Drisapersen: an overview of the clinical programme to date in Duchenne muscular dystrophy

Giles Campion SVP Research and Development
Prosensa Holdings NV
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Prosensa

- Founded in 2002.
- About 120 employees.
- Key partnerships with LUMC and patient groups
- RNA modulation technology platform
- Clinical programmes in Duchenne Muscular Dystrophy
What I Will Cover

- Review of drisapersen trial programme
- Status of re-dosing for programme participants
- Drisapersen regulatory update
- Drisapersen confirmatory clinical trial
- Update on other Prosensa Duchenne programmes
Overview of the drisapersen clinical trial programme

- Comprehensive clinical trial program to assess the safety and efficacy of drisapersen in DMD
  - Two Phase 2 and one Phase 3 randomized, placebo-controlled studies (total N=290)
  - Two open-label extension (OLE) studies (N=245)

PLACEBO-CONTROLLED, REPEAT-DOSE STUDIES

DEMAND III (DMD114044)
- Phase 3, 48 weeks continuous 6 mg/kg/week
- Ambulant boys

DEMAND II (DMD114117)
- Phase 2, 48 weeks continuous 6 mg/kg/week, or intermittent 6 mg/kg
- Ambulant boys

DEMAND V (DMD114876)
- Phase 2, 24 weeks
  - 6 mg/kg/week or 3 mg/kg/week, continuous
  - Ambulant boys

OPEN-LABEL EXTENSION (OLE) STUDIES

DEMAND IV (DMD114349)
- Phase 3
  - 6 mg/kg/week* continuous

DMD115501
- Phase 3
  - 6 mg/kg/week continuous

DMD114673 (Extension phase)
- Phase 1/2
  - 6 mg/kg/week continuous until Week 72 to 80 then intermittent

OTHER SUPPORTIVE STUDIES

PR0051-01
- Phase 1/2, single dose, im uncontrolled
- Ambulant and non-ambulant boys

DMD114118
- Phase 1/2, single dose, sc placebo-controlled
- Non-ambulant boys

DMD114673 (Acute phase, formerly PR0051-02)
- Phase 1/2, multiple dose, sc
  - 5 weeks; uncontrolled
  - Ambulant and non-ambulant boys

*While continuous 6 mg/kg/week was the primary treatment arm for this study, some subjects moved to the intermittent dosing or natural history arms.
im, intramuscular; sc, subcutaneous.
Data shown are for all subjects who completed the test at extension study baseline. One subject (subject 201) was non-ambulant at study entry and did not participate in any 6MWD tests while another subject (subject 103) was unable to complete the 6MWD test at extension study baseline. Data for both of these subjects are not shown here.
Baseline age can also predict decline in ambulation in DMD

Natural History: 36 month changes in boys below 7 years (blue) above 7 years (red)

OLE study DMD114673: 6MWD

Mazzone et al. (PLOS ONE 2014)
### Study DMD114673: percent-predicted 6MWD

<table>
<thead>
<tr>
<th>Subject*</th>
<th>Age (years)</th>
<th>OLE study baseline (% normal)</th>
<th>Week 177 (% normal)</th>
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<tbody>
<tr>
<td>101</td>
<td>9.6</td>
<td>59</td>
<td>79</td>
</tr>
<tr>
<td>102</td>
<td>6.7</td>
<td>69</td>
<td>78</td>
</tr>
<tr>
<td>104</td>
<td>9.1</td>
<td>104</td>
<td>96</td>
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<td>105</td>
<td>8.4</td>
<td>56</td>
<td>78</td>
</tr>
<tr>
<td>106</td>
<td>9.0</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>107</td>
<td>10.9</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>202</td>
<td>6.5</td>
<td>75</td>
<td>74</td>
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<td>205</td>
<td>11.1</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>206</td>
<td>5.1</td>
<td>69</td>
<td>74</td>
</tr>
<tr>
<td>207</td>
<td>9.3</td>
<td>82</td>
<td>46</td>
</tr>
</tbody>
</table>

*Two subjects (103 and 201) unable to complete the 6MWD at OLE baseline are not shown.

