Name of the Sponsor: Cardoz AB

Trial ID: Cardoz-003 (EudraCT Number: 2011-000285-35)

Name of Finished Product: To be determined

Name of Active Ingredient: Pemirolast sodium (Code: CRD007)

TITLE:
An international, multi-centre, randomised, stratified, double-blinded, placebo-controlled, 4-parallel group trial investigating the efficacy and safety of three different dose levels of CRD007 administered twice daily for 1 year to subjects with AAA (The AORTA trial)

INVESTIGATORS / TRIAL CENTRES:
International Coordinating Investigator and National Coordinating Investigator, Denmark:
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Matthew Thompson MD FRCS, Professor of Vascular Surgery, St George's Vascular Institute, 4th Floor St James Wing, St George's Healthcare Trust, Blackshaw Road, SW17 0QT, London, United Kingdom.

There were 15 trial centres: 5 in Denmark, 8 in Sweden and 2 in the UK.

PUBLICATION (REFERENCE):
None

STUDY PERIOD (YEARS):
Date of first patient screened: 16 May 2011
Date of first patient randomised: 24 May 2011
Date of last subject completed: 11 October 2012

PHASE OF DEVELOPMENT:
Phase II

OBJECTIVES:
Primary objective
- To investigate the optimal oral dose of CRD007 (10 mg, 25 mg and 40 mg tablets) in comparison to matching placebo tablets with respect to efficacy in terms of change in maximum aortic diameter after 12 months of treatment (b.i.d.) as assessed by measurement method A (based on measurements performed during systole)

Secondary objectives
- To compare CRD007 (10 mg, 25 mg and 40 mg tablets) to matching placebo tablets with respect to efficacy in terms of change in maximum aortic diameter after 12 months of treatment (b.i.d.) as assessed by measurement method A (based on measurements performed during diastole)
- To compare CRD007 (10 mg, 25 mg and 40 mg tablets) to matching placebo tablets with respect to efficacy in terms of change in maximum aortic diameter after 12 months of treatment (b.i.d.) as assessed by measurement method B
- To compare CRD007 (10 mg, 25 mg and 40 mg tablets) to matching placebo tablets with respect to efficacy in terms of change in maximum aortic diameter after 6 months of treatment (b.i.d.) as assessed by measurement method A and B
- To compare CRD007 (10 mg, 25 mg and 40 mg tablets) to matching placebo tablets with respect to

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efficacy in terms of incidence and time to maximum aortic diameter of 50 mm as assessed by measurement method A and B

- To compare CRD007 (10 mg, 25 mg and 40 mg tablets) to matching placebo tablets with respect to efficacy in terms of change in dilation, strain and distensibility after 6 and 12 months of treatment (b.i.d.) as assessed by measurement method A and B
- To compare aortic diameter data resulting from the different measurement methods and approaches
- To compare CRD007 (10 mg, 25 mg and 40 mg tablets) to matching placebo tablets with respect to efficacy in terms of incidence and time to
  - acute or elective aneurysm repair
  - aneurysm rupture
  - major cardiovascular events
  - other clinical events of special interest
  - all cause mortality

  during 12 months of treatment (b.i.d.)
- To compare CRD007 (10 mg, 25 mg and 40 mg tablets) to matching placebo tablets with respect to efficacy in terms of change in biomarkers during 12 months of treatment (b.i.d.)
- To compare CRD007 (10 mg, 25 mg and 40 mg tablets) to matching placebo tablets with respect to safety and tolerability in terms of adverse events, ECG, vital signs and safety laboratory parameters during 12 months of treatment (b.i.d.)
- To explore the level of CRD007 plasma concentration after 12 months of treatment with CRD007 tablets (10 mg, 25 mg and 40 mg b.i.d.)

METHODOLOGY:

This was an international, multi-centre, randomised, stratified, double-blinded, placebo-controlled, 4-arm parallel group trial. The trial consisted of a 3-week screening period, a 52-week treatment period and a 2-week follow-up period. Potential subjects were identified for screening from hospital outpatient clinics, national screening programmes and abdominal aortic aneurysm surveillance programmes. Eligible subjects were stratified according to self-reported current smoking status (smoker and non-smoker). Within each stratum subjects were equally randomised (1:1:1:1) to receive one of four treatments: CRD007 tablets (10 mg, 25 mg or 40 mg) or matching placebo tablets twice daily.

