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SYNOPSIS

Title of Study:

A Randomized, Double-Blind, Placebo Controlled, Multi Center and Parallel Group Study of the Safety, Tolerability and Efficacy of Darexaban (YM150) in combination with Standard Treatment in Secondary Prevention of Ischemic Vascular Events in Patients with Acute Coronary Syndromes

Responsible Medical Officer/Investigators:

Responsible Medical Officer: [redacted], MD, Astellas Pharma Europe B.V.

Coordinating Investigator: [redacted], MD, FESC, FACC, FCCP, [redacted], France.

Study Centers:

This multicenter study was conducted at 147 sites in 24 countries – Argentina, Australia, Brazil, Canada, Columbia, India, Malaysia, Mexico, Russian Federation, South Africa, South Korea, Ukraine, and the following countries in the European Union: Belgium, Czech Republic, Denmark, France, Germany, Hungary, Latvia, The Netherlands, Poland, Romania, Slovakia, United Kingdom.

Publication (reference):

None.

Study Period:

Date of first enrollment (Study initiation date):

29 September 2009

Date of last evaluation (Study completion date):

06 March 2011

Phase of Development:

Phase 2

Objectives:

The primary objective of this study was to evaluate the safety and tolerability of different doses and dose regimens of darexaban on top of standard treatment with acetylsalicylic acid (ASA) with or without clopidogrel in secondary prevention of ischemic vascular events in patients with recent acute coronary syndromes (ACS).

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The secondary objectives of this study were:

- To evaluate the efficacy of different doses and dose regimens of darexaban on top of standard treatment with ASA with or without clopidogrel in the secondary prevention of ischemic vascular events in patients with recent ACS
- To compare safety, tolerability and efficacy of different doses and dose regimens of darexaban on top of standard treatment with ASA with or without clopidogrel against placebo
- To assess the pharmacokinetic-pharmacodynamic properties in the target population
- To further define the suitable patient population for further development (i.e., Phase 3)

Methodology:

This was a prospective, randomized, double-blind, multi-center, multiple dose, placebo-controlled, parallel-group study in patients presenting with ACS (the index event). After presentation with ACS, patients were managed according to (local) standard of care which included antiplatelet treatment (ASA ± clopidogrel) and were randomized (1:1:1:1:1:1:2) to 1 of 7 treatment groups for 6 months of double-blind treatment (darexaban 5 mg bid, 10 mg qd, 15 mg bid, 30 mg qd, 30 mg bid or 60 mg qd; or placebo).

Number of Patients (planned, enrolled and analyzed):

It was planned that 158 patients would be randomized to each darexaban dose group and 316 patients to the placebo group, making a total of 1264 patients randomized. In total 1264 patients were randomized and received study drug. Of these: 1258 patients were included in the safety analysis set (SAF), which consisted of all randomized patients who took at least 1 dose of study drug; the same 1258 patients were included in the full analysis set (FAS), which was identical to the SAF in the analysis; and 1170 patients were included in the per-protocol set (PPS), which consisted of all patients in the FAS who had no major protocol violations.

Diagnosis and Main Criteria for Inclusion:

- Men or women with a diagnosis of ST-segment elevation ACS (STE-ACS) or non-ST-segment elevation ACS (NSTE-ACS) as index event according to accepted guidelines such as the European Society of Cardiology or American Heart Association guidelines.
- Had elevated cardiac biomarkers (cardiac troponin T or I or creatine kinase myocardial band [CK-MB]) > 2 x upper limit of normal (ULN) for CK-MB or > ULN for troponin.
- Either had STE-ACS, or for patients with a diagnosis of NSTE-ACS, at least one of the following additional high risk factors for ischemic events had to be present: ST deviations on electrocardiogram (ECG) at any time between presentation of the index event and randomization; aged 65 years or older; previous ACS < 12 months prior to randomization; multi vessel coronary artery disease (CAD); ischemic stroke or transient ischemic attack (TIA) > 12 months prior to randomization; type 2 diabetes mellitus; peripheral arterial disease.
- 18 years of age (legal minimum age required per country) or older at time of informed consent.

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

Darexaban was administered as oral tablets containing 5, 10, 15, 30 or 60 mg of darexaban free base equivalent as monomaleate salt. The dosing regimens in the 6 darexaban treatment groups were as follows: 1 x 5 mg tablet twice daily; 1 x 10 mg tablet once daily; 1 x 15 mg tablet twice daily; 1 x 30 mg tablet once daily; 1 x 30 mg tablet twice daily; and 1 x 60 mg tablet once daily. The batch numbers for darexaban were as follows:

	Study No. 150-CL-201		
	General Batch No.	**General Batch No.**	**General Batch No.**
	[redacted]	[redacted]	[redacted]
Bulk Product	**Bulk Batch No.**	**Bulk Batch No.**	**Bulk Batch No.**
Darexaban 5 mg	[redacted]	[redacted]	[redacted]
Darexaban 10 mg	[redacted]	[redacted]	[redacted]
Darexaban 15 mg	[redacted]	[redacted]	[redacted]
Darexaban 30 mg	[redacted]	[redacted]	[redacted]
Darexaban 60 mg	[redacted]	[redacted]	[redacted]
Treatment Group	**Finished Product Batch No.**	**Finished Product Batch No.**	**Finished Product Batch No.**
Darexaban 5 mg bid	[redacted]	[redacted]	[redacted]
Darexaban 10 mg qd	[redacted]	[redacted]	[redacted]
Darexaban 15 mg bid	[redacted]	[redacted]	[redacted]
Darexaban 30 mg qd	[redacted]	[redacted]	[redacted]
Darexaban 30 mg bid	[redacted]	[redacted]	[redacted]
Darexaban 60 mg qd	[redacted]	[redacted]	[redacted]

Duration of Treatment:

Patients were to receive double-blind treatment with 1 of the 6 darexaban dosage regimens or placebo for 26 weeks (6 months).

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

Patients in the placebo group were administered placebo tablets (containing excipient only) that matched the darexaban tablets. All patients were administered placebo tablets so that all patients received the same quantity of tablets of the same appearance each day. The batch numbers for placebo were as follows:

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	Study No. 150-CL-201		
	General Batch No.	**General Batch No.**	**General Batch No.**
	[redacted]	[redacted]	[redacted]
Bulk Product	**Bulk Batch No.**	**Bulk Batch No.**	**Bulk Batch No.**
PTM darexaban 15/30 mg	[redacted]	[redacted]	[redacted]
PTM darexaban 60 mg	[redacted]	[redacted]	[redacted]
Treatment Group	**Finished Product Batch No.**	**Finished Product Batch No.**	**Finished Product Batch No.**
Placebo	[redacted]	[redacted]	[redacted]

Abbreviation: PTM: Placebo to match

Criteria for Evaluation:

The primary endpoint of this study was a safety endpoint: the presence or absence of major and/or clinically relevant non-major (CRNM) bleeding events during 6 months of double-blind treatment according to the RUBY-1 modified International Society on Thrombosis and Hemostasis (ISTH) criteria.

The secondary endpoints were:

- Incidence of major and CRNM bleeding events at 30 days according to RUBY-1 modified ISTH criteria. Additionally, major and CRNM bleeding events at 30 days and 6 months according to unmodified standard ISTH criteria (see Sections 5.1.1.1 and 5.5.5.1)
- Incidence of Thrombolysis in Myocardial Infarction (TIMI) major bleeding events at 30 days and 6 months. Note: For better understanding and to be able to compare to other studies, the bleeding events were classified separately according to the TIMI classification; this classification was not used for the primary analysis. Additionally, the TIMI definitions included as secondary variables were expanded to include the extra categories TIMI requiring medical attention and TIMI insignificant bleeding
- Incidence of the composite of all-cause mortality, non-fatal myocardial infarction (MI), non-fatal stroke, severe recurrent ischemia (SRI) at 30 days and 6 months
- Incidence of the composite of all-cause mortality, non-fatal MI and non-fatal stroke at 30 days and 6 months
- Incidence of individual efficacy variables (all-cause mortality, non-fatal MI, non-fatal stroke, systemic thromboembolic event, transient ischemic attack [TIA], SRI) at 30 days and 6 months
- Incidence of total bleeding events (major, CRNM and minor bleeding) at 30 days and 6 months
- Overall tolerability of darexaban (i.e., serious adverse events [SAEs], AEs, changes in laboratory parameters)
- Incidence of composite of all-cause mortality, non-fatal MI, non-fatal stroke and major bleeding events

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Other outcome variables were the plasma pharmacokinetics of darexaban and its metabolite (darexaban glucuronate), and pharmacodynamics including prothrombin fragment 1+2 (F1+2), D-dimer and FXa inhibition. The findings are presented in a separate report.

Statistical Methods:

For adjudicated efficacy variables and the bleeding events, the cumulative risk and 95 % confidence intervals (CIs) at 30 days and at 6 months were calculated using Kaplan-Meier estimates. These variables were also inferentially analyzed using a Cox regression model. Treatment comparisons were made between darexaban and placebo, between the total daily doses of darexaban, and between darexaban one and twice daily dosing.

EQ-5D and SF-36 were summarized descriptively. EQ-VAS and SF-36 were inferentially analyzed for change from baseline to EOT visit using an analysis of covariance model including standard antiplatelet treatment (clopidogrel or no clopidogrel) and treatment as class variables and baseline EQ-VAS as a covariate.

TEAEs were tabulated to show the number and percentage of patients with TEAEs and the number of TEAEs by SOC and preferred term.

Clinical laboratory variables were presented using summary statistics. Each laboratory result was classified as low (L), normal (N), or high (H) at each visit according to the laboratory who supplied the reference ranges and was summarized using standard summary statistics. Shift tables of changes in classification from baseline to EOT/discontinuation visit were produced. A further shift table to present the changes in classification from baseline to the worst double-blind treatment value was produced.

All other safety variables (Vital signs, 12-lead ECGs, physical examinations) were presented using summary statistics, including tables showing the incidence of normal and abnormal values.

A population pharmacokinetic/pharmacodynamic model was developed to describe the pharmacokinetics of darexaban glucuronide in the patient population and to relate clinical outcomes and FXa data to darexaban glucuronide exposure.

Summary of Results/Conclusions:

Population:

A total of 967 (76.9%) of 1258 patients in the SAF/FAS completed double-blind study treatment, and 291 (23.1%) discontinued. More patients discontinued 30 mg once daily (28.2%) and 30 mg twice daily (32.7%) than the four other darexaban dosing groups (5 mg bid, 18.9%; 10 mg qd, 19.5%, 15 mg bid, 20.1%; and 60 mg qd, 23.5%) and the placebo group (21.3%). The most common primary reasons for discontinuation were AEs (137 patients, 10.9%). More patients discontinued 30 mg once daily (16.0%) and 30 mg twice daily (15.7%) for AEs than the four other darexaban dosing groups (5 mg bid, 8.2%; 10 mg qd, 12.6%, 15 mg bid, 10.1%; and 60 mg qd, 11.1%) and the placebo group (6.9%).

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Demographic characteristics were similar between treatment groups [Table 12.1.2.1]. The SAF/FAS consisted of 79.6% men and 20.4% women. Mean (SD) age was 56.9 (10.40) years and median age was 56.0 years. A total of 75.9% of patients were < 65 years (minimum age 28 years), 18.9% were ≥ 65 to < 75 years, and 5.2% were ≥ 75 years (maximum age 87 years). The majority of patients were white (78.8%); 17.5% were Asian, 0.6% were Black or African American, and 3.1% were of other race. The mean (SD) BMI was 28.1 (4.67) kg/m2. At baseline, 96.7% of patients were taking clopidogrel (with or without ASA), and 3.3% were not taking clopidogrel and taking ASA alone.