Improvement from baseline in percent-predicted 6MWD was observed at Week 177 for 4/10 boys with available data.
Mean change from baseline in 6MWD in the Phase 2 and 3 studies

**DEMAND II (DMD114117)**

- Drisapersen 6mg/kg intermittent (n=17)
- Drisapersen 6 mg/kg/week (n=18)
- Placebo (n=18)

**DEMAND III (DMD114044)**

- Drisapersen 6 mg/kg/week (n=125)
- Placebo (n=61)

**DEMAND V (DMD114876)**

- Drisapersen 3 mg/kg/week (n=17)
- Drisapersen 6 mg/kg/week (n=18)
- Placebo (combined; n=16)

**Difference in change from baseline in 6MWD for drisapersen 6 mg/kg/week versus placebo**

- **DEMAND II (DMD114117)**
  - Week 25: 35 m; p=0.014
  - Week 49: 36 m; p=0.051

- **DEMAND V (DMD114876)**
  - Week 24: 27 m; p=0.069

- **DEMAND III (DMD114044)**
  - Week 48: 10 m; p=0.415
Study population baseline characteristics and timed function test results

Boys in DMD114044 were older with more advanced disease

<table>
<thead>
<tr>
<th></th>
<th>DMD114117</th>
<th>DMD114876</th>
<th>DMD114044</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>7.3</td>
<td>7.8</td>
<td>8.2</td>
</tr>
<tr>
<td><strong>Time since diagnosis, months</strong></td>
<td>46</td>
<td>46</td>
<td>57</td>
</tr>
<tr>
<td><strong>Rise from floor velocity, rises/sec</strong></td>
<td>0.220</td>
<td>0.240</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>4-stair climb-ascent time, stairs/sec</strong></td>
<td>1.37</td>
<td>1.31</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>6MWD, m</strong></td>
<td>409</td>
<td>409</td>
<td>341</td>
</tr>
<tr>
<td><strong>Muscle strength, lbs</strong></td>
<td>124</td>
<td>128</td>
<td>101</td>
</tr>
</tbody>
</table>

*Data shown are mean (range) for total study populations.
†Data shown are mean (95% CI) for total study populations.
6MWD sub-group analysis by feeder study in the extension study DEMAND IV*

**Study DEMAND IV (DMD114349)**

Continuous/intermittent drisapersen: $-66.8$ m
Placebo/delayed drisapersen treatment: $-112.9$ m
Mean treatment difference: +46.1 m

**Feeder study DEMAND II (DMD114117)**

Continuous/intermittent drisapersen: $-5.1$ m
Placebo/delayed drisapersen treatment: $-57.1$m
Mean treatment difference: +52.0 m

**Feeder study DEMAND III (DMD114044)**

Continuous/intermittent drisapersen: $-87.0$ m
Placebo/delayed drisapersen treatment: $-136.2$ m
Mean treatment difference: +49.2 m

*Data presented are from the 6 June 2013 data cut; integrated data for placebo/delayed drisapersen treatment and by feeder study are from 14 October 2013 (using the 6 June data cut).
6MWD sub-group analysis by age group in the extension study DMD114349*

**Subjects ≤7 years old**

- Continuous/intermittent drisapersen: +8.4 m
- Placebo/delayed drisapersen treatment: –28.7 m
- Mean treatment difference: +37.1 m

**Subjects >7 years old**

- Continuous/intermittent drisapersen: –128.1 m
- Placebo/delayed drisapersen treatment: –189.7 m
- Mean treatment difference: +61.6 m

Earlier treatment appears to show more favourable effect on disease progression.

In more progressed patients, longer treatment duration may be required.

*Data presented are integrated data from 14 October 2013 (using the 6 June data cut).*
6MWD pooled analysis of the Phase 2 studies*

A statistically significant treatment difference was observed for the change in 6MWD for the pooled analysis of the two Phase 2 studies.

**Δ6MWD = +35 m**

p=0.014

**Δ6MWD = +27 m**

p=0.069

**Δ6MWD = +31 m**

p=0.003

*The adjusted mean change from baseline in 6MWD for subjects enrolled in studies DMD114117 and DMD114876 was calculated. Error bars show the standard error.
Drisapersen: effect on muscle

Leaky muscle fibres in DMD promote AON uptake

AONs enter nuclei, bind to exon 51 of DMD pre-mRNA, and induce skipping

Exon 51 skipping results in novel dystrophin production

Improved muscle physiology and structure

Leaky muscle fibres in DMD promote AON uptake

AONs enter nuclei, bind to exon 51 of DMD pre-mRNA, and induce skipping

Exon 51 skipping results in novel dystrophin production

Improved muscle physiology and structure

MRI data suggest reduced fat infiltration*

*Subjects were from study DMD114876.

AON, antisense oligonucleotides; BF, bicep femoris; CK, creatine kinase; MRI, magnetic resonance imaging; RF, rectus femoris; ST, semitendinosus; VI, vastus intermedius; VL, vastus lateralis; VM, vastus medialis.
Drisapersen clinical trial programme: key safety data

- Drisapersen is generally well tolerated, with an adverse event (AE) profile consistent with that described previously for this class of molecule.
- 59 serious AEs reported on drisapersen, most considered unrelated: 15/59 serious AEs were considered related or possibly related to drisapersen.
  - 13 of >300 subjects have withdrawn permanently from treatment owing to AEs.
- Most commonly reported AEs include injection-site reactions and renal abnormalities (including subclinical proteinuria).
  - Some cases of (moderate to severe) thrombocytopaenia have been reported.

### AEs of special interest, n (%):

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Any AE of special interest</th>
<th>Injection-site reactions*</th>
<th>Renal abnormalities†</th>
<th>Inflammation</th>
<th>Hepatic</th>
<th>Thrombocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMD114117</td>
<td>Placebo</td>
<td>18</td>
<td>13 (72%)</td>
<td>6 (33%)</td>
<td>7 (39%)</td>
<td>9 (50%)</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>DMD114117</td>
<td>Drisapersen 6 mg/kg/week</td>
<td>18</td>
<td>16 (89%)</td>
<td>14 (78%)</td>
<td>13 (72%)</td>
<td>10 (56%)</td>
<td>2 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>DMD114876</td>
<td>Placebo</td>
<td>16</td>
<td>9 (56%)</td>
<td>5 (31%)</td>
<td>5 (31%)</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>DMD114876</td>
<td>Drisapersen 6 mg/kg/week</td>
<td>18</td>
<td>16 (89%)</td>
<td>13 (72%)</td>
<td>5 (28%)</td>
<td>5 (28%)</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>DMD114044†</td>
<td>Placebo</td>
<td>61</td>
<td>37 (61%)</td>
<td>10 (16%)</td>
<td>20 (33%)</td>
<td>16 (26%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DMD114044†</td>
<td>Drisapersen 6 mg/kg/week</td>
<td>125</td>
<td>114 (91%)</td>
<td>97 (78%)</td>
<td>80 (64%)</td>
<td>33 (26%)</td>
<td>7 (6%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Includes discolouration, erythema, rash, induration; †Includes proteinuria, red blood cells in urine; ‡Two subjects in DMD114044 receiving drisapersen 6 mg/kg/week had severe AEs reported by the investigator as drug-related (glomerulonephritis, intracranial venous sinus thrombosis and spinal pain). No severe AEs were reported in the placebo group.
Conclusions

- Comprehensive clinical trial program (>300 subjects) to assess safety and efficacy of drisapersen in DMD, comprising both placebo-controlled and OLE studies

- Drisapersen was generally well tolerated
  - AEs include sub-clinical proteinuria, local injection-site reactions and thrombocytopenia
  - Overall safety profile is consistent with that described previously for this class of molecule

- The clinical program efficacy data suggest:
  - benefit with drisapersen versus placebo in boys with less severe disease
  - clinically meaningful benefit after longer duration of drisapersen treatment in boys who are, on average, more severely affected
Re-dosing programme
Re-dosing programme

- Prosensa is working to provide access to drisapersen for all previously treated patients where possible

- No biopsies in the re-dosing programme

- For boys who are in a drisapersen clinical trial that is still open
  - DMD114673 Extension study (Belgium & Sweden)
  - DMD115501 (North America)
  - Re-dosing will be implemented via protocol amendments

- For boys who were in a drisapersen clinical trial that is closed
  - Aim to provide continued treatment for boys who wish to continue
  - Time-consuming set-up as each country has a separate, often complex, procedure
Drisapersen re-dosing in Europe

RO051-02 (DMD114673) continuation
PRO051-02 (DMD114673)

A phase I/II, open label, escalating dose, pilot study to assess the effect, safety, tolerability and pharmacokinetics of multiple subcutaneous doses of drisapersen in patients with Duchenne muscular dystrophy

• Dose escalation phase of study was conducted in 2008 – 2009
  • 12 boys (5-16 years on entry, ambulant / non-ambulant, on steroids)

• Extension phase of study started July 2009
  • 12 boys continued into the extension phase
  • Dosing halted by GSK on 20 September 2013
  • Patients have been followed up every 12 weeks (optional)
DMD114673 resumption of dosing

• All 12 boys have been invited to continue in study PRO051-02 with resumption of dosing with drisapersen

• First patient recommenced dosing in Leuven, Belgium on 25 September 2014

• Other boys will follow over the forthcoming weeks

• Regulatory approval in Sweden
Re-dosing North America

- Re-dosing for boys who were in a clinical trial that is still open
  - DMD115501 (extension of DMD114876 US & Canadian sites from DMD114349)
- Boys taking part in DMD115501
  - Originally was 3 US sites from Phase II DMD114876 (DEMAND V) study
  - Now extended to include additional 8 US sites from 876
  - Plus 3 Canadian sites from DMD114349 (DEMAND IV) study (extension of Phase III DMD114044 study)
  - Total 14 sites in North America
  - Up to 72 patients may participate (US & Canada)
- Use of Greenphire to assist with patient travel arrangements
- Use of MRN to provide home-dosing options
  - Try to ease the burden of participation for patients and families
Status re-dosing

- First patient re-dosed at Cincinnati Children’s Hospital on 16th Sept 2014
- 2/14 sites have IRB (Institutional Review Board) approval
- Contract negotiations ongoing with remaining sites
- Submission to Health Canada in preparation
- Canadian sites will submit to IRB in parallel
- Expect to have first Canadian site initiated before year end
- Site set up is dependent on IRB/Regulatory approval and site contracts
Re-dosing outside of clinical trial

- Prosensa currently is working on all countries simultaneously.

- Each country has its own regulations and timelines to start this program; we are currently assessing these.

- Prosensa is working with a company which has significant experience in starting these types of programs.

- Country roll out plans are currently being developed – your doctor will be informed regularly on the progress of the roll out in your country.
How long will the programme run?

