Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Darexaban		
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SYNOPSIS

Title of Study:

A Phase 2, Double-Blind, Double-Dummy, Randomized, Parallel Group Dose Finding Study to Investigate the Safety and Tolerability of Darexaban in Patients with NonValvular Atrial Fibrillation and to Compare the Safety and Tolerability with Warfarin.

Responsible Medical Officer/Investigators:

[redacted], MD, [redacted] The Netherlands.

Study Centers:

This study was conducted in 179 active study centers in 24 countries – Australia, Canada, India, Japan, Malaysia, Russian Federation, South Africa, South Korea, the Philippines, the Ukraine and Thailand; and the following countries in the EU: Austria, Bulgaria, Czech Republic, Estonia, France, Germany, Hungary, Israel, Poland, Slovakia, Spain, the Netherlands and the United Kingdom (UK).

Publication (references):

- Lip GYH, Halperin JL, Petersen P; Rodgers GM4, Renfurm RW. Safety and Tolerability of the Oral Factor Xa Inhibitor, YM150 versus Warfarin in 1297 Patients with Non-Valvular Atrial Fibrillation: A Dose Confirmation Study (OPAL-2). Presented at the XXIII Congress of the International Society on Thrombosis and Haemostasis, July 23–28, 2011, Kyoto, Japan. Oral presentation number O-TH-083.
- Rodgers GM; Renfurm RW; Halperin JL; Petersen P; Lip GYH. Efficacy of the Oral FXa Inhibitor, Darexaban (YM150) on Biomarkers for Thrombogenesis in 1297 Patients with Non-Valvular Atrial Fibrillation: Phase IIb Dose Confirmation Study (OPAL-2). Presented at the XXIII Congress of the International Society on Thrombosis and Haemostasis, July 23-28, 2011, Kyoto, Japan. Poster number P-TH-373.

Study Period: 11 Jun 2009 (first patient screened) to 04 Oct 2010

Date of first enrollment (Study initiation date): 15 Jun 2009

Date of last evaluation (Study completion date): 04 Oct 2010

Phase of Development: Phase 2

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Objectives:

The primary objective of the study was to investigate the optimal daily dose and dose regimen of darexaban (YM150) in patients with nonvalvular atrial fibrillation (NVAF), primarily based on safety and tolerability data. The secondary objectives of the study were as follows:

- To obtain information on the pharmacokinetics and pharmacodynamics (antithrombotic potential) in the target population
- To evaluate the efficacy, safety and tolerability of darexaban in patients with NVAF and
- To evaluate the effects of darexaban and warfarin on: [1] the health status of patients with NVAF; [2] the number of Quality Adjusted Life Years (QALYs) gained (as a means of quantifying the benefit of the intervention); and [3] the health care resource use associated with both treatment options

Methodology:

This was a multi-center, randomized, double-blind, double-dummy, multiple-dose, active control (dose-adjusted warfarin), parallel-group study. Six dose groups of darexaban and 1 control group of dose-adjusted warfarin were evaluated in a double-blind, double-dummy fashion. Patients were stratified by prior anticoagulant use (such as warfarin or heparin use within 8 weeks prior to baseline visit). Patients were randomized to one of the following groups:

- Group 1: Darexaban 15 mg bid
- Group 2: Darexaban 30 mg qd
- Group 3: Darexaban 30 mg bid
- Group 4: Darexaban 60 mg qd
- Group 5: Darexaban 60 mg bid
- Group 6: Darexaban 120 mg qd and
- Group 7: Dose-adjusted warfarin qd

The study organization consisted of a Steering Committee (SC), an Adjudication Committee (AC), and an independent Data and Safety Monitoring Board (DSMB). The SC had participated in the study design and protocol development and advised Astellas regarding the continuation or termination of a dose group of darexaban as well as the overall study, based on the recommendation of the DSMB. A blinded independent AC evaluated the specified study outcomes centrally. An independent DSMB periodically reviewed unblinded data and provided recommendations to the SC and Astellas.

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Number of Patients (planned, enrolled and analyzed):

It was planned that at least 160 patients and up to 165 patients would be randomized in each darexaban dose regimen group and at least 320 patients and up to 330 patients in the warfarin group, for a total of at least 1280 patients and up to 1320 patients. Overall, 1867 patients were screened due to a higher than anticipated screen failure rate and 1312 patients were randomized in the study. Patient disposition in this study is summarized in Table 1.

Table 1 Patient Disposition – All Randomized Patients

	Darexaban						Warfarin
Number (%) of Patients	**15 mg bid n=164**	**30 mg qd n=164**	**30 mg bid n=164**	**60 mg qd n=164**	**60 mg bid n=163**	**120 mg qd n=164**	**qd n=329**
Randomized and received study drug	163 (99.4)	163 (99.4)	162 (98.8)	163 (99.4)	163 (100.0)	164 (100.0)	328 (99.7)
SAF†	162 (98.8)	161 (98.2)	162 (98.8)	163 (99.4)	162 (99.4)	163 (99.4)	324 (98.5)
FAS‡	162 (98.8)	161 (98.2)	162 (98.8)	163 (99.4)	162 (99.4)	163 (99.4)	324 (98.5)
PPS§	151 (92.1)	146 (89.0)	147 (89.6)	147 (89.6)	148 (90.8)	151 (92.1)	285 (86.6)

Abbreviations: SAF: Safety Analysis Set; FAS: Full Analysis Set; PPS: Per Protocol Set.
† All randomized patients with at least 1 dose of double-blind drug taken.
‡ All randomized patients with at least 1 dose of double-blind drug taken.
§ All randomized patients with at least 1 dose of double-blind drug taken and without major protocol violation.
Source: Table 12.1.1.2

Diagnosis and Main Criteria for Inclusion:

Male or female patients with paroxysmal, persistent or permanent NVAF with a Stroke Risk Stratification Score (CHADS2) of 1 to 6, and who had not had recent (within 12 months) stroke or transient ischemic attack (TIA).

Test Product, Dose and Mode of Administration, Batch Numbers:

Darexaban was administered as oral tablets containing 15, 30, 60 or 120 mg of darexaban free base equivalent as monomaleate salt. The treatment groups were as follows:

- Group 1: Darexaban 15 mg bid
- Group 2: Darexaban 30 mg qd
- Group 3: Darexaban 30 mg bid
- Group 4: Darexaban 60 mg qd
- Group 5: Darexaban 60 mg bid
- Group 6: Darexaban 120 mg qd

Darexaban batch numbers are listed in [Appendix 13.1.6].

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Duration of Treatment (or Duration of Study, if applicable):

Darexaban was to be administered for at least 24 weeks for the last patient randomized and up to approximately 14 months for the first patient randomized.

Warfarin was also to be administered for at least 24 weeks for the last patient randomized and up to approximately 14 months for the first patient randomized.

After the end of the double-blind treatment period (or in case of premature discontinuation) patients were to be switched to standard of care open-label warfarin therapy unless medically contraindicated. Treatment with open-label warfarin was to continue throughout the 1-month follow-up period after which subsequent treatment was at the discretion of the managing physician.

Reference Product, Dose and Mode of Administration, Batch Numbers:

Warfarin was administered as oral tablets dose-adjusted to a target International Normalized Ratio (INR) of 2.0 to 3.0 (for patients aged 70 years or older, the dose could be adjusted to a target INR of 1.6 to 2.6, according to local practice). Placebo to match (PTM) darexaban tablets and PTM warfarin tablets were also used.

Warfarin and placebo batch numbers are listed in [Appendix 13.1.6].

Criteria for Evaluation:

Safety variables

The primary variable was the incidence of major and clinically relevant nonmajor (CRNM) bleeding events during the double blind treatment period as adjudicated by the AC.

Safety was additionally assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug)
- Clinical laboratory variables (hematology, biochemistry, and urinalysis)
- Vital signs (systolic and diastolic blood pressure and pulse rate)
- Physical examination
- 12-lead electrocardiogram (ECG)

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Efficacy Variables

Adjudicated Efficacy Events

Interest lies in estimating the incidence rates per 100 patient years of the following events:

- Ischemic stroke
- TIA
- Systemic thromboembolic events (STEs)
- Acute coronary syndrome (ACS)
- Deaths

Thus the presence/absence of the event combined with the time of the first occurrence or time of censoring were considered to be the efficacy variables for this study; note that only the occurrence of the first event was of interest as typically the patient could leave the study or the hazard function could change after the first event.

Each of the above events were adjudicated and classified by the AC. For each of the above events the AC reviewed the data provided by the investigators and determined which event (if any) the patient experienced. The AC remained blinded throughout the treatment period and objectively reviewed the data available.

Definitions for each of these events were provided in the study protocol (Appendix 13.1.1) and further detailed in the AC charter. For each of the above events the AC provided further classification of the exact nature of the event, and could also provide a sub-categorization.

Combination of Adjudicated Events (Composites)

The presence/absence of composite events combined with the time of the first occurrence or time of censoring were also considered to enable the estimation of incidence rates per 100 patient years. The primary composite event was the composite incidence of any ischemic strokes, TIAs, STEs, ACS, and all deaths as defined based on the decisions provided by the AC.

Patient Reported Outcomes

Patient reported outcomes were assessed using the following: EuroQol-5 Dimension Questionnaire (EQ-5D), Hospital Anxiety and Depression Scale (HADS), 36 Item Short-Form Health Survey (SF-36) and the Tablets for Anti-Clot Treatment Questionnaire (TACT-Q).

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Pharmacokinetic/Pharmacodynamic Variables

Pharmacokinetic blood samples were collected for determination of darexaban and darexaban glucuronide (YM-222714) plasma concentrations. The following pharmacodynamic endpoints were measured:

- Hemostasis biomarkers: prothrombin fragment 1+2 (F_{1+2}), D-dimer and activated Factor X (FXa) inhibition
- Coagulation laboratory measurement: prothrombin time (PT)

Statistical Methods:

Safety Analysis

The primary analysis was based on the Safety Analysis Set (SAF), which defined evaluability for the primary analysis; all patients in the SAF were evaluable and included in the primary analysis. The primary hypothesis was: H_0: $\tau_{\text{Group A}} = \tau_{\text{Group B}}$ versus H_A: $\tau_{\text{Group A}} \neq \tau_{\text{Group B}}$ where τ is the incidence rate of at least 1 major bleed and CRNM bleed. Incidence rates were reported as number of events per 100 patient years. Incidence per 100 patient years was summarized by treatment grouping (treatment group, total darexaban daily dose, darexaban dosing frequency and overall). The incidence rates and 95% confidence intervals (CIs) for each event, classification and sub-classification of event were calculated.

The treatment effect was analyzed using a Poisson regression including factors for treatment and prior anticoagulant use (yes/no) as covariates. Time at risk was used as the denominator (or equivalently log of time at risk was an offset). Patients who had an event only contributed the time up to that event as the time at risk. For each comparison, the hazard ratio was presented along with the 95% CI.

Following the event it was expected that patients would be withdrawn from the study or the hazard could change and so only the time up to and including the event was used in the analyses. There was no adjustment for multiplicity in the tests. This was a phase 2 study for dose and regimen selection; each test was used as part of the information for selecting the appropriate dose for phase 3.

The incidence rate analyses were conducted for the double-blind treatment period (on-treatment analysis). The number of events occurring off treatment was investigated at the blinded data review meeting (BDRM), where it was decided whether to also perform an Intention to Treat (ITT) analysis for the primary variable (i.e., also counting events that appear after the last dose of double-blind treatment, within the follow-up period).

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The events that occurred in the follow-up period were listed; they were to be used in the inferential analysis only if the above-mentioned ITT analysis was performed (computing the events for the double-blind and follow-up period together). As a sensitivity analysis the above analyses were also repeated based on the Per Protocol Set (PPS).

Interactions were tested in a separate model. The interaction between treatment and prior anticoagulant therapy was investigated and included in the model if the type 3 estimate was significant at the 0.1 level. The interaction between dose and dosing frequency was also investigated in order to assess whether the dosing frequency effect was homogenous across different total daily doses.

The proportional hazards assumption was verified graphically using a log-cumulative hazard plot against log-survival time.

Efficacy Analysis

The number of patients experiencing each of the efficacy-related events defined in the section "*Efficacy Variables"* (see above) was summarized by treatment grouping (treatment group, total darexaban daily dose, darexaban dosing frequency and overall). The incidence rate per 100 patient years was calculated as follows:

(Number of patients with event)/(Total cumulative time at risk [years]) x 100

If a patient had more than 1 event, only the first occurrence of the event was counted in the above calculation. Note: the total cumulative time at risk included the time up to the event or the time up to censoring as appropriate. If there was a sufficient number of first events, the Poisson regression analysis and incidence rate analysis described above for the primary endpoint, were conducted on each efficacy endpoint. In this case, 95% CIs for the incidence rate (based on the Poisson distribution) were also summarized. If conducted, the analyses were also repeated based on the PPS.

Patient Reported Outcomes

Patient reported outcomes were summarized descriptively overall and by treatment.

Pharmacokinetic/Pharmacodynamic Analysis

Pharmacokinetic and pharmacodynamic parameter estimates supplied were summarized by treatment grouping (treatment group, total darexaban daily dose, darexaban dosing frequency and overall). Pharmacokinetic and pharmacodynamic models used in this study are described in a separate Pharmacokinetic/ Pharmacodynamic Analysis Plan. The results and the model development are described in detail in a separate pharmacokinetic/pharmacodynamic report.

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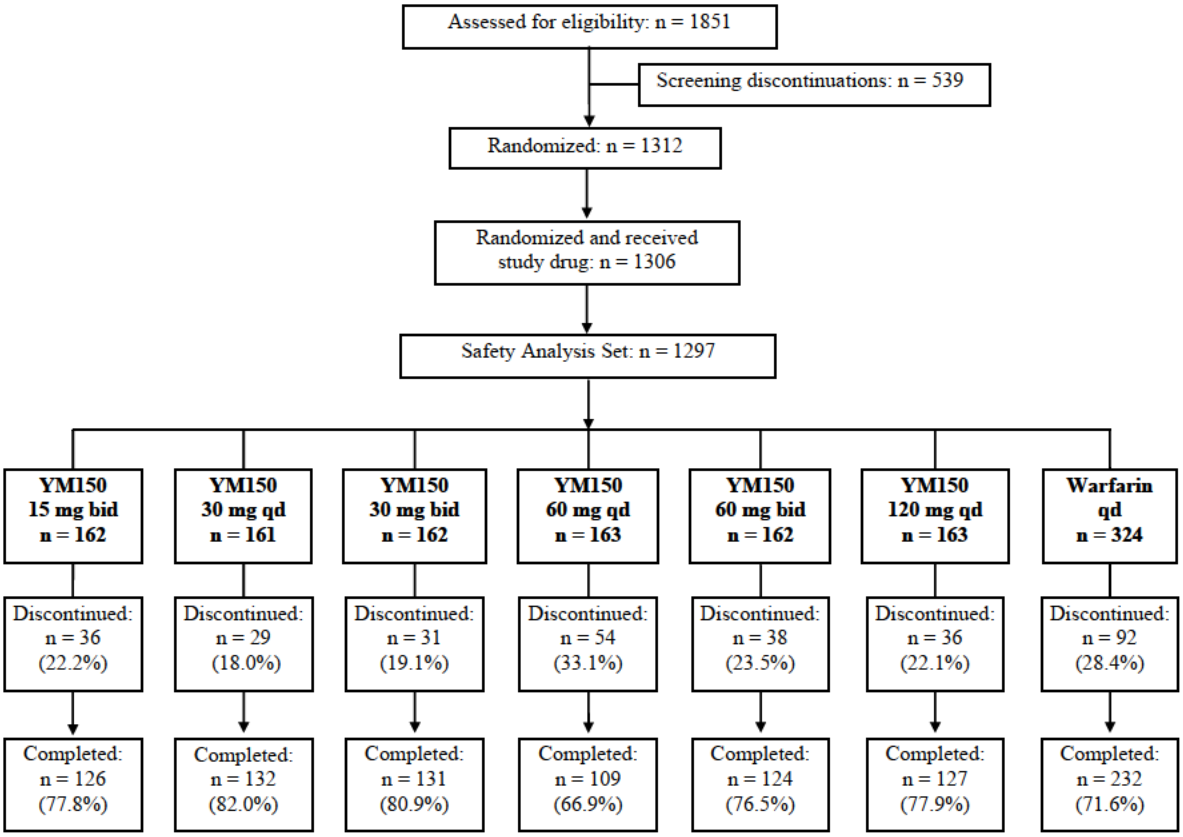
Summary of Results/Conclusions:

Patient Population Results:

The disposition of patients in the double-blind treatment period is presented in [Figure 1]. Refer to [Table 1] above for a summary of patient disposition by study population.

