSQM-9): Convenience

End point title	Rating of Treatment Satisfaction Questionnaire for Medication®-9 (TSQM-9): Convenience[21]

End point description:

End point type	Secondary

End point timeframe:

Completed as soon as possible after termination of the treated PSVT episode

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: point				
arithmetic mean (standard deviation)	72.6 (± 17.6)	70.6 (± 17.7)		

Statistical analyses

Statistical analysis title	Analysis of Treatment Satisfaction Questionnaire
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.414
Method	ANOVA

Secondary: Durability of Conversion/Reoccurrence of PSVT

End point title	Durability of Conversion/Reoccurrence of PSVT[22]

End point description:

End point type	Secondary

End point timeframe:

within the 5-hour observation window after conversion to SR for more than 30 seconds

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The relevant statistics for comparing Etripamil vs Placebo is presented here.

End point values	Etripamil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	100		
Units: patient				
number (not applicable)	5	5		

Statistical analyses

Statistical analysis title	Durability of Conversion of Adjudicated PSVT to SR
Comparison groups	Etripamil v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.832
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomized Treatment Emergent Adverse Events (RTEAEs) were defined as treatment-emergent adverse events that occurred within 24 hours after, or 12 hours prior to, or 25 hours prior to and were drug-related to, taking randomized study drug.

Adverse event reporting additional description:

The data presented here are the treatment-emergent adverse events (RTEAEs) for the Safety Population (N=303). 143 were randomized to Placebo vs 160 randomized to Etripamil.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Etripamil

Reporting group description:

Self Administration of Etripamil following an episode of PSVT.

Reporting group title	Placebo

Reporting group description:

Self Administration of Placebo following an episode of PSVT.

Serious adverse events	Etripamil	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 160 (0.00%)	1 / 143 (0.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 160 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Etripamil	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 160 (51.88%)	27 / 143 (18.88%)	
Cardiac disorders			
Ventricular tachycardia			

subjects affected / exposed	4 / 160 (2.50%)	2 / 143 (1.40%)	
occurrences (all)	4	2	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 160 (2.50%)	2 / 143 (1.40%)	
occurrences (all)	4	2	
Dysgeusia			
subjects affected / exposed	2 / 160 (1.25%)	1 / 143 (0.70%)	
occurrences (all)	2	1	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	6 / 160 (3.75%)	2 / 143 (1.40%)	
occurrences (all)	6	2	
Respiratory, thoracic and mediastinal disorders			
Nasal discomfort			
subjects affected / exposed	39 / 160 (24.38%)	10 / 143 (6.99%)	
occurrences (all)	39	10	
Nasal congestion			
subjects affected / exposed	23 / 160 (14.38%)	1 / 143 (0.70%)	
occurrences (all)	23	1	
Rhinorrhoea			
subjects affected / exposed	17 / 160 (10.63%)	4 / 143 (2.80%)	
occurrences (all)	17	4	
Epistaxis			
subjects affected / exposed	9 / 160 (5.63%)	3 / 143 (2.10%)	
occurrences (all)	9	3	
Sneezing			
subjects affected / exposed	7 / 160 (4.38%)	1 / 143 (0.70%)	
occurrences (all)	7	1	
Throat irritation			
subjects affected / exposed	6 / 160 (3.75%)	0 / 143 (0.00%)	
occurrences (all)	6	0	
Oropharyngeal pain			
subjects affected / exposed	3 / 160 (1.88%)	1 / 143 (0.70%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2020	Defined the separation between NODE 301 Part 2 (RAPID) and NODE-301 Part 1 (conducted under Protocol Versions 5.0 and earlier). Introduced changes into RAPID, including study design changes affecting patient dosing and treatment periods, refinement of the eligibility criteria, and changes to the primary efficacy endpoint and to the statistical methods.
01 March 2021	Allowed all Screening Visit procedures and Test Dose Randomization Visits to be conducted on the same day.
14 January 2022	Modified requirements after questions raised by the BfArM: The following updates were made to the amended protocol: Procedures in Case of Emergency or Serious Adverse Event Reporting was revised with updated contact information Study Description and Site Study Procedures were revised to add precision related to when the Test Dose Randomization Visit could not be performed within 28 days of the Screening visit, that missing Follow-up visits was considered a protocol deviation, and to the window for the final study visit. Selection and Withdrawal of Patients was updated to revise one inclusion criterion, clarify one exclusion criterion, and revise one exclusion criterion. Study Treatments was revised to correct the emergency unblinding procedure. Safety Assessments was revised to clarify the reporting of AESIs, clarify procedures for SAEs related to PSVT, to align the reporting language with the German law, to update the contact information for the Medical Monitors Statistics was revised to clarify the definition of the Test Dose Only population and remove the estimators related to safety assessments from the primary efficacy section. Investigator Requirements and Quality Control was updated with a statement related to the obligation to publish the results of the clinical trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported