A Randomized, Placebo-Controlled Study of Vernakalant (Oral) for the Prevention of Atrial Fibrillation Recurrence After Cardioversion

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Background—Vernakalant, a relatively atrial-selective antiarrhythmic drug, has previously demonstrated efficacy for the acute conversion of atrial fibrillation (AF) to sinus rhythm. This study was designed to determine the most appropriate oral dose of vernakalant for the prevention of AF recurrence postcardioversion.

Methods and Results—Patients with nonpermanent AF were randomized to 150, 300, or 500 mg vernakalant or placebo twice daily for up to 90 days. The efficacy analysis was conducted on 605 of 735 patients who entered the maintenance phase on day 3 after cardioversion. The time to the first recurrence of symptomatic sustained AF was significantly longer in the 500 mg vernakalant group, with a median of >90 days versus 29 days in the placebo group (hazard ratio, 0.735; P=0.0275). No significant effect was seen at the lower doses. The percent of patients in sinus rhythm at day 90 was 41%, 39%, and 49% in the 150-mg (n=147), 300-mg (n=148), and 500-mg (n=150) vernakalant groups, respectively, compared with 36% in the placebo group (n=160). There were no vernakalant-related proarrhythmic events. Related serious adverse events occurred in 2 patients in the 150-mg vernakalant group and in 1 patient in each of the other groups.

Conclusions—Vernakalant, 500 mg twice daily, appears to be effective and safe for the prevention of AF recurrence after cardioversion. The absence of proarrhythmia and favorable safety profile is an important finding for the drug.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00526136.

Key Words: antiarrhythmia agents · arrhythmia · cardioversion · prevention · vernakalant

Maintenence of sinus rhythm is a necessary goal in many patients with paroxysmal or persistent atrial fibrillation (AF). In the Euro Heart Survey,1 77% of patients with paroxysmal or persistent AF received pharmaceutical rhythm control therapy. Currently available antiarrhythmic drugs have important limitations. The most effective compound, amiodarone, is associated with severe noncardiac side effects.2,3 Class 1C antiarrhythmics and sotalol are associated with risks of proarrhythmia, which limit their use.4 Finally, the newly registered dronedarone was significantly inferior to amiodarone for the composite primary end point of time to first AF recurrence or premature study drug discontinuation (due to intolerance or lack of efficacy).5 Thus, there is a continued need to develop safe and efficacious antiarrhythmic drugs.

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Vernakalant represents a novel class of antiarrhythmics being developed for conversion as well as maintenance of sinus rhythm after conversion. The electrophysiological properties differ from currently available compounds. Vernakalant has relative atrial specificity and targets early-activating and acetylcholine-activated potassium channels and has a weak effect on sodium channels in atria and ventricles.6–8 Vernakalant slows conduction at rapid pacing rates and prolongs atrial refractoriness. The intravenous formulation has been demonstrated to rapidly convert recent onset AF to sinus rhythm in several clinical trials9–14 and has recently been approved by regulatory authorities in Europe. Vernakalant is currently being developed for the maintenance of sinus rhythm in the hope that it may deliver efficacious as well as safe therapy. The current study was designed to select the most appropriate oral dose of vernakalant for the prevention of AF recurrence after successful cardioversion.

Methods

Study Design

This was a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study performed in...
compliance with the guidelines for good clinical practice and the Declaration of Helsinki. The study was approved by an institutional review board or ethics committee at each site, and written informed consent was obtained from patients before enrollment in the study.

Eligible patients were men and women 18 to 85 years of age and weighing 45 to 113 kg, with symptomatic AF (sustained for 72 hours to 6 months) for which cardioversion was indicated. Patients were required to be hemodynamically stable (systolic blood pressure >100 mm Hg but <190 mm Hg) at screening and before dosing and adequately anticoagulated in accordance with guidelines.

Patients with any of the following criteria were excluded from the study: known prolonged QT syndrome, QTcB interval >500 ms, familial long-QT syndrome, previous tachycardias de pointes (TdP), ventricular fibrillation, or sustained ventricular tachycardia (VT); QRS interval >140 ms; second- or third-degree atrioventricular block; clinically significant persistent bradycardia with heart rate <50 beats per minute, sick sinus syndrome, or pacemaker; clinically significant moderate or severe aortic valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis; New York Heart Association class III or IV congestive heart failure or hospitalization for heart failure in the previous 6 months; myocardial infarction, cardiac surgery, angio-plasty, unstable angina, or acute coronary syndrome within 30 days before enrollment; serious or end-stage disease states; known temporary secondary causes of AF; uncorrected electrolyte imbalance; digoxin toxicity; concurrent participation in another drug study; or receipt of an investigational drug within 30 days before screening. Women were not pregnant or nursing, and if premenopausal, were using birth control. Patients were also excluded if they had received class I or III antiarrhythmics (including sotalol) within 3 days (oral amiodarone within 4 weeks) of random assignment, or intravenous class I or III antiarrhythmics or amiodarone within 24 hours before dosing. Eligible patients were randomly allocated (in a 1:1:1:1 ratio) to placebo or 1 of 3 doses of oral vernakalant: 300, 600, or 1000 mg daily (150, 300, or 500 mg twice daily [BID]). Patients were stratified according to the use of angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) versus nonuse of these drugs.

Patients were admitted in hospital for at least 3 days from the beginning of the treatment. If sinus rhythm was not restored after 3 days of drug exposure, electric cardioversion was performed. Successfully cardioverted patients (sinus rhythm maintained for >90 minutes) entered the maintenance phase of the study and treatment was continued for up to 90 days. Rate control medications were withheld on the day of electric cardioversion until after the cardioversion procedure and the establishment of an adequate heart rate. Patients were not permitted to receive class I or III antiarrhythmics until at least 48 hours after the completion of dosing. Study drug was to be discontinued if any of the following occurred: failed electric cardioversion on day 3; recurrence of AF (or other atrial tachyarrhythmia) documented by two 12-lead ECGs taken 90 minutes apart (all of these events were to be recorded as adverse events [AEs] or serious adverse events [SAEs]); ventricular fibrillation; sustained monomorphic VT (duration >30 seconds), incessant VT (recurrent VT episodes lasting ≤30 seconds), or polymorphic VT (eg, TdP); symptomatic or clinically significant bradycardia (persistent heart rate <45 beats per minute); QTcB prolongation (>550 ms); persistent systolic blood pressure >190 mm Hg or <85 mm Hg; use of prohibited concomitant medications; seizures; syncope; any changes in cardiac rhythm or atrioventricular conduction that compromised the patient’s safety; or any intolerable side effects.

Study visits in the outpatient clinic were scheduled on days 10, 17, 28, 56, and 90 after random assignment. A final follow-up telephone call was performed 30 days after the last dose of study drug for all patients. Safety assessments included 12-lead ECGs, vital signs, clinical laboratory parameters, and physical examinations. Adverse events were recorded through the final follow-up visit and SAEs were recorded through the final follow-up telephone call. Patients recorded their cardiac rhythm each day until the end of the study using a transtelephonic monitor (TTM) and were also instructed to record the presence or absence of symptoms related to AF in a daily diary.

Study End Points

This study had multiple “time-to-event” endpoints that were assessed through 12-lead ECGs taken at scheduled visits and TTM devices used daily by patients to record a single lead 30-second ECG tracing. Multiple cardiologists (both the treating physician and the core laboratory cardiologist, who were blinded to treatment assignment) assessed the recurrence of AF through the 12-lead ECG and TTM data. Symptoms were assessed through a diary completed by patients on a daily basis; the recurrence of AF was only considered symptomatic if the patient diary was dated the day of or the day before the ECG and/or TTM showing AF.

Efficacy end points included the time to the first documented recurrence of (1) symptomatic sustained AF per TTM or investigator decision (sustained AF required 2 positive TTM recordings taken at least 20 hours apart, and symptoms as defined above); (2) AF determined by investigator assessment only; (3) symptomatic AF based on 12-lead ECG (required two 12-lead ECGs showing AF recorded at least 75 minutes apart, and symptoms as defined above); and (4) any AF recurrence (also required two 12-lead ECGs showing AF recorded at least 75 minutes apart).

Additional efficacy end points included the proportion of patients in sinus rhythm at day 90, improvement in AF symptoms as assessed by an AF symptom checklist, and improvement in quality of life as measured by the Short Form (SF)-36 Health Survey.

Statistical Analyses

Sample size calculation was based on the hypothesis of an AF recurrence rate of 60% on placebo at 90 days and a 40% relative reduction in recurrence rate in at least 1 dose of vernakalant, assessed using a 2-sided log-rank test with a 5% significance level and 80% power. This resulted in an estimated sample size of 500 patients (125 per group) entering the maintenance phase of the study. Assuming a 20% to 25% dropout rate during the first 3 days as a result of failure to achieve sinus rhythm, a minimum of 670 patients was planned.

Two interim analyses were performed to assess the safety and tolerability of the study drug, but did not result in modification or early termination of the study.

There were 2 analysis populations defined in this study. The safety population was used for the safety analyses and consisted of all randomly assigned patients who took at least 1 dose of study drug. The modified intent-to-treat population was used for the efficacy analyses and consisted of all randomly assigned patients who took at least 1 dose of study drug and were discharged in sinus rhythm (by day 3) into the maintenance phase of the study.

Time to event was compared with a log-rank test stratified for ACEI/ARB use. A Cox proportional hazards model, with factors for ACEI/ARB use and treatment group, was used to estimate the hazard ratio and respective 95% confidence interval for each pairwise comparison with placebo.

Treatment group comparisons of the change from baseline for the severity and frequency domains of the symptom checklist and the 8 domains of the SF-36 were based on an analysis of covariance model with treatment group, ACEI/ARB use, and baseline score as covariates.

As this was a phase 2 dose ranging study, all analyses were considered exploratory, and no adjustment for multiplicity was performed.

Results

Patient Characteristics

From April 2007 to July 2008, 735 patients were enrolled into the study at 152 centers in 24 countries. There were 732 patients who received study drug, and 605 patients were discharged in sinus rhythm and were available for efficacy
analyses (Figure 1). All 4 treatment groups were well balanced in regard to baseline characteristics (Table 1).

**Efficacy**

A summary of the end points used to assess the time to first recurrence of AF is presented in Table 2. There was a statistically significant reduction in the recurrence of symptomatic sustained AF with vernakalant 500 mg BID compared with placebo (Figure 2). This effect was not significant at the lower doses. The median time to the first recurrence of symptomatic sustained AF was 29 days in the placebo group and 90 days in the vernakalant 500 mg group (hazard ratio, 0.735; \( P = 0.028 \)).

Based on the investigator’s assessment, vernakalant 500 mg BID resulted in a 26% reduction in the rate of AF recurrence (irrespective of symptoms) (hazard ratio, 0.743; \( P = 0.032 \)). Based on the 12-lead ECG assessment, there was a 45% reduction in the rate of symptomatic AF recurrence with vernakalant 500 mg BID (hazard ratio 0.553, \( P = 0.023 \)). The 150- and 300-mg BID doses did not provide a benefit in reducing the rate of sustained or symptomatic AF recurrence as compared with placebo. There was not a statistically significant reduction in the rate of recurrence of any AF (symptomatic or asymptomatic).

Patients who received vernakalant and in whom sinus rhythm was restored were more likely to be in sinus rhythm after 90 days of treatment than patients who received placebo. There were 57 of 160 patients (36%) in the placebo group, 61 of 147 patients (41%) in the 150-mg vernakalant group; electric cardioversion not performed (1 patient), inclusion/exclusion criteria not met (1 patient), and wrong dosing (1 patient) in the 300-mg vernakalant group; and atrial thrombus (1 patient) in the 500-mg vernakalant group. ECV indicates electric cardioversion; IRAF, immediate recurrence of atrial fibrillation.