Primary diagnosis of ACS (i.e. the proportion of patients with STE-ACS or non-STE ACS) was similar between treatment groups [Table 12.1.3.1]. A total of 894 of 1258 patients (71.1%) had a primary diagnosis (Index Event) of STE-ACS, and 364 (28.9%) had a primary diagnosis of NSTE-ACS. Approximately one quarter of patients (22.5%) had multivessel CAD. Time from presentation after Index Event to first dose was also similar between treatment groups. The mean (SD) time to presentation after Index Event was 4.1 (1.82) days (median time 4.0 days; range 0 to 18 days). No differences in GRACE scores at presentation and discharge were observed between treatment groups. The mean (SD) GRACE risk score was 132.8 (24.15) at presentation and 90.5 (22.67) at discharge from hospital.

Primary Safety Endpoint:

The results show that darexaban added to dual antiplatelet therapy after ACS produces an expected dose related 2-fold increase in bleeding.

In the primary analysis set (SAF), all darexaban treatment arms were associated with higher incidences of major and/or CRNM bleeding after 6 months than placebo [Table 1, Figure 1]. However, in the Cox proportional hazards model the difference from placebo was only statistically significant for darexaban 30 mg twice daily (P = 0.002) with an HR of 3.793 (95% CI: 1.66, 8.67), and this dose regimen also had the greatest cumulative risk (Kaplan-Meier analysis) of an event compared with the other darexaban doses. In the test for a linear dose-response relationship the effect of each addition of 10 mg of darexaban was statistically significant (P = 0.009; HR = 1.147 [95% CI: 1.03, 1.27]) [Table 2].

Data pooled according to frequency of daily dosing showed a trend of a greater cumulative risk of the primary safety endpoint with twice daily dosing (8.4%) compared with once daily dosing (6.2%). This was mainly due to the higher incidence of events seen with the 30 mg twice daily dose [Table 2]. However, the difference between twice and once daily dosing was not statistically significant. Data pooled according to the magnitude of daily dose demonstrated a greater cumulative risk for 60 mg/day (9.3%) compared with 10 mg/day (6.2%) and 30 mg/day (6.5%). This finding was again mainly due to the higher incidence of events with the 30 mg twice daily dose. However, there were no statistically significant differences between total daily doses.

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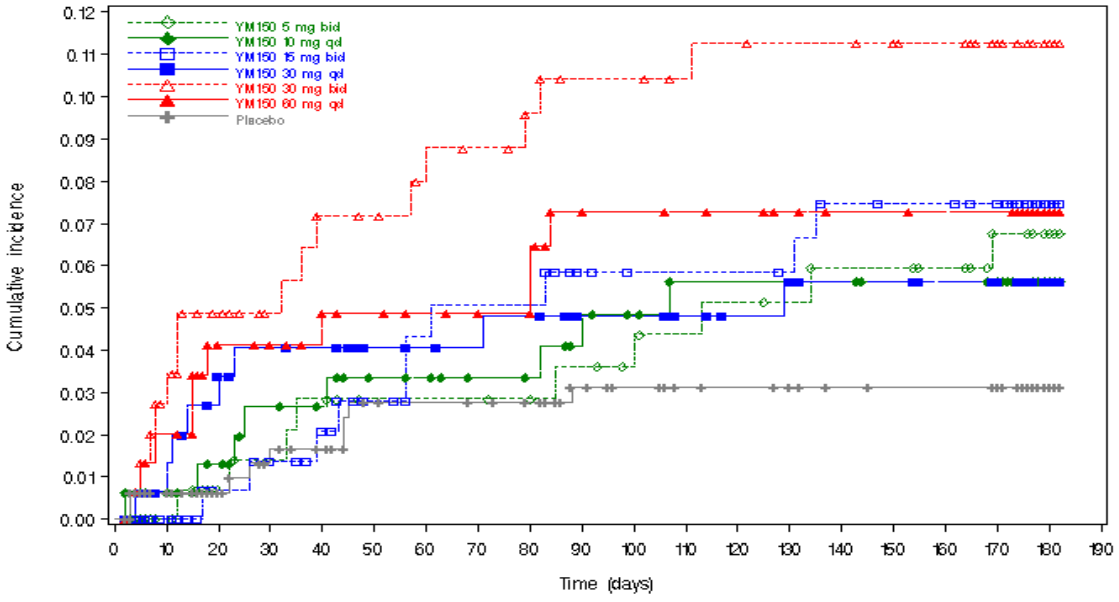
Table 1 Analysis of Major and/or CRNM Bleeding after 6 Months of Double-Blind Treatment According to RUBY-1 Modified ISTH Criteria – All Treatment Groups – Safety Analysis Set

	Darexaban						Placebo
	5 mg bid n=159	10 mg qd n=159	15 mg bid n=159	30 mg qd n=156	30 mg bid n=153	60 mg qd n=153	n=319
Major and/or CRNM bleeding after 6 months of double-blind treatment							
No. patients with event †	9	8	10	8	15	10	9
Cumulative risk, % ‡	6.8%	5.6%	7.5%	5.6%	11.3%	7.3%	3.1%
95% CI	(3.6%, 12.6%)	(2.8%, 11.0%)	(4.1%, 13.5%)	(2.9%, 11.0%)	(6.9%, 18.1%)	(4.0%, 13.1%)	(1.6%, 5.9%)
Cox proportional hazards model analysis							
HR vs. placebo §¶	2.043	1.778	2.270	1.829	3.793	2.422	-
95% CI	(0.81, 5.15)	(0.69, 4.61)	(0.92, 5.59)	(0.71, 4.74)	(1.66, 8.67)	(0.98, 5.96)	-
P-value	0.130	0.237	0.074	0.214	0.002	0.054	-

Abbreviations: CI: confidence interval; CRNM: clinically relevant non-major; HR: Hazard ratio; ISTH: International Society on Thrombosis and Hemostasis.
† Only the first event within the double-blind period contributes for each patient.
‡ Cumulative risk (and 95% CI) was calculated from Kaplan-Meier estimate of survival of last event time prior to 6 months.
§ HR, 95% CI and P-values were obtained from the Cox proportional hazards model with treatment and standard antiplatelet therapy (clopidogrel or no clopidogrel) included as covariates in the model.
¶ HR > 1 represents darexaban having more risk of events
Source: Tables 12.6.6.2.1.1 and 12.6.6.2.1.3

Figure 1 Cumulative Risk of RUBY-1 Modified ISTH Major and/or CRNM Bleeding Events, by Treatment Group – Safety Analysis Set



Source: Figure 12.6.5.1.1

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Table 2 Analysis of Major and/or CRNM Bleeding after 6 Months of Double-Blind Treatment According to RUBY-1 Modified ISTH Criteria – Darexaban Treatment Group Combinations – Safety Analysis Set

	Darexaban					
	bid n=471	**qd n=468**	**10 mg/ day† n=318**	**30 mg/ day† n=315**	**60 mg/ day† n=306**	**Total n=939**
Major and/or CRNM bleeding after 6 months of double-blind treatment						
No. patients with event ‡	34	26	17	18	25	60
Cumulative risk, % §	8.4%	6.2%	6.2%	6.5%	9.3%	7.3%
95% CI	(6.1%, 11.6%)	(4.2%, 8.9%)	(3.9%, 9.8%)	(4.2%, 10.2%)	(6.3%, 13.4%)	(5.7%, 9.3%)
Cox proportional hazards model analysis						
Dosing comparisons	Increasing dose by 10 mg ††	bid vs. qd ‡‡	30 vs. 10 mg/day†	60 vs. 10 mg/day†	60 vs. 30 mg/day†	Doubling dose §§
HR ¶	1.147	1.307	1.069	1.591	1.487	1.182
95% CI	(1.03, 1.27)	(0.78, 2.19)	(0.55, 2.08)	(0.85, 2.96)	(0.81, 2.75)	(0.93, 1.51)
P-value	0.009	0.311	0.844	0.144	0.205	0.176

Abbreviations: CI: confidence interval; CRNM: clinically relevant non-major; HR: Hazard ratio
† These treatment groups included both qd and bid dosing with the total daily dose specified.
‡ Only the first event within double-blind period contributes for each patient.
§ Cumulative risk (and 95% CI) was calculated from Kaplan-Meier estimate of survival of last event time prior to 6 months.
¶ Hazards ratios, 95% CI and P-values were obtained from the Cox proportional hazards model with treatment and standard antiplatelet therapy (clopidogrel or no clopidogrel) included as covariates in the model.
†† HR > 1 indicates positive dose trend assuming linear dose response with placebo as 0 mg.
‡‡ HR > 1 indicates bid having more risk of events (i.e., bid worse than qd).
§§ HR > 1 indicates higher the dose the more events occur.
Source: Tables 12.6.6.2.1.1 and 12.6.6.2.1.3

Secondary Safety Endpoints

Major Bleeding Adverse Events According to RUBY-1 Modified ISTH Criteria

The results showed that after 6 months of double-blind treatment, major bleeding events had been experienced by 10 patients receiving darexaban (cumulative risk 1.3%) and 1 patient receiving placebo (cumulative risk 0.4%). The highest incidence of major bleeding events was observed with 30 mg once daily and 30 mg twice daily (both 3 patients, cumulative risk 2.2%), but there were no statistically significant differences from placebo. There were also no statistically significant differences between twice and once daily dosing and between the total daily doses of darexaban.

All Bleeding Events According to RUBY-1 Modified ISTH Criteria

After 6 months of double-blind treatment, darexaban was associated with a greater cumulative risk (16.6%) of all types of bleeding events compared with placebo (9.3%).

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In the Cox proportional hazards model the differences from placebo were statistically significant for darexaban 15 mg twice daily (P = 0.018), 30 mg twice daily (P <0.001), and 60 mg once daily (P = 0.016). In the analysis of data pooled by daily dosing frequency there were no statistically significant differences between twice and once daily dosing (cumulative risk 18.6% and 14.7%, respectively). Data pooled according to the magnitude of daily dose showed a greater cumulative risk for 60 mg/day (20.1%) compared with 30 mg/day (15.8%) and 10 mg/day (14.2%); a statistically significant difference was observed between 60 and 10 mg/day (P = 0.046; HR = 1.526 [95% CI: 1.01, 2.31]. The test for linear dose-response relationship was statistically significant (P = 0.001; HR = 1.119 [95% CI: 1.05, 1.20]).

Bleeding Events According to ISTH Standard Criteria

Using the RUBY-1 modified ISTH criteria instead of the ISTH standard criteria more patients were classified with minor bleeding events (8.3% vs. 6.9%) and fewer patients were classified with CRNM bleeding events (4.7% vs. 6.5%) , and thus with major and/or CRNM bleeding events (5.5% vs. 7.3%). As a result the rate of major and/or CRNM bleeding events increased. However, in the analyses of the events classified by the standard ISTH similar trends to the results using the RUBY-1 modified criteria were observed.

TIMI Bleeding Events

The TIMI risk score was used to identify high risk patients, and 7 patients were identified with major TIMI bleeding events during the 6-month double blind treatment period. Because of the small number of patients with these events, no statistically relevant findings were observed. By definition, the occurrence of all TIMI events was identical to events defined under the RUBY-1 modified and standard ISTH criteria, as were the results of the Cox proportional hazards model analysis of these variables.

Age and Gender

The analyses of the events by age (< 65, ≥ 65 to < 75, and ≥ 75 years) showed a similar trend as the results overall, and darexaban was associated with higher observed incidence bleeding events than placebo after 6 months of double-blind treatment. However, there were no statistically significant differences apart from between 30 mg twice daily and placebo at 6 months for patients <65 years was (P = 0.006).

