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COMPOUND NUMBER: WAY-214486 (GAP-486)

PROTOCOL NO.: 3163K1-200-WW

PROTOCOL TITLE: A Safety and Efficacy Dose-Ranging Study of GAP-486 in Subjects With Nonsustained Ventricular Tachycardia and Acute Ischemia

Study Centers: A total of 82 centers were involved in the study and 26 centers enrolled subjects (8 in Russia, 6 in Canada, 4 in India, 2 in Romania and 1 each in Croatia, Brazil, Poland, Serbia, Ukraine and the United States).

Study Initiation and Final Completion Dates: 26 July 2005 to 26 October 2006.
The study was terminated due to a lack of efficacy.

Phase of Development: Phase 2

Study Objectives:

Primary Objective: To test the hypothesis that administration of GAP-486 was effective in decreasing the number of non-life-threatening ventricular arrhythmias in subjects who have acute coronary syndrome (unstable angina, ST-elevation myocardial infarction, or non-ST-elevation myocardial infarction subjects).

Secondary Objective: To assess safety and tolerability in subjects with acute coronary syndrome and to identify potentially effective doses for Phase 3 studies.

METHODS

Study Design: This was a multicenter, placebo-controlled, parallel-group, double-blind, randomized, dose-ranging, Phase 2 study in subjects with non-sustained ventricular tachycardia (NSVT) and acute ischemia. Subjects were randomly assigned to receive 1 of 4 GAP-486 doses (0.1 mg, 1 mg, 5 mg, or 25 mg) or placebo. Blood samples (10 mL) for determination of plasma GAP-486 concentrations were collected at Baseline, 4 hours, 23 hours, 28 hours, and 36 hours from all subjects and were analyzed using a validated liquid chromatography/mass spectrometry assay.

Number of Subjects (Planned and Analyzed): The planned sample size for the study was 500 subjects; 100 subjects per cohort. Due to early termination of the study a total of 120 subjects were enrolled, 2 subjects did not receive study drug and 118 subjects received study drug and were analyzed for safety.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged ≥18 years, with a history of coronary artery disease or left ventricular dysfunction and who experienced an acute ischemic event within 24 hours prior to study entry or an episode of NSVT within 24 hours of the index ischemic event were recruited into the study.

Exclusion Criteria: Subjects who had percutaneous coronary intervention, thrombolytics, or open-heart surgery within 48 hours prior to study entry, or who required it during test article administration, subjects taking an antiarrhythmic medication (other than a beta blocker) were required to discontinue such medication for a period of at least 5 half-lives prior to inclusion in this trial, or who had a history of torsades de points, long QT syndrome, corrected QT interval >0.50 were excluded from the study.

Study Treatment: GAP-486 or matching placebo was administered as a bolus dose over approximately 1 minute followed by a continuous intravenous infusion (250 mL) for 24 hours at a rate of 10 mL/h. Subjects were randomly assigned to 1 of the following groups with an approximately equal number of subjects in each group:

- GAP-486: Dose A: 0.01 mg bolus/0.1 mg infusion

  Dose B: 0.1 mg bolus/1 mg infusion

  Dose C: 0.5 mg bolus/5 mg infusion

  Dose D: 2.5 mg bolus/25 mg infusion

- Placebo

Test article administration started after completion of the 3-hour baseline Holter monitor and not later than 24 hours after the clinical signs of acute ischemia that led to hospitalization.

Efficacy Endpoints:

Primary: The total number of ventricular beats recorded by Holter monitoring during the 24 hour on-therapy phase.

Secondary: The total number of NSVT beats, premature ventricular contractions/couplets, NSVT episodes during the 24 hour on-therapy phase and incidence of new-onset atrial fibrillation during the 24 hour on-therapy phase.

Safety Evaluations: Safety monitoring was based on adverse events (AEs), serious adverse events (SAEs) and deaths throughout the study.

Statistical Methods: Data not available.

RESULTS

Subject Disposition and Demography: A total of 120 subjects were enrolled in the study, 118 subjects received test article and 105 subjects completed the study (Table 1). Demography is presented in Table 2.

