Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare Pharmaceuticals Inc.	
Study Number:	12839	NCT00571649
Study Phase:	III	
Official Study Title:	Multicenter, randomized, parallel-group efficacy and safety study for the prevention of venous thromboembolism in hospitalized medically ill patrients comparing rivaroxaban with enoxaparin (The MAGELLAN study)	
Therapeutic Area:	Cardiology/Coagulation	
Test Product		
Name of Test Product:	Rivaroxaban (Xarelto, BAY59-7939)	
Name of Active Ingredient:	Rivaroxban	
Dose and Mode of Administration:	Test drug: Rivaroxaban 10 mg orally, once daily (o.d.) Placebo (for double-dummy design): Rivaroxaban-matched placebo oral tablets	
Reference Therapy/Placebo		
Reference Therapy:	Enoxaparin	
Dose and Mode of Administration:	Active comparator: Enoxaparin 40 mg s.c. injection, o.d. Placebo (for double-dummy design): Enoxaparin-matched placebo solution subcutaneous injection	
Duration of Treatment:	Rivaroxaban: 35 days (29 to 41 days of treatment, inclusive used for efficacy data analysis) Enoxaparin: 10 days (6 to 15 days of treatment, inclusive used for efficacy data analysis)	
Studied period:	**Date of first subjects' first visit:**	04 DEC 2007
	Date of last subjects' last visit:	24 NOV 2010
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 30 APR 2008) was enacted following the European Medicines Agency (EMA) comments. This was a global amendment and affected all study sites. The amendment addressed the EMA's points directly by: • Excluding two controversial subject categories, specifically, diabetes mellitus and "other" • Requiring subjects with infectious and inflammatory diseases, including subjects with acute rheumatic diseases, to have one or more additional venous thromboembolic event (VTE) risk factors • Extending duration of anticipated immobilization to beyond the required 4 days of hospitalization • Including a second, routine lower extremity venous ultrasonography to be performed at the time of parenteral study medication discontinuation. This endpoint was to be tested for non-inferiority of efficacy compared to the enoxaparin regimen as one	

primary endpoint.

All-cause mortality became the major secondary endpoint to be tested confirmatory after the primary endpoints.

Amendment no. 2 (dated 22 MAY 2008) was implemented to comply with the Japanese good clinical practices (GCP) regulations and local requirements. The changes included:

- Expanding the statement regarding monitoring of adverse events (AEs) to include "Adequate medical care will be provided to the subjects for any AEs, and the event will be followed up until resolution or stabilization".
- Clarifying that, in accordance with the Japanese regulatory requirements, a hospital stay of less than 12 hours was reported as a serious adverse event (SAE).
- Expanding the section on unexpected AEs to include "However, any SAE that has already been reported to the regulatory authorities and notified to the centers in writing will be regarded as an "expected" AE although it may not be listed in the investigator's brochure".

Amendment no. 3 (dated 08 JUL 2008) was a global amendment affecting all study sites. The changes made under Amendment 3 included:

- The statement that "Oral contraceptive agents should be carefully assessed to determine if the risk of their use in subjects at increased risk of venous thromboembolic complications is warranted" was added to the exclusion criteria. Because oral contraceptives are known to carry an increased risk of VTEs, this cautionary statement was added to improve subject safety.
- Allowing the use of Lovenox 0.4 mL prefilled syringes (sanofi-aventis Inc., Bridgewater, NJ, USA) in countries outside the USA.

Amendment no. 4 (dated 09 FEB 2009) was a global amendment affecting all study sites. The changes made under Amendment 4 included:

- Including, in the study inclusion criteria, the additional risk factor of acute infectious disease contributing to hospitalization, as this is a known risk factor for the occurrence of VTEs.
- Changing the venue of anticipated immobilization required for inclusion of a subject into the study from the hospital setting exclusively to any type of health care administration setting. This change was made because hospital stay availability and duration vary widely between countries for subjects with identical admitting diagnosis.
- Changing the requirement for anticipated complete immobilization on the first day of hospitalization to any day during the hospital stay to reflect the circumstances when a subject's condition deteriorates during hospitalization.
- Expanding the period of pre-randomization hospitalization from 48 to 72 hours to allow hospital weekend admissions to be screened and randomized on the first day (i.e., Monday) of the following work week.
- Expanding allowed consenting procedures to permit oral informed consent procedures for illiterate subjects.

	• Modifying the Day 5 + 1 visit to a Day 5 + 3 visit to allow increased flexibility in scheduling, in particular when the subject is no longer hospitalized and the scheduling of study visits is more complex. • Changing the reference to assessment of brain natriuretic peptide (BNP) to assessment of BNP fragment because the wrong assay was validated by the Central Laboratory. • Modifying the statistical section of the protocol such that the hierarchy of analyses of secondary efficacy endpoints was now defined in the statistical analysis plan (SAP) rather than the protocol.
Study Centre(s):	This study was conducted at 562 recruiting centers in 52 countries: Austria, 14 sites; Australia, 11 sites; Belgium, 10 sites; Switzerland, 6 sites; Germany, 27 sites; Denmark, 5 sites; Spain, 11 sites; Finland, 2 sites; France, 22 sites; the United Kingdom, 7 sites; Greece, 10 sites; Israel, 10 sites; Italy, 21 sites; Luxembourg, 2 sites; the Netherlands, 4 sites; Norway, 4 sites; New Zealand, 3 sites; Portugal, 10 sites; Sweden, 9 sites; Bulgaria, 8 sites; Czech Republic, 7 sites; Estonia, 4 sites; Croatia, 6 sites; Hungary, 8 sites; Lithuania, 10 sites; Latvia, 6 sites; Poland, 14 sites; Russia, 8 sites; Slovenia, 6 sites; Slovakia, 5 sites; Ukraine, 16 sites; China, 43 sites; Hong Kong, 2 sites; Indonesia, 3 sites; India, 14 sites; Japan, 32 sites; Korea, 7 sites; Malaysia, 3 sites; Pakistan, 3 sites; Singapore, 6 sites; Thailand, 3 sites; Turkey, 6 sites; Taiwan, 5 sites; South Africa, 14 sites; Argentina, 7 sites; Brazil, 8 sites; Canada, 13 sites; Chile, 2 sites; Colombia, 8 sites; Mexico, 12 sites; Peru, 7 sites; the United States, 72 sites.
Methodology:	The study was conducted in a prospective, randomized, double blind, double dummy, active comparator controlled, multi-center and multi-national design. There were 3 independent committees evaluating efficacy and safety. An Ultrasonography Adjudication Committee (UAC) evaluated all ultra-sonograms performed for the presence or absence of thrombi in the deep venous system of the lower extremities. A Clinical Events Adjudication Committee (CEAC) adjudicated the efficacy (acute symptomatic proximal and distal deep vein thrombosis (DVT), pulmonary embolism, VTE related deaths, acute myocardial infarction, and acute ischemic stroke) and safety (all bleeding) clinical events. Subjects were randomized as soon as possible and received the first dose of study drug within 72 hours of hospital admission. Study drug was taken with or without food and at approximately the same time each day. During treatment, subjects participated in study-related visits to undergo a clinical assessment for VTEs and bleeding on Days 1, 5, 10, and 35 and a bilateral lower extremity venous ultrasound was performed on Days 10 (stop of parenteral study drug) and 35 (stop of oral study drug). A final visit was performed on Day 90. The treatment period (i.e., rivaroxaban-enoxaparin-placebo phase) was followed by a follow-up period, which started the day after the last intake of study medication, and ended on Day 90. A full-profile pharmacokinetic/pharmacodynamic (PK/PD) sub-study, which included, assessment of rivaroxaban serum concentrations, prothrombin time (PT), prothrombinase-induced clotting time (PiCT), and D-dimer was conducted. Venous blood samples for assessment of

	coagulation parameters were collected. All coagulation parameters were assessed by the central laboratory.
Indication/ Main Inclusion Criteria:	Indication: Prevention of venous thromboembolism in hospitalized medically ill adult subjects. Main Inclusion Criteria: • Men and women ≥40 years of age • Subjects at risk for VTE being hospitalized for acute medical conditions as follows: ▪ Heart failure (New York Heart Association [NYHA] Class III or IV) ▪ Active cancer (e.g., admitted for chemotherapy or for the treatment of a complication of active cancer) ▪ Acute ischemic stroke ▪ Acute infectious and inflammatory diseases, including acute rheumatic diseases ▪ Acute respiratory insufficiency • At least one additional risk factor for VTE: ▪ Severe varicosis (varicosities) ▪ Chronic venous insufficiency ▪ History of cancer ▪ History of DVT or pulmonary embolism (PE) ▪ History of heart failure (NYHA Class III or IV) ▪ Thrombophilia (hereditary or acquired) ▪ Recent major surgery (6 to 12 weeks) ▪ Recent serious trauma (6 to 12 weeks) ▪ Hormone replacement therapy ▪ Advanced age ≥75 years ▪ Morbid obesity (body mass index ≥35 kg/m^2) ▪ Acute infectious disease contributing to hospitalization
Study Objectives:	**Overall:** The objective of this study was to compare the efficacy and safety of VTE prophylaxis with oral rivaroxaban 10 mg once daily administered for 35 ± 4 days (hereafter referred to as 35 days or Day 35) to subcutaneous enoxaparin 40 mg once daily administration for 10 ± 4 days (hereafter referred to as 10 days or Day 10) in men and women aged 40 years or above who have been hospitalized for a medical illness. **Primary:** The primary efficacy objectives of this study were to: • To demonstrate the superior efficacy of a 35-day treatment period of oral rivaroxaban (10 mg o.d. for 29 to 41 days, inclusive) for VTE prophylaxis compared with a 10-day treatment period with s.c. enoxaparin (40 mg o.d. for 6 to 15 days, inclusive) in men and women greater than or equal to 40 years of age who were hospitalized for a medical illness and at risk for VTE. • To demonstrate the non-inferiority of a 10-day treatment period of oral rivaroxaban (10 mg o.d. for 6 to 15 days, inclusive) for VTE prophylaxis compared with a 10-day treatment period of s.c. enoxaparin (40 mg o.d., for 6 to 15 days, inclusive) in this subject population.

	The primary safety objective of the study was the evaluation of major bleeding events and clinically relevant non-major bleeding events. **Secondary:** Not applicable
Evaluation Criteria:	**Efficacy (Primary):** The primary efficacy variable was a composite of the number of events of: • asymptomatic proximal DVT in lower extremity detected by mandatory bilateral lower extremity venous ultrasonography • symptomatic DVT in lower extremity, proximal or distal • symptomatic, non-fatal pulmonary embolism (PE) • VTE-related death. VTE-related death was defined as either a well-documented fatal PE, or sudden death with no other plausible explanation The two primary efficacy endpoints were (i) test of superiority at Day 35 (Days 29 to 41, inclusive) and (ii) test of non-inferiority at Day 10 (Days 6 to 15, inclusive). The analyses of the primary efficacy endpoints were based solely on the assessments made by the UAC and the CEAC. **Efficacy (Secondary):** The first major secondary efficacy endpoint was defined as a composite of the test of superiority at Day 35 with the component of VTE-related death substituted by all-cause mortality, up to Day 35. The second major secondary efficacy endpoint was the test for superiority at Day 10 using the same composite endpoint as the Day 10 non-inferiority test. Additional secondary endpoints included: • Incidence of symptomatic VTE (DVT or PE) up to Day 10, 35, and 90± 7 • Net clinical benefit at Day 35 comprising the endpoint of the test of superiority at Day 35 plus treatment-emergent major bleeding or non-major clinically relevant bleeding • Incidence of the composite of cardiovascular (CV) death, acute myocardial infarction or acute ischemic stroke up to Day 35 • Incidence of each of the components of the primary efficacy endpoint at Day 35 • Incidence of the composite of the primary efficacy endpoint at Day 10, with the component of VTE-related death substituted by all-cause mortality, up to Day 10 • Net clinical benefit as assessed by the primary efficacy endpoint at Day 10 and treatment-emergent major bleeding or non-major clinically relevant bleeding • Incidence of the composite of CV death, acute myocardial infarction or acute ischemic stroke up to Day 10 • Incidence of each of the components of the primary efficacy endpoint at Day 10

	• Incidence of all-cause mortality up to Day 90 ± 7 days • Incidence of the composite of CV death, acute myocardial infarction or acute ischemic stroke up to Day 90 ± 7 days • Percentage of participants with major vascular events up to Day 10, 35 and 90 • Net clinical benefit as assessed by the primary efficacy endpoint at Day 10, 35 and treatment-emergent major bleeding or non-major clinically relevant bleeding • Health Care Resource Utilization and Quality of Life data An additional study endpoint was health care resource utilization, as assessed by reason and duration of hospitalization, any visit to health care professionals not required by the protocol, any re-hospitalization and/or emergency room visit during the entire study period, any outpatient surgery/consultation not required by the protocol, and rehabilitation center stays following hospital discharge. The final efficacy endpoint related to quality of life and subject reported outcomes, collected using the 12-item Short Form Health Survey (SF-12), Version 2.0, and the European Quality of Life five dimensions questionnaire (EQ-5D). **Safety:** Evaluation of major bleeding events and clinically relevant non-major bleeding events were done. The primary safety outcome of the study was the treatment-emergent clinically relevant bleeding events, which were a composite of treatment-emergent adjudicated major bleeding events and clinically relevant non-major bleeding events.
	Pharmacokinetics: A subset of approximately 125 subjects was to be stratified into 5 groups (of 25 subjects) based on the major diagnoses. The following PK parameters were calculated on Day 1 and Day 10: area under the plasma concentration curve (AUC), area under the curve normalized to body weight (AUC_{norm}), area under the curve for the expected dosing interval obtained after single dose administration (AUC_{τ}), $AUC_{\tau,norm}$, maximum serum concentration (C_{max}), maximum and normalized serum concentration ($C_{max,norm}$), time to reach maximum concentration in plasma (t_{max}), half-life ($t_{1/2}$), and total body clearance of drug from plasma calculated after oral administration (CL/F). **Other:** Pharmacodynamics: Full profile PD sampling was performed in parallel to the PK samples on Day 1 and Day 10. In addition, sparse PD sampling was performed in nearly all subjects at 5 predefined time points: prior to study drug administration, around the time of peak plasma concentrations (2 to 4 hours after intake of the rivaroxaban tablets or rivaroxaban placebo tablet) on the first, 10^{th} and 35^{th} day of study drug administration, and before study drug administration on day 10. Coagulation parameters assessed included international normalized ratio (INR), PT, PiCT, and the fibrin degradation product, D-dimer. Pharmacodynamic parameters assessed included changes to baseline of the maximal effect (E_{max}) and changes to baseline at trough

	(E_{trough}).
Statistical Methods:	**Efficacy (Primary):** All statistical tests were formally performed at a one-sided level of 0.025. However, following general conventions, p-values for superiority testing were presented as two-sided and p-values for noninferiority testing were presented as one-sided. For primary endpoints the multiple testing approach according to Hochberg was employed. If both primary efficacy endpoints were significant at the one-sided level of 2.5%, both primary efficacy endpoints were declared statistically significant. Otherwise, if the p value for one of the primary endpoints was larger than 2.5% (one-sided), the p-value for the other primary endpoint must have been below 1.25% (one-sided) in order to declare statistical significance (for this primary endpoint alone). For both primary efficacy endpoints, the relative risk ratio (rivaroxaban/enoxaparin) with respect to the incidence rates of the primary efficacy endpoint was estimated based on a stratified estimator using Mantel-Haenszel weights (based on sample sizes by geographic region). The corresponding asymptotic 2-sided 95% confidence interval based on the approximation to the normal distribution was determined. Sensitivity analyses were performed for the primary efficacy endpoints. **Efficacy (Secondary):** The first major secondary efficacy endpoint was evaluated by estimating the relative risk of the incidence rates between the treatment groups and calculating the corresponding confidence interval (CIs) and p-values using the same method described for the Day 35 primary efficacy endpoint. This analysis was based solely on the assessments made by the UAC and the CEAC. The population was modified intent-to-treat (mITT) Day 35+ all subjects who died (all-cause mortality) upto Day 41. The second major secondary efficacy variable was the test for superiority at Day 10 of the same composite endpoint as used for Day 10 non-inferiority testing. The population was subjects who were valid for mITT Day 10 or subjects who died (all-cause mortality) up to Day 15. This analysis was based solely on the assessments made by the UAC and the CEAC. Incidence of symptomatic VTE (DVT or PE) up to Day 35 + 6 days, net clinical benefit (including the primary efficacy endpoint and treatment-emergent major bleeding events and treatment-emergent clinically relevant non-major bleeding events) at Day 10 and Day 35 and incidence of the composite of CV death, acute myocardial infarction or acute ischemic stroke up to Day 35 + 6 days, all these endpoints were analyzed in the same way as for the primary efficacy endpoint, Day 35. **Safety:** The primary safety endpoint was the incidence of the composite of

	treatment-emergent major bleeding events and non-major clinically relevant bleeding events observed during treatment and not later than 2 days after the last intake of double-blind study drug.
	Pharmacokinetics: Pharmacokinetic parameters were calculated by non-compartmental analysis. **Other:** Pharmacodynamic parameters were calculated by descriptive statistics.
Number of Subjects:	Planned: 7190 to 8220 total randomized subjects to ensure 2876 evaluable subjects per treatment group. Analyzed: In total, 8428 potential subjects signed an informed consent form and were screened for eligibility. Of these, 327 subjects failed screening and were not randomized. The remaining 8101 subjects were randomized at 562 study centers in 52 countries to one of the two treatment groups: 4050 were randomized to active rivaroxaban and 4051 were randomized to active enoxaparin.

Study Results

Results Summary — Disposition and Baseline

There were generally no differences between the two treatment groups with respect to subject disposition, demographics, and baseline characteristics. Subjects in both treatment groups had a similar medical history. The mean number of days of hospitalization prior to treatment was 1.4 days (median 1.0 days). Median post-randomization hospitalization time was 11 days, and median post-randomization complete immobilization time was 4 days. The most common medical condition for hospitalization was acute infectious disease (47.3%), followed by heart failure (32.4%), and acute respiratory insufficiency (27.9%) (safety population). Overall in the safety population, the mean age was 69 years (range: 40 to 105 years), and mean body mass index (BMI) was 28.2 kg/m^2 (range: 12.7 to 72.7 kg/m^2). Sixty-nine percent of subjects were White, 20% were Asian, and 2% were Black. Of note, there were statistically significantly more males in the rivaroxaban group than in the enoxaparin group in all analysis sets (p = 0.0061, safety set).

A total of 6005 subjects completed the full 35-day treatment period, 2958 (73.0%) in the active rivaroxaban group and 3047 (75.2%) in the active enoxaparin group. Mean duration of treatment for the entire treatment period was 32.4 days for active rivaroxaban and 8.6 days for active enoxaparin in the efficacy modified intent-to-treat (mITT) Day 35 population. Mean compliance over the entire treatment period was 98.6% for rivaroxaban and 99.4% for enoxaparin (mITT Day 35). The mean time from randomization to the Day 10 visit ultrasonogram was 8.8 days (median 8.0 days) in both treatment groups, and to the Day 35 visit ultrasonogram was 35.2 days for rivaroxaban and 35.1 days for enoxaparin (median time 35 days in both treatment groups).

Results Summary — Efficacy

Rivaroxaban 10 mg o.d. for a duration of 35 days was shown to be effective for the prevention of VTE in subjects with acute medical illnesses at risk for VTE. The primary efficacy variable was a composite of the number of events of (1) asymptomatic proximal DVT in lower extremity detected by mandatory bilateral lower extremity venous ultrasonography; (2) symptomatic DVT in lower extremity, proximal or distal; (3) symptomatic, nonfatal PE; and (4) VTE-related death. Efficacy was analyzed during the following phases of the study:

- Rivaroxaban-enoxaparin phase: Each treatment group received both active treatment and placebo; Day 1 to Day 10 (Day 6 to Day 15, inclusive used for efficacy data analysis).
- Rivaroxaban-placebo phase: Rivaroxaban subjects continued to receive active treatment; enoxaparin subjects continued to receive placebo; Day 10 to Day 35 (Day 16 to Day 41, inclusive used for efficacy data analysis).
- Rivaroxaban-enoxaparin/placebo phase: Rivaroxaban subjects received active treatment (35 days total), while enoxaparin subjects received active treatment for the first 10 days only, and then placebo for the remaining 25 days; Day 1 to Day 35; (Day 1 to Day 41 inclusive used for efficacy data analysis).
- Follow-up phase: Subjects did not receive study drug. Started the day after the last intake of study medication, regardless of the duration of study-drug administration, and ended on Day 90; (Last intake of study drug to Day 97 inclusive used for efficacy data analysis).
- Observational phase: The entire treatment period and the subsequent follow-up period. Randomization until Day 90 Visit (Day 1 to Day 97 inclusive used for efficacy data analysis).

The primary efficacy evaluation of the composite primary efficacy variable was performed at Day 35 and Day 10 endpoints.

At Day 35, the end of the rivaroxaban-enoxaparin/placebo phase (treatment phase), rivaroxaban (10 mg o.d. for 35 days) was statistically significantly superior to enoxaparin (40 mg SC for 10 days) in the mITT Day 35 population ($p = 0.0211$). The relative risk was 0.771 with the CI ranging from 0.618 to 0.962. The relative risk reduction was 22.89%, (95% CI: 3.83% to 38.17%). The incidence rate of the primary efficacy composite outcome events at Day 35 was higher in the enoxaparin group (5.7% [175/3057]) than in the rivaroxaban group (4.4% [131/2967]) (mITT Day 35 population).

At Day 10, the end of the rivaroxaban-enoxaparin phase (active control treatment phase), rivaroxaban 10 mg o.d. was statistically significantly non-inferior (with a relative margin of 1.5, one-sided $p = 0.0015$) to enoxaparin 40 mg SC in the per protocol (PP) Day 10 population. The relative risk was 0.968 with 95% CI ranging from 0.713 to 1.314. The relative risk reduction was 3.25% (95% CI -31.38% to 28.75%). The incidence rate of the primary efficacy composite outcome events at Day 10 was identical in both treatment groups in the per-protocol (PP) Day 10 population (rivaroxaban, 2.7% [78/2938]); enoxaparin, 2.7% [82/2993]).

In addition, the incidence of each of the individual components of the composite primary efficacy endpoint at Day 35 was lower in the rivaroxaban group than in the enoxaparin group in the mITT Day 35 population. The enoxaparin group had a numerically higher incidence of VTE-related death (1.0%) than the rivaroxaban group (0.6%) at Day 35. At Day 35, the majority of events in both treatment groups were in the category asymptomatic proximal DVTs in lower extremity (rivaroxaban, 3.5%; enoxaparin, 4.4%).

The incidence of each of the individual components of the composite primary efficacy endpoint at Day 10 in the rivaroxaban group was similar to the enoxaparin group in the PP Day 10 population as summarized in Table 1.

Table 1: Incidence rates of primary endpoint

Primary endpoint / components	Treatment group	
	Rivaroxaban	Enoxaparin
Day 35 + 6: Modified intent-to-treat Day 35	**N = 2967 (100%)**	**N = 3057 (100%)**
Any event	**131 (4.4%)**	**175 (5.7%)**
Symptomatic non-fatal pulmonary embolism	10 (0.3%)	14 (0.5%)
Symptomatic deep vein thrombosis in lower extremity	13 (0.4%)	15 (0.5%)
Asymptomatic proximal deep vein thrombosis in lower extremity	103 (3.5%)	133 (4.4%)
Venous thromboembolism related death	19 (0.6%)	30 (1.0%)
Death (pulmonary embolism)	1 (<0.1%)	1 (<0.1%)
Death (pulmonary embolism cannot be excluded)	18 (0.6%)	29 (0.9%)
Day 10 + 5: Per protocol Day 10	**N = 2938 (100%)**	**N = 2993 (100%)**
Any event	**78 (2.7%)**	**82 (2.7%)**
Symptomatic non-fatal pulmonary embolism	6 (0.2%)	2 (<0.1%)
Symptomatic deep vein thrombosis in lower extremity	7 (0.2%)	6 (0.2%)
Asymptomatic proximal deep vein thrombosis in lower extremity	71 (2.4%)	71 (2.4%)
Venous thromboembolism related death	3 (0.1%)	6 (0.2%)
Death (pulmonary embolism cannot be excluded)	3 (0.1%)	6 (0.2%)

In the rivaroxaban-placebo phase (placebo control treatment phase), evaluated using a sensitivity analysis, rivaroxaban was statistically significantly superior to enoxaparin (p = 0.0035) at Day 35 (mITT [Day 10 to Day 35] population). The relative risk was 0.649, with the 95% CI ranging from 0.485 to 0.867. The relative risk reduction was 35.14% (95% CI: 13.27% to 51.50%). The incidence rate of the primary efficacy composite outcome events at Day 35 for the mITT (Day 10 to Day 35) population was higher in the enoxaparin group (3.8%) than in the rivaroxaban group (2.5%). The enoxaparin group had a numerically higher incidence of VTE-related death (0.5%) than the rivaroxaban group (0.3%). The majority of events in both treatment groups were in the category asymptomatic lower proximal DVTs (rivaroxaban, 2.1%; enoxaparin, 2.9%).

Table 2: Incidence rates of primary endpoint (mITT population; Day 10 to Day 35)

Events (Day 10 + 5 up to Day 35 + 6 days)	Treatment group	
Primary endpoint / components	**Rivaroxaban**	**Enoxaparin**
Modified intent-to-treat (Day 10 to Day 35) population	**N = 2934 (100%)**	**N = 3017 (100%)**
Any event	**72 (2.5%)**	**114 (3.8%)**
Symptomatic non-fatal pulmonary embolism	1 (<0.1%)	10 (0.3%)
Symptomatic deep vein thrombosis in lower extremity	3 (0.1%)	7 (0.2%)
Asymptomatic proximal deep vein thrombosis in lower extremity	61 (2.1%)	89 (2.9%)
Venous thromboembolism related death	9 (0.3%)	15 (0.5%)
Death (pulmonary embolism)	1 (<0.1%)	0
Death (pulmonary embolism cannot be excluded)	8 (0.3%)	15 (0.5%)

Additional sensitivity analyses confirmed the results of the primary efficacy analyses.

Subgroup analyses: At Day 35 rivaroxaban was generally more effective in reducing the incidence of VTE compared with enoxaparin across a diverse range of primary medical illnesses, other risk factors, demographic factors, and geographic regions. Of note:

- Rivaroxaban appeared to be more effective in subjects in Western Europe (including Australia, New Zealand, and Israel) than in other regions compared with enoxaparin, with a relative risk of 0.5, 95% CI: 0.319 to 0.783; (mITT Day 35 population).
- Rivaroxaban appeared to be more effective than enoxaparin in the age subgroup ≥75 years compared with enoxaparin (relative risk 0.624; 95% CI: 0.458 to 0.848; mITT Day 35 population) than in other age subgroups.
- Rivaroxaban appeared to be more effective in subjects with acute infectious and inflammatory disease (relative risk 0.657; 95% CI: 0.475 to 0.909; mITT Day 35 population) than other medical conditions.

An exception was:

- Rivaroxaban appeared to be less effective in subjects with active cancer (relative risk 1.340; 95% CI: 0.706 to 2.542; mITT Day 35 population), compared with enoxaparin.

- With few exceptions, at Day 10 rivaroxaban was generally as effective as enoxaparin in reducing the incidence of VTE across a diverse range of primary medical illnesses, other risk factors, demographic factors, and geographic regions. Some exceptions were:
- Rivaroxaban appeared to be less effective than enoxaparin for the age subgroup ≥65 to <75 years (relative risk = 1.88; 95% CI: 1.017 to 3.461; PP Day 10 population) than other age subgroups.
- Rivaroxaban appeared to be less effective in subjects with duration of complete immobilization post randomization of 4 - 6 days (relative risk = 1.75; 95% CI: 0.914 to 3.363; PP Day 10 population) compared with enoxaparin.
- Rivaroxaban appeared to be more effective in subjects with duration of complete immobilization >6 days post randomization (relative risk = 0.671; 95% CI: 0.369, to 1.222; PP Day 10 population), compared with enoxaparin.
- Rivaroxaban appeared to be less effective in subjects with active cancer (relative risk 2.500; 95% CI: 0.797 to 7.847; PP Day 10 population) compared with enoxaparin.

An evaluation of secondary efficacy endpoints led to the following results:

When the component of VTE-related death (in the primary variable) was substituted by all-cause mortality, rivaroxaban appeared to be more effective than enoxaparin, but statistically significant superiority of rivaroxaban over enoxaparin in the mITT Day 35 population (expanded to include all subjects with cause of death not VTE-related) was not demonstrated.

In the rivaroxaban-enoxaparin/placebo phase, the incidence rate of the composite endpoint, including all-cause mortality at Day 35 was 8.6% (266/3096) in the rivaroxaban group and 9.2% (293/3169) in the enoxaparin group, and the relative risk was 0.931, with the 95% CI ranging from 0.795 to 1.091. The second major efficacy endpoint (superiority at Day 10 using the same composite endpoint as the Day 10 non-inferiority test) was also not met.

For the incidence of symptomatic VTE, excluding VTE-related death, numerical results favored rivaroxaban at Day 35 (rivaroxaban, 0.6%; enoxaparin, 0.7%) and Day 90 (rivaroxaban, 0.7%; enoxaparin, 0.9%), and enoxaparin at Day 10 (rivaroxaban, 0.5%; enoxaparin, 0.3%); there was no statistical significance difference. A similar pattern was found for symptomatic VTE including death: Day 35 (rivaroxaban, 1.0%; enoxaparin, 1.4%) and Day 90 (rivaroxaban, 1.7%; enoxaparin, 1.9%), and Day 10 (rivaroxaban, 0.7%; enoxaparin, 0.6%).

The net clinical benefit, which was defined as a composite of the primary efficacy endpoint plus major and clinically relevant non-major bleeding events, rivaroxaban had a less favorable profile, compared with enoxaparin, mainly due to the higher number of bleeding events in the rivaroxaban group: net clinical benefit at Day 35 (rivaroxaban, 9.4%; enoxaparin, 7.8%; mITT Day 35, statistically significant in favor of enoxaparin [two-sided p-value 0.0224]) and at Day 10 (rivaroxaban, 4.5%; enoxaparin, 3.9%; PP Day 10).

Table 3: Net clinical benefit

Net clinical benefit endpoint/components	Treatment group Rivaroxaban	Enoxaparin
Day 35 + 6: Modified intent-to-treat Day 35 plus major and clinically relevant bleeds (primary population)	**N = 3042 (100%)**	**N = 3082 (100%)**
Any event	**286 (9.4%)**	**240 (7.8%)**
Symptomatic non-fatal pulmonary embolism	10 (0.3%)	14 (0.5%)
Symptomatic deep vein thrombosis in lower extremity	13 (0.4%)	15 (0.5%)
Major bleeding	43 (1.4%)	15 (0.5%)
Clinically relevant non-major bleeding	124 (4.1%)	52 (1.7%)
Asymptomatic lower proximal deep vein thrombosis	104 (3.4%)	133 (4.3%)
Venous thromboembolism related death	19 (0.6%)	30 (1.0%)
Death (pulmonary embolism)	1 (<0.1%)	1 (<0.1%)
Death (pulmonary embolism cannot be excluded)	18 (0.6%)	29 (0.9%)
Day 10 + 5: Per protocol Day 10 plus major and clinically relevant bleeds (primary population)[a]	**N = 2950 (100%)**	**N = 3007 (100%)**
Any event	**134 (4.5%)**	**118 (3.9%)**
Symptomatic non-fatal pulmonary embolism	6 (0.2%)	2 (<0.1%)
Symptomatic deep vein thrombosis in lower extremity	7 (0.2%)	6 (0.2%)
Major bleeding	9 (0.3%)	4 (0.1%)
Clinically relevant non-major bleeding	51 (1.7%)	32 (1.1%)
Asymptomatic lower proximal deep vein thrombosis	71 (2.4%)	71 (2.4%)
Venous thromboembolism related death	3 (0.1%)	6 (0.2%)
Death (pulmonary embolism)	3 (0.1%)	6 (0.2%)

The incidence of major vascular events (CV death, acute myocardial infarction, or acute ischemic stroke) was the same in both treatment groups at Day 10 (1.0%) and at Day 90 (2.8%), and slightly higher in the rivaroxaban group at Day 35 (rivaroxaban, 1.8%; enoxaparin, 1.6%).

The incidence of all-cause mortality at Day 90 was slightly higher in the rivaroxaban group (rivaroxaban, 6.7%; enoxaparin, 6.2%), but no statistically significant difference between treatment groups was seen (p-value 0.400).

Health economics and outcomes analyses did not reveal any notable differences between the treatment groups, but confirmed the fact that these subjects were severely ill, with a duration of hospitalization of 11 days and an average of 4 days of complete immobilization.

Results Summary — Safety

The safety analysis was performed on 7998 randomized subjects who received at least one dose of study drug, rivaroxaban (3997 subjects) or enoxaparin (4001 subjects).

The primary safety outcome of the study was the assessment of clinically relevant bleeding events which are a composite of treatment-emergent adjudicated major bleeding events and clinically relevant non-major bleeding events.

Overall, the incidence of all adjudicated bleeding events (major, clinically relevant non-major, and minimal) was higher in the rivaroxaban group when compared with the enoxaparin group in all phases of the study: the rivaroxaban-enoxaparin/placebo phase (Day 1 to 35), the rivaroxaban-enoxaparin phase (Day 1 to 10), and the rivaroxaban-placebo phase (Day 10 to 35). In the follow-up phase of the study (Day 35 to 90), the bleeding events were comparable in the two treatment groups.

The incidence of clinically relevant bleeding events in the rivaroxaban and enoxaparin groups was reported in 164 (4.1%) and 67 (1.7%) subjects in the rivaroxaban-enoxaparin/placebo treatment phase (relative risk of 2.455, p <0.0001), 111 (2.8%) and 49 (1.2%) subjects in the rivaroxaban-enoxaparin treatment phase (relative risk of 2.272, p <0.0001), and 56

(1.4%) and 19 (0.5%) subjects in the rivaroxaban-placebo treatment phase (relative risk 2.958, p <0.001), respectively. The confidence intervals and p-values for the weighted relative risks of bleeding events in the three treatment phases were of significance in favor of enoxaparin.

Major bleeding events were reported in 64 (1.6%) subjects in the rivaroxaban group (74 major bleeding events) and 37 (0.9%) subjects in the enoxaparin group (42 major bleeding events). By phase, the major bleeding events in the rivaroxaban-enoxaparin/placebo phase were reported in 43 (1.1%) vs 15 (0.4%) subjects, in the rivaroxaban-enoxaparin treatment phase in 24 (0.6%) vs 11 (0.3%) subjects, in the rivaroxaban-placebo treatment phase in 19 (0.5%) and 4 (< 0.1%) subjects in the rivaroxaban and enoxaparin groups, respectively. In the follow-up phase the incidence was the same in either treatment group (23 [0.6%] subjects).

- A total of 8 (0.1%) subjects were reported with treatment-emergent (Day 1 to 35) fatal bleeding events leading to death, 7 in the rivaroxaban group (3 due to pulmonary site bleeding, 2 due to intracranial bleeding events, and 1 each due to retroperitoneal and gastrointestinal bleeding event) and 1 in the enoxaparin group (due to tracheal bleeding event). Majority of the fatal bleeding events occurred during the rivaroxaban-enoxaparin treatment phase (Day 1 to 10) with 5 cases in the rivaroxaban group and 1 in the enoxaparin group.

  In the rivaroxaban-enoxaparin/placebo treatment phase, the most prominent difference in the incidence of bleeding events was reported (rivaroxaban vs enoxaparin) for the intracranial bleeding site (4 [0.1%] vs 2 [<0.1%] subjects), retroperitoneal bleeding site (3 [<0.1%] vs 0 subjects), and pulmonary bleeding site (3 [<0.1%] vs 0 subjects).
- The incidence of critical site bleeding events was also higher in the rivaroxaban group when compared with enoxaparin. In the rivaroxaban-enoxaparin/placebo treatment phase, the most prominent difference in the incidence of critical site bleeding events was reported (rivaroxaban vs enoxaparin) for the intracranial bleeding site (4 [0.1%] vs 2 [<0.1%] subjects), retroperitoneal bleeding site (3 [<0.1%] vs 0 subjects), and pulmonary bleeding site (3 [<0.1%] vs 0 subjects).
- Bleeding events that resulted in a fall of hemoglobin (Hb) to ≥2 g/dL (0.8% vs 0.2%) or that required blood transfusions of ≥2 units (0.6% vs 0.2%) were also higher in the rivaroxaban group when compared with the enoxaparin group.

The number of subjects with multiple bleeding events was slightly higher in the rivaroxaban group in comparison to enoxaparin.

Clinically relevant non-major bleeding events were higher in rivaroxaban (158 [4.0%] subjects with 184 bleeding events) in comparison to enoxaparin (83 [2.1%] subjects with 90 bleeding events). However, the incidence of minimal bleeding events was comparable in the two treatment groups with reports of 382 (9.6%) subjects in the rivaroxaban group and 330 (8.2%) subjects in the enoxaparin group.

The incidence rates for adjudicated treatment-emergent bleeding events analyzed in the four geographic regions (Western-Europe, Eastern-Europe, Asia/Africa, and America) did not show any consistent subgroup findings. Analysis of treatment-emergent bleeding events was also performed for numerous specified covariates grouped into demography, immobilization, active and acute illness (such as cancer), history of disease (including cancer, infections, DVT or PE, obesity, heart failure, etc), and inhibitors and inducers of the cytochrome P450 enzyme, CYP3A4. Descriptive values consistently favored enoxaparin over rivaroxaban.

The investigator-reported bleeding events were consistent with the adjudicated bleeding events showing a higher incidence in the rivaroxaban group in comparison to enoxaparin. The

incidence rates of the AEs without bleeding and the AEs with bleeding were similar.

In the rivaroxaban-enoxaparin/placebo (treatment-emergent) phase of the study, the investigator-reported an incidence of 12.5% treatment-emergent adverse events (TEAEs), 6.9% drug-related TEAEs, and 2.0% SAEs in the rivaroxaban group and an incidence of 8.5% TEAEs, 4.2% drug-related TEAEs, and 0.8% SAEs in the enoxaparin group. The incidence of investigator-reported TEAEs leading to permanent discontinuation of the study drug was 3.1% (rivaroxaban) and 1.5% (enoxaparin).

The incidence of investigator-reported deaths in the entire study duration (Day 1 to 90) was comparable in both treatment groups with 280 (7.0%) deaths in the rivaroxaban group and 262 (6.5%) deaths in the enoxaparin group. The incidence of VTE-related deaths was 39 (1.0%) subjects in the rivaroxaban group and 48 (1.2%) subjects in the enoxaparin group. Pulmonary embolism was confirmed in 3 subjects (2 rivaroxaban and 1 enoxaparin).

The incidence of hepatic disorders was lower in the rivaroxaban group compared to enoxaparin. The liver-related laboratory test abnormalities showed notable elevations in the hepatic enzymes and total bilirubin (TBL) in the enoxaparin group during the treatment-emergent phase.

The adjudicated CV events were comparable in the two treatment groups, both in the treatment-emergent and the follow-up phase of the study.

The changes in laboratory parameters including amylase, lipase, and platelet number were similar in both treatment groups. There were no notable findings in any of the clinical laboratory investigations (other than the hepatic enzyme elevations), or other safety evaluations such as vital signs or electrocardiograms (ECGs).

Results Summary — Pharmacokinetics

No evidence of relevant drug accumulation beyond steady state was observed between Day 1 and Day 10 in all subject groups, although drug exposure at Day 1 (overall, AUC 1642 ug*h/L; C_{max} 176 ug/L) tended to be higher than at Day 10 (overall, AUC 1355 ug*h/L; C_{max} 189 ug/L) for all subject subgroups.

Drug exposure was comparable between subject groups. No relevant differences in AUC and C_{max} were observed, with subjects with acute infectious disease at the lower end (Day 10: AUC 1192 ug*h/L; C_{max} 178.9 ug/L) and subjects with congestive heart failure (CHF) NYHA IV at the upper end (Day 10: AUC 1436 ug*h/L; C_{max} 191.8 ug/L) of the overall subject data. The tendency to higher AUC (i.e., lower clearance) data, especially for some subject subgroups (such as CHF and acute respiratory insufficiency), may be explained by the varying severity of the underlying disease.

Drug exposure at steady state and CL/F for this study population in general were in the range of results previously obtained with 10 mg rivaroxaban in both healthy adults (phase 1 data pool; age ranging from 18 to 83 years) as well as in VTE-major orthopedic surgery (MOS) subject populations.

Rivaroxaban plasma concentration/PT response relationship was comparable between subject groups and again similar to data reported for VTE-MOS subjects.

Results Summary — Other

Pharmacodynamic evaluation:
Two sets of samples were evaluated for PD parameters: Full profile PD sampling in parallel to the PK samples on Day 1 and Day 10. In addition sparse PD sampling in nearly all subjects at 5 predefined time points: prior to study drug administration, approximately the time of peak

plasma concentrations (2 to 4 hours after intake of the rivaroxaban tablets or rivaroxaban placebo tablet) on the first, 10th and 35th day of study drug administration, and before study drug administration on Day 10.

Prothrombin times from full profile sampling following administration of 10 mg rivaroxaban were comparable between the subgroups (overall median values, peak Day 1, 23.5 sec; peak Day 10, 23.2 sec).

The PT data from sparse and full sampling schemes were comparable for medically ill subjects and also did not differ from data obtained from previous studies in other study populations (subjects with acute decompensated heart failure, chronic stable heart failure, orthopedic surgery subjects).

Enoxaparin had no influence on PT, as expected from previous investigations. Prothrombin times from sparse data sampling were: Baseline, 14.4 sec; Day 1 peak 14.8 sec; Day 10 peak 14.2 sec, Day 35 peak, 13.8 sec (median values). Corresponding rivaroxaban median values: Baseline, 14.3 sec; Day 1 peak 19.3 sec; Day 10 peak 19.3 sec, Day 35 peak, 18.6 sec.

An overall decrease in D-dimer following administration of rivaroxaban over the course of the treatment was observed in the entire study population (rivaroxaban median values: Baseline, 0.94 µg/ml; Day 1 peak 0.90 µg/ml; Day 10 peak 0.64 µg/ml, Day 35 peak, 0.45 µg/ml; enoxaparin median values: baseline, 0.95 µg/ml; Day 1 peak 0.94 µg/ml; Day 10 peak 0.66 µg/ml, Day 35 peak, 0.67 µg/ml).

Subgroup analysis from subjects classified as NYHA III and IV with full PD sampling were consistent with the overall results. In subjects with acute infectious disease or acute respiratory insufficiency, D-dimer appeared to be unaffected by rivaroxaban (acute infectious disease, median values: Baseline, 1.76 µg/ml; Day 1 peak 2.07 µg/ml; Day 10 trough 1.74 µg/ml, Day 10 peak 2.13 µg/ml; acute respiratory insufficiency, median values: baseline, 1.48 µg/ml; Day 1 peak 1.44 µg/ml; Day 10 trough 1.18 µg/ml, Day 10 peak 1.37 µg/ml). This was probably due to the low number of rivaroxaban subjects and high variability of the test. D-dimers appeared also to be unaffected by enoxaparin in subjects with acute respiratory insufficiency (median values: Baseline, 0.57 µg/ml; Day 1 peak 0.66 µg/ml; Day 10 trough 0.46 µg/ml, Day 10 peak 0.70 µg/ml).

The prothrombinase induced clotting time (one step) data from sparse sampling was performed in both rivaroxaban- and enoxaparin-treated subjects. Rivaroxaban prolonged the PiCT one step assay by 14.6 seconds at Day 1, and by 13.1 seconds on Day 10. No change in the clotting time was observed for enoxaparin-treated subjects. Expressed in units of µg/L, mean peak concentration of rivaroxaban were 199.41 µg/L on Day 1, 202.96 µg/L on Day 10 and 169.07 µg/L on Day 35. Trough values could not be assessed due to the lower limit of quantitation set to 33.33 µg/L.

The PiCT (two step) data from sparse sampling was performed in both rivaroxaban- and enoxaparin-treated subjects. Rivaroxaban had little effect on the PiCT two step assay and no difference was observed between baseline and peak measurements on Day 1 and between trough and peak values on Day 10. Enoxaparin prolonged the PiCT assay by 23.6 seconds on Day 1 and by 19.8 seconds on Day 10. No change in the clotting time was observed for rivaroxaban-treated subjects. Expressed in units of IU/mL, mean peak concentration of enoxaparin was 0.32 IU/mL on Day 1 and 0.31 IU/mL on Day 10. The baseline value was below the lower limit of quantitation on Day 1 and trough was reported to be 0.11 IU/mL on Day 10. For rivaroxaban-treated subjects, peak values were below the lower limit of quantitation on both Day 1 and Day 10.

Conclusion(s)			
The MAGELLAN study met its protocol specified primary efficacy outcomes for rivaroxaban versus enoxaparin/placebo at both Day 10 and Day 35. Bleeding rates in MAGELLAN were low overall and consistent with rates in prior trials. The enoxaparin bleeding rate in MAGELLAN was comparable to that reported in prior trials in this indication. Nonetheless, the incidences of clinically relevant bleeding events including both the component of major bleeding events as well as the component of non-major clinically relevant bleeding events were increased in rivaroxaban treated subjects compared to enoxaparin followed by placebo treated subjects in a statistically significant manner during all three specified study phases. The non-bleeding safety of rivaroxaban in this subject population was in line with previous clinical experience, and not different from enoxaparin followed by placebo. There was no imbalance of drug-related treatment-emergent AE, SAE, CV events, or hepatic diseases evaluated using the Standard Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs), or liver function tests (LFTs).			
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Date Created or Date Last Updated:	13 Jun 2013	**Date of Clinical Study Report:**	21 NOV 2011

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93	Drum Tower Hospital of Nanjing University Medical School	Respiratory Dept. No.321 Zhongshan Road,	210008	Nanjing	CHINA
94	first affiliated hospital of guangzhou medical college	Respiratory Dept. first affiliated hospital of guangzhou medical college/ guangzhou insitute of respiratory disease, No. 151,yanjiang Road,	510120	Guangzhou	CHINA
95	General Hospital of Shenyang Military Area	Respiratory Dept. No 82, CultureStreet, ShenHe District,	110015	Shenyang	CHINA

96	Jiangsu Province Hospital	Neurology Dept. No. 300, Guangzhou Rd.		Nanjing	CHINA
97	No.1 Hospital of Jilin University	Neurology Dept. No 71.Xinmin Road,		Changchun	CHINA
98	Peking Union Medical College Hospital	Cardiology Dept. No.53 Dong Dan North Road,	100005	Beijing	CHINA
99	Peking Univ. People's Hosp.	Cardiovascular Dept. No.11 South Avenue, Xizhimen, Xicheng District,	100044	Beijing	CHINA
100	Renji Hosp. Shanghai Jiao Tong Univ. School of Medicine	Neurology Dept. No.1630 Dongfang Rd.	200127	Shanghai	CHINA
101	Respiratory Diseases Institute, Beijing Chaoyang Hospital	Respiratory Dept. 8 Bai Jiazhuang Road, Chaoyang District,	100020	Beijing	CHINA
102	Second Affiliated Hospital of Guangzhou Medical College	Neurology Dept. No.250,Chang Gang East Road,		Guangzhou	CHINA
103	Shanghai Changzheng Hospital	Respiratory Dept. 25 Floor, No.415, Fengyang Road,	200003	Shanghai	CHINA
104	Shanghai Changzheng Hospital	Neurology dept. Shanghai Changzheng Hospital 16 Floor, No.415, Fengyang Road,	200003	Shanghai	CHINA

105	Shanghai Tongji Hospital of Tongji University	Cardiology Dept. No.389, Xincun Road		Shanghai	CHINA
106	Shengjing Hosp. of China Medical Univ.	Cardiology Dept. No.36 Sanhao Rd. Heping District	110004	Shenyang	CHINA
107	Southwest Hospital of 3rd Military Medical University.	Neurology Dept.No.30, Gaotan Yanzheng Street,Shapingba District	400038	Chongqing	CHINA
108	The 6th People's Hospital of Shanghai Jiao Tong University	Respiratory Dept. No.600, yishan road,	200233	Shanghai	CHINA
109	The First hospital of China Medical University	Cardiology Dept. No.155 North Nanjing street, heping district,	110001	Shenyang	CHINA
110	The General Hospital of Guangzhou Military Command	No.111,Linhua Road,		Guangzhou	CHINA
111	The Second Artillery General Hospital of PLA	Cardiology Dept. No.16 Xinjiekou Wai Avenue, Xicheng District,	100088	Beijing	CHINA
112	The Second Artillery General Hospital of PLA	Respiratory Dept. No.16 Xinjiekou Wai Avenue, Xicheng District,	100088	Beijing	CHINA
113	The Third Xiangya Hospital of Central South University	Cardiology Dept. No.138,Tongzipo Road,	410013	Changsha	CHINA

114	The Third Xiangya Hospital of Central South University	Respiratory Dept. No.138, Tongzipo Road,	410013	Changsha	CHINA
115	West China Hospital of Sichuan University	Respiratory Dept. No.37, Guoxue Alley	610041	Chengdu	CHINA
116	Xuanwu Hospital of the Capital University of Medical Science	Cardiology Dept. No.45 Chang Chun Avenue, XuanWu District,	100053	Beijing	CHINA
117	Centro Médico Imbanaco	Oficina 408 Carrera 38 A No. 5A-100		Cali	COLOMBIA
118	Clínica del Country	Centro de Investigación Clinica del Country Calle 83 No. 16A - 43 Primer Piso		Bogotá	COLOMBIA
119	Clínica Las Américas	Diagonal 75 B # 2 A 80 -140 Octavo Piso		Medellín	COLOMBIA
120	Clínica Medellín	Office 1509 Clinica Medellin Calle 54 No. 46 - 27		Medellín	COLOMBIA
121	Fundación Cardioinfantil	Calle 163 A No. 13B-60 Edificio Nuevo-Tercer Piso Departamento de Investigaciones		Bogota	COLOMBIA
122	Hospital Mario Correa	Carrera 78 Oeste No.2A00		Cali	COLOMBIA
123	Hospital Militar Central	Medicina Interna Transversal 3A #49-00 Piso 6to Norte		Bogotá	COLOMBIA

124	Hospital San Vicente de Paul	Laboratorio Vascular Calle 64 con Carrera 51D		Medellín	COLOMBIA
125	KB Osijek	Interna klinika Huttlerova 4	310 00	Osijek	CROATIA
126	Klinicka bolnica Dubrava	Zavod za bolesti srca i krvnih zila Avenija Gojka Suska 6	10000	Zagreb	CROATIA
127	Klinicki Bolnicki Centar Zagreb	Klinika za neurologiju Kispaticeva 12	1000	Zagreb	CROATIA
128	Klinicki Bolnicki Centar Zagreb	Zavod za hematologiju Kispaticeva 12	10000	Zagreb	CROATIA
129	Klinika za plucne bolesti Jordanovac	Klinika za Pulmologiju Jordanovac 104	10000	Zagreb	CROATIA
130	Opca bolnica Zadar	Odjel za interne bolesti B. Pericica 5	23000	Zadar	CROATIA
131	Fakultni nemocnice Plzen	II. Interni klinika E. Benese 13	305 99	Plzen	CZECH REPUBLIC
132	Nemocnice Nove Mesto na Morave	Interni Oddeleni Zdarska 610	592 31	Nove Mesto na Morave	CZECH REPUBLIC
133	Nemocnice Znojmo	Interni oddeleni Jana Janskeho 11	669 02	Znojmo	CZECH REPUBLIC
134	Vseobecna fakultni nemocnice	IV Interni Klinika u Nemocnice 2	128 08	Praha 2	CZECH REPUBLIC
135	Vseobecna fakultni nemocnice	II Interni Klinika VFN a 1.LF UK U nemocnice 499/2	12800	Praha 2	CZECH REPUBLIC
136	Vseobecna Fakultni Nemocnice Olomouc	II Interni klinika I.P. Pavlova 6	775 20	Olomouc	CZECH REPUBLIC
137	Vseobecna fakultni nemocnice v Praze	Neurologicka klinika Katerinska 30	128 21	Praha 2	CZECH REPUBLIC

138	Amtssygehuset Roskilde	Nefrologisk Afsnit Medicinsk Afd	4000	Roskilde	DENMARK
139	Esbjerg Hospital	Esbjerg Hospital Kardiologisk Afdeling Finsensvej 35	6700	Esbjerg	DENMARK
140	Frederiksberg Hospital	Frederiksberg Hospital Ndr. Fasanvej 57	2000	Frederiksberg C	DENMARK
141	H:S Amager Hospital	Medicinsk Center Italiensvej 1	2300	København S	DENMARK
142	H:S Bispebjerg Hospital	Kardiologisk Klinik Y21, Bygning 40 Bispebjerg Bakke 23	2400	København NV	DENMARK
143	Clinic of Internal Diseases Tartu University Hospital	Internal Medicine Clinic Tartu University Hospital L.Puusepa 6	EE-51014	Tartu	ESTONIA
144	East Tallinn Central Hospital	Internal Medicine Clinic Ravi 18	10138	Tallinn	ESTONIA
145	Regional Hospital of North Estonia	J. Sutiste tee 19	13419	Tallinn	ESTONIA
146	West Tallinn Central hospital	Paldiski mnt. 68	EE-10617	Tallinn	ESTONIA
147	HUS, Meilahden sairaala	Haartmaninkatu 4	00290	Helsinki	FINLAND
148	Raisio Hospital	Sairaalakatu 5	21200	Raisio	FINLAND

149	Centre Hospitalier Lyon Sud - Pierre Bénite	Hospices civils de Lyon Centre Hospitalier Lyon Sud Service de Médecine Interne et Angiologie 165, chemin du Grand Revoyet	69495	PIERRE BENITE	FRANCE
150	Centre Hospitalier - Saint Philibert - Lomme	Centre Hospitalier Service de Cardiologie Rue Grand But	59160	LOMME	FRANCE
151	CH TOURCOING	135, rue du président COTY BP619	59208	TOURCOING cedex	FRANCE
152	Clinique Bon Secours	2, rue du Dr FORGEOIS	62000	ARRAS	FRANCE
153	Clinique du Parc	Clinique du PARC Service de Médecine Vasculaire 50 rue Emile Combes	34170	CASTELNAU LE LEZ	FRANCE
154	Hôpital Albert Calmette - CHRU de Lille	Pôle des maladies Respiratoires Boulevard du Professeur Jules Leclerc	59307	Lille	FRANCE
155	Hopital Carrémeau - Nimes	Consultations de Pneumologie Carémeau Nord Tour D 3ème étage Place du Professeur Robert Debré	30029	Nimes	FRANCE

156	Hôpital Civil - Strasbourg	Hôpitaux Universitaires Hôpital Civil Service d'Hypertension et Maladies Vasculaires 1, place de l'Hôpital	67091	STRASBOURG CEDEX	FRANCE
157	Hôpital Claude Huriez - Lille	CHU Lille Hopital Huriez Service de Medecine Interne Place de Verdun	59037	Lille	FRANCE
158	Hôpital de Cimiez/Hôpital Pasteur	Soins Intensifs 30, voie Romaine	06280	NICE	FRANCE
159	Hôpital de Rangueil - Toulouse	C.H.U. Hôpital de Rangueil Service de Cardiologie A 1, avenue Poulhes	31403	TOULOUSE	FRANCE
160	Hopital d'instruction des Amées Desgenettes	Hopital d'instruction des Amées Desgenettes108 Boulebard Pinel	69003	Lyon	FRANCE
161	Hôpital du Bocage - Dijon	CHRU de Dijon Hôpital du Bocage Service de Médecine Interne et immunologie clinique 2 boulevard du Maréchal de Lattre de Tassigny	21000	DIJON	FRANCE

162	Hôpital Dupuytren - Limoges Cedex	C.H.R.U. Hôpital Dupuytren Service de Chirurgie Thoracique et cardiovasculaire 2, avenue Martin Luther King	87042	LIMOGES	FRANCE
163	Hôpital Gabriel Montpied - Clermont Ferrand	Hôpital Gabriel Montpied Service d'Accueil des Urgences 58 rue Montalembert	63000	CLERMONT FERRAND	FRANCE
164	Hôpital La Cavale Blanche - Brest Cedex	Hôpital La Cavale Blanche Service de Médecine Interne et Pneumologie Boulevard Tanguy Prigent	29609	BREST CEDEX	FRANCE
165	Hôpital Lariboisière - Paris	Groupe Hospitalier Lariboisière - F. Widal - St Lazare Hôpital Lariboisière Service de Médecine Interne 2, rue Ambroise Paré	75475	PARIS	FRANCE
166	Hôpital Louis Mourier - Colombes Cedex	Hôpital Louis Mourier Service de Médecine Interne V 178, rue des Renouillers	92701	COLOMBES CEDEX	FRANCE

