



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 occurrences (all) | 4 / 160 (2.50%) 4 | 2 / 143 (1.40%) 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 | <p>Defined the separation between NODE 301 Part 2 (RAPID) and NODE-301 Part 1 (conducted under Protocol Versions 5.0 and earlier).</p> <p>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.</p> |
| 01 March 2021 | <p>Allowed all Screening Visit procedures and Test Dose Randomization Visits to be conducted on the same day.</p> |
| 14 January 2022 | <p>Modified requirements after questions raised by the BfArM: The following updates were made to the amended protocol:</p> <p>Procedures in Case of Emergency or Serious Adverse Event Reporting was revised with updated contact information</p> <p>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.</p> <p>Selection and Withdrawal of Patients was updated to revise one inclusion criterion, clarify one exclusion criterion, and revise one exclusion criterion.</p> <p>Study Treatments was revised to correct the emergency unblinding procedure.</p> <p>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</p> <p>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.</p> <p>Investigator Requirements and Quality Control was updated with a statement related to the obligation to publish the results of the clinical trial.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported