Name of the Sponsor: Cardoz AB

Trial ID: Cardoz-004 (EudraCT Number: 2011-004667-76)

Name of Finished Product: To be determined

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

TITLE:
An open-label, un-controlled, single-centre trial investigating the efficacy and safety of CRD007 tablets administered twice daily for 12 weeks in children with Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD) or children being symptomatic carriers for DMD or BMD

INVESTIGATOR / TRIAL CENTRE:
Principal Investigator
Thomas Sejersen, MD PhD, Professor in Pediatric Neurology, Department of Women's and Children's Health, Karolinska University Hospital, Astrid Lindgrens Barnsjukhus Q2:07, SE-171 76 Stockholm, Sweden

PUBLICATION (REFERENCE):
None

STUDY PERIOD (YEARS):
Date of first patient screened: 01 March 2012
Date of first patient enrolled: 01 March 2012
Date of last subject completed: 28 September 2012

PHASE OF DEVELOPMENT:
Phase II

OBJECTIVES:
Primary objective:
- To assess the ability of CRD007 to decrease plasma creatine kinase activity levels in subjects with DMD or BMD and in subjects being carriers for DMD or BMD.

Secondary objectives:
- To asses the ability of CRD007 to decrease the level of a range of other disease related biomarkers
- To assess the ability of CRD007 to improve the outcome of functional tests
- To assess the safety of CRD007
- To assess the safety margins of CRD007 in relation to plasma concentrations of pemirolast observed in clinical and pre-clinical studies.

METHODOLOGY:
This was an open-label, un-controlled, single-centre trial consisting of an initial single-dose, dose-escalation part (Part A) followed by a multiple-dose part (B). Part A was added to the trial by the Medical Products Agency (MPA) to document pharmacokinetics in support of the dose rationale for Part B. Part A included an enrolment visit and a dosing visit. Part B included an enrolment visit, a 12-week treatment period and a 2-week post-treatment follow-up period.

NUMBER OF SUBJECTS (planned and analysed):
Part A:
It was planned to enroll 6 subjects divided into two cohorts, each of 3 subjects. A total of 6 subjects were screened and enrolled, 3 in each dose cohort. No subjects withdrew prematurely. All enrolled subjects were included in the analysis data set.

Part B:
It was planned enroll a sufficient number of subjects to achieve 12 subjects completing Part B. A total of

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12 subjects were screened and enrolled, and all 12 subjects completed Part B. No subject withdrew prematurely. All enrolled subjects were included in the safety analysis set, the intention-to-treat analysis set and the per-protocol analysis set.

Five subjects who participated in Part A participated also in Part B. These 5 subjects received new subject ID numbers in Part B (see Table 1).

Table 1: Subjects participating in both Part A and Part B

Subject ID in Part A	Subject ID in Part B
1001	1017
1002	1009
1004	1014
1005	1008
1006	1012

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Male subjects with a diagnosis of Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD) and female subjects being symptomatic carrier for DMD or BMD.

Subjects had to have elevated defined as >5 x Upper Limit of Normal (ULN).

Subjects had to have an age of maximum creatine kinase 11 years (females in the pre-pubertal stage as defined by Tanner criterion I) and a body weight of minimum 14 kg.

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

Part A:

Test product was CRD007 tablets, 10 mg (batch number 81002-1012-31), grinded into oral powder. One batch of oral powder was prepared for each subject, each batch containing oral powder micro weighted according to the individual subject's body weight and the intended dose level (Cohort 1: 0.35 mg/kg and Cohort 2: 0.70 mg/kg). Batch numbers of CRD007 oral powder prepared for the individual subjects are listed in Table 2 below.

The grinning process resulted in some loss of CRD007 and therefore content analyses were performed and conversion factors, giving the percentage of CRD007 contents, were derived (see Table 2).

Conversion factors were taken into account in the pharmacokinetic analyses for Part A, when calculating the dose per kilo body weight.

Table 1: Batch numbers and conversion factors of CRD007 oral powder

Subject ID	Batch Number	Conversion factor (%)
1001	81002-1202-24	94,5
1002	81002-1202-25	94,6
1003	81002-1202-26	92,9
1004	81002-1203-27	97,7
1005	81002-1203-28	95,8
1006	81002-1203-29	95,0

Each subject received a single dose of CRD007 oral powder, administered at the clinic. Subjects enrolled

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into Cohort 1 received 0.35 mg/kg and subjects enrolled into Cohort 2 received 0.70 mg/kg. The study nurse dispensed the oral powder into a spoon full of yoghurt and ensured that the spoon was emptied by the child. The study nurse ensured that all yoghurt including the oral power was swallowed by the child by letting the child drink some water and/or eat some more yoghurt.

Part B:
CRD007 tablets, 10 mg (batch number 81002-1012-30).

The dosage will be adjusted according to the subject's body weight at the Enrolment Visit (Visit 1):

Body weight of 14 to 25 kg: One CRD007 10 mg tablet b.i.d.
Body weight of 26 kg or above: Two CRD007 10 mg tablets b.i.d.

The subjects' parents were instructed to administer the CRD007 tablets to their child as home treatment twice daily, i.e. one or two tablets in the morning and one or two tablets in the evening with 12 (±2) hours between administrations. CRD007 tablets were to be swallowed with minimum 50 mL of water or beverages in connection with a meal. If the subject was unable to swallow tablets, it was allowed that tablets were crushed and taken with some yoghurt or other kind of food, as appropriate.

DURATION OF TREATMENT:
Part A: Single dose
Part B: 12 weeks

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:
No reference therapy was administered.