No significant differences between treatment groups were observed for the frequency or severity scores of the symptom checklist or in any of the 8 domains of the SF-36. An exploratory analysis of the frequency and severity scores from the symptom checklist showed that patients (regardless...
of treatment) had fewer and less severe symptoms when in sinus rhythm compared with when in AF.

Safety
Table 3 outlines the incidence of treatment-emergent AEs, SAEs, and discontinuations due to AEs for the safety population. Four deaths were reported in this study (none of which were considered to be related to treatment): 2 in the placebo group and 1 each in the 150- and 300-mg vernakalant groups. The 2 placebo deaths consisted of a 58-year-old man who died after myocardial infarction and a 70-year-old man who died after an ischemic stroke. In the 150-mg group, a

| Table 3. Incidence of Treatment-Emergent AEs, SAEs, and Discontinuations Due to AEs for the Safety Population |
|---------------------------------------------------------------|----------------|----------------|----------------|----------------|
| Safety outcomes                                              | Placebo (n=184) | 150 mg BID (n=183) | 300 mg BID (n=183) | 500 mg BID (n=182) |
| Incidence of treatment-emergent AEs                          |                |                |                |                |
| Safety analysis                                              |                |                |                |                |
| SAEs                                                         |                |                |                |                |
| Discontinuations due to AEs                                   |                |                |                |                |
Table 2. Summary of End Points to Assess the Time to First AF Recurrence

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (n=160)</th>
<th>Vernakalant (Oral) (BID)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>150 mg (n=147)</td>
</tr>
<tr>
<td>Symptomatic* sustained†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or investigator decision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to event, d</td>
<td>36</td>
<td>26</td>
</tr>
<tr>
<td>KM estimate of patients in SR at day 90, %</td>
<td>62</td>
<td>76</td>
</tr>
<tr>
<td>Hazard ratio for each dose vs placebo‡</td>
<td>0.906</td>
<td>1.009</td>
</tr>
<tr>
<td>P value§</td>
<td>0.438</td>
<td>0.859</td>
</tr>
<tr>
<td>AF recurrence per investigator’s assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to event, d</td>
<td>&gt;90</td>
<td>&gt;90</td>
</tr>
<tr>
<td>KM estimate of patients in SR at day 90, %</td>
<td>50</td>
<td>29</td>
</tr>
<tr>
<td>Hazard ratio for each dose vs placebo‡</td>
<td>0.802</td>
<td>0.792</td>
</tr>
<tr>
<td>P value§</td>
<td>0.416</td>
<td>0.283</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; KM, Kaplan-Meier; SR, sinus rhythm; and TTM, transtelephonic monitor.
*Based on symptoms recorded in the patient diary.
†Based on 2 consecutive TTMs showing AF, recorded ≥20 hours apart.
‡Placebo or lower doses are the denominator of hazard ratios.
§P value comparing the distribution of the Kaplan Meier curves based on a 2-sided log-rank test.
|| Required 2 ECGs ≥75 minutes apart.

70-year-old woman died of cervical cancer, which was undiagnosed before entering the study. In the 300-mg group, a 59-year-old woman died of pneumonia and pulmonary embolism after mitral valveplasty and annuloplasty, approximately 4 weeks after her last dose of study drug.

The incidence of SAEs was similar among treatment groups. The most common SAE was hospitalization associated with the recurrence of AF, reported in 11 of 184 patients (6.0%) in the placebo group, 7 of 183 patients (3.8%) in each of the 150- and 300-mg groups, and 9 of 182 patients (4.9%) in the 500-mg group. Five patients (1 placebo, 4 vernakalant) had SAEs that were considered by the investigator to be related to treatment: ventricular tachycardia before electric cardioversion (during the induction of anesthesia) in the placebo group; angina pectoris and conduction disorder in the 150-mg BID group; atrial flutter in the 300-mg BID group; and sinus arrest at the time of electric cardioversion in the 500-mg BID group.

