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)

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Ethical review	Approved WMO
Status	Completed
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON52096

Source
ToetsingOnline

Brief title
RAPID - NODE-301

Condition

- Cardiac arrhythmias

Synonym
heart rhythm disorder, Paroxysmal Supraventricular Tachycardia

Research involving
Human

Sponsors and support

Primary sponsor: Milestone Pharmaceuticals
Source(s) of monetary or material Support: Industry: Milestone Pharmaceuticals

Intervention

Keyword: Nasalspray, Paroxysmal Supraventricular Tachycardia, Self-administration

Outcome measures

Primary outcome

The primary efficacy endpoint is defined as time to an adjudicated termination

of a positively adjudicated episode of PSVT and conversion to SR for at least

30 seconds within 30 minutes of start of study drug dosing.

Secondary outcome

Additional efficacy endpoints include:

• Time to conversion at time points prior to, and later than, 30 minutes;

• Time to conversion in patients with the option of repeat administration;

• The percentage of patients requiring additional medical intervention in

emergency department to terminate an episode of PSVT

• Relief of specific symptoms (i.e., heart palpitations, rapid pulse feeling,

chest pain, anxiety, shortness of breath, dizziness, and fainting) potentially

associated with an episode of PSVT;

• Rating of TSQM;

• The repeat of key efficacy endpoints in various subgroups of interest (e.g.,

concomitant medications).

During the etripamil test dose period, vital signs, SBP, DBP, HR measurements,

arrhythmia, conduction disorders on the ECGs, and clinical AEs will be

recorded. These data will be reported in the Overall Safety Population.

During the Treatment Periods, safety variables will be recorded, as detailed in

Sections 6.5 and 6.7 of the protocol.

Study description

Background summary

Etripamil, an L-type calcium channel antagonist and short-acting verapamil analog, is being developed by Milestone Pharmaceuticals Inc. (hereinafter Milestone) for the treatment of paroxysmal supraventricular tachycardia (PSVT), used in reference to both the disorder and its associated tachyarrhythmia. A relatively common disorder, PSVT is characterized by episodes of tachyarrhythmia typically with a heart rate (HR) over 100 bpm and a QRS duration of <120 msec. Etripamil is directed towards the 2 most common subtypes of PSVT, atrioventricular (AV) nodal reentrant tachycardia (AVNRT) and AV reentrant tachycardia (AVRT), together accounting for approximately 90% of PSVT cases. In both conditions, a pharmaceutical agent capable of transiently prolonging AV conduction time can result in arrhythmia termination and restoration of normal sinus rhythm (SR). Historically, intravenous (IV) verapamil has been used as an effective agent for treatment of acute episodes of PSVT. However, it has been
replaced in recent years by IV adenosine, which is equally effective in terminating acute episodes of PSVT. Adenosine has the advantage of having a very short half-life, as it is rapidly metabolized during the time required to terminate an episode of PSVT. However, the short half-life of adenosine renders it ineffective when given via routes of administration other than IV. As both of these medications require the establishment of IV access, they are not appropriate for a patient self-administration paradigm in an outpatient setting.

Study objective

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 PSVT in an at-home setting.
The secondary objective of this study is to evaluate the safety of etripamil when self administered by patients without medical supervision.

The exploratory objectives of the study are:
• To evaluate the safety, hemodynamic, and cardiac conduction effects of a test dose of etripamil NS,
• To evaluate the safety and efficacy of etripamil NS in various subgroups of interest (e.g., concomitant medications), and
• To evaluate the safety and efficacy of a treatment regimen of etripamil NS which allows a repeat dose of etripamil to terminate episodes of PSVT in an at-home setting.

Study design

NODE-301 is a multi-centre, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etripamil NS self-administered by patients who experience an episode of PSVT in an at-home setting. Each episode will be documented by an ambulatory CMS that will be placed on the chest by the patient or caregiver when symptoms begin and will record at least 5 hours of continuous ECG. Each CMS will be identified by a unique number.
The study will comprise of 2 parts, Part 1 and Part 2.
• Part 1 describes the conduct of NODE-301 up to the date of the adjudication of the 150th positively adjudicated PSVT episode (January 15th, 2020).
• Part 2 describes the conduct of NODE-301 following the completion of Part 1.
NODE-301 - Part 1
Part 1 was conducted under protocol versions 1 through 5, and has been completed. Part 1 has the same general study design as Part 2 of the study, with the key differences being that Part 2 includes a repeat dosing option during the randomized treatment phaseTreatment Period, as well as during an added open-label treatment phaseOpen-Label Treatment Period (test dose procedures have been amended in Part 2 to assess a repeat dose of etripamil NS 70 mg).

NODE-301 - Part 2 (the RAPID Study)
RAPID (NODE-301 Part 2) will consist of:
• New patients enrolled following protocol version 6.0 (and subsequent versions) implementation
• Patients enrolled prior to protocol version 6.0 implementation and who werehad not dosed with the double-blind study drug, or havehad not discontinued the study before the adjudication of the 150th positively adjudicated PSVT episode, and in Part 1.
• Patients enrolled into the study following the completion of Part 1.
The RAPID study will test the treatment effect of etripamil (a dosing regimen of either single dose or second dose, if symptoms persist after 10 minutes), in a population of patients having a perceived episode of PSVT in an at-home setting, as measured by time to conversion to sinus rhythm for at least 30 seconds.