- The programme aims to bridge the gap between end of clinical trials and potential commercial access

- Boys may continue in the study until certain conditions apply:
  - They elect not to continue
  - Drisapersen is granted regulatory approval and becomes commercially available for the treatment of DMD in their country
  - Prosensa or regulatory agencies terminate the program for reasons such as safety issues or ethical issues
Rolling NDA submission is well underway (fast track & breakthrough therapy designation)

First module has been submitted

Multiple interactions with the Agency have taken place since June 2\textsuperscript{nd} guidance letter was issued

We are working as swiftly and diligently as we can to ensure a high quality and timely submission that could potentially lead to an approval in 2015 under the accelerated approval pathway

EMA - interactions ongoing, plan to file MAA for conditional approval shortly after submission of file with FDA
Confirmatory Studies - FDA Guidance

- Ongoing discussions with regulatory agencies
- Confirmatory studies that will support an accelerated approval for drisapersen are anticipated to begin in H1 2015 (prior to a potential approval)

1. Open-label study of drisapersen with historical control
   - Prosensa’s fully enrolled Natural History Study (269 patients) may serve as a control

2. Randomized, placebo-controlled trial of another exon-skipping drug with a similar mechanism of action, directed at a different exon
   - PRO044 may serve this purpose
What is the Natural History study?

- **Study Title:** A Prospective Natural History Study of progression of physical impairment, activity limitation and quality of life in Duchenne Muscular Dystrophy (DMD)

- **Aim:** To address the needs of Investigators and Patients for a better understanding of Duchenne Muscular Dystrophy

- There is no study drug administered
Why is the Natural History data important?

- To characterize the natural history and progression of DMD
- Determine whether rates of decline are influenced by mutation and steroid use, as well as other factors
- To capture biomarkers of safety and disease progression
- Identification of outcome measures for sub-populations
- To provide comparative data for patients with rare exon deletions/mutations for which formal controlled trials are not feasible
- May serve as control in drisapersen confirmatory study
Natural history study

Sites for natural history study
Currently 269 patients enrolled
The study has enrolled 269 boys with confirmed DMD between the ages of 3 and 18.

- 10 countries involved across 16 centers in America and Europe.
- Both ambulatory and non-ambulatory boys.
- Duration: 3 years with site visits and assessments every 6 months.
- Assessments: Investigators will evaluate the boys on a number of physical tests. These parameters are meant to assess how the disease affects their overall Quality of Life (QoL) as the condition evolves over time.
PRO044 and other DMD compounds
PRO044 Escalating Dose Study Design

- Open-label, 5 week dosing (+13 week FU), escalating dose study.
- 18 subjects were to be studied in 9 cohorts
  - 6 SC administration cohorts
  - 3 IV administration cohorts.

SC cohorts 1-6

0.5 mg/kg
1.5 mg/kg
5 mg/kg
8 mg/kg
10 mg/kg
12 mg/kg

IV cohorts 7-9

1.5 mg/kg
5 mg/kg
12 mg/kg

N.B subjects in IV cohorts previously dosed in a SC cohort
Baseline characteristics (n=3) per cohort

<table>
<thead>
<tr>
<th></th>
<th>6 SC cohorts</th>
<th>3 IV Cohorts</th>
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<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Overall</td>
</tr>
<tr>
<td></td>
<td>N=18</td>
<td>N=9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.2</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>(5.6-15.3)</td>
<td>(6.5-15.2)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>124</td>
<td>127</td>
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<tr>
<td></td>
<td>(103-146)</td>
<td>(108-151)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>(15.0-51.5)</td>
<td>(16.6-56.5)</td>
</tr>
<tr>
<td>BMI</td>
<td>20</td>
<td>19</td>
</tr>
</tbody>
</table>
Safety Summary

• PRO044 was **generally well tolerated** up to dose levels of 12mg/kg for 5 weeks by SC or IV administration

• Safety findings are consistent with the **known class safety profile**:
  - *Sub-clinical proteinuria* reported for individual subjects (high baseline values were also reported in some subjects)
  - No clinically significant changes seen in:
    - Hepatic parameters
    - Thrombocyte counts
    - Effects on coagulation (aPTT)
  - *Injection site reactions* reported more often after SC administration
  - No indicators of systemic inflammation seen