The analyses of the events by gender (men and women) showed a similar trend as the results overall, and darexaban was associated with a higher incidence of bleeding events than placebo after double-blind treatment. For men the differences from placebo were statistically significant at 6 months for 5 mg twice daily (P = 0.024), 30 mg twice daily (P = 0.001 and 60 mg once daily (P = 0.022), and the test for linear dose-response relationship was statistically significant (P = 0.009; HR = 1.186 [95% CI: 1.04, 1.35]).

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Efficacy Endpoints

Composite Efficacy Endpoint of Adjudicated All-Cause Mortality, Non-Fatal MI, Non-Fatal Stroke and SRI

Overall only a small number of patients experienced events that made up the composite efficacy endpoint of adjudicated all-cause mortality, non-fatal MI, non-fatal stroke and SRI: 67 of 1258 patients in the FAS (5.3%) shown by treatment group in [Table 3]. The data did suggest a dose-response trend with increasing doses of darexaban. It would appear though this trend was mainly driven by a small number of SRI events.

Table 3 Overview of On-Treatment Adjudicated Efficacy Endpoints at Month 6 – Full Analysis Set

No. patients (%)	Darexaban						Placebo
	5 mg bid n=159	10 mg qd n=159	15 mg bid n=159	30 mg qd n=156	30 mg bid n=153	60 mg qd n=153	n=319
Composite† of adjudicated efficacy endpoints after 6 months of double-blind treatment							
Death, MI, stroke & SRI	6 (3.8)	6 (3.8)	10 (6.3)	10 (6.4)	9 (5.9)	12 (7.8)	14 (4.4)
Death, MI & stroke	4 (2.5)	5 (3.1)	4 (2.5)	5 (3.2)	5 (3.3)	4 (2.6)	7 (2.2)
Death, MI, stroke, & major bleeding events	5 (3.1)	6 (3.8)	6 (3.8)	8 (5.1)	8 (5.2)	4 (2.6)	8 (2.5)
Individual adjudicated efficacy endpoints after 6 months of double-blind treatment							
MI	4 (2.5)	4 (2.5)	4 (2.5)	5 (3.2)	4 (2.6)	4 (2.6)	6 (1.9)
Fatal	0	1 (0.6)	0	3 (1.9)	0	1 (0.7)	1 (0.3)
Non-fatal	4 (2.5)	3 (1.9)	4 (2.5)	2 (1.3)	4 (2.6)	3 (2.0)	5 (1.6)
STEMI	3 (1.9)	2 (1.3)	1 (0.6)	1 (0.6)	0	2 (1.3)	1 (0.3)
Non-STEMI	0	1 (0.6)	3 (1.9)	1 (0.6)	4 (2.6)	2 (1.3)	4 (1.3)
ECG unavailable	1 (0.6)	1 (0.6)	0	3 (1.9)	0	0	1 (0.3)
SRI	2 (1.3)	1 (0.6)	6 (3.8)	5 (3.2)	4 (2.6)	8 (5.2)	7 (2.2)
Deaths	0	2 (1.3)	0	3 (1.9)	1 (0.7)	1 (0.7)	2 (0.6)
Sudden cardiac death	0	1 (0.6)	0	3 (1.9)	0	0	1 (0.3)
Acute MI	0	0	0	0	1 (0.7)	1 (0.7)	1 (0.3)
Unknown	0	1 (0.6)	0	0	0	0	0
TIA	0	0	0	0	1 (0.7)	1 (0.7)	0
Stent thrombosis probable	0	0	0	1 (0.6)	0	0	0
Stent thrombosis definite	3 (1.9)	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.7)	0	1 (0.3)

Abbreviations: MI: myocardial infarction; Non-STEMI: non-ST segment elevation MI; SRI: severe recurrent ischemia; STEMI: ST segment elevation MI; TIA: transient ischemic attack.
† Includes all-cause mortality, non-fatal MI, non-fatal stroke
Source: Tables 12.3.1.1.1.2, 12.3.1.1.1.3 and 12.3.1.2.1

After 6 months of double-blind treatment the cumulative risk of the composite efficacy endpoint ranged from 4.3% for the lowest daily doses of 5 mg twice daily and 10 mg once daily to 6.9% for 30 mg twice daily and 9.3% for 60 mg once daily [Tables 12.3.1.3.1 and 12.3.1.3.3]. In the Cox proportional hazards model, the test for linear dose-response relationship was statistically significant (P = 0.045) and the HR that expressed the effect of each addition of 10 mg of darexaban was 1.116 (95% CI: 1.00, 1.24) [Tables 12.3.1.3.1 and 12.3.1.3.3].

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There were no statistically significant differences in the comparisons of total daily doses of 10 mg/day, 30 mg/day and 60 mg/day, and no differences in the comparisons of dosing frequency, i.e., twice daily vs. once daily. The cumulative risk of the primary efficacy endpoint was greater overall for the higher doses of darexaban than the lower doses compared with placebo (5.2%). There were no statistically significant differences between darexaban and placebo.

Secondary Efficacy Composite Endpoints

The composite variable of all-cause mortality, non-fatal MI and non-fatal stroke was associated with more events occurring with darexaban (2.9% for pooled data) than with placebo (2.2%) after 6 months of double-blind treatment. Overall the incidence of this endpoint (that did not include the small number of SRI events included in the primary variable) was not different between the darexaban treatment groups.

The composite endpoint of all-cause mortality, non-fatal MI, non-fatal stroke and major bleeding events was also associated with more events occurring with darexaban (3.9%) compared with placebo (2.5%). The results showed a possible trend of more events occurring with darexaban 30 mg twice daily (5.2%), which was most probably because of the inclusion of major bleeding events in this endpoint, since in the primary endpoint of incidence of major and CRNM bleeding events at 6 months there was some indication of a higher occurrence of bleeding at this dose (see Section 9.1.1).