167	Hôpital Nord-SAINT ETIENNE	Hôpital Nord Consultations Médecine et Thérapeutique Batiment A, Niveau 0 CHU de St-Etienne	42000	SAINT-ETIENNE	FRANCE
168	Hôpital Saint-Eloi - Montpellier Cedex	Hôpital Saint Eloi Service de Médecine Interne et Maladies Vasculaires 80 avenue Augustin Fliche	34295	MONTPELLIER CEDEX	FRANCE
169	Hôpital Saint Louis - Paris	Hôpital Saint Louis Service de Médecine interne Avenue Claude Vellefaux	75010	PARIS	FRANCE
170	Hôtel Dieu - Paris	Hôtel Dieu Service de Médecine Interne 1, place du Parvis de Notre Dame	75004	PARIS	FRANCE
171	Berufsgenossenschaftl. Kliniken Bergmannstrost	Innere Medizin Merseburger Str. 165	06112	Halle	GERMANY
172	Bethesda Krankenhaus Wuppertal gGmbH	Medizinische Klinik Innere Medizin Hainstr. 35	42109	Wuppertal	GERMANY
173	Bethlehem-Krankenhaus	Innere Medizin Steinfeldstr. 5	52222	Stolberg	GERMANY
174	Brüderkrankenhaus St. Josef	Innere Medizin Husener Str. 46	33098	Paderborn	GERMANY
175	Caritas Krankenhaus GmbH	Medizinische Klinik I Uhlandstr. 7	97980	Bad Mergentheim	GERMANY

176	Franziskus-Krankenhaus	Innere Medizin Budapester Str. 15-19	10787	Berlin	GERMANY
177	Johannes-Gutenberg-Universität Mainz	II. Med. Klinik und Poliklinik Angiologie Langenbeckstr. 1	55131	Mainz	GERMANY
178	Johannes-Gutenberg-Universität Mainz	III. Medizinische Klinik und Poliklinik Langenbeckstr. 1	55131	Mainz	GERMANY
179	Kliniken der Stadt Köln gGmbH- Krankenhaus Holweide	Innere Medizin Neufelder Str. 32	51067	Köln	GERMANY
180	Kliniken der Stadt Köln - Städt. Krankenhaus Köln-Merheim	Lungenklinik - Haus 23/24 Ostmerheimer Straße 200	51109	Köln	GERMANY
181	Kliniken Maria Hilf GmbH	Krankenhaus St. Franziskus Innere Medizin II Klinik für Kardiologie Viersener Straße 450	41063	Mönchengladbach	GERMANY
182	Kliniken Nordoberpfalz AG - Klinikum Weiden	Klinik für Urologie und Kinderurologie Söllnerstr. 16	92637	Weiden	GERMANY
183	Klinikum Bremen Mitte gGmbH	Institut für Klinische Pharmakologie St.-Jürgen-Strasse 1	28177	Bremen	GERMANY
184	Klinikum Esslingen GmbH	Klinik für Kardiologie, Angiologie und Pneumologie Hirschlandstr. 97	73730	Esslingen	GERMANY
185	Klinikum Frankfurt/Oder	Medizinische Klinik II Müllroser Chaussee 7	15236	Frankfurt/Oder	GERMANY

186	Klinikum Leverkusen gGmbH	Medizinische Klinik IV Dhünnberg 60	51375	Leverkusen	GERMANY
187	Krankenhaus Dresden-Friedrichstadt	Städtisches Klinikum Innere Medizin II Friedrichstraße 41	01067	Dresden	GERMANY
188	Medizinische Fakultät Carl Gustav Carus	Technische Universität Dresden Medizinische Klinik III Fetscherstraße 74	01307	Dresden	GERMANY
189	SRH Klinikum-Karlsbad-Langensteinbach gGmbH	Innere Medizin Guttmannstr. 1	76307	Karlsbad	GERMANY
190	Städtische Kliniken Neuss	Lukaskrankenhaus GmbH Medizinische Klinik II Preußenstr. 84	41464	Neuss	GERMANY
191	St. Elisabeth-Krankenhaus GmbH	Medizinische Klinik Werthmannstraße 1	50935	Köln	GERMANY
192	St. Irmgardis-Krankenhaus Süchteln	Innere Medizin Tönisvorster Straße 26	41749	Viersen	GERMANY
193	St.-Johannes-Hospital Dortmund	Innere Medizin II Johannesstr. 9-17	44137	Dortmund	GERMANY
194	St. Johannes Krankhaus gGmbH	Innere Medizin Wilhelm-Busch-Straße 9	53844	Troisdorf	GERMANY
195	St. Josef-Hospital	Innere Medizin Mülheimer Str. 83	46045	Oberhausen	GERMANY
196	Universitätsklinikum Heidelberg	Neurologische Universitätsklinik Im Neuenheimer Feld 400	69112	Heidelberg	GERMANY

197	Universitätsklinikum Leipzig AöR	Herzzentrum Leipzig GmbH - Universitätsklinik Klinik für Innere Medizin / Kardiologie Strümpellstraße 39	04289	Leipzig	GERMANY
198	Constantopoulio General Hospital of Nea Ionia - Agia Olga	Cardiology Department, 3-5 Agia Olga street	14233	Nea Ionia	GREECE
199	Evangelismos General Hospital of Athens	45-47, Ipsilantou Str.	106 76	Athens	GREECE
200	KAT General Hospital of Athens	Cardiology Clinic, KAT General Hospital of Athens, 2 Nikis street	14561	Kifisia / Athens	GREECE
201	Korgialenio Benakio Red Cross General Hospital of Athens	1 Athanasaki & Erythrou Stavrou Str.	115 22	Abelokipi - Athens	GREECE
202	Laiko General Hospital of Athens	1st Propedeutic Clinic of Internal Medicine 17, Agiou Thomas Str.,	115 27	Athens	GREECE
203	Sotiria General State Hospital of Chest Diseases	2nd Pneumonological Clinic, 152 Messogeion Avenue	156 69	Athens	GREECE
204	Sotiria General State Hospital of Chest Diseases	6th Pneumonological Clinic 152 Messogion Avenue	156 69	Athens	GREECE
205	Thriassio General Hospital of Elefsina	Georgios Gennimatas Avenue	19018	Elefsina	GREECE

206	Tzaneio General Hospital of Piraeus	Zanni & Afentouli street	18536	Piraeus	GREECE
207	University General Hospital of Patras	Department of Internal Medicine	265 04	Rio	GREECE
208	Prince of Wales Hospital	Department of Medicine & Therapeutics, 9/F Clinical Sciences Building, 30-32 Ngan Shing Street,		Shatin	HONG KONG
209	Prince of Wales Hospital	30-32 Ngan Shing Street,		Shatin	HONG KONG
210	AEK Orszagos Haemophilia Kozpont	Ideggyogyaszati es Stroke Osztalay Robert K. krt.44	1134	Budapest	HUNGARY
211	Bacs-Kiskun Country Hospital	Neurologiai es Stroke Osztalay Nyiri ut. 38	6000	Kecskemet	HUNGARY
212	Bajai Varosi Korhaz	Belgyogyaszati Osztalay Rokus u. 10	6500	Baja	HUNGARY
213	D.Kenessey A Hospital	Intensive Care Unit I Rakoczi ut 125-127	2660	Balassagyarmat	HUNGARY
214	National Scientific Institute of Neurosurgery and Neurology	Epilepsia es Stroke Osztaly Amerikai ut. 57	1145	Budapest	HUNGARY
215	Szent Borbala Hospital	Neurologiai Osztalay (II/E ep.) Dozsa Gyorgy ut.77	2800	Tatabanya	HUNGARY
216	Uzsoki utkai Korhaz	Neurologia Uzsoki u. 29	1145	Budapest	HUNGARY
217	Zala Megyei Korhaz	Zala Megyei Korhaz Neurologiai Osztaly Zrinyi u. 1	H-8900	Zalaegerszeg-Pozva	HUNGARY

218	Apollo Hospital Tondiarpet	No.645 & 646 TH Road Thandiarpet	600081	Chennai	INDIA
219	Baby Memorial Hospital	Baby Memorial Hospital, Indira Gandhi Road,	673 004	Calicut	INDIA
220	Bhagwan Mahaveer Jain Heart Centre	# 8 Millers Tank Bund Road	560052	Bangalore	INDIA
221	CARE Hospital	Road No.1, Banjara Hills	500034	Hyderabad	INDIA
222	Dayanand Medical College& Hospital	Tagore Nagar, Civil Lines	141001	Ludhiana	INDIA
223	King Edward Memorial Hospital	4th Floor, T. D. H. Building, Rasta Peth	411011	Pune	INDIA
224	Lokmanya Tilak Municipal Hospital	Department of Medicine, LTMMC & LTMGH, Sion	400022	Mumbai	INDIA
225	Metro Centre for Respiratory Diseases,	Metro Hospitals & Critical Care L-94, Sector-11		Noida	INDIA
226	Narayana Hrudayalaya	258/A, Bommasandra Industrial Area,	560099	Bangalore	INDIA
227	Prime Hospital	Department of Cardiology Plot No: 4, Behind Mythrivanam Building Besides Blue Fox Hotel Ameerpet	600 038	Hyderabad	INDIA
228	PSG Hospital	Department of Pulmonology Avinashi road, Peelamedu,	641 004	Coimbatore	INDIA
229	Ruby Hall Clinic	40 Sasson Road,	411001	Pune	INDIA

230	S.A.L Hospital & Medical Institute	Opposite Doordarshan Drive-in Road,	380 054	Ahmedabad	INDIA
231	Yashodha Hospital	Department of Cardiology,Rajbhavan Road, Somajiguda	500082	Hyderabad	INDIA
232	Cardiac Centre Harapan Kita Hospital	Pusat Jantung Nasional Harapan Kita (National Cardiovascular Center Harapan Kita) Jl. LetJen. S. Parman Kav. 87, Slipi	11420	Jakarta	INDONESIA
233	Cipto Mangunkusumo Hospital	Division of Hematology-Medical Oncology Department of Internal Medicine, University of Indonesia, Jl Salemba Raya No. 6,	10430	Jakarta	INDONESIA
234	Dr Soetomo Hospital	Department of Neurology, Faculty of Medicine, Airlangga University Jl. Mayjen Prof. Dr. Moestopo 6-8	60286	Surabaya	INDONESIA
235	Barzilai Medical Center	3, Hahistadrut Street	78306	Ashkelon	ISRAEL
236	Bnai Zion Medical Center	47, Golomb Street P.O.B. 4940	31048	Haifa	ISRAEL
237	Edith Wolfson Medical Center	62 Halochamim Street P.O.B. 5	58100	Holon	ISRAEL
238	Haemek Medical Center	Rabin Road	18101	Afula	ISRAEL

239	Kaplan Medical Center	P.O.B. 1	76100	Rehovot	ISRAEL
240	Meir Medical Center	59 Tchernichovsky Street	44281	Kfar Saba	ISRAEL
241	Rambam Medical Center	Neurology Department Rambam Medical Center P.O.B 9602, 8, Haaliya Hashniya St. Bat Galim	31096	Haifa	ISRAEL
242	Rambam Medical Center	8, Haaliya Hashniya St. Bat Galim	31096	Haifa	ISRAEL
243	Tel Aviv Sourasky Medical Center	6, Weizman Street	64239	Tel Aviv	ISRAEL
244	Ziv Medical Center	P.O.B. 1008	13100	Safed	ISRAEL
245	A.O. di Perugia	Medicina Interna e Cardiovascolare - Stroke Unit Ospedale Santa Maria della Misericordia Via G. Dottori - Località Sant'Andrea delle Fratte	06156	Perugia	ITALY
246	A.O. di Reggio Emilia	Centro Emostasi e Trombosi - Medicina Interna I Arcispedale Santa Maria Nuova Viale Risorgimento, 80	42100	Reggio Emilia	ITALY
247	A.O. Osp Circolo e Fond.Macchi	Medicina Interna I Viale L.Borri, 57	21100	Varese	ITALY
248	A.O. Ospedali Riuniti Bergamo	Emostasi e Trombosi Largo Barozzi, 1	24128	Bergamo	ITALY

249	A.O. Osp Niguarda Ca' Granda	Ematologia - Centro Trombosi ed Emostasi Piazza Ospedale Maggiore, 3	20162	Milano	ITALY
250	A.O.U. di Parma	Medicina Interna ad indir. Angiologico e Coagulativo Via Gramsci, 14	43100	Parma	ITALY
251	A.O.U. Policlinico Giaccone	Ematologia Via del Vespro, 127	90127	Palermo	ITALY
252	ASL VCO - Piemonte	Ambulatorio Emostasi, Trombosi e Angiologia Medica Medicina Interna P.O. San Biagio Largo Caduti Lager Nazisti, 1	28845	Domodossola	ITALY
253	AULSS 06 Vicenza - Veneto	Ematologia e Trombosi Ospedale S. Bortolo Via Rodolfi, 37	36100	Vicenza	ITALY
254	AUSL 1 Perugia - Umbria	Medicina Interna P.O. Alto Chiascio Largo San Francesco, 7/a - Località Branca	06024	Gubbio	ITALY
255	AUSL 4 Terni - Umbria	Medicina Generale P.O. S.Maria della Stella Località Ciconia	05019	Orvieto	ITALY
256	AUSL Latina - Lazio	Ematologia Ospedale Santa Maria Goretti Via G.Reni, 1	04100	Latina	ITALY

257	AUSL Modena - Emilia Romagna	Medicina Cardiovascolare Nuovo Ospedale Civile S.Agostino Estense Via Giardini, 1355 - Località Boggiovara	41100	Modena	ITALY
258	AUSL Parma - Emilia Romagna	Medicina Interna 2 Ospedale di Fidenza Via Don E.Tincati, 5	43036	Fidenza	ITALY
259	AUSL Piacenza - Emilia Romagna	Centro Emostasi e Trombosi Medicina Interna Area Critica Ospedale Guglielmo da Saliceto Via Taverna, 49	29100	Piacenza	ITALY
260	Azienda Policlinico Umberto I	Medicina Interna H Policlinico Umberto I Viale del Policlinico, 155	00161	Roma	ITALY
261	E.O. Ospedali Galliera	Centro Trombosi - Malattie Tromboemboliche Dip. Medicina Via A. Volta, 8	16128	Genova	ITALY
262	IRCCS Ist Clinico Humanitas	Centro Trombosi Via Manzoni, 56	20089	Rozzano	ITALY
263	IRCCS Istituto Nazionale Tumori	Oncologia Medica 2 Via G.Venezian, 1	20133	Milano	ITALY