• No subject withdrew from treatment

• No drug-related SAEs reported
Biochemical outcome measures

- Dystrophin expression determined in tibialis anterior biopsy before and after 5 injections
- Immunofluorescence analysis performed by a reproducible operator-independent imaging method
- In the PRO044 population all fibers express trace dystrophin and show a high number of revertant fibers
- Increase in dystrophin after 5 weeks of treatment small but observed in 6 of the 13 (46%) evaluable biopsies in SC cohorts and 6 of the 8 (75%) evaluable biopsies in IV cohorts.
- Biopsies show also improvement in emerging miRNA biomarkers
Dystrophin increase following treatment with PRO044

**DMD** (deletion 45): 5 weekly SC injections with 12 mg/kg PRO044

MANDYS106

- **PRE**
- **POST**

ab15277

- **PRE**
- **POST**

![Graphs showing dystrophin mean membrane intensity](image)

- **PRE-treatment**
- **post-treatment**
Concurrent changes in muscle miRNA profile following treatment with PRO044

DMD Subject (deletion 45) after 5 weekly SC injections with 12 mg/kg PRO044

- miR-1, 133a, 206 involved in dystrophin signalling and muscle cell differentiation
- miR-31 suppresses dystrophin expression

In DMD patients:
- miR-1 & 133a: down regulated
- miR-206 & 31: up regulated partially restored after PRO044
Conclusions

- Pre-treatment biopsy evaluation demonstrates trace dystrophin present in all fibers.

- Despite high trace & revertant fibers in the exon 44 flanking deletion population, a positive dystrophin response has been detected in 12 of 21 evaluable biopsies.

- Dose exposure modelling predicts an effective dose range at 6-9 mg/kg IV, which will be employed in an extension study.

- Safety findings are consistent with the known class safety profile and no drug related SAE’s reported.
Other DMD compounds

PRO045

- Dose finding study ongoing; 5 cohorts completed (15 patients)
- Initial results expected in Q4 2014
- Will explore iv dosing

PRO053

- Dose finding study ongoing; 3 cohorts completed (9 patients)
- Results expected in Q1 2015
- Will explore iv dosing

PRO052/PRO055/PROSPECT

- Preclinical studies ongoing
Our current target patient populations & mutations
PROSPECT (SPECtrin Truncation)
Multiple exon skipping with single AONs
PROSPECT (SPECtrin Truncation)
Multiple exon skipping with single AONs

DMD Patient Muscle Cells ($\Delta$22-29)
RT-qPCR Analysis

Total IF products: 23.4%
PROSPECT (SPECtrin Truncation)
Multiple exon skipping with single AONs

Mandys1 (central rod domain)
Ab15277 (C-terminal)

DMD patient cells Δ22-29
PROSPECT (SPECtrin Truncation)
Multiple exon skipping with single AONs

DMD Patient Muscle Cells (∆12-16)

RT-qPCR Analysis

Total IF products: 30.3%
PROSPECT (SPECtrin Truncation)  
Multiple exon skipping with single AONs

- A single specifically designed AON can induce multiple exon skipping in the exon 10-40 region of the dystrophin transcript

- The broad mutation applicability of this MSK approach was demonstrated in various myotube cultures from DMD patients with different mutations outside the deletion hot spot region (including deletions of exons 12-16, exons 22-29, exons 14-43, exons 18-41, and a 4 bp deletion in exon 21)

- Per mutation a specific pattern of multiple exon skipping products was reproducibly obtained, with up to 30% in-frame transcripts (after 24-48 hrs post-transfection) which allowed expression of novel dystrophin proteins at the myotube membrane.

- Several multiple exon skipping products reached beyond the deletion hot spot region which extends the applicability to more frequent mutations

- *Mdx* mouse studies have been initiated to obtain *in vivo* proof-of-concept
Conclusions

- We are working hard to provide access to drisapersen as quickly as possible
- We continue to progress our other compounds to increase the number of patients we can help
- We thank you, the patient community, for your unwavering and steadfast support
- You can find further information on our website at www.prosensa.com or by email by contacting:

patientinfo@prosensa.nl