The most frequent related AE was bradycardia, occurring in 5 patients (2.7%) in the 500-mg group and in 2 patients (1.1%) in each of the other groups. Most of the discontinuations due to AEs were for the recurrence of AF, which occurred more frequently in the placebo group. There were 8 (1.5%) vernakalant patients who discontinued study drug due to related AEs (other than AF recurrence or atrial flutter). In the placebo group, there was 1 (0.5%) premature discontinuation for a related AE of AF recurrence.

In terms of cardiovascular side effects, no treatment-related proarrhythmic events (including TdP) were reported with vernakalant. In addition to the aforementioned related SAE of VT in the placebo group, an unrelated episode of VT (7-beat monomorphic run) was reported 2 days after discontinuation of vernakalant 500 mg BID.

There was no effect of vernakalant on QRS duration; however, the QTcF interval showed a mean prolongation of 5.8 ms (95% confidence interval, 3.54–7.96) in the vernakalant 500-mg group compared with placebo after steady state was reached. No significant increases were observed in the 150- or 300-mg groups. The proportion of patients with a QTcF interval >500 ms at day 10 was 0.7% (1 patient), 0.8% (1 patient), 2.3% (3 patients), and 1.5% (2 patients) in the placebo, 150-, 300-, and 500-mg groups, respectively. On subsequent visits, there was only 1 patient in each of the placebo and 300-mg groups with a QTcF interval >500 ms.

There were no clinically significant trends over time or differences between treatment groups in vital signs, laboratory parameters, or physical examination findings.

Discussion

Main Study Findings

The results of this study demonstrate that after conversion to sinus rhythm, vernakalant at a dose of 500 mg BID signifi-
cantly delayed the time to first AF recurrence when compared with placebo. The drug was safe and well tolerated during exposure up to 90 days, and no proarrhythmic reactions were observed.

**Antiarrhythmic Efficacy**
Vernakalant at a dose of 500 mg BID prolonged the time to the first recurrence of symptomatic sustained AF by 3-fold compared with placebo, from a median of 29 to 90 days. This was associated with a sinus rhythm maintenance rate at 90 days of 49% in vernakalant-treated patients, compared with the placebo rate of 36%. Consistent with other postcardioversion studies, our study population appears to be at high risk for AF recurrences. The efficacy analyses were based on relatively frequent hospital visits in conjunction with a daily recording on a TTM device and a daily symptom diary, allowing for robust detection of early symptomatic and sustained AF recurrences.

**Safety**
There was no evidence for vernakalant-associated proarrhythmia in this study. Importantly, no cases of TdP were observed, which is consistent with vernakalant’s relatively atrial-selective electrophysiological profile. The effect of vernakalant on the QTc interval was small at the highest dose. Vernakalant also proved to be hemodynamically well tolerated. The incidence of related SAEs was very low (0.5% at 500 mg BID), with no dose relationship or target organ system.

**Other Antiarrhythmics**
It has been estimated that over 50% of patients have a recurrence of AF within 1 year of restored sinus rhythm on most currently available antiarrhythmics. Of the various class I and III antiarrhythmics that have been studied in controlled trials for the maintenance of sinus rhythm, amiodarone has shown the highest rate of efficacy. However, amiodarone has numerous side effects and has reported discontinuation rates due to side effects in up to 23% of patients over the course of 1 to 2 years. Dronedarone appeared to have a better safety profile compared with amiodarone in patients with persistent AF; however, dronedarone was significantly less effective than amiodarone in decreasing the recurrence of AF. In the large outcome study, ATHENA, dronedarone reduced all-cause mortality and cardiovascular hospitalization compared with placebo in AF patients at risk for a cardiovascular event; however, questions still remain about dronedarone’s place in the treatment of AF.