Figure 1 Patient Disposition by Treatment



Note: Total number of patients, discontinuations and completions are reported for the double-blind treatment period.

Safety Results:

Primary Safety Endpoint

In the primary analysis set (SAF), the incidence rate of major and/or CRNM bleeding adverse events (BAEs) was lower in the darexaban groups (6.9%/y to 15.8%/y) than in the warfarin group (22.5%/y) [Table 2].

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Incidence rates of 6.9%/y, 9.2%/y, 7.0%/y, 14.3%/y, 15.8%/y and 11.7%/y were observed in the darexaban groups (15 mg bid, 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid and 120 mg qd, respectively). Statistically significant differences in incidence rates were observed in the darexaban 15 mg bid (hazard ratio: 0.308, P=0.008), 30 mg qd (hazard ratio: 0.409, P=0.022) and 30 mg bid (hazard ratio: 0.309, P=0.008) groups compared with the warfarin group. Consistent statistically significant findings were observed for the PPS.

Analysis of pooled data for qd and bid regimens indicated a decreased risk of events with bid dosing compared to qd dosing (hazard ratio: 0.793, P=0.411). In contrast, analysis of pooled data for dose response based on total daily dose indicated an increased risk of events with doubling the dose (hazard ratio: 1.305, P=0.120). These results, which were not statistically significant, should be interpreted with caution given the inconsistent patterns observed at different dose levels.

Table 2 Poisson Regression Analysis of Major and/or Clinically Relevant NonMajor Bleeding Adverse Events – Safety Analysis Set

	Darexaban						**Warfarin**
	15 mg bid n=162	**30 mg qd n=161**	**30 mg bid n=162**	**60 mg qd n=163**	**60 mg bid n=162**	**120 mg qd n=163**	**qd n=324**
Number of patients with event	6	8	6	11	13	10	35
Total cumulative time at risk (years)†	89.588	89.087	88.860	79.748	83.901	88.660	159.849
Incidence rate:‡ n (%/y)	6.9	9.2	7.0	14.3	15.8	11.7	22.5
95% CI	3.1, 15.5	4.6, 18.4	3.1, 15.5	7.9, 25.9	9.2, 27.3	6.3, 21.9	16.1, 31.5
	vs. warfarin						
Hazard ratio	0.308	0.409	0.309	0.633	0.702	0.520	-
95% CI	0.130, 0.732	0.190, 0.881	0.130, 0.734	0.322, 1.247	0.371, 1.326	0.258, 1.051	-
P-value	0.008*	0.022*	0.008*	0.186	0.275	0.069	-

Abbreviations: CI: Confidence interval; dashes (-) indicate no data are applicable to these table cells
* Value is statistically significant compared to warfarin ($P < 0.05$).
† Time up to the first event or time in double-blind treatment period for patients without event.
‡ Incidence rates were estimated as number of events per 100 patient years based on a Poisson regression model with factors for treatment and prior anticoagulant use (yes/no) and log of time at risk as offset.
Source: Table 12.6.6.2.1.1

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Secondary Safety Endpoints

The incidence rates for individual types of adjudicated BAEs i.e., major, CRNM, minor and any BAEs were assessed as secondary safety endpoints [Table 3].

Table 3 Overview of Adjudicated Bleeding Events – Safety Analysis Set

	Darexaban						**Warfarin**
	15 mg bid n=162	**30 mg qd n=161**	**30 mg bid n=162**	**60 mg qd n=163**	**60 mg bid n=162**	**120 mg qd n=163**	**qd n=324**
	#PY=90	**#PY=91**	**#PY=90**	**#PY=83**	**#PY=87**	**#PY=91**	**#PY=167**
	n (%/y)	n (%/y)	n (%/y)	n (%/y)	n (%/y)	n (%/y)	n (%/y)
Major BAE	1 (1.1)	0	3 (3.3)	2 (2.4)	5 (5.8)	4 (4.4)	8 (4.8)
CRNM BAE	5 (5.6)	8 (9.0)	4 (4.5)	9 (11.3)	8 (9.5)	6 (6.8)	31 (19.4)
Minor BAE	7 (8.0)	6 (6.8)	8 (9.1)	4 (4.9)	11 (13.3)	13 (15.1)	27 (17.3)
Any BAE	13 (15.0)	13 (15.0)	13 (14.9)	15 (19.2)	22 (27.6)	21 (25.0)	57 (38.2)

BAE: Bleeding adverse event; CRNM: Clinically relevant non-major; #PY: Number of patient-years of exposure to double-blind treatment in the Safety Analysis Set
Source: Table 12.6.6.1.1

Major Bleeding Adverse Events

The incidence of major BAEs was 3.3%/y; 2.8%/y for patients treated with darexaban and 4.8%/y for patients treated with warfarin. The incidence of major BAEs was lower in the darexaban 15 mg bid, 30 mg bid, 60 mg qd and 120 mg qd groups (1.1%/y, 3.3%/y, 2.4%/y, 4.4%/y, respectively) than in the warfarin group (4.8%/y) but higher in the darexaban 60 mg bid group (5.8%/y). No major BAEs occurred in the darexaban 30 mg qd group. No statistically significant difference in incidence rates was observed between any darexaban group and warfarin for major BAEs.

The most frequent major BAEs were BAEs warranting treatment cessation of more than 7 days; the incidence rate of these BAEs was 2.6%/y; 2.1%/y for patients treated with darexaban and 4.2%/y for patients treated with warfarin.

