I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**Clinical Study Report Synopsis**
Study title	**Evaluation of the effect of the oral administration of perindopril orodispersible at a dose of 0.150 mg/kg/day on the muscular and myocardial function in early stage Duchenne muscular dystrophy.** **Double blind two years study, randomised *versus* placebo.**
Study drug	**S 90652**
Studied indication	**Duchenne muscular dystrophy**
Development phase	**Phase III**
Protocol code	**CL3-90652-004**
Study initiation date	**11 March 2009**
Study completion date	**19 October 2011**
Main coordinator	[redacted]
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 06 April 2012**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study: Evaluation of the effect of the oral administration of perindopril orodispersible at a dose of 0.150 mg/kg/day on the muscular and myocardial function in early stage Duchenne muscular dystrophy. Double blind two years study, randomised *versus* placebo. Protocol No.: CL3-90652-004		
National coordinator: [redacted].		
Study centres: 16 centres located in France, were opened and 14 centres included at least one patient.		
Publication (reference): Not applicable		
Studied period: Initiation date: 11 March 2009 Completion date: 19 October 2011	**Phase of development of the study:** Phase III	
Objectives: The main objective of the study was to assess the benefit *versus* placebo of the administration of perindopril arginine salt orodispersible at a dose of 0.150 mg/kg/day in a morning dose during 2 years, on peripheral muscular function in children suffering from Duchenne Muscular Dystrophy (DMD). The secondary objectives were: - To measure the benefit of the administration of perindopril arginine salt orodispersible at a dose of 0.150 mg/kg/day in a morning dose during 2 years, *versus* placebo on the myocardial and respiratory function in children suffering from DMD. - To quantify the endomysial fibrosis during the study on a new biopsy in patients who need to undergo surgery for medical reasons (tenotomy, etc.). - To measure the myocardial and muscular fibrosis by Nuclear Magnetic Resonance (NMR) with a T1, T2 and delayed time study after injection of gadolinium *(Note: This auxiliary study was not set up).* - To quantify the endomysial fibrosis on the initial muscle biopsy that allowed calibrating the NMR fibrosis measurement and also looking for ACE inhibitor response predictive factors (data not available at the time of the report).		
Methodology: Phase III, multi-centric, double-blind, randomised, comparative study *versus* placebo, conducted in France, with 2 parallel groups, in children with DMD.		
Number of patients: Planned: 40 patients *i.e.* 20 patients in each group Included: 40 patients *i.e.* 20 patients in each group		
Diagnosis and main criteria for inclusion: Children under 7 years old suffering from confirmed DMD, capable of performing a 6 minute walking test, who did not take corticosteroid therapy in the long term, angiotensin converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor antagonists (ARA II) treatments.		
Study drug: Perindopril: orodispersible arginine salt tablets dosed at 0.625 mg and 2.5 mg for a posology of 0.150 mg/kg/day *per os* administered fasting in the morning. Batch No.: L0022643, L0025990, L0036962, L0021422 and L0028847		
Reference product: Placebo: orodispersible tablets *per os* administered fasting in the morning.		
Duration of treatment: Active treatment period: 2 years		

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Criteria for evaluation:

Efficacy measurements:

Primary assessment criterion: the 6-minute walking distance

This test was performed every 6 months in the morning on the day of the visit.

Secondary criteria: all secondary criteria were assessed every 6 months.

- Other parameters of 6 minute walking test
- The 3-minute stair climbing test: This test was performed in the afternoon on the day of the visit.
- The 18-point muscle testing: combination score of 9 muscles with a measure of the left (9 points) and the right (9 points) side of the body. Muscular testing score for each muscle was determined using a numerical scale from 0 through 5. Higher score is related to greater muscular strength. Upper limb included shoulders (3 muscles) & elbows (2 muscles) and lower limb included thigh-bottom (2 muscles) & legs (2 muscles).
- The cardiac echocardiography
- The Doppler
- The pulmonary function tests and the Sniff test

Safety measurements:

- Adverse events: assessed at each visit.
- Laboratory tests: Biological tests (biochemistry and haematology) performed at M0, M6, M12, M18 and M24 were assessed.
- Vital signs: weight, BMI, blood pressure and heart rate were measured at M0, M6, M12, M18 and M24.