**Study Limitations**
The relatively small sample size was a limitation. The 90-day treatment and assessment period was too short to assess any long-term benefit or difficulties that patients with AF could expect from vernakalant treatment. Using time to first relapse and having a single relapse result in treatment termination does not capture the potential benefits or futility that additional cardioversions and treatment courses may have in influencing a patient’s AF burden over time. Another limitation was that no adjustments for multiplicity were performed.

**Conclusions**
This dose-ranging study demonstrated that vernakalant was safe and well tolerated in patients with symptomatic sustained AF, and that 500 mg BID was effective for the maintenance of sinus rhythm after cardioversion. The favorable safety profile associated with vernakalant appears to be a significant advancement in the treatment of AF.

**Acknowledgments**
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DISCLOSURES

Dr Torp-Pedersen received consulting fees, honoraria, and speaker’s fees from Cardiome Pharma Corp and Merck and has been an advisory board and steering committee member for Cardiome Pharma Corp and Merck. Dr Raev was a principal investigator in this clinical trial. Dr Dickinson is a paid consultant for Cardiome Pharma Corp. Drs Butterfield, Mangal, and Beatch are full-time employees of Cardiome Pharma Corp.

REFERENCES


CLINICAL PERSPECTIVE

Maintenance of sinus rhythm is the preferred therapeutic goal in many patients with paroxysmal or persistent atrial fibrillation (AF). It has been estimated that over 50% of patients have a recurrence of AF within 1 year of restored sinus rhythm on most currently available antiarrhythmics, many of which have important safety limitations. Vernakalant represents a new class of antiarrhythmic drugs with a preferential effect on atrial refractoriness. Intravenous vernakalant was recently approved in Europe for the conversion of AF to sinus rhythm, and an oral formulation is in development for the maintenance of sinus rhythm. In this dose-ranging study, after conversion to sinus rhythm, vernakalant at a dose of 500 mg BID significantly delayed the time to first AF recurrence when compared with placebo (median of >90 days versus 29 days, respectively). The drug was safe and well tolerated during exposure up to 90 days, and no proarrhythmic reactions were observed. The current study is the first to demonstrate that vernakalant is effective and safe for the maintenance of sinus rhythm.
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Hospital, Frederiksberg, Tuxen—Estonia: Viimsi Hospital, Haabneeme, Kaik—Tartu University Hospital, Tartu, Kolk—North Estonia Regional Hospital, Talinn, Laks—Parnu Hospital, Parnu, Vahula—Germany: Evangelisches Krankenhaus, Witten, Horacek—Herzzentrum Bad Krozingen, Bad Krozingen, Kalusche—Kerckhoff-Klinik, Bad Nauheim, Mitrovic—