Enrollment into RAPID will continue until the adjudication of the 180th positively adjudicated PSVT episode in Part 2 patients treated with

double-blind study drug during the Randomized Treatment period required for the study*s pivotal analysis.

Intervention

Before randomization in the RAPID study, all patients will receive a test dose of an etripamil NS dosing regimen (an initial dose of etripamil NS 70 mg followed by a second dose of etripamil NS 70 mg not earlier than 10 minutes and not later than 15 minutes after the first dose) to evaluate tolerability and to train patients on the study procedures.

First PSVT episode during study; Self-administration of the study drug regimen during a PSVT episode is as follows: an initial dose of etripamil NS 70 mg (or placebo) followed by a second dose 10 minutes later if the patient continues to experience PSVT symptoms.

Second PSVT episode during study: Self-administration of the study drug regimen during a PSVT episode is as follows: an initial dose of etripamil NS 70 mg followed by a second dose 10 minutes later if the patient continues to experience PSVT symptoms.

Study burden and risks

the burden and risk of the study mainly consist out of extra time spend in comparision to standard treatment (going to the study site and completing surveys) and side effects.
possible side effects of etripamil NS:
• Nasal congestion (stuffy nose)
• Nasal discomfort
• Eyes watering
• Rhinorrhea (runny nose)
• Sore throat
• Cough
• Sneezing
• Bleeding from the nose
• Decrease in heart rate and/or a drop in blood pressure (hypotension), with symptoms that include dizziness and fainting. In severe cases, low blood pressure can be life-threatening.
• A condition called heart block, where a naturally occurring electrical signal that controls the heartbeat is partially or completely blocked from reaching the heart*s ventricles (the 2 large chambers in the heart that collect and distribute blood from the heart to the rest of the body). In severe cases, heart block can be life-threatening.
Patients have the benefit of the possibility to self administer the study drug to stop a PSVT episode and do not need to go to a hospital directly when having a PSVT episode.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients who meet all of the following criteria will be 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., electrocardiogram [ECG] obtained during an episode of PSVT, Holter monitoring, loop recorder, etc.). If patient had a prior ablation for PSVT, patient must have 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 are sexually active with a male partner who is not surgically sterile (i.e., vasectomy) must agree to use a highly effective form of contraception from the time of signed informed consent

until 30 days after the last administration of study drug. Females of childbearing potential should have a negative serum pregnancy test result at the Screening Visit and at the Final Study Visit, a negative urine pregnancy test at the Test Dose Randomization Visit and must use a highly effective form of contraception between the visits.
The following categories define females who are NOT considered to be of childbearing potential:
• Premenopausal females with 1 of the following:
a. Documented hysterectomy;
b. Documented bilateral salpingectomy or tubal ligation; or
c. Documented bilateral oophorectomy; or

• Postmenopausal females, defined as having amenorrhea for at least 12 months without an alternative medical cause;
5. Male patients, except those who are surgically sterile, must use a highly effective form of contraception during the 3 days after any study drug administration; and
6. Signed written informed consent.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from participation in the study:
1. Systolic blood pressure (SBP) <90 mmHg after a 5-minute rest in 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 may be stopped for at least the equivalent of 5 half-lives, patients may be rescreened once, and chronic use of the drug cannot be restarted after randomization.
2. History of severe symptoms of hypotension, especially syncope, during episodes of PSVT;
3. History of atrial arrhythmia that does not involve the atrioventricular (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 are stopped at least the equivalent of 5 half-lives before the Test Dose Randomization Visit;
6. Current chronic therapy with oral amiodarone, or have taken oral amiodarone within 30 days prior to the Test Dose Randomization Visit;
7. Evidence of ventricular pre-excitation (e.g., delta waves, short PR interval <100 msec, 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. Stroke in the last within 6 months of screening;
12. Evidence of hepatic dysfunction defined as alanine aminotransferase or aspartate aminotransferase >3 × the upper limit of normal (ULN) or total bilirubin >2 × ULN 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 <15mL/min/1.73m2 or requiring hemodialysis;
14. Females who are 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 has the ability to exclude a patient if for any reason the Investigator judges the patient is not a good candidate for the study or will 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; or
17. Previously enrolled in a clinical trial for etripamil and received study drug during a perceived episode of PSVT.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	08-04-2021

Enrollment:	72
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Etripamil Nasal Spray
Generic name:	Etripamil Nasal Spray

Ethics review

Approved WMO Date:	07-10-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-12-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-04-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-04-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-04-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-06-2021

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-06-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-07-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-07-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-02-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-03-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-000308-41-NL
ClinicalTrials.gov	NCT03464019
CCMO	NL75081.100.20

Study results

Date completed:	14-12-2022
Results posted:	16-11-2023
Actual enrolment:	21

First publication
06-09-2023