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Clinically Relevant Non Major Bleeding Adverse Events

The incidence of CRNM BAEs was 10.4%/y; 7.7%/y for patients treated with darexaban and 19.4%/y for patients treated with warfarin. The incidence of CRNM BAEs was lower in all darexaban treatment groups (5.6%/y, 9.0%/y, 4.5%/y, 11.3%/y, 9.5%/y, 6.8%/y in the 15 mg bid, 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid and 120 mg qd, respectively) compared with the warfarin group (19.4%/y). No individual statistical analysis was performed for individual CRNM events.

The most frequent CRNM BAEs were BAEs of epistaxis ≥ 5 minutes; the incidence rate of these events was 3.3%/y; 3.0%/y for patients treated with darexaban and 4.2%/y for patients treated with warfarin. These BAEs occurred more frequently in the darexaban 15 mg bid and 120 mg qd (4.5%/y in each) than in the other darexaban groups (30 mg qd: 3.3%/y, 30 mg bid: 1.1%/y, 60 mg qd:2.4%/y and 60 mg bid:2.3%/y) and the warfarin group (4.2%/y).

Minor Bleeding Adverse Events

The incidence of minor BAEs was 11.3%/y; 9.5%/y for patients treated with darexaban and 17.3%/y for patients treated with warfarin. The incidence of minor BAEs was lower in all darexaban treatment groups (8.0%/y, 6.8%/y, 9.1%/y, 4.9%/y, 13.3%/y, 15.1%/y in the 15 mg bid, 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid and 120 mg qd, respectively) compared with the warfarin group (17.3%/y). No individual statistical analysis was performed for minor BAEs.

Any Bleeding Adverse Events

The incidence of any BAEs was 23.6%/y; 19.3%/y of patients treated with darexaban and 38.2%/y of patients treated with warfarin. The incidence of any BAEs was lower in all darexaban treatment groups (15.0%/y, 15.0%/y, 14.9%/y, 19.2%/y, 27.6%/y, 25.0%/y in the 15 mg bid, 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid and 120 mg qd, respectively) compared with the warfarin group (38.2%/y). The difference in incidence rates compared to warfarin was statistically significant for the darexaban 15 mg bid (hazard ratio: 0.395; P=0.003), 30 mg qd (hazard ratio: 0.392; P=0.002) and 30 mg bid (hazard ratio: 0.391; P=0.002) groups, consistent with the primary endpoint finding.

Analysis of pooled data for qd and bid regimens indicated a similar risk of events with bid and qd dosing (hazard ratio: 0.948, P=0.796). Analysis of pooled data for dose response based on total daily dose indicated an increased risk of events with doubling the dose (hazard ratio: 1.325, P=0.023), which was statistically significant.

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Efficacy Results:

Primary Composite Endpoint for Adjudicated Events

The primary composite endpoint consisted of adjudicated ischemic strokes, TIAs, STEs, ACSs and any deaths [Table 4]. The primary composite event occurred infrequently during the double-blind treatment period in 18 patients (2.6%/y) in the FAS; 15 patients (2.8%/y) treated with darexaban and 3 patients (1.8%/y) treated with warfarin. The primary composite event occurred more frequently the darexaban 15 mg bid (6 patients, 6.7%/y) group than in the darexaban 30 mg qd (3 patients, 3.3%/y), 30 mg bid (2 patients, 2.2%/y), 60 mg qd (1 patient, 1.2%/y), 60 mg bid (2 patients, 2.3%/y) and 120 mg qd (1 patient, 1.1%/y) groups, and the warfarin group (3 patients, 1.8%/y).

Table 4 Overview of Adjudicated Efficacy Events during Double-Blind Treatment – Full Analysis Set

Frequency (incidence rate)† Event	**Darexaban**						**Warfarin**
	15 mg bid n=162	**30 mg qd n=161**	**30 mg bid n=162**	**60 mg qd n=163**	**60 mg bid n=162**	**120 mg qd n=163**	**qd n=324**
	#PY=90	**#PY=91**	**#PY=90**	**#PY=83**	**#PY=87**	**#PY=91**	**#PY=167**
	n (%/year)	n (%/year)	n (%/year)	n (%/year)	n (%/year)	n (%/year)	n (%/year)
Primary composite event (ischemic strokes, TIAs, STEs, ACS, and/or deaths)	6 (6.7)	3 (3.3)	2 (2.2)	1 (1.2)	2 (2.3)	1 (1.1)	3 (1.8)
Any strokes:	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.2)	2 (2.3)	0	1 (0.6)
Ischemic stroke	1 (1.1)‡	1 (1.1)	0	0	1 (1.2)	0	0
Hemorrhagic strokes	0	0	1 (1.1)	1 (1.2)	1 (1.2)§	0	1 (0.6)
Fatal and/or disabling strokes	1 (1.1)‡	0	0	0	1 (1.2)§	0	0
TIA	1 (1.1)	0	0	1 (1.2)	0	0	0
Stroke and/or STE¶	1 (1.1)‡	1 (1.1)	1 (1.1)	1 (1.2)	2 (2.3)	0	2 (1.2)
ACS	4 (4.4)	2 (2.2)	2 (2.2)	0	0	0	2 (1.2)
Death due to cardiovascular reason††	2 (2.2)	0	0	0	1 (1.2)	1 (1.1)	0

ACS: Acute coronary syndrome; #PY: Number of patient years of exposure to double-blind treatment; STE: Systemic thromboembolic event; TIA: Transient ischemic attack

† The number of patients with an on-treatment event and the incidence rate per 100 patient years (% per year)

‡ The ischemic stroke was fatal and disabling.

§ The hemorrhagic stroke was fatal and disabling.

¶ All patients had strokes as broken down under "any strokes" category, except for 1 patient in the warfarin group who had an STE.