Statistical methods:

The main set for efficacy criteria was the FAS based on intention-to-treat and defined as all randomised patients having taken at least one dose of study treatment, having one available baseline evaluation and at least one available post baseline evaluation for the 6 minute walking distance.

Efficacy analysis:

All efficacy analyses were carried out primarily on the FAS and secondarily on the PPS.

Primary criterion: 6 minute walking distance

The *main analysis* was the comparison between treatments groups, perindopril *versus* placebo, in terms of the change from baseline to last post-baseline value on the period M000-M024.

An analysis of covariance adjusted on 6 minute walking distance baseline value, height baseline value and growth was used.

Non-parametric approach without adjustment, based on the Hodges-Lehmann's estimator was tested using a Mann-Whitney-Wilcoxon test as a *sensitivity analysis*.

The *secondary analyses* consisted of:

- A comparison between treatments groups of the relative change from baseline to last post-baseline value on the period M000-M024, using an analysis of covariance adjusted on height baseline value and growth.
- A comparison between treatments groups of the ratio change from baseline to last post-baseline value on the period M000-M024, using a Student t test.

Non-parametric approach without adjustment as described for the main analysis was carried out as a sensitivity analysis for these secondary analyses of main criterion.

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Statistical methods (Cont'd):

Secondary criteria

- Other parameters of 6 minute walking test: descriptive analysis.

- 3 minute stairs test

The same analyses (except the sensitivity analysis) as those for the main criterion were carried out for the number of stairs climbed in 3 minutes.

For other parameters of 3 minute stairs test (patient leaned on ramp/wall, number of stops, unfinished exercise duration and other difficulties): descriptive analysis.

- Muscular testing

Comparison between treatments groups of the change from baseline to last post-baseline value on the period M000-M024 for the overall muscular testing global score (18 points) and for upper (10 points) / lower (8 points) limbs score, using an analysis of covariance adjusted on baseline score, height baseline value and growth.

- Echocardiography parameters

Comparison between treatments groups of the change from baseline to last post-baseline value on the period M000-M024 for the Simpson biplan ejection fraction and shortening fraction, using an analysis of covariance adjusted on baseline value of the considered parameter, height baseline value and growth.

- Doppler: descriptive analysis.

- Spirometry

Comparison between treatments groups of the change from baseline to last post-baseline value on the period M000-M024 for the spirometry parameters (forced vital capacity and functional residual capacity), using a Student t test for independent samples.

- Sniff test: descriptive analysis.

Safety analysis:

Descriptive statistics were carried out on the Safety Set.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 40 children suffering from DMD were included in the study and randomly assigned to one of the 2 groups. The disposition of patients is summarised in the following table.

Disposition of patients

		Perindopril	Placebo	All
Included (Randomised Set)	n	20	20	40
Lost to Follow-up	n	-	-	-
Withdrawn due to	n (%)[a]	5 (25.0)	2 (10.0)	7 (17.5)
protocol deviation	n (%)[a]	3 (15.0)	2 (10.0)	5 (12.5)
non-medical reason	n (%)[a]	2 (10.0)	-	2 (5.0)
Completed	n (%)[a]	15 (75.0)	18 (90.0)	33 (82.5)
Full Analysis Set (FAS)	n (%)[a]	19 (95.0)	20 (100)	39 (97.5)
Per Protocol Set (PPS)	n (%)[b]	13 (68.4)	17 (85.0)	30 (76.9)
Safety set	n	19	20	39

a: % of the Randomised Set , b: % of the FAS

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Overall, 4 patients (10.0%) presented each one protocol deviation at inclusion and 28 patients (70.0%) presented at least one protocol deviation after inclusion: 14 patients (70.0%) in each group.

