Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Intranasal Etripamil, a Short-Acting Calcium Channel Blocker, in Healthy Japanese and non-Japanese Adults

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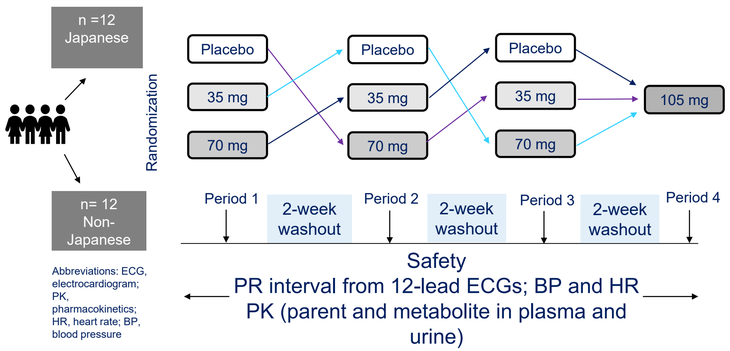
BACKGROUND

Paroxysmal supraventricular tachycardia (PSVT) is a clinical syndrome characterized by the presence of a regular tachycardia (heart rate in excess of 100 beats per minute at rest) of abrupt onset and termination. Common clinical symptoms include palpitations, chest discomfort, light-headedness, and anxiety. For acute termination of supraventricular tachycardia, vagal maneuvers are the first line of intervention, although their success rates are low. When vagal maneuvers are unsuccessful, intravenous administration of adenosine or verapamil is required to restore normal sinus rhythm. At this time, there is no short-acting, non-injectable drug approved for the treatment of acute episodes of PSVT. Etripamil is a fast-acting, intranasally-administered, non-dihydropyridine calcium channel blocker, under investigation for the acute termination of PSVT in a non-medically supervised setting. Etripamil is rapidly converted into an inactive metabolite, MSP-2030.

METHODS



Abbreviations: ECG, electrocardiogram; PK, pharmacokinetics; HR, heart rate; BP, blood pressure

A randomized, double-blind, 4-way crossover, single-dose study was conducted in healthy Japanese and non-Japanese male and female adults. Drug or placebo was delivered intranasally via the Aptar Pharma's Bidose System. Parent drug and metabolite (MSP-2030) were measured in plasma and urine. Etripamil and MSP-2030 plasma concentrations were determined using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. Incidence of adverse events, changes in clinical lab tests, physical examinations, vital signs, and electrocardiograms (ECGs) were used to assess the safety and tolerability of etripamil. PK and PD parameters were calculated by standard noncompartmental methods using Phoenix WinNonlin and were summarized using descriptive statistics.

DISCLOSURE INFORMATION

Doug Wight and Francis Plat: Milestone Employees. Corinne Seng Yue and David Nguyen: Consultants to Milestone.

- Etripamil was **safe** and **well-tolerated** in both Japanese and non-Japanese subjects.
- Etripamil showed comparable safety and tolerability profile in Japanese and non-Japanese male and female adults, indicating **no ethnic differences**.
- All the TEAEs experiences were **mild** or **moderate** in intensity.
- When **dose**- and **weight-normalized**, the **etripamil exposure** in the two groups was **comparable**, suggesting that differences in exposure were simply due to differences in weight between the two groups (Fig. 1, 2, and Table 1, 2).
- The effect of etripamil on **HR**, **PR interval**, and **BP** was similar between the groups at all dose levels.
- The effect of etripamil on **PR interval** was similar between the ethnic groups and lasted for up to 30-45 minutes.
- **PR prolongation** greater than 10% relative to baseline was achieved in less than 10 minutes (Fig. 3).
- These data suggest that etripamil is suitable for investigational use in Japanese and non-Japanese PSVT patients.

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Milestone Pharmaceuticals Inc funded this research.

TABLE 1

Baseline Demographics and Subject Characteristics

		Japanese	Non-Japanese
Age (years)	Mean (Min, Max)	43.75 (26.0, 53.0)	35.67 (21.0, 46.0)
Sex	Male n (%) Female n (%)	6 (50.0) 6 (50.0)	6 (50.0) 6 (50.0)
Ethnicity	No Hispanic or Latino n (%) Hispanic or Latino n (%)	12 (100.0) 0 (0.0)	7 (58.3) 5 (41.7)
BW (kg)	Mean (Min, Max)	64.63 (49.3, 87.4)	73.88 (55.8, 91.0)
BMI (kg/m^2)	Mean (Min, Max)	22.63 (19.7, 26.2)	25.24 (22.2, 29.0)

BW = Body weight; BMI = Body mass index; n = number of subjects.