264	PR S.Pietro e OR S.Giovanni Fatebenefratelli	Medicina Generale Ospedale Buon Consiglio Fatebenefratelli Via A. Manzoni, 220	80123	Napoli	ITALY
265	Università Cattolica del Sacro Cuore	Malattie Emorragiche e Trombotiche Istituto Medicina Interna e Geriatria Policlinico Universitario A. Gemelli Largo A. Gemelli, 8	00168	Roma	ITALY
266	Ebina General Hospital	Cardiology 1320 Kawaharaguchi	243-0433	Ebina	JAPAN
267	Ehime National Hospital	Cardiology 366 Yokogawara	791-0281	Toon	JAPAN
268	Ehime Prefectural Central Hospital	Cardiovascular Internal Medicine 83 Kasugamachi	790-0024	Matsuyama	JAPAN
269	Fukui General Hospital	Neurosurg 58-16-1 Egami-cho	910-8561	Fukui	JAPAN
270	General Hanamaki Hospital	Neurology 4-28 Kajomachi	025-0075	Hanamaki	JAPAN
271	JA Kochi Hospital	Department of Cardiology 526-1 Nakano Myokenaza	783-8509	Nangoku	JAPAN
272	Kanagawa Cardiovascular and Respiratory Center	Cardiovascular 6-16-1 Tomiokahigashi Kanazawa-ku	236-0051	Yokohama	JAPAN
273	Kanazawa Medical Center	Department of Circulatory System 1-1 Shimoishibiki-machi	920-8650	Kanazawa	JAPAN

274	Kansai Rosai Hospital	Obstetrics and gynaecology 3-1-69 Inabaso	660-8511	Amagasaki	JAPAN
275	Kumamoto Medical Center	Cardiology 1-5 Ninomaru	860-0008	Kumamoto	JAPAN
276	Kusatsu General Hospital	Cardiovascular Internal Medicine 1660 Yabase-cho	525-8585	Kusatsu	JAPAN
277	Kyoto University Hospital	Department of Multidisciplinary Cancer Treatment 54, Shogoin-kawahara-cho, Sakyo-ku	606-8507	Kyoto	JAPAN
278	Matsusaka City Hospital	Internal Medicine 1550 Tonomachi	515-8544	Matsusaka	JAPAN
279	Medical Corporation Daiyukai Daiyukai General Hospital	Neurosurgical 1-9-9 Sakura	491-8551	Ichinomiya	JAPAN
280	Mie Central Medical Center	Respiratory 2158-5 Hisaimyojin-cho	514-1101	Tsu	JAPAN
281	Mie University Hospital	Cardiology 2-174, Edobashi	514-8507	Tsu	JAPAN
282	Nagoya Tokushukai Genaral Hospital	Thoracic Surgery 2-28-1 Kozoji-cho	487-0013	Kasugai	JAPAN
283	National Center for Geriatrics and Gerontology	Department of Cardiology 35 Gengo Moriokamachi	474-8511	Obu	JAPAN
284	National Center for Global Health and Medicine Hospital	Cardiology 1-21-1 Toyama	162-8655	Shinjuku-ku	JAPAN

285	National Hospital Organization Ibaraki Higashi Hospital	Department of Internal Medicine 825 Terunuma Tokaimura Nakagun	319-1113		JAPAN
286	Niigata National Hospital	Internal Medicine 3-52 Akasaka-cho	945-8585	Kashiwazaki	JAPAN
287	Nozaki Tokushukai Hospital	Neurosurgery 2-10-50 Tanigawa	574-0074	Daito	JAPAN
288	Saiseikai Futsukaichi Hospital	Division of Cardiology 3-13-1 Yumachi	818-8516	Chikushino	JAPAN
289	Sapporo Higashi Tokushukai Hospital	Neurosurgery 14-3-1 Kita33jo-higashi Higashi-ku	065-0033	Sapporo	JAPAN
290	Shimonoseki Kosei Hospital	Cranial Nerve Internal Medicine 3-3-8 Kamishinchi-cho	750-0061	Shimonoseki	JAPAN
291	Shonan Kamakura General Hospital	Hematology 1370-1 Okamoto	247-0072	Kamakura	JAPAN
292	Takasaki General Medical Center	Internal Medicine 36 Takamatsu-cho	370-0829	Takasaki	JAPAN
293	Tokyo Medical Center	Cardiology 2-5-1 Higashigaoka	152-8902	Meguro-ku	JAPAN
294	Tomishiro Central Hospital	Internal Medicine 25 Ueta aza	901-0243	Tomigusuku	JAPAN
295	Urasoe General Hospital	Heart Center 4-16-1 Iso	901-2132	Urasoe	JAPAN
296	Urasoe General Hospital	Neurosurgery 4-16-1 Iso	901-2132	Urasoe	JAPAN

297	Yao Tokushukai General Hospital	Neurosurgery 1-17 Wakakusa-cho	581-0011	Yao	JAPAN
298	Asan Medical Center	# 388-1, Pungnap-dong, Songpa-gu	138736	Seoul	KOREA, REPUBLIC OF
299	BUNDANG CHA HOSPITAL	Division of Hemato-oncology, Department of Internal Medicine, , 351 Yatapdong, Bundanggu, Sungnamsi		Kyunggido	KOREA, REPUBLIC OF
300	Chonnam National University Hospital	Dept of Hematology - Oncology 160 Iisimri Hwasun-eup	519-809	Hwasun-Gun Jeonnam	KOREA, REPUBLIC OF
301	Samsung Medical Center	Samsung Medical Center, 50 Ilwon-dong, Kangnam-ku,	135-710	Seoul	KOREA, REPUBLIC OF
302	Seoul Metropolitan Boramae Hospital	425 Shindaebang-2-dong Dongjak-ku	156-707	Seoul	KOREA, REPUBLIC OF
303	Seoul National Univ. Bundang Hospital	Division of Hemato-oncology, Department of Internal Medicine, 300 Gumi-dong, Bundang-gu, Seongnam-si ,	463-707	Gyeongi-do	KOREA, REPUBLIC OF
304	Seoul National University Hospital	101 Daehang-ro, Jongno-gu	110-744	Seoul	KOREA, REPUBLIC OF
305	1st Riga Hospital	Bruninieku 5		Riga	LATVIA
306	Central Hospital of Liepaja	Slimnicas street 25	3402	Liepaja	LATVIA

307	Daugavpils Regional Hospital	Vasarnicas 20	LV-5417	Daugavpils	LATVIA
308	Latvian Maritime Medicine Center	Patversmes 23	1005	Riga	LATVIA
309	Paula Stradina Kliniskas Universitates slimnica	Pilsonu iela 13	1002	Riga	LATVIA
310	Valmiera Hospital	Jumaras street 195	LV-4201	Valmiera	LATVIA
311	Kaunas 2nd Clinical Hospital	Department of Diagnostics of Internal Diseases Josvainiu 2	LT-3026	Kaunas	LITHUANIA
312	Kaunas District Hospital	Department of Internal Diseases Hipodromo 13	LT-3002	Kaunas	LITHUANIA
313	Kaunas Red Cross Clinical Hospital	Department of Internal Diseases I Laisves al. 17	LT-3000	Kaunas	LITHUANIA
314	Klaipeda District Hospital	S.Neries 3	LT-92231	Klaipeda	LITHUANIA
315	Klaipeda University Hospital	Department of Diagnostics of Internal Diseases Liepojos 41	LT-5800	Klaipeda	LITHUANIA
316	Siauliai County Hospital	Dept of Internal Diseases V. Kudirkos 99	76231	Siauliai	LITHUANIA
317	University Hospital of Vilnus City	Dept of Internal Diseases Antakalnio 57	10207	Vilnius	LITHUANIA
318	Utena District Hospital	Aukstakalnio 3	LT-28142	Utena	LITHUANIA
319	Vilnius Center University Hospital	Department of Diagnostics of Internal Diseases Zygimantu 3	LT-2001	Vilnius	LITHUANIA

320	Vilnius University Hospital of Emergency Care	Dept of Therapy Siltnamiu 29	04130	Vilnius	LITHUANIA
321	Centre Hospitalier du Kirchberg	Service de Cardiologie Rue Edward Steichen 9	2540	KIRCHBERG	LUXEMBOURG
322	Centre Hospitalier Emile Mayrisch	Site Niederkorn Médecine Interne Avenue de la Liberté 187	4602	NIEDERKORN	LUXEMBOURG
323	Mawar Renal Medical Centre	No. 71, Jalan Rasah , Seremban,	70300	Negeri Sembilan,	MALAYSIA
324	Sarawak General Hospital	Sarawak General Hospital Heart Centre 94300 Kota Samarahan	93400	Sarawak	MALAYSIA
325	University Malaya Medical Centre	Lembah Pantai	59100	Kuala Lumpur	MALAYSIA
326	Antiguo Hospital Civil de Guadalajara "Fray Antonio Alcalde"	Calle del Hospital No. 278 Col. El Retiro Sector Hidalgo	44280	Guadalajara	MEXICO
327	Central Médico Quirúrgica de Aguascalientes	5a Avenida 702-202 Col. Agricultura	20234	Aguascalientes	MEXICO
328	Hospital Ángeles Torreón	Paseo del Tecnológico # 909 Col. Residencial Tecnológico (Torre de Consultorios, Módulo 610)	27250	Torreón	MEXICO
329	Hospital Central Universitario	Rosales 3302 Col. Obrera	31350	Chihuahua	MEXICO

330	Hospital de la Mujer	Calle Guillermo Roquet 250 esq. Miguel Arreola Col. Poblado de Ocolusen	58270	Morelia	MEXICO
331	Hospital General Balbuena	Cecilio Robelo y Sur 103 Colonia Aeronáutica Militar. Delegación Venustiano Carranza	15900	Mexico D.F.	MEXICO
332	Hospital General del Estado de Sonora "Eduardo Ramos Bours"	Blvd. Luis Encinas Jonhson S/N y Reyes Col. San Benito	83000	Hermosillo	MEXICO
333	Hospital General de Urgencias "La Villa" DDF-S.S.	Calz. San Juan de Aragón No. 285 Col. Granja Moderna Delegación Gustavo A. Madero	07460	México, D.F	MEXICO
334	Hospital General Dr. Rafael Pascacio Gamboa	Calle Central Esq. Av. 9na. Sur, S/N Col. Centro	29000	Tuxtla Gutiérrez	MEXICO
335	Hospital Juárez de México SS	Av. Instituto Politécnico Nacional 5160 Col. Magdalena de las Salinas	07760	México, D.F.	MEXICO
336	Hospital Metropolitano "Dr. Bernardo Sepúlveda"	Av. López Mateos 4600 Col. Bosques del Nogalar	66480	Monterrey	MEXICO
337	Hospital Universitario de Puebla	25 Poniente y 13 Sur, Col. Los Volcanes	72410	Puebla	MEXICO

338	Academisch Ziekenhuis Maastricht	Afd. Inwendige Geneeskunde - P. Debyelaan 25	6229 HX	MAASTRICHT	NETHERLANDS
339	Ikazia Ziekenhuis	Afdeling Inwendige Geneeskunde, Montessoriweg 1	3083 AN	ROTTERDAM	NETHERLANDS
340	Meander Medisch Centrum Locatie Elisabeth	Afdeling Interne Geneeskunde, Ringweg Randenbroek 110	3816 CP	Amersfoort	NETHERLANDS
341	St. Lucas Andreas Ziekenhuis,	Afd. Interne Geneeskunde - J. Tooropstraat 164	1061 AE	AMSTERDAM	NETHERLANDS
342	Auckland City Hosptial	2 Park Road Grafton	1023	Auckland	NEW ZEALAND
343	Middlemore Hospital	Hospital Road Mangere East	2024	Auckland	NEW ZEALAND
344	North Shore Hospital	Shakespeare Road Takapuna North Shore City	0622	Auckland	NEW ZEALAND
345	Diakonhjemmets sykehus	Medisinsk avdeling Visiting address:Diakonveien 12	0319	Oslo	NORWAY
346	Sykehuset Innlandet HF Gjøvik	Medisinsk avdeling Sykehuset Innlandet HF Gjøvik	2819	Gjøvik	NORWAY
347	Sykehuset Innlandet HF Hamar	Medisinsk avdeling Skolegata 32	2326	Hamar	NORWAY
348	Sykehuset Østfold HF Fredrikstad	Poliklinikk for kreft & blodsykdommer. Besøksadr.:Cicignongata 19, 1606 Fredrikstad	1603	Fredrikstad	NORWAY

349	Hameed Latif Hospital	Department of Oncology, Hameed Latif Hospital, 14 Abu Bakr Road, New Garden Town,		Lahore	PAKISTAN
350	Jinnah Postgraduate Medical Centre	Department of Chest Medicine Jinnah Postgraduate Medical Centre (JPMC) Rafiqui Shaheed Road Karachi	75500	Karachi	PAKISTAN
351	Lahore General Hospital	Ferozpur Road,		Lahore	PAKISTAN
352	Centro Médico Naval	Av. Venezuela s/n	CALLAO 2	Callao	PERU
353	Hospital Alberto Sabogal Sologuren	Avenida Colina 1081	CALLAO 2	Callao	PERU
354	Hospital Dos de Mayo	Parque Historia de La medicina Peruana S/N Cercado de Lima	01	Lima	PERU
355	Hospital Edgardo Rebagliati Martins	Av. Edgardo Rebagliati Martins S/N JESUS MARIA	LIMA 11	Lima	PERU
356	Hospital Guillermo Almenara	Av. Grau 800	LIMA 1	Lima	PERU
357	Hospital Nacional Arzobispo Loayza	Av. Alfonso Ugarte N°. 848 Lima 1	LIMA 1	Lima Cercado	PERU
358	Hospital Nacional Cayetano Heredia	Av. Honorio Delgado 530	31	Lima	PERU
359	109 Szpital Wojskowy z przychodnia SPZOZ	Oddzial Kardiologiczny ul. Piotra Skargi 9/11	70-965	Szczecin	POLAND