Table 1. Summary of Conclusion of Subjects' Participation by Primary Reason – MITT Population

Conclusion Status Reason Total[a]	Overall p-Value[b]	GAP-486 0.1 mg (N=24) n (%)	GAP-486 1 mg (N=22) n (%)	GAP-486 5 mg (N=25) n (%)	GAP-486 25 mg (N=24) n (%)	Placebo (N=23) n (%)	Total (N=118) n (%)
Study completed	0.451	21 (87.5)	21 (95.5)	23 (92.0)	22 (91.7)	18 (78.3)	105 (89.0)
Discontinued	0.451	3 (12.5)	1 (4.5)	2 (8.0)	2 (8.3)	5 (21.7)	13 (11.0)
Death	0.562	2 (8.3)	0	2 (8.0)	1 (4.2)	3 (13.0)	8 (6.8)
Discontinuation of study by Sponsor	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Failed to return	0.599	0	1 (4.5)	0	1 (4.2)	1 (4.3)	3 (2.5)
Other	0.381	0	0	0	0	1 (4.3)	1 (0.8)

MITT = modified intent-to-treat; N = total number of subjects in each treatment group; n = number of subjects meeting specified criteria.
a. Total discontinued was the sum of individual reasons because they were mutually exclusive by subject.
b. Overall p-value: Fisher exact test, p-value (2-tail).

Table 2. Summary of Demographic Characteristics

Characteristic	p-Value	GAP-486 0.1 mg (N=24)	GAP-486 1 mg (N=22)	GAP-486 5 mg (N=25)	GAP-486 25 mg (N=24)	Placebo (N=23)	Total (N=118)
Age (years)							
Mean	0.602[a]	64.75	61.59	61.00	64.42	60.04	62.38
Standard deviation		11.21	13.00	13.15	12.82	11.55	12.31
Minimum		48.00	34.00	35.00	40.00	43.00	34.00
Maximum		84.00	88.00	85.00	86.00	80.00	88.00
Median		63.50	62.00	61.00	67.00	61.00	63.00
Sex, n (%)	0.892[b]						
Male		18 (75.0)	16 (72.7)	18 (72.0)	20 (83.3)	17 (73.9)	89 (75.4)
Female		6 (25.0)	6 (27.3)	7 (28.0)	4 (16.7)	6 (26.1)	29 (24.6)

N = total number of subjects; n = number of subjects with specified criteria.
a. One (1)-way analysis of variance with treatment as factor.
b. Fisher exact test p-value (2-tail).

Efficacy Results: Data not available. This study was terminated prematurely for futility due to lack of efficacy and only safety data is reported.

Safety Results: During the study, 44 subjects (37.3%) reported treatment-emergent adverse events (TEAEs). The number and percentage of subjects reporting TEAEs in the modified intent-to-treat population is summarized in Table 3. Data regarding treatment-related AEs is not available as the study was terminated prematurely for futility.

Seventeen (17) subjects (14.4%) had SAEs during the study. The number and percentage of subjects reporting SAEs in the MITT population is presented in Table 4. Data regarding treatment-related SAEs are not available as the study was terminated prematurely for futility.

Table 3. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events - MITT Population

System Organ Class[a] Preferred Term	Overall p-Value[b]	GAP-486				Placebo (N=23)	Total (N=118)
		0.1 mg (N=24)	1 mg (N=22)	5 mg (N=25)	25 mg (N=24)		
Any adverse event	0.513	11 (45.8)	5 (22.7)	11 (44.0)	9 (37.5)	8 (34.8)	44 (37.3)
Cardiac disorders	0.353	3 (12.5)	2 (9.1)	6 (24.0)	4 (16.7)	1 (4.3)	16 (13.6)
Accelerated idioventricular rhythm	0.788	0	0	0	1 (4.2)	0	1 (0.8)
Atrial fibrillation	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Atrioventricular block second degree	0.194	0	0	2 (8.0)	0	0	2 (1.7)
Atrioventricular block third degree	1.000	0	0	1 (4.0)	0	0	1 (0.8)
Bradycardia	1.000	1 (4.2)	0	1 (4.0)	0	0	2 (1.7)
Cardiac failure	0.936	1 (4.2)	0	1 (4.0)	2 (8.3)	1 (4.3)	5 (4.2)
Cardiac hypertrophy	0.186	0	1 (4.5)	0	0	0	1 (0.8)
Cardiac valve vegetation	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Cardiorespiratory arrest	0.788	0	0	0	1 (4.2)	0	1 (0.8)
Myocardial infarction	0.186	0	1 (4.5)	0	0	0	1 (0.8)
Pericarditis	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Tachycardia	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Ventricular extrasystoles	1.000	0	0	1 (4.0)	0	0	1 (0.8)
Ventricular fibrillation	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Ventricular tachycardia	0.508	0	0	2 (8.0)	1 (4.2)	0	3 (2.5)
Gastrointestinal disorders	0.607	1 (4.2)	0	0	2 (8.3)	1 (4.3)	4 (3.4)
Constipation	0.659	0	0	0	1 (4.2)	1 (4.3)	2 (1.7)
Dry mouth	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Gastroduodenitis	0.788	0	0	0	1 (4.2)	0	1 (0.8)
General disorders and administration site conditions	0.298	1 (4.2)	2 (9.1)	5 (20.0)	2 (8.3)	5 (21.7)	15 (12.7)
Asthenia	1.000	0	0	1 (4.0)	0	0	1 (0.8)
Chest pain	0.454	0	0	2 (8.0)	0	1 (4.3)	3 (2.5)
Fatigue	0.420	0	1 (4.5)	0	1 (4.2)	0	2 (1.7)
Pyrexia	0.758	1 (4.2)	1 (4.5)	2 (8.0)	1 (4.2)	3 (13.0)	8 (6.8)
Sudden cardiac death	1.000	0	0	1 (4.0)	0	0	1 (0.8)
Vessel puncture site bruise	0.381	0	0	0	0	1 (4.3)	1 (0.8)
Infections and infestations	0.958	1 (4.2)	0	2 (8.0)	1 (4.2)	1 (4.3)	5 (4.2)
Cystitis	0.788	0	0	0	1 (4.2)	0	1 (0.8)
Pneumonia	0.743	0	0	1 (4.0)	0	1 (4.3)	2 (1.7)
Respiratory tract infection viral	1.000	0	0	1 (4.0)	0	0	1 (0.8)