Subjects were evaluated with respect to the maximum abdominal aortic diameter by ultrasonography at screening (Visit 1) and at 26 and 52 weeks of treatment (Visits 5 and 7). Two different methods of diameter measurement were applied (Table 1).

Table 1: Method of Diameter Measurement

Method	Description
A	Maximum diameter assessed as measured in anterior-posterior (AP) plane from leading edge adventitia (anterior wall) to leading edge media/adventitia border (posterior wall)
B	Maximum diameter assessed in the AP plane from leading edge adventitia (anterior wall) to leading edge intima (posterior wall)

The Core Ultrasound Laboratory performed 5 measurements for each method, both during systole and diastole, on ultrasound scans obtained at Visits 1, 5 and 7. Additionally, for each method a non-adjudicated and an adjudicated approach were followed (Table 2).

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Table 2: Non-adjudicated and Adjudicated Approaches by Core Ultrasound Laboratory

Non-adjudicated	A Central Reader determines the aortic diameter from Visits 1, 5 and 7 ultrasound scans sequentially, blinded to treatment allocation and blinded to previous measurement results and anatomical information without the option to modify previous measurement results.
Adjudicated	A Central Adjudicator determines the aortic diameter from Visits 1, 5 and 7 ultrasound scans sequentially, blinded to treatment allocation but un-blinded to previous measurements with the option to modify previous measurement results based on a holistic evaluation of all scans across all visits.

An imaging charter described the procedures to be followed by the Core Ultrasound Laboratory to ensure a central, blinded measurement of the maximum aortic diameter on the ultrasound scans provided by ultrasound operators. A standardised image acquisition protocol was specified and required to be followed by ultrasound operators.

An independent data monitoring committee monitored safety data and the overall risk/benefit of the subjects during the trial.

A steering committee assisted and advised the sponsor with regard to scientific and operational aspects of the trial.

There was no option for continued treatment with CRD007 after completion of or withdrawal from trial treatment.

NUMBER OF SUBJECTS (planned and analysed):

It was planned to randomise a total of 300 subjects. A total of 484 subjects were screened, of which 326 were randomised. All randomised subjects, except one subject in the placebo group, received at least one dose of IMP. The number of subjects who completed the trial was 291 and the number of subjects who withdrew from the trial was 35. Subject disposition per dose group is given in Table 3.

The most common reasons for withdrawal were subjects' wish to discontinue and infra-renal aortic repair/ surgery.

Table 3: Subject Disposition per dose group

	Placebo	CRD007 10 mg	CRD007 25 mg	CRD007 40 mg	Total
Screened					484
Randomised	84	80	78	84	326
Dosed	83	80	78	84	325
Completed	69	72	73	77	291
Withdrawn	15	8	5	7	35

The intention to treat analysis set consisted of 326 subjects, the safety analysis set of 325 subjects, the full analysis set of 321 subjects, and the per-protocol analysis set of 283 subjects.

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Male and female subjects aged ≥50 years with a diagnosis of infra-renal abdominal aortic aneurysm (AAA) and an infra-renal AAA diameter (anteroposterior or lateral) between ≥39 mm and ≤49 mm. The subjects were self-reported current smokers or non-smokers.

TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER :

CRD007 tablets, 10 mg (batch number 81002-1012-30), 25 mg (batch number 81002-1012-32), and 40 mg (batch number 81002-1012-34).

The subjects were instructed to administer the investigational medicinal product (IMP) twice daily as home treatment, i.e. one tablet in the morning and one tablet in the evening with 12 (±2) hours between administrations. The subjects were instructed to swallow the IMP with minimum 50 mL of water or non-alcoholic beverages after intake of a meal in the morning and in the afternoon/evening.

DURATION OF TREATMENT:

52 weeks.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Placebo tablets (batch number 81002-1012-28).