TABLE 2

Summary statistics of Dose-normalized, Weight-Normalized PK Parameters of Etripamil

Parameter Statistic n	35 mg Etripamil Japanese n=11	 Non-Japanese n=10	70 mg Etripamil Japanese	 Non-Japanese	105 mg Etripamil Japanese	 Non-Japanese
C_{max} BW/dose mean (CV%)	161.33 (59.5)	133.03 (100.5)	n=12 156.55 (65.97)	n=11 121.97 (38.6)	n=11 82.72 (57.1)	n=12 82.70 (62.4)
$AUC_{0\text{-last}}$BW/dose mean (CV%)	6850.67 (44.7)	7101.33 (98.2)	6564.89 (46.0)	6479.41 (43.5)	4576.5 (51.2)	4544.71 (66.9)
$AUC_{0\text{-inf}}$ BW/dose mean (CV%)	7485.46 (44.7)	8184.58 (100.0)	7054.39 (43.8)	6941.1 (45.5)	4939.7 (49.3)	4931.5 (63.8)
CL/F (L/min) mean (CV%)	12.68 (92.2)	17.6 (102.2)	10.91 (50.6)	12.72 (54.96)	19.37 (96.6)	24.98 (97.6)
t_{max} (min) median (range)	5 (3.0, 10.0)	8.4 (5.0, 15.0)	6.0 (5.0, 15.0)	7.0 (2.9, 25.0)	7.0 (5.0, 10.0)	7.0 (1.2, 15.0)
$t_{1/2}$ (min), median (range)	93.74 (42.8, 672)	82.67 (27.2, 685.2)	198.71 (86.3, 382.9)	178.05 (27.3, 223.7)	167.43 (87.3, 269.9)	148.11 (30.8, 226.3)

CV, Coefficient of variation; BW, Body weight, C_{max}, Maximum plasma concentration; t_{max}, The time at which C_{max} occurs; $t_{1/2}$, Half-life; CL/F, Apparent total body clearance; $AUC_{0\text{-last}}$, Area under the plasma concentration-time curve from 0 to the last measurable concentration; $AUC_{0\text{-inf}}$, Area under the concentration-time curve from 0 to infinity; n=number of subjects with observations.

FIGURE 1

Mean dose- and weight-normalized plasma etripamil concentration.

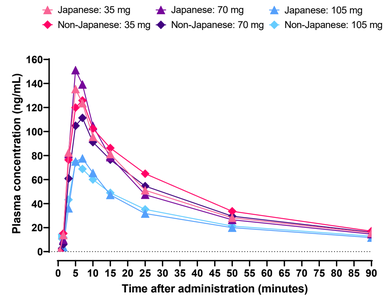


FIGURE 2

Mean dose- and weight-normalized plasma MSP-2030 concentration, an inactive metabolite of etripamil.

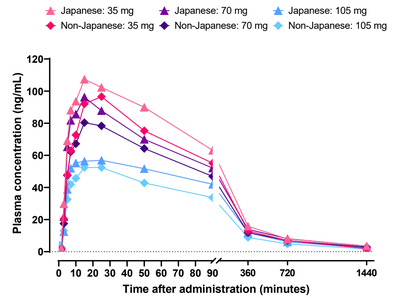
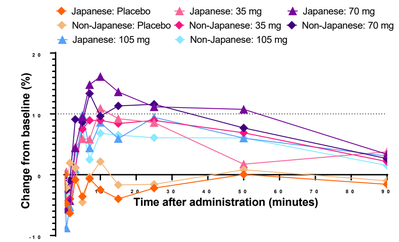


FIGURE 3

Mean percent change in PR interval from baseline to 90 minutes post-dose.



SAFETY DATA

- There were no serious adverse events.
- Treatment-emergent adverse events (>10%) were increased lacrimation, burning nose sensation, and rhinorrhea (occurring with all etripamil doses and placebo).