Individual Adjudicated Events

On-treatment, no differences were observed between the darexaban treatment groups, and no differences from placebo in the incidence of individual adjudicated events apart possibly from SRI (darexaban 5 mg bid 2 patients, 1.3%; 10 mg qd 1 patient, 0.6%; 15 mg bid 6 patients, 3.8%; 30 mg qd 5 patients, 3.2%; 30 mg bid 4 patients, 2.6%; 60 mg qd 8 patients, 5.2%; and placebo 7 patients, 2.2%). However, the number of patients affected was low. The incidence of MI was similar across all study treatment groups, ranging from 1.9% with placebo to 3.2% with darexaban 30 mg once daily. No patients experienced stroke during the double-blind treatment period and only 2 patients had TIA; in the follow-up period , 1 patient experienced a stroke from which [redacted] recovered with sequelae. Definite or probable stent thrombosis occurred in 8/939 (0.9%) of patients receiving darexaban and 1/319 (0.3%) patients receiving placebo.

No trend was observed in the incidence of deaths during the study in relation to study treatment. The 15 deaths that occurred in the study were mainly cardiovascular (12 patients, 1.0%), of which 9 (0.7%) were sudden cardiac death and 3 (0.2%) were acute MI. Of the 3 remaining deaths, 2 were non-cardiovascular and 1 was due to an unknown cause.

Duration of Hospitalization

Mean (SD) duration of hospitalization in the FAS was 3.9 (6.10) days (median 2.0 days). No difference between treatment groups was observed.

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Patient Outcomes

Patient EQ-5D responses and SF-36 scores were similar between treatment groups. By end of treatment visit an improvement in all responses from baseline was observed, including a mean (SD) improvement in EQ-VAS by 5.2 (19.32) mm and SF-36 score improved by 4.4 (16.32).

Summary

A low number of events occurred in the study, but the increase of events with dose of darexaban may be driven by an effect of darexaban on SRI events. This is to be further examined. This study was not powered to detect differences in any of the efficacy endpoints.

Pharmacokinetic and Pharmacodynamic Results:

To be presented in separate report.

Other Safety Endpoints

Treatment-Emergent Adverse Events

Regarding the incidence of TEAEs, apart from the expected increased bleeding, no safety concerns have arisen from the study.

TEAEs were reported by 61.9% of patients; 63.7% treated with darexaban and 56.7% treated with placebo. TEAEs occurred more frequently in all individual darexaban groups (range: 61.5% [30 mg qd group] to 66.0% [30 mg bid group]) compared with the placebo group (56.7%) [Table 4]. Most TEAEs were of mild to moderate severity; 6.0% of patients had severe TEAEs; 6.7% treated with darexaban and 4.1% treated with placebo.

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Table 4 Overview of Incidence Treatment-Emergent Adverse Events – Safety Analysis Set

No. patients (%)	Darexaban						Placebo
	5 mg bid n=159	10 mg qd n=159	15 mg bid n=159	30 mg qd n=156	30 mg bid n=153	60 mg qd n=153	n=319
Any TEAE	100 (62.9)	102 (64.2)	100 (62.9)	96 (61.5)	101 (66.0)	99 (64.7)	181 (56.7)
Drug-related TEAE	34 (21.4)	27 (17.0)	34 (21.4)	26 (16.7)	37 (24.2)	33 (21.6)	51 (16.0)
Deaths	0	2 (1.3)	4 (2.5)	4 (2.6)	2 (1.3)	1 (0.7)	2 (0.6)
Serious TEAEs	13 (8.2)	22 (13.8)	28 (17.6)	26 (16.7)	26 (17.0)	26 (17.0)	40 (12.5)
Drug-related serious TEAEs	3 (1.9)	6 (3.8)	5 (3.1)	3 (1.9)	4 (2.6)	4 (2.6)	3 (0.9)
TEAEs that led to permanent discontinuation of study drug	16 (10.1)	25 (15.7)	21 (13.2)	27 (17.3)	29 (19.0)	25 (16.3)	31 (9.7)
Drug-related TEAEs that led to permanent discontinuation of study drug	9 (5.7)	10 (6.3)	10 (6.3)	8 (5.1)	14 (9.2)	10 (6.5)	14 (4.4)
Mild TEAEs	58 (36.5)	61 (38.4)	62 (39.0)	46 (29.5)	48 (31.4)	57 (37.3)	108 (33.9)
Moderate TEAEs	36 (22.6)	28 (17.6)	29 (18.2)	36 (23.1)	41 (26.8)	33 (21.6)	60 (18.8)
Severe TEAEs	6 (3.8)	13 (8.2)	9 (5.7)	14 (9.0)	12 (7.8)	9 (5.9)	13 (4.1)
Mild drug-related TEAEs	22 (13.8)	15 (9.4)	26 (16.4)	17 (10.9)	27 (17.6)	21 (13.7)	39 (12.2)
Moderate drug-related TEAEs	11 (6.9)	8 (5.0)	7 (4.4)	8 (5.1)	10 (6.5)	8 (5.2)	9 (2.8)
Severe drug-related TEAEs	1 (0.6)	4 (2.5)	1 (0.6)	1 (0.6)	0	4 (2.6)	3 (0.9)
Hepatic TEAEs	6 (3.8)	3 (1.9)	2 (1.3)	3 (1.9)	5 (3.3)	2 (1.3)	10 (3.1)

Abbreviations: TEAE: treatment-emergent adverse event.
Source: Tables 12.6.1.1, 12.6.1.7 and 12.6.1.8

The most frequent TEAEs by SOC were cardiac disorders (16.5%), gastrointestinal disorders (13.0%), general disorders and administration site conditions (11.9%), respiratory, thoracic and mediastinal disorders (11.7%) and vascular disorders (134 patients, 10.7%). The most common TEAEs are summarized in [Table 12.6.1.11]. The most frequent TEAEs by preferred term were hypertension (5.3%), cough (3.9%), angina pectoris (3.3%), epistaxis (3.2%), headache (3.1%) and chest pain (38 patients, 3.0%). It can be concluded that no hepatic safety risk has been observed in the study. Hepatic TEAEs were reported by 2.5% of patients overall; 2.2% treated with darexaban and 3.1% treated with placebo.