The subjects were instructed to administer the investigational medicinal product (IMP) twice daily as home treatment, i.e. one tablet in the morning and one tablet in the evening with 12 (±2) hours between administrations. The subjects were instructed to swallow the IMP with minimum 50 mL of water or non-alcoholic beverages after intake of a meal in the morning and in the afternoon/evening.

CRITERIA FOR EVALUATION

EFFICACY

Primary endpoint, efficacy:

- Absolute change in maximum aortic diameter from screening (Visit 1) to 12 months of treatment (Visit 7) as assessed by measurement method A (based on the arithmetic mean of 5 consecutive measurements performed during systole)

The primary endpoint was based on adjudicated measurements. Secondary endpoints on maximum aortic diameter (below) were based on both adjudicated and non-adjudicated measurements.

Secondary endpoints, efficacy:

- Absolute change in maximum aortic diameter from screening (Visit 1) to 12 months of treatment (Visit 7) as assessed by measurement method A (based on the arithmetic mean of 5 consecutive measurements performed during diastole)
- Absolute change in maximum aortic diameter from screening (Visit 1) to 12 months of treatment (Visit 7) as assessed by measurement method B (based on the arithmetic mean of 5 consecutive measurements performed during both systole and diastole)
- Absolute change in maximum aortic diameter from screening (Visit 1) to 6 months of treatment (Visit 5) as assessed by measurement method A and B (based on the arithmetic mean of 5 consecutive measurements performed during both systole and diastole)
- Incidence and time to maximum aortic diameter of 50 mm as assessed by measurement method A and

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B (based on the arithmetic mean of 5 consecutive measurements performed during both systole and diastole)

- Absolute change in dilatation, strain and distensibility from screening (Visit 1) to 12 months of treatment (Visit 7) as assessed by measurement method A and B (based on the arithmetic mean of 5 consecutive measurements performed during both systole and diastole)
- Absolute change in dilatation, strain and distensibility from screening (Visit 1) to 6 months of treatment (Visit 5) as assessed by measurement method A and B (based on the arithmetic mean of 5 consecutive measurements performed during both systole and diastole)
- Incidence and time to clinical events of special interest:
  - Acute or elective aneurysm repair
  - Aneurysm rupture
  - Major cardiovascular events
  - Other clinical events of special interest
  - Death (any cause)
- Biomarkers
- Plasma concentration of CRD007

SAFETY

Secondary endpoints, safety:

- Adverse events
- ECG assessments
- Blood pressure and pulse
- Haematology, serum chemistry and liver function parameters

STATISTICAL METHODS:

The primary efficacy endpoint, change in maximum aortic diameter from screening to 12 months of treatment, measured according to measurement method A (based on the arithmetic mean of 5 consecutive measurements performed during systole) by the Core Ultrasound Laboratory, was analysed using analysis of variance (ANOVA) adjusted for self-reported current smoking status (stratification factor). Missing data for the 12 months endpoint was imputed using the most recent post baseline value (Last Observation Carry Forward, LOCF). The type I error was controlled using the principle of closed testing by first testing the hypothesis of no difference between treatments arms and subsequently testing for no difference between each active dose level versus placebo starting with the highest dose level.

SUMMARY AND CONCLUSION(S)

EFFICACY RESULTS:

There was no statistically significant difference (p=0.19) in change in maximum aortic diameter from screening to 12 months of treatment using Last Observation Carry Forward (LOCF) on the Full Analysis Set. Analysis of the secondary endpoints did not indicate differences between treatment arms.

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Maximum aortic diameter: Change from screening to 12 months as assessed by measurement method A during systole [LOCF], Full analysis set (FAS)

	Placebo (N=81)	CRD007 10 mg (N=80)	CRD007 25 mg (N=76)	CRD007 40 mg (N=84)	Total (N=321)
Number of subjects included in the analysis	81	80	76	84	
Mean (SD) at Screening	44.000 (2.816)	44.376 (2.909)	44.025 (2.608)	44.108 (2.787)	
Mean (SD) at 12 months	46.016 (3.590)	46.929 (3.766)	46.327 (3.403)	46.791 (3.399)	
Adjusted mean change (95% CI)	2.039 (1.577, 2.501)	2.581 (2.115, 3.047)	2.335 (1.856, 2.813)	2.707 (2.253, 3.161)	
p-value (Test for common mean)					0.1892

SD = Standard deviation, CI = Confidence interval

Adjusted mean change from ANOVA model with self-reported smoking status at baseline as factor.

