# Clinical trial results: CELL THERAPY OF DUCHENNE MUSCULAR DYSTROPHY BY INTRA-ARTERIAL DELIVERY OF HLA-IDENTICAL ALLOGENEIC MESOANGIOBLASTS

## Summary

| | |
|---|---|
| EudraCT number* | **2011-000176-33** |
| Trial protocol | Cell therapy of Duchenne Muscular Dystrophy (DMD) by intra-arterial delivery of HLA-identical allogeneic mesoangioblasts (DMD03) |
| Global end of trial date* | 29.01.2025 |

# Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code* | DMD03 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | if available |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors details*

| | |
|---|---|
| Sponsor organisation name | Fondazione Centro San Raffaele del Monte Tabor |
| Sponsor organisation address | Via Olgettina, 60, Milano, Italy, 20132 |
| Public contact | ciceri.fabio@hsr.it |
| Scientific contact | cossu.giulio@hsr.it |

Notes:

### Paediatric regulatory details*

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

### Results analysis stage

| | |
|---|---|
| Analysis stage* | Final |
| Date of interim/final analysis* | 01.12.2016 |
| Is this the analysis of the primary completion data?* | No |
| Global end of trial reached?* | Not applicable |
| Global end of trial date* | Not applicable |
| Was the trial ended prematurely? | No |

## General information about the trial

- Main objective of the trial*:

Safety:

1. evaluation of the incidence of adverse events in DMD patients treated with intra-arterial injections of allo-MABS from an HLA-identical family donor;

Efficacy:

2. to test the efficacy of intra-arterial injections of allo-MABS from an HLA-identical family donor in improving muscle strength in DMD patients;

| | |
|---|---|
| Actual start date of recruitment* | 04-Mar-2011 |
| Long term follow-up planned* | Yes |
| If Yes, rationale: | Safety |
| Duration | Total duration of the study expected of 3 years after the last patient enrolled and treated<br>(After month +12, all patients enrolled in the study expected to continue long term follow-up for at least 8 years from infusion I according to Italian law for cellular and gene therapy trials DM02-03-2004) |
| Independent data monitoring committee (IDMC) involvement?* | Yes |
| Protection of trial subjects*: | Written informed consent from each patient or patient's parent(s) or legal guardian(s), if applicable, and written assent from each patient, if applicable, were obtained before any study-specific screening or baseline period evaluations were performed. The anonymity of participating patients will be maintained to the extent required by applicable laws. This study was designed and monitored in accordance with Sponsor procedures, which complied with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki. |
| Background therapy: | Standard |
| Evidence for comparator: | Not applicable |

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: | Italy |
| Planned number of subjects | 6 |
| Actual Number of subjects enrolled* | 5 |
| Worldwide total number of subjects | 5 |
| EEA total number of subjects | 5 |

### Subjects enrolled per age group

| | |
|---|---|
| In utero* | 0 |
| Preterm newborn - gestational age < 37wks* | 0 |
| Newborns (0-27 days)* | 0 |
| Infants and toddlers (28 days-23months)* | 0 |
| Children (2-11 years)* | 3 |
| Adolescents (12-17 years)* | 2 |
| Adults (18-64 years)* | 0 |
| From 65 to 84 years* | 0 |
| 85 years and over* | 0 |

# Subject disposition

**Recruitment details:**

recruitment period 2 years of patients affected by DMD with proven diagnosis as evidenced by a clinical history of early onset and progressive muscle weakness confirmed by increased serum creatine kinase (CK) levels (at least 10 times the upper limit of normal), muscle biopsy and dystrophin analysis

*Enter key information relevant to the recruitment process for the trial (eg gates of recruitment period and territories)*

**Pre-assignment - *Screening details*:**

Patients have been screened among 28 patients enrolled in the clinical trial DMD01, Outcome measures validation study for children affected by DMD. Force measurement on enrolled patients according to North-Star Scale (NS), 6 minutes-walking test (6MWT) and Kin Com force measurements (quantitative measurement tests -QMT).

*Enter relevant information related to screening (eg screening criteria, significant events and approaches)*

**Period 1**

| | |
|---|---|
| Period title* | Overall trial |
| Is this the baseline period? | No |
| Allocation method* | Not applicable |
| Blinding used* | Not applicable |

**Arms**

| | |
|---|---|
| **Arm title*** | Treatment |
| Arm description: | CELL THERAPY BY INTRA-ARTERIAL DELIVERY OF HLA-IDENTICAL ALLOGENEIC MESOANGIOBLASTS |
| Arm type* | Treatment |
| Investigational medicinal product name* | MABS ex-vivo expanded from an HLA identical sibling donor muscle biopsy. |
| Investigational medicinal product code | Not available |
| Other name | Not available |
| Pharmaceutical forms* | Cell suspension of hMABs |
| Routes of administration* | Intra-arterial left femoral artery delivery |
| Dosage and administration details* | - Intra-arterial left femoral artery delivery:<br>o Month 0: I infusion 1x108 cells§ (suspended in approximately 20 ml)<br>o Month2: II infusion 2x108 cells§ (suspended in approximately 40 ml)<br>- Intra-arterial multiple infusions:<br>o Month 4: III infusion 6x108 cells§ (total dose, suspended in approximately 120 ml)<br>o Month 6: IV infusion 6x108 cells§ (total dose suspended in approximately 120 ml)<br>One ml of cellular product will contain approximately 5x106 cells.<br>§The reported dose is calculated for a patient weighing 30 kg and adjusted depending on the actual weight at infusion:<br>1° infusion: CELL DOSE: **1 x 108** x patient's weight/30 kg.<br>2° infusion: CELL DOSE: **2 x 108** x patient's weight/30 kg.<br>3° infusion: CELL DOSE: **6 x 108** x patient's weight/30 kg.<br>4° infusion: CELL DOSE: **6 x 108** x patient's weight/30 kg.<br>In case of overweight patients, a mean between actual and ideal weight will be considered.<br>Initial dose has been calculated based upon the initial dose |

| | |
|---|---|
| | administered to distrophic mice and dogs (on a pro-kg bases) in the pre-clinical work. |

| **Number of subjects in period** | Arm Title (Treatment ) |
|---|---|
| Started* | 6 |
| Completed* | 5 |
| Subject non-completion reason (if applicable) | |
| AE, non fatal | |
| AE, fatal | |
| Consent withdrawn by subject | |
| Lack of efficacy | |
| Lost to follow up | |
| Physician decision | |
| Pregnancy | |
| Protocol Deviation | |
| Other | Screening failure (1) |

# Baseline characteristics

| **Reporting groups*** | |
|---|---|
| Reporting group title* | Overall cohort |
| Number of subjects at the baseline* | 5 |

Reporting group description: INTRA-ARTERIAL DELIVERY OF HLA-IDENTICAL ALLOGENEIC MESOANGIOBLASTS

*You can report per arm in the baseline period or for the overall baseline period*

**Subject analysis sets**

*Add a subject analysis set if you wish to report on groups different from the reporting group defined above (repeat if applicable)*

| | |
|---|---|
| Subject analysis set title* | |
| Subject analysis set type* | Intention to treat<br>Per protocol<br>Safety analysis<br>Sub-group analysis |
| Subject analysis set description* | *Enter a clear description which defines this set of subjects* |
| Number of subjects in subjects analysis set* | |

## Age characteristics*

*Complete either the age categorical, age continuous or complete both these characteristics in order to collect values for the reporting groups and optionally the subject analysis sets.*

| | Characteristic title* | Units* | Age categories* |
|---|---|---|---|
| **Age categorical** | Children | Subjects | (2-11 years) |
| **Age categorical** | Adolescents | Subjects | (12-17 years) |

| | Characteristic title* | Units* | Central tendency* | Dispersion type* |
|---|---|---|---|---|
| **Age continuous** | | Years<br>Months<br>Weeks<br>Days | Arithmetic Mean<br>Median<br>least square mean<br>geometric mean<br>log mean | full range (min-max)<br>standard deviation<br>inter quartile range |
| | Overall cohort | Years | Arithmetic Mean<br>10.38 | 8.5 – 12.4<br>full range (min-max) |

## Gender characteristics*

| | Characteristic title* | Units* | Gender categories* |
|---|---|---|---|
| **Gender categorical** | Overall cohort | Subjects | Male |

## Study specific characteristics NA

| | Characteristic title* | Units * | Categories* | Number of subject for each categories |
|---|---|---|---|---|
| **Study specific categorical** | | | | |

| | | | | |
|---|---|---|---|---|
| **Study specific categorical** | | | | |
| **Study specific categorical** | | | | |

## End points

*Add subject analysis set if you wish to report on groups different form reporting groups defined above*

| | |
|---|---|
| Subject analysis set title* | |
| Subject analysis set type* | Full Analysis<br>Intention to treat<br>Per protocol<br>Safety analysis<br>Sub-group analysis |
| Subject analysis set description* | |
| Number of subject in subject analysis set * | |

### End points definitions

| | | |
|---|---|---|
| End point title* | Safety: Incidence and severity of local and systemic adverse events (tolerated grade I-II) in DMD patients treated with intra-arterial injections of allo-MABS during immunosuppressive treatment with FK506 (tacrolimus) up to 1 year from the first infusion | |
| | | Values |
| Countable or measurable?* | *Select countable when the end point represents data that contains distinct values.*<br>**Countable** | Adverse events<br>Adverse drug reactions<br>Serious adverse events |
| If countable, Countable units*: | Number of the events | 6 |
| If measurable, Measurable units* | | |
| Measure type*: | Number<br>Arithmetic Mean<br>Median<br>least square mean<br>geometric mean<br>log mean | |
| Precision/dyspersion type* | | |

| | |
|---|---|
| End point type* | **Primary**<br>Secondary<br>Other pre-specified<br>Post Hoc |

End point timeframe*: up to 1 year from the first infusion

Use categories only if the data for the end point can be categorized

### Category title

Specify the groups of subjects applicable to this end point

| | | | |
|---|---|---|---|
| **Reporting groups*** | Overall cohort | | |
| Period | Overall trial | | |
| Arms | Treatment | | |

| | | | |
|---|---|---|---|
| subject analysis sets | | | |

| End point title* | Efficacy.<br>2. Improvement or stabilization of muscle strength in DMD patients treated with intra-arterial injections of allo-MABS during immunosuppressive treatment with FK506 (tacrolimus) evaluated 1 year from the first infusion. | |
|---|---|---|
| | | Values |
| Countable or measurable?* | *Select countable when the end point represents data that contains distinct values.*<br>**Measurable** | muscle strength |
| If countable, Countable units*: | | |
| If measurable, Measurable units* | North-Star Scale (NS) | Pt 02 and Pt 05 showed score stabilization throughout 8 months of MAB infusions; Pt 05 showed stabilization even in the subsequent period, whereas Pt 02 showed progressive deterioration until loss of ambulation. Pt 03 showed progressive deterioration throughout MAB infusion and lost ambulation soon after the end of the trial. |
| | 6 minutes-walking test (6MWT) | Pt 02 and Pt 05 showed time stabilization throughout 8 months of MAB infusions; Pt 05 showed stabilization even in the subsequent period, whereas Pt 02 showed progressive increase of time until loss of ambulation. Pt 03 showed progressive increase of time throughout MAB infusion and lost ambulation soon after the end of the trial. |
| | Kin Com force measurements (quantitative measurement tests - QMT) | Quantitative measures with Kin-Com ergometer did not show significant changes after cell infusions in all the patients except for Pt 05. This patient showed an attenuated decrease in all the Kin-Com parameters after the infusions, as compared with his own previous slope before age 7.5 years |
| Measure type*: | Number<br>Arithmetic Mean<br>Median<br>least square mean<br>geometric mean<br>log mean | |
| Precision/dyspersion type* | | |

| End point type* | **Primary**<br>Secondary<br>Other pre-specified<br>Post Hoc |
|---|---|

End point timeframe*: 1 year from the first infusion

Use categories only if the data for the end point can be categorized

**Category title**

Specify the groups of subjects applicable to this end point

| **Reporting groups*** | Overall cohort | | |
|---|---|---|---|
| Period | Overall trial | | |
| Arms | Treatment | | |
| subject analysis sets | | | |

| End point title* | Safety.<br>3. Long term incidence and severity of local and systemic adverse events (tolerated grade I-II) in DMD patients treated with intra-arterial injections of allo-MABS during immunosuppressive treatment with FK506 (tacrolimus). | |
|---|---|---|
| | | Values |
| Countable or measurable?* | *Select countable when the end point represents data that contains distinct values.*<br>**Countable** | Adverse events<br>Adverse drug reactions<br>Serious adverse events |
| If countable, Countable units*: | Number of the events | 0 |
| If measurable, Measurable units* | | |
| Measure type*: | Number<br>Arithmetic Mean<br>Median<br>least square mean<br>geometric mean<br>log mean | |
| Precision/dyspersion type* | | |

| End point type* | Primary<br>**Secondary**<br>Other pre-specified<br>Post Hoc |
|---|---|