At inclusion, children were aged from 2.5 to 7.0 years with a mean age of 5.31 ± 1.19 years. Their weight ranged from 9.5 to 27.7 kg with a mean of 18.90 ± 3.25 kg and the height ranged from 88 to 125 cm with a mean of 109.3 ± 8.3 cm. The mean supine SBP/DBP values were 98.9 ± 9.2 mmHg / 56.2 ± 8.8 mmHg and the mean heart rate was 92.1 ± 14.2 bpm. No relevant difference between groups was noted in demographic data and vital signs.

At inclusion, children have suffered from DMD for 21.7 ± 16.3 months in average; this mean time since diagnosis of the disease was longer in the perindopril group (24.8 ± 19.1 months) than in the placebo group (18.5 ± 12.4 months).

Overall, in around three quarters of patients (72.5%), stairs climbing was possible with help; in one quarter, it was possible without help and only one patient in the perindopril group could not climb stairs. Around two thirds of patients (67.5%) could run. Overall, only one patient in the perindopril group received levoglutamide and uridine triphosphate sodium as DMD previous treatments. In all, 82.5% of children had kinesitherapy session until 6 months before inclusion. All these patients, except one in the placebo group, continued the kinesitherapy sessions during the study. No relevant between-group difference was noted for these parameters.

Regarding the evaluation of the peripheral muscular function of children at inclusion, the mean distance covered in the 6 minutes of the walking test was 319.4 ± 78.3 meters without relevant difference between groups.

Patients climbed in average 69.1 ± 33.3 stairs during the 3 minutes of the stairs climbing test: 64.6 ± 29.6 stairs (median = 73.0 stairs) in the perindopril group and 73.5 ± 36.9 stairs (median = 68.0 stairs) in the placebo group.

The mean of the muscular testing global score was 3.9 ± 0.6, without relevant difference between groups.

Overall, more than half of the patients (55.0%) reported at least one medical history other than DMD, mainly (≥ 15.0% of patients) respiratory, thoracic and mediastinal disorders (20.0% of patients) and infections and infestations (15.0%).

A total of 31 patients (77.5%) received at least one concomitant treatment during the treatment period, main concomitant treatments (≥ 40.0% of patients in either group) being analgesics (exclusively paracetamol), antibacterials for systemic use and vaccines. Systemic corticosteroids were used (all less than 1 month) in 6 patients in the placebo group *versus* none in the perindopril group.

In the Safety Set, treatment duration ranged between 351 and 750 days with a mean of 688.6 ± 96.8 days (median = 721.5 days). The mean treatment duration was slightly shorter in the perindopril group (667.2 ± 122.6 days) than in the placebo group (707.8 ± 63.0 days), the median values being similar.

In the Safety Set, overall compliance ranged between 51 and 101% with a mean of 95.2 ± 8.8%, without relevant difference between groups.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Primary assessment criterion: 6 minute walking distance

The main analysis was the comparison between groups on the change of the distance covered in 6 minutes from baseline to last post-baseline value in the FAS, using an analysis of covariance adjusted on 6 minutes walking distance baseline value, height baseline value and growth. The results are presented in the following table.

Distance covered in 6 minutes - Change from baseline to last post-baseline value - FAS

		Perindopril (N = 19)	Placebo (N = 20)
	n	19	20
Baseline	Mean ± SD	320.4 ± 58.2	324.4 ± 92.8
	Median	313.0	333.0
	Min ; Max	201 ; 400	100 ; 500
END	Mean ± SD	275.4 ± 141.0	240.3 ± 142.1
	Median	325.0	268.0
	Min ; Max	0 ; 440	0 ; 414
END-Baseline	Mean ± SD	-44.9 ± 132.7	-84.1 ± 134.3
	Median	-43.0	-63.0
	Min ; Max	-300 ; 197	-335 ; 145
Statistical analysis			
Main analysis: parametric approach	E (SE) (1.1)	60.39 (44.95)	
	95% CI (2)	[-30.96 ; 151.74]	
	p-value (3.1)	0.188	
Sensitivity analysis: non-parametric approach	E (1.2)	40.50	
	95% CI (2)	[-44.00 ; 124.00]	
	p-value (3.2)	0.339	