Hungary: Magyar Imre Hospital, Ajka, Amer—Nyiro Gyula Hospital, Budapest, Barsi—Hetenyi Geza County Hospital, Szolnok, Benczur—Petz Aladar County Teaching Hospital, Gyor, Dezsi—Baja City Community Hospital, Baja, Kovacs—Bugat Pal Hospital, Gyongyos, Lippai—Zala County Hospital, Zalaegerszeg, Lupkovics—Bacs-Kiskun County Hospital, Kecskemet, Nagy—Peterfy Sandor Hospital, Budapest, Ronaszeki—Fejer Megyei Szent Gyorgy Korhaz, II., Szekesfehervar, Sereg—Szent Istvan Hospital, Budapest, Vertes—Lithuania: Vilnius University Hospital, Vilnius, Aidietis—Klaipeda Seamen’s Hospital, Klaipeda, Jarasuniene—Kaunas Medical University Hospital, Kaunas, Sakalyte—Netherlands: VU Medisch Centrum, Amsterdam, Allaart—Martini Ziekenhuis, Groningen, Bartels—Stichting Sint Antonius Ziekenhuis, Nieuwegein, Boersma—Isala Klinieken, Zwolle, Maas—Catharina Ziekenhuis, Eindhoven, Michels—Academisch Ziekenhuis Maastricht, Maastricht, Tieleman—Reinier de Graaf Groep, Delft, Withagen—New Zealand: Nelson Hospital, Nelson, Hamer—North Shore Hospital, Takapuna, Hart—Waikato Hospital, Hamilton, Heald—Dunedin Hospital, Dunedin, Wilkins—Poland: Wojewodzki Specjalistyczny Szpital, Lodz, Chojnowska-Jezierska—Szpital Specjalistyczny, Tarnow, Derlaga—Wielospecjalistyczny Szpital Miejski, Bydgoszcz, Hoffman—SP Szpital Kliniczny Nr 2, Szczecin, Kornacewicz-Jach—Wojskowy Instytut Medyczny, Warszawa, Kubik—Szpital Wojewodzki Nr 2 w Rzeszowie, Rzeszow, Kuzniar—III Klinika Chorob, Warszawa, Makowiecki—Szpital Miejski im. J. Brudzinskiego w Gdyni, Gdynia, Miekus—Szpital Powiatowy w Chrzanowie, Chrzanow, Nowak—IV Wojskowy Szpital,
Wroclaw, Ponikowski—Instytut Kardiologii AMG, Gdansk, Rynkiewicz—Okregowy Szpital Kolejowy, Lublin, Trojnar—Portugal: Hosp. de Santa Marta, Lisbon, Oliveira—Centro Hospitalar, Vila Nova de Gaia, Rui Da Gama Ribeiro—Romania: Spitalul Clinic Judetean de Urgenta Brasov, Brasov, Bobescu—Institutul de Cardiologie C.C. Iliescu, Bucuresti, Coman—Spitalul Clinic Colentina Cardiologie, Bucuresti, Dan—Spitalul Clinic Judetean de Urgenta Sf. Spiridon, Iasi, Datcu—Spitalul Clinic Judetean de Urgenta Targu Mures, Targu Mures, Dobreanu—Spitalul Clinic Judetean de Urgenta Arad, Arad, Olariu—Spitalul Clinic Judetean de Urgenta Ploiesti, Ploiesti, Predescu—Spitalul Clinic Judetean Oradea, Oradea, Salajan—Spitalul Clinic de Urgenta Sf. Pantelimon, Bucuresti, Stamate—Spitalul Clinic Municipal de Urgenta Timisoara, Timisoara, Tomescu—Russia: Moscow Medical Academy City Hospital #20, Moscow, Bokarev—St-Petersburg GUZ City Hospital #15, St. Petersburg, Goloshchekin—Moscow City Hospital #29, Moscow, Gratsiansky—MI of Health City Clinical Hospital #2, Yaroslavl, Khokhlov—Yaroslavl Regional Clinical Hospital, Yaroslavl, Khrustalev—Moscow SHI City Clinical Hospital #52, Moscow, Konyakhin—Botkin City Clinical Hospital, Moscow, Libov—War Veteran’s Hospital #3, Moscow, Mkrtchian—Med Centre of RF President Central Clinical Hospital, Moscow, Sidorenko—Pokrovskya City Hospital, St. Petersburg, Vishnevsky—SI Cardiology Research-and-Production Complex of FA of HTMC, Moscow, Zagray—FSI EMC of the President of RF, b.o. City Hospital #51, Moscow, Zateyshchikov—Serbia & Montenegro: Institute of CV Diseases, Sremska Kamenica, Dodic—Clinical Center of Serbia Cardiology III., Belgrade, Grujic—Clinical Center for Cardiovascular Diseases, Niska Banja, Ilic—Clinical Center Bezanijska Kosa, Zemun, Krotin—Dedinje Cardiovascular Institute, Belgrade, Otasevic—Clinical Center Zemun Cardiology, Zemun, Putnikovic—Institute of CV Diseases, Belgrade, Seferovic—Clinical Center of Serbia Emergency Hospital, Belgrade,