The most frequent hepatic TEAEs by preferred term were ALT increased (0.7%); GGT increased and hepatic enzyme increased (each in 0.4% of patients); and hepatic steatosis (0.3% of patients). No differences between treatment groups were observed.

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It can be concluded that discontinuations due to TEAEs were more common for darexaban (143 patients, 15.2%) than for placebo (31 patients, 9.7%), but no specific type of event was identified that drove the difference in discontinuation rate between darexaban and placebo.

The most frequent TEAE resulting in discontinuation was increased blood creatinine and MI. However, both were reported in a low percentage of the population assigned to darexaban. Other reasons for discontinuation varied widely in the population with no differences evident between the darexaban treatment groups or placebo.

Drug-related TEAEs were reported in 19.2% of patients; 20.3% treated with darexaban and 16.0% treated with placebo. Drug-related TEAEs occurred most frequently in the darexaban 30 mg twice daily group (24.2%), followed by the 60 mg once daily group (21.6%); the 5 mg twice daily and 15 mg twice daily groups (21.4% in each); and the 10 mg once daily group (17.0%). It appears that the difference was due to the occurrence of bleeding events, the most common being epistaxis, which occurred in 3.3% of patients treated with darexaban and 1.3% treated with placebo.

Serious TEAEs were reported by 14.4% of patients in the SAF; 15.0% of patients treated with darexaban and 12.5% of patients treated with placebo. Unstable angina was the most common serious TEAEs which was reported by 1.7% of patients; 1.8% treated with darexaban and 1.6% treated with placebo. The small numeric difference between darexaban and placebo was mainly driven by a higher rate of unstable angina which was reported more frequently in the 30 mg once daily and the 60 mg once daily groups. However, as the numbers were small, no definite conclusions could be drawn.

Deaths

Fifteen patients (1.2%) in the SAF died during the study; 13 patients (1.4%) treated with darexaban and 2 patients (0.6%) treated with placebo. There is a numerical difference in death rate between darexaban and placebo, however there were no bleeding related deaths, and the death rate was driven by death due to cardiovascular events, endemic to the population under study.

Laboratory Parameters

Hematology, clinical chemistry and urinalysis parameter findings were generally unremarkable; no notable trends were observed across the treatment groups with regard to shifts from baseline in laboratory data and no clear dose dependent effects were observed across the darexaban groups.

In this population, there were no numerical differences in hepatic TEAE's or moderate/marked hepatic abnormalities between darexaban and placebo and across the darexaban groups [Table 5]. The laboratory parameters normalized in all patients after discontinuation of study drug.

Two concurrent increases of ALT/AST and bilirubin were observed in patients who received darexaban, but strong confounders were present.

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Table 5 Incidence of Clinically Significant Values in Hepatic Function Laboratory Tests – Safety Analysis Set

		Darexaban						Placebo
		5 mg bid n=159	10 mg qd n=159	15 mg bid n=159	30 mg qd n=156	30 mg bid n=153	60 mg qd n=153	n=319
		n/n (%)	n/n (%)	n/n (%)	n/n (%)	n/n (%)	n/n (%)	n/n (%)
ALT or AST	> 3 x ULN	5/ 139 (3.6%)	4/ 144 (2.8%)	2/ 143 (1.4%)	0	1/ 133 (0.8%)	2/ 134 (1.5%)	6/ 284 (2.1%)
	> 5 x ULN	2/ 143 (1.4%)	2/ 150 (1.3%)	0	0	0	1/ 141 (0.7%)	1/ 295 (0.3%)
	> 10 x ULN	1/ 146 (0.7%)	1/ 151 (0.7%)	0	0	0	1/ 142 (0.7%)	1/ 298 (0.3%)
	> 20 x ULN	0	1/ 151 (0.7%)	0	0	0	0	0
Total bilirubin	> 1.5 x ULN	2/ 145 (1.4%)	1/ 146 (0.7%)	3/ 143 (2.1%)	0	2/ 134 (1.5%)	3/ 139 (2.2%)	4/ 288 (1.4%)
	> 2 x ULN	1/ 145 (0.7%)	1/ 146 (0.7%)	0	1/ 143 (0.7%)	1/ 134 (0.7%)	1/ 139 (0.7%)	0
	> 3 x ULN	0	1/ 146 (0.7%)	0	0	0	0	0
	> 5 x ULN	0	1/ 146 (0.7%)	0	0	0	0	0
Moderate or marked hepatic abnormality† ‡		4/ 144 (2.8%)	2/ 145 (1.4%)	2/ 144 (1.4%)	1/ 135 (0.7%)	2/ 134 (1.5%)	2/ 135 (1.5%)	5/ 285 (1.8%)
Marked hepatic abnormality‡		2/ 143 (1.4%)	2/ 150 (1.3%)	0	0	0	1/ 141 (0.7%)	1/ 294 (0.3%)
Concurrent hepatic abnormality§		0	1/ 151 (0.7%)	0	0	0	0	0

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase
† Moderate hepatic abnormality is defined as total bilirubin >2 x ULN, ALT > 3 x ULN, and/or AST > 3 x ULN, including marked abnormalities.
‡ Marked hepatic abnormality is defined as total bilirubin >3 x ULN, ALT > 5 x ULN, and/or AST > 5 x ULN; or concurrent hepatic abnormality.
§ Concurrent hepatic abnormality is defined as total bilirubin >2 x ULN with ALT or AST >3 x ULN on the same day.
Source: Table 12.6.2.5

Significant changes from baseline in serum creatinine occurred to a similar extend in all groups without any differences between darexaban total darexaban dose or dosing regimen. Marked renal events were observed in all treatment groups without any significant differences between darexaban and placebo or between a once or twice daily darexaban dose regimen. Most of the observed renal abnormalities recovered before the final follow-up visit and most of the events did not require any specific intervention. A single patient died, but death was not related to [redacted] renal abnormality. Apart from the patient that died who was treated for a septic shock, only one patient had a renal event that required treatment. Oral rehydration was advised in this patient. None of the events required a significant medical intervention such as a change in treatment regimen, dietary measure or dialysis.