Two-sided type I error rate: 0.05
(1.1) Estimate (Standard Error) of the difference between adjusted groups means : perindopril minus placebo
(1.2) Estimate of Hodges-Lehmann for the difference between groups means : perindopril minus placebo
(2) 95% Confidence Interval of the estimate
(3.1) p-value for General linear model
(3.2) p-value for Mann-Whitney-Wilcoxon test

The mean distance covered in 6 minutes decreased from baseline to last post-baseline value in both groups. This mean decrease was smaller in the perindopril group (-44.9 ± 132.7 meters) (median = -43 meters) as compared to that in the placebo group (-84.1 ± 134.3 meters) (median = -63 meters), although the between-group estimated difference (SE) of 60.39 (44.95) meters (95% CI [-30.96 ; 151.74]) was not statistically significant. However, this between-group difference was close to the one expected as a clinically significant difference and used in the calculation of sample size (difference of at least 65 m between the groups). The observed variances were higher than those expected, which could be explained by the age range at inclusion and the loss of walking in some patients (3 in both groups).
Even not statistically significant, these results suggested a potential improvement of the peripheral muscular function under perindopril as compared to placebo.

The same trend was shown in the sensitivity analysis (non-parametric approach, without adjustment), with a non-statistically significant between-group estimated difference of 40.50 meters.

Consistently, regarding the relative change, the mean distance covered in 6 minutes decreased from baseline to last post-baseline value by 13.5% in the perindopril group and by 25.0% in the placebo group. The between-group estimated difference was not statistically significant (E (SE) = 19.10 (15.93)%, 95%CI [-13.24 ; 51.43]).

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

The complementary analysis on the change of the distance covered in 6 minutes from baseline to last post-baseline, excluding patients with distance equal to 0 at END, showed similar non-statistically significant between-group difference as that of the main analysis: E (SE) = 58.19 (33.93) meters, 95% CI [-11.32 ; 127.69]. It should be noted that SD clearly decreased as compared to those of the main analysis, in both groups, respectively in perindopril and placebo group from 132.7 to 96.8 and from 134.3 to 101.0.

The evolution of the distance covered in 6 minutes according to age and growth, respectively, was examined.
The treatment effect of perindopril as compared to placebo on the change of distance covered in 6 minutes between baseline and the last post-baseline value was particularly pronounced in young children and in children with a small growth (≤ 10 cm) (complementary analyses).

Secondary criteria

- 3 minute stairs test

The results of the 3 minute stairs test also suggested that perindopril could improve the peripheral muscular function in comparison with placebo. The number of stairs climbed in 3 minutes decreased between baseline and last post-baseline value in both groups, but this decrease tended to be smaller in the perindopril group than in the placebo group: -15.7 ± 34.6 stairs (median = -13.0 stairs) corresponding to a relative decrease of 18.4% (median = -29.9%) in the perindopril group *versus* -27.4 ± 41.8 stairs (median = -41.0 stairs) corresponding to a relative decrease of 30.5% (median = -48.1%) in the placebo group (non-statistically significant between-group difference, E (SE) = 13.15 (12.05) stairs, 95% CI [-11.33 ; 37.63]).