CRITERIA FOR EVALUATION
EFFICACY
Primary endpoint:
- The relative change in creatine kinase from enrolment (Visit 1) to 12 weeks of treatment (Visit 5)

Secondary endpoints:
- The relative change in other disease related biomarkers between baseline and 12 weeks of treatment
  a. Myoglobin
  b. miR-1, miR-133 (subtypes miR-133a and miR-133b), miR-206
  c. Tryptase
  d. hs-CRP
- The relative change in the total North Star Ambulatory Assessment score
- The relative change in the time needed to perform "Rise from floor", "Run (10 m)", "Climb 4 steps"
- Change in safety related assessments between baseline and 12 weeks
  a. Blood pressure (diastolic and systolic) and pulse
  b. Electrocardiogram
  c. Biochemistry laboratory values
  d. Hematology laboratory values
- Incidence of adverse events by type and severity
- $C_{pl(CRD007)}$ and derived pharmacokinetic parameters

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STATISTICAL METHODS:
All statistical analyses were performed using SAS® (Version 9.3, SAS Institute Inc., Cary, NC, USA).

Continuous data were summarized using descriptive statistics where the following parameters were reported: Number of observations and missing observations, mean and standard deviation, minimum, 1st quartile, median, 3rd quartile and maximum. Categorical data were presented using frequency and percentage and total number of subjects.

All confidence intervals were two-sided and at a 95% level.

Since there was only one primary endpoint, no adjustment for multiplicity was performed. The main analysis on the primary endpoint was performed on the intention-to-treat analysis set. For the secondary endpoints no adjustment for multiple comparisons was performed.

Creatine kinase activity level at baseline (Visit 1) and at 12 weeks of treatment (Visit 5) and relative change ($\Delta_{rel} = (CK_{12w} - CK_{base})/CK_{base}$) were presented descriptively for subjects with both a baseline and a 12-week recording. A 95% two-sided confidence interval for the estimated mean relative change in creatine kinase activity level was presented. This corresponded to a one-sample two-sided test of whether the change could considered statistically significantly different from zero or not.

The relative change in creatine kinase activity level from baseline (Visit 1) to 6 weeks of treatment (Visit 3) was summarized with descriptive statistics and 95% confidence interval as for the primary endpoint.

The relative change between baseline (Visit 1) and 12 weeks of treatment (Visit 5) for other disease related biomarkers (myoglobin, miR-1, miR-133a, miR-133b, miR-206, tryptase, hs-CRP) and for functional test results (total North Star Ambulatory Assessment score, time needed to perform "Rise from floor", to perform "Run (10 m)" and to perform "Climb 4 steps") was summarized and analysed in the same manner as for the primary endpoint.

The relationship between dose and effect was analysed by plotting dose by body weight against the 12-week relative change in creatine kinase activity level.

CRD007 plasma concentration profiles were subjected to non-compartmental pharmacokinetic analysis using validated PC-based software, WinNonlin v. 5.3 (Pharsight Corporation, Mountain View, CA, USA).

SUMMARY AND CONCLUSION(S)

EFFICACY RESULTS:
The mean creatine kinase activity level was 272.4 mikrokat/L (SD=122.3) at baseline (Visit 1) and 254.3 mikrokat/L (SD=121.5) at 12 weeks of treatment (Visit 5), resulting in a mean relative change of -0.018 (95% confidence interval: -0.201 - 0.164). This relative change was not statistically significant.

With respect to other disease related biomarkers, only myoglobin showed as statistically significant change (increase) from baseline (Visit 1) to 12 weeks of treatment (Visit 5). Relative change from baseline was 0.55 (95% confidence interval: 0.17 – 0.94). However, since no adjustment for multiplicity was performed this could be a chance finding and should therefore be interpreted with caution.

Functional tests did not show any change from baseline (Visit 1) to 12 weeks of treatment (Visit 5).

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SAFETY RESULTS:
In Part A, no adverse events were reported.

In Part B, 13 adverse events were reported for 7 of the 12 subjects (58.3%). Of these, 11 adverse events were assessed as not related to the test product and were of mild intensity. The 2 adverse events judged related to the test product were of mild and moderate intensity, respectively.

No serious adverse events were reported.

No other safety related assessments showed any clinically relevant changes from baseline (Visit 1) to 12 weeks of treatment (Visit 5).

OTHER RESULTS:
For Part A, total body clearance following extravascular administration (CL/f) was almost identical for the two cohorts (59.0±30.0 ml/h/kg for Cohort 1 versus 60.6±19.2 ml/h/kg for Cohort 2), indicating linear pharmacokinetics. A short terminal elimination half-life ($t_{½}$) was shown (2.98±0.50 h for Cohort 1 and 2.88±0.58 h for Cohort 2), predicting minimal accumulation during b.i.d. administration.

For Part B, multiple b.i.d. administration resulted in minimal accumulation as expected from the $t_{½}$ shown in Part A.

CONCLUSIONS:
CRD007 did not decrease plasma creatine kinase levels during the treatment period investigated.

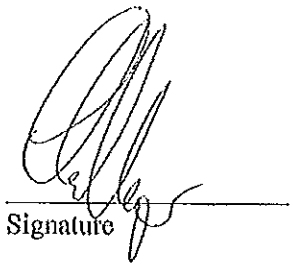
No other disease related biomarkers showed a decrease over this period and no improvements on functional test results were demonstrated.

Safety related assessments, including adverse events, did not reveal any safety concerns with respect to CRD007 in the dose range investigated.

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 trial.



Sponsor's Medical Responsible
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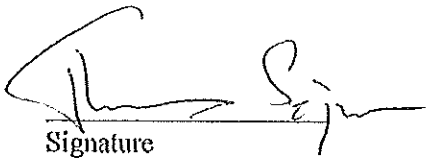
Signature

25-MARS-2013
Date



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25 MAR 2013
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