†† The total number of adjudicated deaths was 4 patients; 15 mg bid group: 2 deaths - 1 due to ischemic stroke, 1 due to other cardiovascular death; 60 mg bid group: 1 due to hemorrhagic stroke; and 120 mg qd: 1 due to other cardiovascular death.

Source: Tables 12.3.1.1 and 12.3.1.2

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Pooled darexaban data based on the total daily dose (i.e., 30 mg/day, 60 mg/day and 120 mg/day) indicated that the primary composite endpoint occurred more frequently with 30 mg/day dosing (9 patients, 5.0%/y) compared with 60 mg/day (3 patients, 1.7%/y) and 120 mg/day dosing (3 patients, 1.7%/y). Pooled darexaban data for bid and qd regimens indicated that the primary composite event occurred more frequently with bid dosing than qd dosing (10 patients, 3.8%/y vs. 5 patients, 1.9%/y).

The data suggest a dose-response trend with increasing doses of darexaban for the primary composite endpoint; however, the apparent trend is mainly driven by a small number of ACS events in the darexaban 15 mg bid treatment group and is of uncertain relevance.

This study was not powered to detect differences in any of the efficacy endpoints and the total number of events is very low. In summary, the results of analysis of the composite endpoint of stroke, TIAs, STEs, ACS and any deaths do not show meaningful differences due to the low number of events in this study.

Patient Reported Health Status

Responses to the EQ-5D questionnaire indicated no remarkable differences in the health status of patients from baseline to Week 12, Week 24 or end of study/early discontinuation. The majority of patients in all treatment groups indicated that they had no problems in mobility, self-care or performance of usual activities; and that they were not anxious or depressed. No statistically significant difference in least squares mean changes from baseline in EuroQol visual analogue scale (EQ-VAS) score was observed for any darexaban group compared with warfarin, except for the darexaban 30 mg bid group (difference: 2.9 mm, P=0.038).

SF-36 scores also indicated no remarkable differences in the health status of patients from baseline to Week 12, Week 24 or end of study/early discontinuation. No statistically significant differences from warfarin were observed for any of the darexaban groups.

HADS scores also indicated no remarkable differences in the health status of patients from baseline to Week 12, Week 24 or end of study/early discontinuation. No statistically significant differences from warfarin were observed for any of the darexaban groups, except for the 60 mg bid group, which indicated a statistically significant difference in anxiety score in favour of the warfarin group from baseline to Week 12 (difference: 0.7; P=0.016).

TACT questionnaire data also indicated no remarkable differences in the health status of patients from baseline to Week 12, Week 24 or end of study/early discontinuation.

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Other Safety Results

Treatment-Emergent Adverse Events

TEAEs were reported by 58.4% of patients in this study; 57.7% of patients treated with darexaban and 60.8% treated with warfarin [Table 5]. These were reported less frequently in the darexaban 60 mg/day groups (30 mg bid: 53.1%; 60 mg qd: 55.2%) than in the 30 mg/day (15 mg bid: 58.6%; 30 mg qd: 59.0%) and 120 mg/day (60 mg bid: 59.3%; 120 mg qd: 60.7%) groups. The most frequent TEAEs by system organ class (SOC) were infections and infestations; investigations; and gastrointestinal disorders, which occurred in 15.8%, 13.0%, 12.7% of patients, respectively. The most frequent TEAEs by preferred term in the SAF were nasopharyngitis, blood creatinine increased, hematuria, epistaxis, which occurred in 5.0%, 4.2%, 4.1% and 3.8% of patients, respectively. Most were of mild or moderate severity; severe TEAEs occurred in 4.1% of patients; 3.8% of patients treated with darexaban and 4.9% of patients treated with warfarin.

Hepatic Events

Hepatic TEAEs were reported by 4.1% of patients; 4.5% of patients treated with darexaban and 2.8% of patients treated with warfarin. These were reported more frequently in the higher dose darexaban groups (60 mg bid: 5.6%; 120 mg qd: 6.7%) than in the lower dose groups (15 mg bid: 4.3%, 30 mg qd: 3.1%, 30 mg bid: 3.1% and 60 mg qd: 4.3%) and the warfarin group (2.8%). The most frequent were increased gamma-glutamyl transferase (GGT), increased alanine aminotranferase (ALT), increased blood bilirubin and increased aspartate aminotransferase (AST), which occurred in 1.3%, 0.8%, 0.6% and 0.5% of patients, respectively.

Events Leading to Permanent Discontinuation of Study Drug

TEAEs led to permanent discontinuation of study drug in 11.2% of patients; 10.3% of patients treated with darexaban and 13.9% of patients treated with warfarin; most commonly increased blood creatinine (1.7%), which was reported by 1.5% of patients treated with darexaban and 2.2% of patients treated with warfarin.

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Table 5 Overview of Treatment-Emergent Adverse Events – Safety Analysis Set