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Confounding factors that could contribute to the renal abnormality were observed in virtually all patients with a marked renal abnormality. The most frequent confounders were the recent MI either or not accompanied by PCI and the concurrent use (with recent changes) of ACE-inhibitors, angiotensin-II inhibitors and/or diuretics.

There were no medically significant differences between the abnormalities observed in groups with an acute marked, a non-acute marked or a concurrent acute and non-acute marked abnormality.

Physical Examinations, Vital Signs and ECGs

Physical examination findings were generally unremarkable with no notable differences being observed across the treatment groups and no dose dependent effects observed across the darexaban groups. Vital signs abnormalities were reported at a similarly increased frequency in patients treated with darexaban and those treated with placebo at EOT/VD compared with baseline; however, no clear conclusions can be drawn given the lower number of evaluable patients at EOT/VD compared with baseline.

ECG data indicated that the majority of patients in all treatment groups had abnormal 12-lead ECG results at baseline and throughout the study as expected for this disease indication (ACS). Most abnormalities were assessed as not clinically significant by the Investigator. No notable differences were observed across the treatment groups with regard to 12-lead ECG abnormalities and no dose dependent effects were observed across the darexaban groups. Clinically significant abnormalities were less frequent post-baseline, at the EOT/VD visit and at the follow-up visit compared with the baseline visit for both patients treated with darexaban and those treated with placebo.

CONCLUSIONS:

Primary Study Endpoint – Incidence of Major and/or CRNM Bleeding Events at 6 Months

- The primary study endpoint of incidence of major and/or CRNM bleeding events during 6 months of double-blind treatment was higher in the darexaban groups (patients receiving darexaban plus standard antiplatelet therapy of clopidogrel and/or ASA) compared with placebo (patients receiving only standard antiplatelet therapy of clopidogrel and/or ASA). The HRs for darexaban versus placebo ranged from 1.8 to 3.8.
- A statistically significant linear association (P = 0.009) was observed between increments in total daily dose of darexaban and an increasing frequency of major and/or CRNM bleeding during 6 months of double-blind treatment.
- The cumulative risk of major and/or CRNM bleeding during 6 months of double-blind treatment ranged from 3.1% with placebo to 11.3% with darexaban 30 mg twice daily. With the exception of darexaban 30 mg twice daily, which showed a higher incidence, the incidence of these bleeding events was comparable across the darexaban dosing groups (ranging from 5.6% to 7.5%).

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- The cumulative incidence was higher with twice daily dosing than a once daily regimen in all three darexaban total daily dose groups of 10, 30 and 60 mg/day. The HR of the darexaban twice daily arms versus darexaban once daily arms was 1.307 (95% CI: 0.78, 2.19), although not statistically significant.
- The results for all patients who were receiving clopidogrel (with or without ASA) were similar to the overall results, as were the analyses using the PPS.

Secondary Bleeding Endpoints

- For the secondary endpoint of events adjudicated as any type of bleed, the incidence in all darexaban groups was higher compared with placebo. In general this endpoint showed a very similar trend to the primary endpoint.
- The incidence of bleeds adjudicated as major in all treatment groups ranged from 0% to 2.0%. The incidence in the darexaban groups was higher than in the placebo group, with the exception of the darexaban 60 mg once daily where no major bleeds occurred. The study was not powered to detect differences in this endpoint.

Efficacy Endpoints

- For the composite efficacy endpoint of all-cause mortality, MI, stroke and SRI during 6 months of double-blind treatment, the cumulative incidence was increased in the darexaban 30 and 60 mg/day dose groups compared with placebo. For the lowest doses of darexaban (10 mg/day), the incidence was comparable to placebo.
- Although the study was not powered to detect effects in this endpoint, these data do not provide any signal of a possible clinical benefit of darexaban on top of dual antiplatelet therapy.
- For the composite of all-cause mortality, non-fatal MI and non-fatal stroke, there is no evidence of a difference between darexaban doses or between darexaban and placebo.
- Although the number of events was limited, the incidence of SRI was observed to increase with the higher doses of darexaban. This suggests that the association observed between higher darexaban doses and the composite endpoint of all-cause mortality, non-fatal MI, non-fatal stroke and SRI might be driven by an effect of darexaban on SRI events.
- The incidence of deaths was 1.4% for darexaban patients (range: 0% in 5 mg bid group to 1.9% in the 30 mg qd group) and 0.6% for placebo patients. There was no clear trend for this endpoint.
- The incidence of on-treatment MI was similar across all treatment groups, ranging from 1.9% with placebo to 3.2% with darexaban 30 mg once daily.
- The results for all patients who were receiving clopidogrel (with or without ASA) were similar to the overall results, as were the analyses using the PPS.

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Other Safety Endpoints

- AEs showed no trend across the darexaban doses, but placebo was generally associated with a lower incidence of AEs than in the darexaban groups.
- Moderate liver abnormalities were observed in all treatment groups without any sign of a dose related.
- There were only 6 marked hepatic abnormalities (including 1 concurrent increases), 1 in the placebo group and 5 in darexaban groups. All recovered after discontinuation of treatment without any complications. In most patients, an alternative explanation for the event was present.
- There were only 2 concurrent elevations of bilirubin with elevated ALT/AST. Both were secondary to an underlying condition.
- Serum creatinine increases were similar across all treatment groups.

Overall Conclusion

The results show that darexaban added to dual antiplatelet therapy after ACS, produces an expected dose related 2-fold increase in bleeding with a strong trend towards more bleeding events in the twice daily dose groups. Although the study was not powered for this objective, no efficacy signal was observed in the study.

Date of Report: January 2012