360	10 Wojskowy Szpital Kliniczny z Poliklinika SPZOZ	Klinika Kardiologii ul. Powstancow Warszawy 5	85-681	Bydgoszcz	POLAND
361	10 Wojskowy Szpital Kliniczny z Poliklinika SPZOZ	Klinika Chorob Wewnetrznych Oddzial Kliniczny Chorob Wewnetrznych ul. Powstancow Warszawy 5	85-681	Bydgoszcz	POLAND
362	Miedzyleski Szpital Specjalistyczny	Oddzial Kardiologii i Chorob Naczyn ul. Bursztynowa 2	04-749	Warszawa	POLAND
363	Samodzielny Szpital Wojew. im. Kopernika	Oddzial Kardiologii ul. Rakowska 15	97-300	Piotrkow Trybunalski	POLAND
364	Specjalistyczny Szpital Sw. Jana	Oddzial Kardiologiczny ul. Balewskiego 1	83-200	Starogard Gdanski	POLAND
365	SP Szpital Kliniczny AM w Bialymstoku	Klinika Endokrynologii, Diabetologii i Chorob Wewnetrznych AM ul. Sklodowskiej-Curie 24a	15-276	Bialystok	POLAND
366	Szpital Praski p.w.Przemienienia Panskiego , SPZOZ	II Oddzial Chorob Wewnetrznych z pododdzialem Nefrologii Al. Solidarnosci 67	03-401	Warszawa	POLAND

367	Szpital Specjalistyczny im. J. Dietla	Oddzial Kardiologiczny ul. Skarbowa 1	31-121	Krakow	POLAND
368	Szpital Uniwersytecki w Krakowie	Oddzial Kliniczny Kliniki Alergologii i Oddzial Kliniczny Kliniki Pulmunologii ul. Skawinska 8	31-066	Krakow	POLAND
369	Szpital Wojewodzki	I Oddzial Chorob Wewnetrznych ul. Wieniecka 49	87-800	Wloclawek	POLAND
370	Szpital Wojewódzki im. Sw. Lukasza	Oddzial Wewnetrzny I i Nefrologii z Osrodkiem Dializ i Oddzial II Wewnetrzny i Ostrych Zatruc ul. Lwowska 178 a	33-100	Tarnów	POLAND
371	Wojewodzki Szpital Specjalistyczny im. S. Wyszynskiego SPZOZ	Oddzial Chorob Wewnetrznych, Endokrynologii i Diabetologii ul. Krasnicka 100	20-178	Lublin	POLAND
372	Wojskowy Instytut Medyczny	Zaklad Immunologii i Alergologii Klinicznej ul. Szaserow 128	04-141	Warszawa	POLAND
373	ZOZ MSWiA z Warminsko-Mazurskim Centrum Onkologii	Oddzial chorob Wewn. z Pododdzialem Kardiologii ul. Wojska Polskiego 37	10-228	Olsztyn	POLAND

374	Centro Hospitalar de Lisboa Norte - Hospital Santa Maria	Serviço de Medicina 1 D, piso 5, Elevador 12, Avenida Professor Egas Moniz	1649-035	Lisboa	PORTUGAL
375	CentroHospitalar de Lisboa Ocidental EPE-Hospital Egas Moniz	Consultas Externas de Medicina I Serviço de Medicina I, Rua da Junqueira 126	1349-019	Lisboa	PORTUGAL
376	Centro Hospitalar do Alto Minho, EPE	Serviço de Medicina 1, Estrada de Santa Lúzia	4901-585	Viana do Castelo	PORTUGAL
377	Hospitais da Universidade de Coimbra	Serviço de Medicina 1, Piso 7 Praceta Mota Pinto +351 965405011 /	3000-075	Coimbra	PORTUGAL
378	Hospitais da Universidade de Coimbra	Unidade de Investigação Clínica em Cardiologia / Serviço de Cardiologia, Praceta Mota Pinto	3000-075	Coimbra	PORTUGAL
379	Hospital de Santarém	Serviço de Medicina 1 Av. Bernardo Santareno	2005	Santarém	PORTUGAL
380	Hospital de São João	Serviço de Medicina Interna, Piso 4 Alameda Prof. Hernani Monteiro	4200-319	Porto	PORTUGAL
381	Hospital Pedro Hispano	Serviço de Medicina Interna Rua Doutor Eduardo Torres	4454-509	Matosinhos	PORTUGAL

382	Hospital SAMS do Sindicato dos Bancarios do Sul e Elhas	Departamento de Medicina, Piso 7 Rua Cidade de Gabela, 1	1849- 017	Lisboa	PORTUGAL
383	Hospital Santo António Oporto	Serviço de Medicina 1 - Unidade A Largo Professor Abel Salazar	4099-001	Porto	PORTUGAL
384	City Clinical Hospital n.a. Botkin	Cardiology Dept. 2nd Botkinskiy proezd, 5 building 20	125101	Moscow	RUSSIA
385	City Clinical Hospital n.a. Botkin	Neurology Dept. 2nd Botkinskiy proezd, 5 building 20	125101	Moscow	RUSSIA
386	Clinical Hospital for Emergency Care n.a. N.V.Solovyov	Zagorodny sad str. 11	150003	Yaroslavl	RUSSIA
387	Medical-Rehabilitation Center of Roszdrav	Neurology dept. Ivankovskoye shosse, 3	125367	Moscow	RUSSIA
388	Municipal Healthcare Institution "Clinical Hospital No 8"	39 Suzdalskoe highway	150030	Yaroslavl	RUSSIA
389	Municipal Hospital N 4	Cardiology Dept. Pavlovskaya street 25	115093	Moscow	RUSSIA
390	Municipal Hospital N 59	Cardiology dept. Dostoevskogo str. 31-33	103030	Moscow	RUSSIA
391	Municipal Hospital N 64	Cardiology Dept. Vavilova 61	117292	Moscow	RUSSIA
392	Changi General Hospital	2 Simei Street 3	529889		SINGAPORE

393	National Heart Centre	National Heart Centre Dept of Cardiovascular Medicine Level 4 Mistri Wing 17 Third Hospital Avenue	168752	Singapore	SINGAPORE
394	National University Hospital	5 Lower Kent Ridge Road, Main Building Level 2	119074	Singapore	SINGAPORE
395	Singapore General Hospital	Department of Internal Medicine, Block 6, Level 7; Outram Road	169608	Singapore	SINGAPORE
396	Singapore General Hospital	Dept of Respiratory & Critical Care Medicine Block 6, Level 6 Outram Road	169608	Singapore	SINGAPORE
397	Tan Tock Seng Hospital	Department of Respiratory, 11 Jalan Tan Tock Seng, Singapore 308433	308433	Singapore	SINGAPORE
398	Fakultna nemocnica s poliklinikou Zilina	Interne oddelenie ul. Vojtecha Spanyola 43	012 07	Zilina	SLOVAKIA
399	Univerzitna nemocnica Bratislava, Nemocnica Ruzinov	V Interna klinika LF UK Ruzinovska 6	826 06	Bratislava	SLOVAKIA
400	Univerzitná nemocnica Bratislava, Nemocnica Stare Mesto	II Interna klinika Mickiewiczova 13	813 69	Bratislava	SLOVAKIA
401	Univerzitna nemocnica Martin	I.Interna klinika Kollarova 2	036 59	Martin	SLOVAKIA

402	Vseobecna nemocnica s poliklinikou Lucenec	namestie Republiky 15	984 39	Lucenec	SLOVAKIA
403	Hospital Golnik	Klinicni oddelek za pljucne bolezni in alergije Golnik 36	4204	Golnik	SLOVENIA
404	Infekcijska klinika	Klinika za infekcijske bolezni in vrocinska stanja Japljeva 2	1000	Ljubljana	SLOVENIA
405	Klinicni center	Nevrolska klinika Klinicni oddelek za vaskularno nevrologijo in intenzivno nevrolsko terapijo Zaloska cesta 7	1000	Ljubljana	SLOVENIA
406	Klinicni center	Klinika za zilne bolezni Zaloska cesta 7	1000	Ljubljana	SLOVENIA
407	Klinicni center	Klinicni oddelek za torakalno kirurgijo Zaloska cesta 7	1000	Ljubljana	SLOVENIA
408	Klinicni center	KO za intenzivno interno medicino Zaloska cesta 7	1000	Ljubljana	SLOVENIA
409	Clinical Projects Research SA	42 Russell Street	6850	Worcester	SOUTH AFRICA
410	Clinresco Kempton Park	ARWYP Medical Suites 4th Floor 22 Pine Avenue	1610	Kempton Park	SOUTH AFRICA
411	Emmed Research	641 5th Avenue Eloffsdal	0084	Pretoria	SOUTH AFRICA

412	Little Company of Mary Hospital	50 Totius St Groenkloof	0181	Pretoria	SOUTH AFRICA
413	Mayo Clinic	Mayo Clinic Mayo 7 2nd Floor William Nicol Drive Floracliffe	1724	Roodepoort	SOUTH AFRICA
414	Medcial Oncology Centre Rosebank	129 Cnr Oxford and Norhtworld Roads Saxonworld	2196	Johannesburg	SOUTH AFRICA
415	Morningside Clinic Rocherster Place	Morningside Clinic Rochester Place 173 Rivonia Road Cnr Hill Morningside, Sandton	2057	Johannesburg	SOUTH AFRICA
416	N1 City Hospital	N1 City Mews Unit B1 Cnr Frans Conradie & Marnus Gerber Street	7460	Goodwood	SOUTH AFRICA
417	National Hospital	Department of Family Medicine Roth Avenue	9301	Bloemfontein	SOUTH AFRICA
418	Pretoria Academic Hospital New	Corner Malan & Voortrekkers Street Gezina	0084	Pretoria	SOUTH AFRICA
419	Sandton Medi Clinic	Kopano Clinical Trials Suite 10, North Block, Medical Centre Peter Place	2196	Sandton, Gauteng	SOUTH AFRICA
420	Unitas Hospital	Unitas Hospital Clifton Ave Lyttleton Centurion	0157	Pretoria	SOUTH AFRICA

421	University of Pretoria, Prinshof Campus	Dr Savage Road HW Snyman South Building Riviera	0084	Pretoria	SOUTH AFRICA
422	University of Stellenbosch	Tygerberg Campus Clinical Building Lung Research Unit Room 3013 3rd Floor	7505	Stellenbosch	SOUTH AFRICA
423	Vergelegen Medi-Clinic	Dr. J.M. Engelbrect Block 1 Vergelegen MediClinic Main Road	7130	Somerset West	SOUTH AFRICA
424	Corporació Sanitària Parc Taulí	Servicio de Medicina Interna Parc Taulí, s/n	08208	Sabadell	SPAIN
425	Hospital Clínic i Provincial de Barcelona	Servicio de Medicina Interna C/ Villarroel, 170	08036	Barcelona	SPAIN
426	Hospital Clínico Universitario Lozano Blesa	Servicio de Neumología Avds. San Juan Bosco, 15	50009	Zaragoza	SPAIN
427	Hospital Comarcal de la Axarquía	Servicio de Medicina Interna Urb. El Tomillar, s/n	29700	Vélez	SPAIN
428	Hospital Infanta Margarita	Servicio de Medicina Interna Av. Góngora, s/nº	14940	Cabra	SPAIN
429	Hospital Josep Trueta	Servicio de Medicina Interna 8ª Planta B Avda. de França, s/n	17007	Girona	SPAIN

430	Hospital Quirón	Servicio de Medicina Interna Plaza Alfonso Comín, 5-7	08023	Barcelona	SPAIN
431	Hospital Santa Lucía	Servicio de Medicina Interna c/Mezquita, s/n. Paraje Los Arcos. Barrio de Santa Lucía	30202	Cartagena	SPAIN
432	Hospital Sant Jaume de Olot	Servicio de Medicina Interna C/ Mulleres, 15	17800	Olot	SPAIN
433	Hospital Universitari Germans Trias i Pujol	Servicio de Medicina Interna Ctra. del Canyet, s/n	08916	Badalona	SPAIN
434	Hospital Virgen de la Luz	Servicio de Medicina Interna C/ Hermandad Donantes de Sangre,1	16002	Cuenca	SPAIN
435	Centralsjukhuset Kristianstad	Medicinklinikens Forskningsenhet	29185	Kristianstad	SWEDEN
436	Danderyds sjukhus	Strokeenheten	182 88	Stockholm	SWEDEN
437	Hässleholms Sjukhus	Medicinkliniken	281 25	Hässleholm	SWEDEN
438	Kärnsjukhuset i Skövde	Avd 51	541 85	Skövde	SWEDEN
439	Karolinska Universitetssjukhuset i Solna	AVA 1, A3:02	171 76	Stockholm	SWEDEN
440	Länssjukhuset Sundsvall-Härnösand	Medicinkliniken	851 86	Sundsvall	SWEDEN
441	Norrlands Universitetssjukhus	Medicinkliniken	90185	Umeå	SWEDEN
442	Skånes Universitetssjukhus	Onkologkliniken	221 85	Lund	SWEDEN

443	Universitetssjukhuset MAS	Medicinkliniken/Koagulationsmott	205 02	Malmö	SWEDEN
444	Inselspital Bern	Department Herz und Gefässe Abteilung Angiologie Freiburger Str. 4	3010	Bern	SWITZERLAND
445	Kantonsspital Bruderholz	Medizinische Universitätsklinik Angiologie Batteriestrasse 1	4101	Bruderholz	SWITZERLAND
446	Kantonsspital Liestal	Medizinische Universitätsklinik Innere Medizin Rheinstr. 26	4410	Liestal	SWITZERLAND
447	Luzerner Kantonsspital	Angiologie Spitalstrasse	6000	Luzern	SWITZERLAND
448	SRO AG Spital Langenthal	St. Urbanstrasse 67	4901	Langenthal	SWITZERLAND
449	Universitätsspital Basel	Departement Innere Medizin Medizinische Klinik B Petersgraben 4	4031	Basel	SWITZERLAND
450	Chang Gung Memorial Hospital Kaohsiung	Chang Gung Memorial Hospital No. 123, TaPei Road Niao-Sung Hsiang	833	Kaohsiung	TAIWAN
451	Chi- Mei Medical Hospital, Tai-Nan Hsien	Dep of Medical Research, No. 901, Chung Hwa Rd. Yung Kang City,	710	Tainan	TAIWAN
452	National Taiwan University Hospital	Department of Internal Medicine, No.7, Chung-Shan South Rd.,	10016	Taipei	TAIWAN