End point timeframe*: from 1 year to 8 years from the first infusion

Use categories only if the data for the end point can be categorized

**Category title**

Specify the groups of subjects applicable to this end point

| **Reporting groups*** | Overall cohort | | |
|---|---|---|---|
| Period | Overall trial | | |
| Arms | Treatment | | |
| subject analysis sets | | | |

| End point title* | Efficacy.<br>4. Presence of signs of engraftment of allo-MABS on muscular biopsy at 8 months from the first infusion. | |
|---|---|---|
| | | Values |
| Countable or measurable?* | *Select countable when the end point represents data that contains distinct values.*<br>**Measurable** | Engraftment of donor MABS |
| If countable, Countable units*: | | |
| If measurable, Measurable units* | STR chimerism | The DNA chimerism analysis |

| | | |
|---|---|---|
| | in muscle tissue biopsy specimen | revealed minimal donor cell engraftment, ranging from 0.00 to 0.69% |
| Measure type*: | Number<br>Arithmetic Mean<br>Median<br>least square mean<br>geometric mean<br>log mean | |
| Precision/dyspersion type* | | |

| | |
|---|---|
| End point type* | Primary<br>**Secondary**<br>Other pre-specified<br>Post Hoc |

End point timeframe*: at 8 months from the first infusion.

Use categories only if the data for the end point can be categorized

**Category title**

Specify the groups of subjects applicable to this end point

| **Reporting groups*** | Overall cohort | | |
|---|---|---|---|
| Period | Overall trial | | |
| Arms | Treatment | | |
| subject analysis sets | | | |

| End point title* | Efficacy.<br>5 Presence of dystrophin in the *gastrocnemius* muscle derived from allo-MABS during immunosuppressive treatment with FK506 (tacrolimus), 8 months after the first infusion | |
|---|---|---|
| | | Values |
| Countable or measurable?* | *Select countable when the end point represents data that contains distinct values.*<br>**Measurable** | Presence of dystrophin |
| If countable, Countable units*: | | |
| If measurable, Measurable units* | biochemical assays such as RT-PCR Western Blot, immunocytochemistry and functional assays on isolated fibers derived from muscular biopsy of the *gastrocnemius* muscle | Pt 01 and Pt 03 showed virtually no dystrophin expression by **immunohistochemistry**. Pt 02 showed scattered, faint, dystrophin positivity in some muscle fibers in post-treatment biopsies. Fiber staining was discontinuous, but revealed also with antidys1 antibody, which recognizes a portion of deleted protein absent in revertant fibers. Pt 05 and Pt 06 showed some fibers positive for dystrophin in both pre- and post-treatment samples.<br>**Western blot analysis** did not show any band corresponding to full-length dystrophin (427 kD) in Pt 01 and Pt 03. Pt 02 did not show full-length dystrophin in pre-treatment sample, whereas a faint band corresponding to full-length dystrophin was observed with anti- |

| | | |
|---|---|---|
| | | mandys18 and manex46e antibodiesì only in post-treatment samples. Pt 05 and Pt 06 (point mutations) showed bands corresponding to dystrophin in both pre and post-treatment samples. The amount of protein did not differ in pre- to post treatment sample in Pt 06, whereas it was increased in post treatment sample in Pt 05 |
| Measure type*: | Number<br>Arithmetic Mean<br>Median<br>least square mean<br>geometric mean<br>log mean | |
| Precision/dyspersion type* | | |

| | |
|---|---|
| End point type* | Primary<br>**Secondary**<br>Other pre-specified<br>Post Hoc |

End point timeframe*: at 8 months from the first infusion.

Use categories only if the data for the end point can be categorized

**Category title**

Specify the groups of subjects applicable to this end point

| **Reporting groups*** | Overall cohort | | |
|---|---|---|---|
| Period | Overall trial | | |
| Arms | Treatment | | |
| subject analysis sets | | | |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events*: *Enter the time point(s) or time period for AE assessment*
up to 8 year from the first infusion

*First patient first visit:* 04/03/2011
*Last recruitment date:* 04/12/2012
*Study closure:* 29.01.2025

Adverse event reporting additional description: *Enter information about the AE collection and provide details about the method of assessment and monitoring*

All adverse events were recorded and correlation with infusion of alloMABs were evaluated according to the Naranjo algorithm.
The occurrence of Severe Adverse Events (SAE) or adverse drug reactions were immediately reported to the Regulatory Authorities.