SAFETY RESULTS:

There were no difference in adverse events between the three CRD007 dose levels and placebo.

	Placebo (N=83)		CRD007 10 mg (N=80)		CRD007 25 mg (N=78)		CRD007 40 mg (N=84)		Total (N=325)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Any pre-treatment adverse event	4 (4.8%)	4	2 (2.5%)	2	6 (7.7%)	6	1 (1.2%)	1	13 (4.0%)	13
Any treatment-emergent adverse event	68 (81.9%)	195	62 (77.5%)	156	67 (85.9%)	183	67 (79.8%)	188	264 (81.2%)	722
Any serious treatment-emergent AE	15 (18.1%)	19	16 (20.0%)	19	14 (17.9%)	16	15 (17.9%)	18	60 (18.5%)	72
Treatment-emergent AEs by severity										
Mild	57 (68.7%)	128	49 (61.3%)	99	60 (76.9%)	141	62 (73.8%)	140	228 (70.2%)	508
Moderate	29 (34.9%)	53	28 (35.0%)	50	27 (34.6%)	38	24 (28.6%)	39	108 (33.2%)	180
Severe	12 (14.5%)	14	7 (8.8%)	7	4 (5.1%)	4	8 (9.5%)	9	31 (9.5%)	34
Treatment-emergent AEs by relationship										
Not Related	67 (80.7%)	171	59 (73.8%)	146	61 (78.2%)	157	63 (75.0%)	162	250 (76.9%)	636
Related	14 (16.9%)	24	8 (10.0%)	10	20 (25.6%)	26	15 (17.9%)	26	57 (17.5%)	86
Treatment-emergent AEs by outcome										
Recovered	53 (63.9%)	117	52 (65.0%)	97	58 (74.4%)	125	51 (60.7%)	118	214 (65.8%)	457
Recovering	10 (12.0%)	11	7 (8.8%)	7	10 (12.8%)	13	12 (14.3%)	14	39 (12.0%)	45
Not Recovered	33 (39.8%)	61	31 (38.8%)	51	24 (30.8%)	38	32 (38.1%)	50	120 (36.9%)	200
Recovered with sequelae	1 (1.2%)	1	1 (1.3%)	1	2 (2.6%)	2	2 (2.4%)	2	6 (1.8%)	6
Death	2 (2.4%)	2	0	0	1 (1.3%)	1	0	0	3 (0.9%)	3
Unknown	2 (2.4%)	3	0	0	3 (3.8%)	4	3 (3.6%)	4	8 (2.5%)	11

n is the number of subjects, m is the number of events.
Percentages are based on the number of subjects in the Safety analysis set.

For ECG assessments, blood pressure, pulse, haematology and liver function parameters no differences between the three CRD007 dose levels and placebo were seen.

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For serum chemistry no differences between the three CRD007 dose levels and placebo were seen except for creatinine. The mean creatinine level increased with dose, however, the change was within normal range and without clinical significance. Furthermore, no difference between the three CRD007 doses and placebo was seen for shifts from normal at baseline to high at post-baseline measurements.

OTHER RESULTS:
Plasma concentrations of CRD007 seemed to increase reasonably with dose. There were no obvious difference in plasma concentrations between genders or between smokers and non-smokers.

CONCLUSIONS:
For efficacy in terms of change in maximum aortic diameter after 12 months of treatment (b.i.d.) as assessed by measurement method A (based on measurements performed during systole) there was no difference between the three CRD007 dose levels and placebo. For safety no difference between the three CRD007 dose levels and placebo except for Creatinine where the mean creatinine level increased with dose within the normal range, without clinical significance or safety concerns.

DATE OF CLINICAL STUDY REPORT SYNOPSIS:

Signature Page

I, the undersigned, have read this report and confirms to the best of my knowledge that it accurately describes the conduct and results of the study.

Sponsor's Medical Responsible
Christian Meyer MD, PhD
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Signature Date

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Signature Date