- Muscular testing

The mean global score tended to remain stable from baseline to the last post-baseline value in both groups (-0.3 ± 0.6 in the perindopril group and -0.4 ± 0.7 in the placebo group), without statistically significant difference between groups.
The mean global score for upper limb remained stable from baseline to the last post-baseline value in both groups (-0.2 ± 0.4 in the perindopril group and -0.1 ± 0.5 in the placebo group), without statistically significant difference between groups.
On the other hand, the mean global score for lower limb remained stable in the perindopril group (-0.1 ± 0.9) whereas it tended to decrease in the placebo group (-0.8 ± 0.8), the between-group difference was close to the statistical significance (E (SE) = 0.53 (0.27), 95% CI [-0.03 ; 1.08], p = 0.063).

The trend in favour of perindopril observed in the 6-minute walking test and the 3-minute stairs test was consistent with the results of the muscular testing for lower limb. Indeed, those results are consistent with the natural development of the DMD which damages the lower limbs first and with an anti-fibrosis potential effect of perindopril in the youngest patients.

- Echocardiography

The Simpson biplan mean ejection fraction and the mean shortening fraction assessed by echocardiography remained stable between baseline and the last post-baseline value in both groups (-1.8 ± 4.2% in the perindopril group and -2.2 ± 6.5% in the placebo group for the Simpson biplan ejection fraction and -0.88 ± 5.04% *versus* -1.23 ± 4.36%, respectively, for the shortening fraction), without statistically significant difference between groups.

- Doppler parameters

No relevant difference between groups in the evolution of Doppler parameters was observed between baseline and M024, with some fluctuations depending on the visit.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- Spirometry

Results should be interpreted with caution due to small sample size.

The mean increase of the forced vital capacity from baseline to last post-baseline value tended to be smaller in the perindopril group (186.3 ± 263.0 mL) (median = 225.0 mL) than in the placebo group (mean = 288.5 ± 156.3 mL) (median = 270.0 mL) and the mean increase of the functional residual capacity from baseline to last post-baseline value tended to be higher in the perindopril group (242.7 ± 135.9 mL) (median = 220.0 mL) than in the placebo group (70.8 ± 490.2 mL) (median = 169.5 mL). No statistically significant difference between groups was noted for these 2 parameters.

SAFETY RESULTS

Overall summary of safety results

		Perindopril (N = 19)	**Placebo (N = 20)**	**All (N = 39)**
Patients having reported				
at least one emergent adverse event	n (%)	17 (89.5)	17 (85.0)	34 (87.2)
at least one treatment-related emergent adverse event	n (%)	3 (15.8)	2 (10.0)	5 (12.8)
Patients having experienced				
at least one serious adverse event (including death)	n (%)	6 (31.6)	3 (15.0)	9 (23.1)
at least one treatment-related serious adverse event	n (%)	-	-	-
Patients withdrawn due to an adverse event	n (%)	-	-	-
Patients who died	n (%)	-	-	-

Overall, 34 patients (87.2%) reported at least one **emergent adverse event** (EAE) during the study. The rate of patients having at least one EAE was similar between treatment groups (89.5% *versus* 85.0%, respectively) while the number of EAEs reported in the perindopril group (107 EAEs) was higher than that reported in the placebo group (69 EAEs).

Considering both groups, the most frequently affected system organ classes (> 20.0% of patients in each group) were Infections and infestations (12 patients [63.2%] in the perindopril group *versus* 14 patients [70.0%] in the placebo group) and Respiratory, thoracic and mediastinal disorders (5 patients in each group, ***i.e.*** 26.3% *versus* 25.0%, respectively), without relevant difference between groups.

The following SOCs were also reported in more than 20.0% of patients in the perindopril group and thus more frequently reported than in the placebo group: Gastrointestinal disorders (6 patients [31.6%] *versus* 3 patients [15.0%]), Injury, poisoning and procedural complications (6 patients [31.6%] *versus* 3 patients [15.0%]), General disorders and administration site conditions (6 patients [31.6%] *versus* 2 patients [10.0%]), Nervous system disorders (5 patients [26.3%] *versus* 1 patient [5.0%]) and Musculoskeletal and connective tissue disorders (4 patients [21.1%] *versus* 1 patient [5.0%]).