| | |
|---|---|
| Assessment type* | Systematic or Non Systematic |
| Frequency threshold for reporting non-serious adverse events* | *Enter the frequency of non SAE that are reported in the results database for all arms or reporting groups*<br>Every follow up visit |

### Dictionary used

| | |
|---|---|
| Dictionary name* | National Cancer Institute (NCI) Common Terminology Criteria for adverse events (CTCAe) |
| Dictionary version* | v3.0, 2006 |

### Adverse events reporting group definition

Use arms from baseline period as reporting groups
**OR**

Reporting group title*: Overall cohort

For this reporting group, provide the following totals:

| | |
|---|---|
| Subject exposed* | 5 |
| Subjects affected by non -SAE* | 2 |
| Total number of deaths (all causes)* | 0 |
| Total number of deaths resulting from adverse event* | 0 |

### Serious adverse event details and values

System organ class*: cardiovascular system

Event term*: Transient atrial fibrillation

### Values for serious adverse event per reporting group *

| Reporting groups | Subjects affected number | Subjects exposed number | Occurrences all number | Occurrences causally related to treatment number | Fatalities number | Fatalities causally related to treatment Number |
|---|---|---|---|---|---|---|
| Overall cohort | 1 | 5 | 1 | 0 | 0 | 0 |

## Serious adverse event details and values

System organ class*: Central Nervous System

Event term*: 1 cm ischemic lesion in the thalamic region

### Values for serious adverse event per reporting group *

| Reporting groups | Subjects affected number | Subjects exposed number | Occurrences all number | Occurrences causally related to treatment number | Fatalities number | Fatalities causally related to treatment Number |
|---|---|---|---|---|---|---|
| Overall cohort | 1 | 5 | 1 | 0 | 0 | 0 |

## Non - Serious adverse event details and values

System organ class*: Musculoskeletal system

Event term*: left leg pain

### Values for non-serious adverse event per reporting group*

Threshold for non-serious adverse event reporting is:

| Reporting groups | Subjects affected number | Subjects exposed number | Occurrences all number |
|---|---|---|---|
| Overall cohort | 1 | 5 | 1 |

## Non - Serious adverse event details and values

System organ class*: Skin Systems

Event term*: cutaneous reticulum of the right upper hand face

### Values for non-serious adverse event per reporting group*

Threshold for non-serious adverse event reporting is:

| Reporting groups | Subjects affected number | Subjects exposed number | Occurrences all number |
|---|---|---|---|
| Overall cohort | 1 | 5 | 1 |

## Non - Serious adverse event details and values

System organ class*: Skin Systems

Event term*: skin abdominal reticulum in the left lower quadrant

### Values for non-serious adverse event per reporting group*

Threshold for non-serious adverse event reporting is:

| Reporting groups | Subjects affected number | Subjects exposed number | Occurrences all number |
|---|---|---|---|
| Overall cohort | 1 | 5 | 1 |

## Non - Serious adverse event details and values

System organ class*: Skin Systems

Event term*: livedo reticularis on the back of the hands and wrists bilaterally

### Values for non-serious adverse event per reporting group*

Threshold for non-serious adverse event reporting is:

| Reporting groups | Subjects affected number | Subjects exposed number | Occurrences all number |
|---|---|---|---|
| Overall cohort | 1 | 5 | 1 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol*? Yes

| Date | Amendment |
|---|---|
| 23-06-2011 | Use of a different cell growth medium in IMP production |
| 05-10-2011 | Protocol changes (infusion modalities), IB change, IMPD (cell growth medium) change and CRF update |
| 11-09-2012 | Protocol changes (infusion modalities and doses), IB change, IMPD (culture medium and cellular growth rate) change, CI and CRF update |
| 15-11-2012 | IMP change: due to change in FBS supplier (from Lonza to PAA) |
| 14/02/2014 | Substantial amendment aimed at introducing changes in the Protocol (permission of additional infusions upon fulfilment of patient specific conditions), in the IMPD (change of the FBS, of a cell culture reagent and re introduction of the cell culture medium Megacell commercialized by Sigma), and in IC, IB, CRF and CTA form. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial*? No

If Yes, Interruption date

Interruption descrption

## Limitations and caveats

None reported

## Online references

Enter PubMed identifier (PMID)

PMID: 27908983
PMID: 27606343