Table 3. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events - MITT Population

System Organ Class[a] Preferred Term	Overall p-Value[b]	GAP-486				Placebo (N=23)	Total (N=118)
		0.1 mg (N=24)	1 mg (N=22)	5 mg (N=25)	25 mg (N=24)		
Upper respiratory tract infection	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Investigations	0.567	2 (8.3)	1 (4.5)	1 (4.0)	0	0	4 (3.4)
Blood creatinine increased	0.186	0	1 (4.5)	0	0	0	1 (0.8)
Blood pressure decreased	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Blood urea increased	0.186	0	1 (4.5)	0	0	0	1 (0.8)
Electrocardiogram QT corrected interval prolonged	1.000	0	0	1 (4.0)	0	0	1 (0.8)
White blood cell count increased	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Metabolism and nutrition disorders	0.688	1 (4.2)	1 (4.5)	1 (4.0)	0	2 (8.7)	5 (4.2)
Diabetes mellitus	0.381	0	0	0	0	1 (4.3)	1 (0.8)
Hyperglycaemia	0.186	0	1 (4.5)	0	0	0	1 (0.8)
Hyperkalaemia	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Hyperuricaemia	1.000	0	0	1 (4.0)	0	0	1 (0.8)
Hypokalaemia	0.381	0	0	0	0	1 (4.3)	1 (0.8)
Musculoskeletal and connective tissue disorders	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Arthritis	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Nervous system disorders	0.516	1 (4.2)	0	1 (4.0)	3 (12.5)	2 (8.7)	7 (5.9)
Dizziness postural	0.381	0	0	0	0	1 (4.3)	1 (0.8)
Headache	0.936	1 (4.2)	0	1 (4.0)	2 (8.3)	1 (4.3)	5 (4.2)
Psychomotor hyperactivity	0.788	0	0	0	1 (4.2)	0	1 (0.8)
Psychiatric disorders	0.788	0	0	0	1 (4.2)	0	1 (0.8)
Confusional state	0.788	0	0	0	1 (4.2)	0	1 (0.8)
Disorientation	0.788	0	0	0	1 (4.2)	0	1 (0.8)
Renal and urinary disorders	0.420	0	1 (4.5)	0	1 (4.2)	0	2 (1.7)
Haematuria	0.788	0	0	0	1 (4.2)	0	1 (0.8)
Proteinuria	0.186	0	1 (4.5)	0	0	0	1 (0.8)
Renal failure	0.186	0	1 (4.5)	0	0	0	1 (0.8)
Respiratory, thoracic and mediastinal disorders	0.613	0	2 (9.1)	1 (4.0)	1 (4.2)	1 (4.3)	5 (4.2)
Chronic obstructive pulmonary disease	0.186	0	1 (4.5)	0	0	0	1 (0.8)
Dyspnoea	0.659	0	0	0	1 (4.2)	1 (4.3)	2 (1.7)
Dyspnoea exertional	1.000	0	0	1 (4.0)	0	0	1 (0.8)

Table 3. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events - MITT Population