In the perindopril group, the most frequently reported (> 3 patients) emergent adverse events were ear infection (6 patients, 31.6% in the perindopril group *versus* 3 patients, 15.0% in the placebo group), gastroenteritis (5 patients, 26.3% *versus* 2 patients, 10.0%, respectively), fall (5 patients, 26.3% *versus* none, respectively) and rhinitis (4 patients, 21.1% *versus* 3 patients, 15.0%, respectively). Most of these EAEs are expected diseases in a population of children from 2.5 to 7 years of age.

Falls reported in 5 patients in the perindopril group were not related to hypotension reported as EAE. None of these falls was considered as related to the study drug according to the investigator.

No adverse events (emergent or not) led to treatment stopped.

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Most of EAEs were rated as mild in both groups: 82.2% of EAEs in the perindopril group *versus* 78.3% in the placebo group. Overall, only 2 EAEs were rated as severe in the perindopril group: myopathy and osteoporosis in the same patient. Both EAEs were serious and did not recover. The first one was considered as related to lack of efficacy and the second one as not related to the study drug but related to medical history.

Few EAEs were considered as related to the study drug by the investigator:

- 9 EAEs in 3 patients in the perindopril group: polydipsia, cough (4 EAEs in the same patient), rhinorrhoea, dry mouth, asthenia and headache, reported in one patient each.
- 3 EAEs in 2 patients in the placebo group: hypertriglyceridaemia, cough and accidental overdose, reported in one patient each.

In most of the cases *i.e.* 154/176 EAEs (87.5% of EAEs), a total recovery was observed: 92 EAEs (86.0%) in the perindopril group and 62 EAEs (89.9%) in the placebo group.

No patient died during the study.

Overall 8 patients (20.5%) had 15 **emergent SAEs**: 5 patients (26.3%) with 12 SEAEs in the perindopril group and 3 patients (15.0%) with 3 SEAEs in the placebo group. The most frequent SEAEs were Infections and infestations reported in 3 patients in the perindopril group *versus* none in the placebo group. No SEAE was considered as related to the study drug by the investigators, only one in the perindopril group (myopathy) was related to a lack of efficacy. All SEAEs, except 2 in the same patient in the perindopril group (osteoporosis and myopathy) and one in the placebo group (myopathy), recovered.

An accidental study drug overdosage without signs and symptoms in patient's sister reported as SEAE in the placebo group led to blind broken; in addition in the same group, an other accidental overdosage due to a mistake in patient's weight without clinical signs was not considered as serious but had an immediate notification as required in the protocol.

Regarding **biology**, 5 patients in the perindopril group and 6 patients in the placebo group presented at least one emergent PCSA biochemical value for high values of ASAT, ALAT, CPK, triglycerides or low values of creatinine and 1 patient in the perindopril group presented an emergent low PCSA value for WBC.

Concerning the **vital signs**, the weight of children expectedly increased from baseline to last post-baseline value under treatment: 2.7 kg in the perindopril group and 3.3 kg in the placebo group. The BMI remained stable during this period.

The mean values of supine SBP, DBP and heart rate also remained stable between baseline and the last post-baseline value under treatment.

CONCLUSION

In summary, results of this study performed in children (2.5 - 7 years) suffering from DMD, who did not take corticosteroid therapy in the long term, ACE inhibitors or ARA II treatments, suggested that orodispersible perindopril arginine salt, administered at a dose of 0.150 mg/kg/day in a morning dose during 2 years, could improve the peripheral muscular function as compared to placebo, assessed by the 6 minute walking test, by the 3 minute stairs test, and by the muscular testing of the lower limbs, although without reaching the statistical significance.

Globally, the reported adverse events in the orodispersible perindopril arginine salt group were in accordance with the safety profile of perindopril and the age of children.

Date of the report: 06 April 2012