453	Shing-Kong Wu Ho-Su Memorial Hospital	Dep of Internal Medicine, Division of Cardiology, No.95, Wen Chang Rd.,		Taipei	TAIWAN
454	Tri-Service General Hospital	Dep of Internal Medicine, Division of Cardiology No. 325, Sec. 2, Cheng Gung Rd.	114	Taipei	TAIWAN
455	Maharaj Nakorn Chiang Mai Hospital	110 Intravarorot Road, Sripum, Muang,Chiang Mai	50200	Chiangmai	THAILAND
456	Pramongkutklao Hospital	Department of medicine 315 Rajavithi Rd. Rajathevee	10400	Bangkok	THAILAND
457	Siriraj Hospital, Mahidol	Siriraj Hospital, 2 Prannok Road Bangkoknoi	10700	Bangkok	THAILAND
458	Dokuz Eylul Universitesi Tip Fakultesi	Hematoloji Onkoloji Bilim Dali Inciralti	35340	Izmir	TURKEY
459	Ege Universitesi Tip Fakultesi	Onkoloji Bilim Dali Bornova	35100	Izmir	TURKEY
460	Ege Universitesi Tip Fakultesi	Nöroloji Anabilim Dali Bornova	35100	Izmir	TURKEY
461	Ege Universitesi Tip Fakultesi	Kardiyoloji Anabilim Dali Bornova	35100	Izmir	TURKEY
462	Istanbul Universitesi Cerrahpasa Tip Fakultesi	Kardiyoloji Anabilim Dali Cerrahpasa, Fatih	34098	Istanbul	TURKEY
463	Istanbul Universitesi Kardiyoloji Enstitusu	Kardiyoloji Anabilim Dali Haseki	34304	Istanbul	TURKEY

464	City Clinical Hospital # 1	Dept of Cardiology Kharkovskoye Shosse 121	02 091	Kiev	UKRAINE
465	City Clinical Hospital # 17	Department of Cardiology Koskovskiy Av. 195	61037	Kharkiv	UKRAINE
466	City Clinical Hospital # 8	Department of Rehabilitation of neurological Patients Kondratyuka str. 8	01105	Kyiv	UKRAINE
467	Clinic of Odesa State Medical University	Dept. of Therapy Tinysta str 8	65009	Odessa	UKRAINE
468	Crimean Republican Cardiological Clinical Hospital	Gagarina str. 15	95 026	Simferopol	UKRAINE
469	Crimiean Republican Clinical Oncology Dispensary	Department of Oncology A. Bespalova str. 49A	95023	Simferopol	UKRAINE
470	Donetsk state medical university	Chair of Child and General Neurology Ilicha ul. 16	83003	Donetsk	UKRAINE
471	Institute of Cardiology AMS	Viddil sertsevoi nedostatnosti Narodnogo Opolechania str. 5	03680	Kiev	UKRAINE
472	Institute of Cardiology AMS	Viddil arterialnoyi hypertensiyi Narodonogo opolcheniya 5	03680	Kiev	UKRAINE
473	Institute of Urgent and Recovery Surgery n.a. V.K.Gusak AMS	Department of Urgent Cardiology and Rehabilitation 47 Leninsky ave,	83045	Donetsk	UKRAINE
474	Kyiv City Clinical Hospital #9	1 Ryzhska str.	04112	Kiev	UKRAINE

475	Lviv City Clinical Hospital #8	Navrotskogo 23 Str.	790 34	Lviv	UKRAINE
476	Miska Klinichna likarnya No 8	3rd Department of Cardiology Saltovskoe shose 266	61178	Kharkiv	UKRAINE
477	Oblasnyi klinichnyi kardiologychnyi dyspanser	Dept of Myocardial Infraction no 2 Mazepy str 114	76000	Ivano-Frankivsk	UKRAINE
478	Regional Clinical Hospital	Zabolotnogo str. 26	65065	Odessa	UKRAINE
479	Regional Clinical Hospital	Department of Vascular Surgery Fed'kovycha str. 91	76000	Ivano-Frankivsk	UKRAINE
480	Dumfries & Galloway Royal Infirmary	Bankend Road	DG1 4EP	Dumfries	UNITED KINGDOM
481	Kings College Hospital	Department of Vascular Sugery 2nd Floor, West Entresol (off Hambledon Wing) Bessemer Road Denmark Hill	SE5 9RS	London	UNITED KINGDOM
482	North Middlesex Hospital	Sterling Way Edmonton	N18 1QX	London	UNITED KINGDOM
483	Royal Victoria Infirmary	Queen Victoria Road	NE1 4LP	Newcastle Upon Tyne	UNITED KINGDOM
484	St James' Hospital	Beckett Street	LS9 7TF	Leeds	UNITED KINGDOM
485	University College London Hospitals	Whitfield Street Laboratories 60 Whitfield Street	W1T 4EU	London	UNITED KINGDOM
486	University Hospital Aintree	Longmoor Lane	L9 7JU	Liverpool	UNITED KINGDOM

487	Advanced Neurology Specialists	400 15th Avenue South Suite 206	59405	Great Falls	UNITED STATES
488	Alabama Clinical Therapeutics	52 Medical Park East Drive Suite 203	35235	Birmingham	UNITED STATES
489	Anaconda Internal Medicine Clinic	1102 East Commercial Avenue	59711-2718	Anaconda	UNITED STATES
490	Atlanta Institute for Medical Research, Inc.	495 Winn Way Suite 220	30030	Decatur	UNITED STATES
491	Baptist Medical Center South	2105 East South Boulevard	36111	Montgomery	UNITED STATES
492	Bay Area Chest Physicians	616 E Street	33756	Clearwater	UNITED STATES
493	Bendel Medical Research Center, LLC	227 Bendel Road Suite 300	70503	Lafayette	UNITED STATES
494	Candler Hospital/St. Joseph's Candler Health System	Office of Research 5353 Reynolds Street	31405	Savannah	UNITED STATES
495	Cardiology Consultants	601 N Congress Avenue Suite 402	33445	Delray Beach	UNITED STATES
496	Carolina Research Specialists	111-A Medical Drive	27909	Elizabeth City	UNITED STATES
497	Christiana Care Health Services	4755 Ogletown Stanton Road Room 1140	19718	Newark	UNITED STATES
498	Clinical Research Limited	4565 Dressler Drive NW Suite 103	44718	Canton	UNITED STATES
499	Community Clinical Research Center	1221 Medical Arts Boulevard	46011	Anderson	UNITED STATES
500	Corsicana Medical Research, LLC	301 Hospital Drive Suite 165	75110	Corsicana	UNITED STATES

501	Creighton University Medical Center-St. Joseph Hospital	601 North 30th Street Suite 3820	68131	Omaha	UNITED STATES
502	Doctors Hospital at Renaissance	5501 S. McColl Road	78539	Edinburg	UNITED STATES
503	Drogue Medical, LLC	3550 Lutheran Parkway W. Suite 102-C	80033-6017	Wheat Ridge	UNITED STATES
504	eStudySite	3998 Vista Way Suite F	92056	Oceanside	UNITED STATES
505	eStudySite	752 Medical Center Court Suite 105	91911	Chula Vista	UNITED STATES
506	Franklin Square Hospital Center	Medical Arts Building 9101 Franklin Square Drive Suite 320	21237	Baltimore	UNITED STATES
507	Geisinger Wyoming Valley Medical Center	Center for Health Research-Wyoming Valley 1000 East Mountain Boulevard	18711-3752	Wilkes-Barre	UNITED STATES
508	George Washington University Medical Center	University Hospital 900 23rd Street NW	20037	Washington	UNITED STATES
509	Harbor - UCLA Medical Center	1000 West Carson Street	90502-2004	Torrance	UNITED STATES
510	Henry Ford Health System	Henry Ford Hospital K-15 2799 West Grand Boulevard	48202	Detroit	UNITED STATES
511	Heritage Cardiology Associates	425 North 21st Street	17011	Camp Hill	UNITED STATES
512	Holy Name Medical Center	718 Teaneck Road	07666	Teaneck	UNITED STATES

513	Hunter Holmes McGuire Veterans Affairs Medical Center	Research Institute Code: 151 1201 Broad Rock Boulevard Room 5D-127	23249	Richmond	UNITED STATES
514	Intercoastal Medical Group	943 S. Beneva Road Suite 102	34232	Sarasota	UNITED STATES
515	Jamaica Hospital Medical Center	8900 VanWyck Expressway	11418	Jamaica	UNITED STATES
516	Jobst Vascular Institute	ProMedica Health Sytem-The Toledo Hospital 2109 Hughes Drive Jobst Tower - Suite 400	43606	Toledo	UNITED STATES
517	Kansas City VA Medical Center	Medical Service (111) 4801 East Linwood Boulevard	64128	Kansas City	UNITED STATES
518	LeBauer HealthCare	520 N. Elam Avenue	27403	Greensboro	UNITED STATES
519	LSU Health Sciences Center	1541 Kings Highway	71130-4228	Shreveport	UNITED STATES
520	McKay-Dee Hospital Center	4401 Harrison Boulevard	84403	Ogden	UNITED STATES
521	Medical University of South Carolina	Department of Medicine Division of Hematology-Oncology 96 Jonathan Lucas Street CSB-903	29425	Charleston	UNITED STATES
522	Memorial Hermann Memorial City Hospital	921 Gessner Road	77024	Houston	UNITED STATES
523	Memorial Sloan-Kettering Cancer Center	1275 York Avenue	10065	New York	UNITED STATES

524	MeritCare Hospital	801 Broadway North Route:32	58122	Fargo	UNITED STATES
525	Minneapolis VA Medical Center	Hematology / Oncology (111E) One Veterans Drive	55417	Minneapolis	UNITED STATES
526	New York Medical College	Munger Pavilion Room 414	10595	Valhalla	UNITED STATES
527	New York Methodist Hospital	506 Sixth Street	11215	Brooklyn	UNITED STATES
528	New York-Presbyterian Hospital	Weill Cornell Medical Center G4-313D 525 East 68th Street	10065	New York	UNITED STATES
529	Northern Michigan Regional Hospital	NISUS Research Department 416 Connable Avenue	49770-2297	Petoskey	UNITED STATES
530	Novellus Research Sites, Inc.	11190 Warner Avenue Suite 300	92708	Fountain Valley	UNITED STATES
531	Oakwell Clinical Research, LLC	3338 Oakwell Court Suites 107 & 110	78218	San Antonio	UNITED STATES
532	Office of Dr. John Simmons, MD	915 West Hospital Drive	36340	Geneva	UNITED STATES
533	Office of John Suen, MD., PA	1355 37th Street Suite 302	32960	Vero Beach	UNITED STATES
534	Overlook Hospital	99 Beauvoir Avenue	07901	Summit	UNITED STATES
535	Penobscot Bay Medical Center	6 Glen Cove Drive Clinical Research, Room 046	04856	Rockport	UNITED STATES
536	Providence Regional Medical Center Everett	Clinical Research 1330 Rockefeller Avenue Suite 140	98201	Everett	UNITED STATES

537	Pulmonary Associates of Mobile, PA	6701 Airport Boulevard Suite B-131	36608	Mobile	UNITED STATES
538	Redlands Community Hospital	350 Terracina Boulevard	92373	Redlands	UNITED STATES
539	Saint Luke's Hospital	5901 Monclova Road	43537-1899	Maumee	UNITED STATES
540	San Diego Clinical Trials	6719 Alvarado Road Suite 201	92120	San Diego	UNITED STATES
541	Santa Barbara Cottage Hospital	Pueblo at Bath Streets	93102	Santa Barbara	UNITED STATES
542	Sinai Hospital of Baltimore	2435 West Belvedere Avenue	21215	Baltimore	UNITED STATES
543	Somerset Medical Center	110 Rehill Avenue	08876-2598	Somerville	UNITED STATES
544	Southern Clinic	1901 Melba Drive	36301	Dothan	UNITED STATES
545	Southern Illinois University School of Medicine	701 North 1st Street Suite D-346	62702	Springfield	UNITED STATES
546	South Texas Institutes of Health	901 East Vermont Suite B	78503	McAllen	UNITED STATES
547	St. John's Mercy Medical Center	621 S. New Ballas Road Suite 4006	63141	St. Louis	UNITED STATES
548	St. Joseph Mercy Hospital	5301 East Huron River Drive	48106	Ann Arbor	UNITED STATES
549	Tacoma General Hospital	315 Martin Luther King Jr Way Mail Stop 315C2-RS	98405	Tacoma	UNITED STATES
550	Thomas Jefferson University Hospitals	833 Chestnut Street Suite 701	19107	Philadelphia	UNITED STATES

551	University of Arkansas for Medical Sciences	General Internal Medicine Research Slot 712 4301 West Markham Street	72205	Little Rock	UNITED STATES
552	University of California Davis Medical Center	Ticon 1 Building 2000 Stockton Boulevard Suite 100-B	95817	Sacramento	UNITED STATES
553	University of Medicine & Dentistry of New Jersey	Robert Woods Johnson Med School Department of Neurology 125 Paterson Street	08901	New Brunswick	UNITED STATES
554	University of Miami School of Medicine	1120 NW 14th Street 935 CRB (C216)	33136	Miami	UNITED STATES
555	Vanderbilt University Medical Center	1161 21st Ave. South T-1218 MCN	37232-2650	Nashville	UNITED STATES
556	VA North Texas Healthcare System	Dallas VA Medical Center Department of Medicine (111-E) 4500 South Lancaster Road	75216-7167	Dallas	UNITED STATES
557	Virgiania Commonwealth University Health System	VCU Medical Center - West Hospital 1200 E. Broad Street 5th Floor/South Wing/Room 307	23298	Richmond	UNITED STATES

558	Washington University-St. Louis	WU Medical Center Center for Advanced Medicine Center for Clinical Studies 4921 Parkview Place - Suite 11B	63110	St. Louis	UNITED STATES
559	Wayne State University	Department of Neurology 8C-UHC 4201 St. Antoine	48201	Detroit	UNITED STATES
560	West Alabama Research, Inc.	100 Rice Mine Road Loop Suite 104	35406	Tuscaloosa	UNITED STATES
561	West Alabama Research, Inc.	2018 Brookwood Medical Center Drive Suite 314	35209	Birmingham	UNITED STATES
562	West Alabama Research, Inc.	2018 Brookwood Medical Center Drive Suite 314	35209	Birmingham	UNITED STATES

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Xarelto
Brand/Trade Name(s) ex-US	Xarelto
Generic Name	rivaroxaban
Main Product Company Code	BAY59-7939
Other Company Code(s)	
Chemical Description	IUPAC Name: 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide
Other Product Aliases	

Date of last Update/Change: 04 Mar 2013