Treatment-Emergent Adverse Events	Darexaban						Warfarin
	15 mg bid n=162	30 mg qd n=161	30 mg bid n=162	60 mg qd n=163	60 mg bid n=162	120 mg qd n=163	qd n=324
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	95 (58.6)	95 (59.0)	86 (53.1)	90 (55.2)	96 (59.3)	99 (60.7)	197 (60.8)
Drug-related AE	27 (16.7)	29 (18.0)	27 (16.7)	38 (23.3)	38 (23.5)	43 (26.4)	80 (24.7)
Deaths	2 (1.2)	0	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)	0
SAEs	22 (13.6)	11 (6.8)	16 (9.9)	8 (4.9)	12 (7.4)	15 (9.2)	41 (12.7)
Drug-related SAEs	3 (1.9)	0	2 (1.2)	2 (1.2)	4 (2.5)	2 (1.2)	7 (2.2)
AEs that led to permanent discontinuation of study drug	16 (9.9)	8 (5.0)	19 (11.7)	24 (14.7)	17 (10.5)	16 (9.8)	45 (13.9)
Drug-related AEs that led to permanent discontinuation of study drug	7 (4.3)	2 (1.2)	9 (5.6)	12 (7.4)	10 (6.2)	7 (4.3)	16 (4.9)
Mild AEs	60 (37.0)	65 (40.4)	50 (30.9)	41 (25.2)	61 (37.7)	60 (36.8)	109 (33.6)
Moderate AEs	27 (16.7)	27 (16.8)	32 (19.8)	40 (24.5)	30 (18.5)	31 (19.0)	72 (22.2)
Severe AEs	8 (4.9)	3 (1.9)	4 (2.5)	9 (5.5)	5 (3.1)	8 (4.9)	16 (4.9)
Mild drug-related AEs	23 (14.2)	23 (14.3)	16 (9.9)	20 (12.3)	26 (16.0)	33 (20.2)	56 (17.3)
Moderate drug-related AEs	2 (1.2)	5 (3.1)	10 (6.2)	12 (7.4)	10 (6.2)	9 (5.5)	20 (6.2)
Severe drug-related AEs	2 (1.2)	1 (0.6)	1 (0.6)	6 (3.7)	2 (1.2)	1 (0.6)	4 (1.2)
Hepatic AEs	7 (4.3)	5 (3.1)	5 (3.1)	7 (4.3)	9 (5.6)	11 (6.7)	9 (2.8)

Abbreviations: AE: adverse event; SAE: Serious adverse event.
Source: Table 12.6.1.1, 12.6.1.7 and 12.6.1.8

Drug-Related Events and Serious Adverse Events

Drug-related TEAEs were reported by 21.7% of patients; 20.8% of patients treated with darexaban and 24.7% of patients treated with warfarin. These were reported more frequently in the higher darexaban dose groups (60 mg qd: 23.3%; 60 mg bid: 23.5%; 120 mg qd: 26.4%) and the warfarin group (24.7%) than in the lower dose darexaban groups (15 mg bid: 16.7%; 30 mg qd: 18.0%; and 30 mg bid: 16.7%) although individual drug-related TEAEs were infrequent in all groups. The most common drug-related TEAE was epistaxis, which

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occurred in 3.2% of patients; 2.5% of patients treated with darexaban and 5.2% of patients treated with warfarin.

Treatment-emergent SAEs were reported by 9.6% of patients; 8.6% of patients treated with darexaban and 12.7% treated with warfarin. Atrial fibrillation (AF) was the most frequent SAE, which occurred in 1.2% of patients; 0.8% of patients treated with darexaban and 2.5% of patients treated with warfarin. Drug-related SAEs occurred in 1.5% of patients; 1.3% of patients treated with darexaban and 2.2% of patients treated with warfarin. Drug-related SAEs occurred in no more than 1 patient in any treatment group.

Six patients (0.5%) died during the study, all of whom received darexaban: 2 patients from the 15 mg bid group (1 died due to stroke; 1 died due to acute coronary insufficiency); 1 patient from the 30 mg bid died due to metastatic ovarian cancer; 1 patient from the 60 mg qd group died due to hepatic carcinoma, 1 patient from the 60 mg bid group died due to intracranial hemorrhage and 1 patient from the 120 mg qd died due to an unknown cause. All causes of death were assessed as unrelated to the study drug, except for stroke and intracranial hemorrhage, which were assessed as possibly related to the study drug.

Laboratory Parameters

Hematology, clinical chemistry and urinalysis parameter findings were generally unremarkable with no notable differences occurring across the treatment groups and no dose dependent effects observed across the darexaban groups.

Although shifts from normal at baseline to high or low postbaseline occurred for many parameters, few resulted in TEAEs and most had resolved by the end of treatment.

Clinically significant liver function abnormalities occurred to some extent in all treatment groups during the double-blind treatment period. The most frequent abnormality was abnormal total bilirubin (> 1.5 x upper limit of normal [ULN]), which occurred in 3 patients, 1.9% (30 mg qd group) to 12 patients, 7.6% (120 mg qd group) treated with darexaban and 4 patients, 1.3% treated with warfarin.

Clinically significant moderate liver abnormalities (defined as total bilirubin > 2 x ULN, ALT > 3 x ULN and/or AST > 3 x ULN) and/or marked liver abnormalities (defined as total bilirubin > 3 x ULN, ALT > 5 x ULN and/or AST > 5 x ULN, or total bilirubin > 2 x ULN with ALT or AST > 3 x ULN) occurred in 2 patients, 1.3% (30 mg bid group) to 7 patients, 4.5% (120 mg qd group) treated with darexaban and 4 patients, 1.3% treated with warfarin.

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Clinically significant combined liver abnormalities/concurrent elevations (defined as total bilirubin > 2 x ULN with ALT or AST > 3 x ULN) occurred in 5 patients (0.4%) during the double-blind treatment period; 1 patient (0.6%) each in the darexaban 15 mg bid, 30 mg qd, 60 mg qd and 120 mg qd groups and 1 patient (0.3%) in the warfarin group.

Clinically significant changes from baseline in serum creatinine were reported to a similar extent in the darexaban and warfarin groups during the double-blind treatment period, and most had resolved by the end of treatment. Changes from baseline of > 25% were reported in 15 patients, 9.5% (120 mg qd group) to 33 patients, 20.8% (30 mg qd group) of patients in the darexaban groups and 71 patients (22.1%) in the warfarin group. Changes from baseline of > 50% were reported by 3 patients, 1.9% (30 mg bid group) to 8 patients, 5.0% (60 mg qd group) of patients treated with darexaban and 3.7% of patients treated with warfarin.