System Organ Class[a] Preferred Term	Overall p-Value[b]	GAP-486				Placebo (N=23)	Total (N=118)
		0.1 mg (N=24)	1 mg (N=22)	5 mg (N=25)	25 mg (N=24)		
Pulmonary oedema	0.186	0	1 (4.5)	0	0	0	1 (0.8)
Skin and subcutaneous tissue disorders	0.826	1 (4.2)	0	0	1 (4.2)	0	2 (1.7)
Ecchymosis	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Urticaria	0.788	0	0	0	1 (4.2)	0	1 (0.8)
Vascular disorders	0.468	2 (8.3)	1 (4.5)	0	1 (4.2)	0	4 (3.4)
Aortic stenosis	0.186	0	1 (4.5)	0	0	0	1 (0.8)
Haematoma	0.788	0	0	0	1 (4.2)	0	1 (0.8)
Hypotension	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Phlebitis	0.788	1 (4.2)	0	0	0	0	1 (0.8)

Non SAE/SAE results are not separated out.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
MITT = modified intent-to-treat; N = total number of subjects; SAE = serious adverse event.
a. Totals at a higher level are not necessarily the sum of those at the lower levels because a subject may have reported 2 or more different adverse events within the higher-level category.
b. Overall p-value: Fisher exact test, p-value (2-tail).

Table 4. Number (%) of Subjects Reporting Serious Adverse Events - MITT Population

System Organ Class[a] Preferred Term	Overall p-Value[b]	GAP-486				Placebo (n=23)	Total (N=118)
		0.1 mg (n=24)	1 mg (n=22)	5 mg (n=25)	25 mg (n=24)		
Any adverse event	0.159	2 (8.3)	1 (4.5)	4 (16.0)	3 (12.5)	7 (30.4)	17 (14.4)
Cardiac disorders	0.789	2 (8.3)	1 (4.5)	1 (4.0)	2 (8.3)	3 (13.0)	9 (7.6)
Angina unstable	0.743	0	0	1 (4.0)	0	1 (4.3)	2 (1.7)
Cardiac arrest	0.788	0	0	0	1 (4.2)	0	1 (0.8)
Cardiac failure	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Cardiac tamponade	0.381	0	0	0	0	1 (4.3)	1 (0.8)
Cardiac valve vegetation	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Cardiorespiratory arrest	0.788	0	0	0	1 (4.2)	0	1 (0.8)
Coronary artery disease	0.788	0	0	0	1 (4.2)	0	1 (0.8)
Myocardial infarction	0.186	0	1 (4.5)	0	0	0	1 (0.8)
Supraventricular tachycardia	0.381	0	0	0	0	1 (4.3)	1 (0.8)
Tachycardia	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Ventricular fibrillation	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Ventricular tachycardia	0.381	0	0	0	0	1 (4.3)	1 (0.8)
Gastrointestinal disorders	1.000	0	0	1 (4.0)	0	0	1 (0.8)
Retroperitoneal haemorrhage	1.000	0	0	1 (4.0)	0	0	1 (0.8)
General disorders and administration site conditions	0.216	1 (4.2)	0	2 (8.0)	0	3 (13.0)	6 (5.1)
Chest discomfort	0.381	0	0	0	0	1 (4.3)	1 (0.8)
Pyrexia	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Sudden cardiac death	0.255	0	0	1 (4.0)	0	2 (8.7)	3 (2.5)
Sudden death	1.000	0	0	1 (4.0)	0	0	1 (0.8)
Infections and infestations	0.381	0	0	0	0	1 (4.3)	1 (0.8)
Pneumonia	0.381	0	0	0	0	1 (4.3)	1 (0.8)
Respiratory, thoracic, and mediastinal disorders	0.870	1 (4.2)	0	1 (4.0)	1 (4.2)	2 (8.7)	5 (4.2)
Mediastinal haemorrhage	0.381	0	0	0	0	1 (4.3)	1 (0.8)
Pleural effusion	0.788	0	0	0	1 (4.2)	0	1 (0.8)
Pulmonary embolism	0.788	1 (4.2)	0	0	0	0	1 (0.8)
Pulmonary oedema	0.743	0	0	1 (4.0)	0	1 (4.3)	2 (1.7)

Table 4. Number (%) of Subjects Reporting Serious Adverse Events - MITT Population

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
MITT = modified intent-to-treat.

a. Totals at higher levels are not necessarily the sum of those at the lower levels because a subject may report 2 or more different adverse events within the higher-level category.

b. Overall p-value: Fisher exact test, p-value (2-tail).

During the study, 8 subjects died: 1 subject due to cardiac failure, 1 subject due to pulmonary embolism, 1 subject due to sudden death, 1 subject due to pyrexia, third degree atrioventricular block and sudden cardiac death, 1 subject due to cardiorespiratory arrest, 1 subject due to pulmonary edema and 2 subjects due to sudden cardiac death.

CONCLUSION: This study was terminated due to lack of efficacy and not due to any safety issues or concerns.