Clinically significant troponin T values (>0.03 mcg/L) were reported during the double-blind treatment period in all treatment groups and more frequently in the darexaban groups (4 patients, 2.5% [15 mg bid] to 6 patients, 3.8% [30 mg qd]) than the warfarin group (3 patients, 0.9%). All patients with increased troponin T were adjudicated by the independent AC in order to confirm or exclude possible ACS.

INR Monitoring

Patients treated with dose-adjusted warfarin had an INR value between 2 and 3 (i.e., within the therapeutic range) 45.4% of the on-treatment time, below the therapeutic range (< 2) 42.3% of the on-treatment time and above the therapeutic range (≥ 3) 12.3% of the on-treatment time.

Physical Examination, Vital Signs and ECGs

Physical examination data were unremarkable; abnormal cardiovascular system (including peripheral vascular pulsations) findings were mostly considered not clinically significant. Potentially clinically significant changes in vital sign parameters occurred to a similar extent in all treatment groups during treatment; however, most resolved by the end of treatment. Abnormal 12-lead ECG results were observed in the majority of patients at baseline and throughout the study as expected for this disease indication; most were assessed as not clinically significant by the Investigator. Clinically significant 12-lead ECG abnormalities increased slightly during treatment to a similar extent across the treatment groups; however, most resolved by the end of treatment.

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CONCLUSIONS:

Conclusions

Primary Safety Endpoint

- For the primary endpoint, the incidence of adjudicated major and/or CRNM BAEs was lower in all darexaban arms compared to warfarin. Statistically significant incidence rate ratios were observed for the darexaban 15 mg bid, 30 mg qd and 30 mg bid groups compared with warfarin; similar significant findings were observed for any BAEs.
- The incidence of adjudicated major and/or CRNM BAEs, and any BAEs, increased with increasing total daily dose (30 mg/day, 60 mg/day or 120 mg/day); the effect of doubling the dose was statistically significant for any BAEs. However, this result is inconclusive given the inconsistent dose patterns observed in individual dose groups.
- The incidence of adjudicated major and/or CRNM BAEs was slightly lower in pooled bid than pooled qd groups, while the incidence of any BAEs was similar in the pooled bid and qd groups; however, neither of these results were statistically significant.
- The incidence rate of major BAEs was lower than warfarin for all darexaban groups, except the darexaban 60 mg bid group (5.8%/y of patients); no statistically significant difference from warfarin in incidence rates was observed for any darexaban group.
- The incidence rate of CRNM BAEs was lower than warfarin for all darexaban groups.

Efficacy Endpoint

- The study was not powered to detect differences in any of the efficacy events. The data indicate a possible dose-response trend with increasing doses of darexaban for the first efficacy endpoint (composite endpoint of adjudicated ischemic strokes, TIAs, STEs, ACS, and any deaths). However, no firm conclusions can be drawn on efficacy because the apparent trend is mainly driven by a small number of ACS events.

Other Safety Endpoints

- The incidence of TEAEs (overall 58.4%) was less frequent in the darexaban 60 mg/day groups (30 mg bid: 53.1%; 60 mg qd: 55.2%) than in the 30 mg/day (15 mg bid: 58.6%; 30 mg qd: 59.0%) and 120 mg/day (60 mg bid: 59.3%; 120 mg

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qd: 60.7%) groups, and the warfarin group (60.8%). Individual TEAEs generally occurred to a similar extent across all treatment groups.

- Treatment-emergent SAEs were reported for 9.6% of patients, most frequently in the darexaban 15 mg bid (13.6%) and warfarin (12.7%) groups. Small differences were observed across the darexaban groups but no dose-dependent pattern was observed.
- Six patients (0.5%) died due to TEAEs: 2 patients from the 15 mg bid group (1 died due to stroke; 1 died due to acute coronary insufficiency); 1 patient from the 30 mg bid died due to metastatic ovarian cancer; 1 patient from the 60 mg qd group died due to hepatic carcinoma, 1 patient from the 60 mg bid group died due to intracranial hemorrhage and 1 patient from the 120 mg qd died due to an unknown cause. No deaths occurred in the YM10 30 mg qd group or warfarin group.
- Drug-related TEAEs were reported (overall 21.7%) were reported more frequently in the higher darexaban dose groups (60 mg qd: 23.3%; 60 mg bid: 23.5%; 120 mg qd: 26.4%) and the warfarin group (24.7%) than in the lower dose darexaban groups (15 mg bid: 16.7%; 30 mg qd: 18.0%; and 30 mg bid: 16.7%); however, individual drug-related TEAEs were infrequent in all treatment groups and this difference seems to be driven by a lower rate of bleeding events in the lower dose arms.
- There were 5 cases of concurrent increases in transaminases and total bilirubin and these were distributed over the different treatment arms (1 patient each in the darexaban 15 mg bid, 30 mg qd, 60 mg qd and 120 mg qd groups) including the warfarin arm (1 patient) with no more than one case per treatment arm. Further independent adjudication of these events is planned.
- Elevated total bilrubin >1.5 x ULN, and moderate and/or marked liver abnormalities, occurred most frequently in the darexaban 120 mg qd group (7.6% and 4.5% of patients, respectively), which were comparably lower in the warfarin group (both in 1.3% of patients).
- The occurrence of serum creatinine abnormalities was of a similar frequency in all treatment groups including warfarin.
- The occurrence of troponin T elevations was higher in the darexaban groups compared with the warfarin group.

Date of Report:

Oct 2011