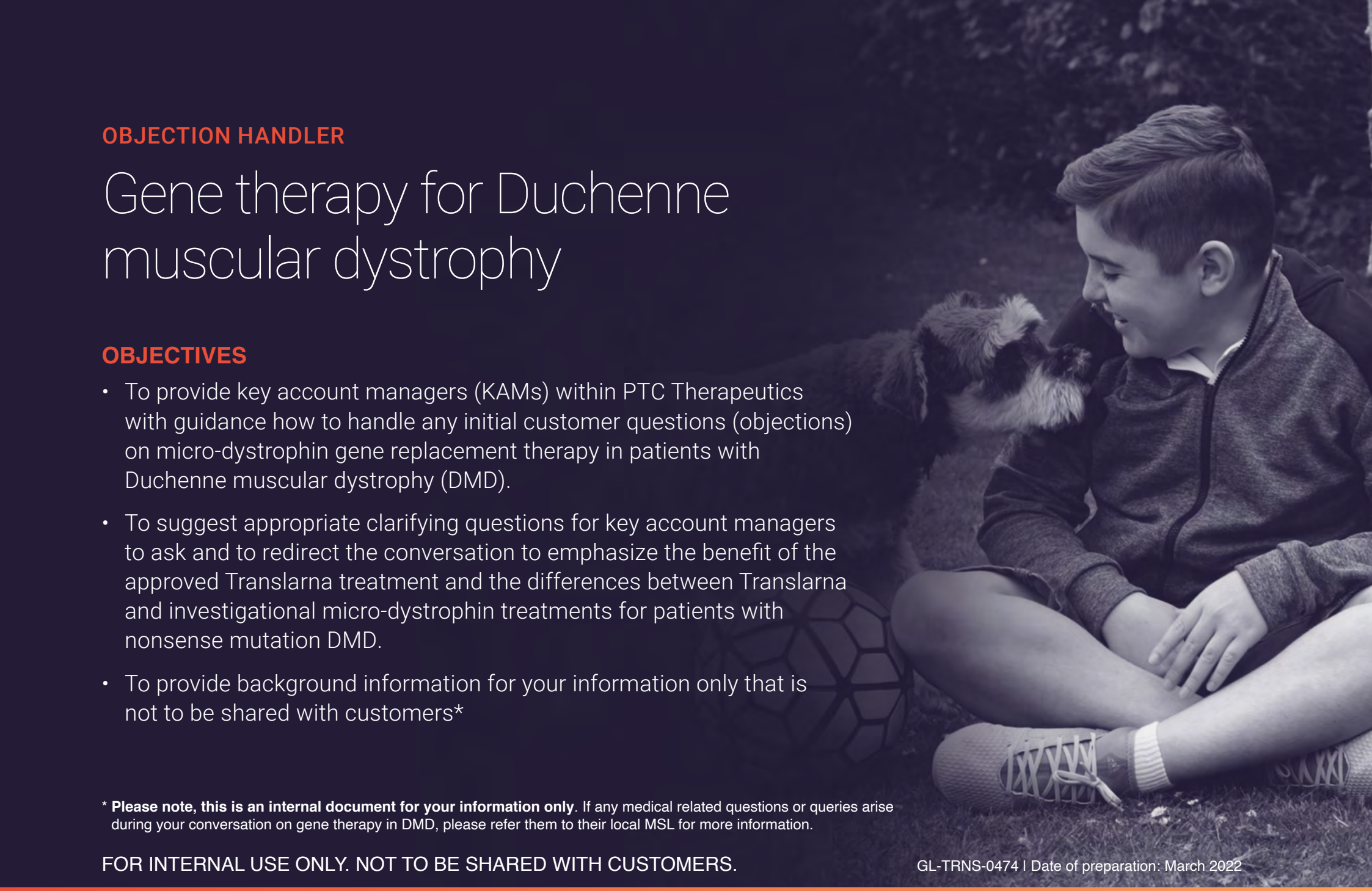
OBJECTION HANDLER

Gene therapy for Duchenne muscular dystrophy



OBJECTIVES

- To provide key account managers (KAMs) within PTC Therapeutics with guidance how to handle any initial customer questions (objections) on micro-dystrophin gene replacement therapy in patients with Duchenne muscular dystrophy (DMD).
- To suggest appropriate clarifying questions for key account managers to ask and to redirect the conversation to emphasize the benefit of the approved Translarna treatment and the differences between Translarna and investigational micro-dystrophin treatments for patients with nonsense mutation DMD.
- To provide background information for your information only that is not to be shared with customers*

* **Please note, this is an internal document for your information only**. If any medical related questions or queries arise during your conversation on gene therapy in DMD, please refer them to their local MSL for more information.

FOR INTERNAL USE ONLY. NOT TO BE SHARED WITH CUSTOMERS.

GL-TRNS-0474 I Date of preparation: March 2022

Contents

1. Will gene therapy for DMD replace the mutated dystrophin gene with a full-length copy?

Initial response

- It is important to note that even the most functional micro-dystrophins will not be as effective as wild-type (full-length) dystrophin.[1]
- Micro-dystrophin gene replacement therapy should not be seen as a cure for DMD, but rather as a way to lessen DMD severity to a level similar to that seen in patients with Becker muscular dystrophy (BMD).[2,3]

Clarifying questions

- What is the reason you are asking about this?
- What is your comfort level in considering Translarna as a treatment option for your patients with nonsense mutation DMD?
- How will you discuss this topic with the families of your patients?

1. Will gene therapy for DMD replace the mutated dystrophin gene with a full-length copy?

Key points to communicate

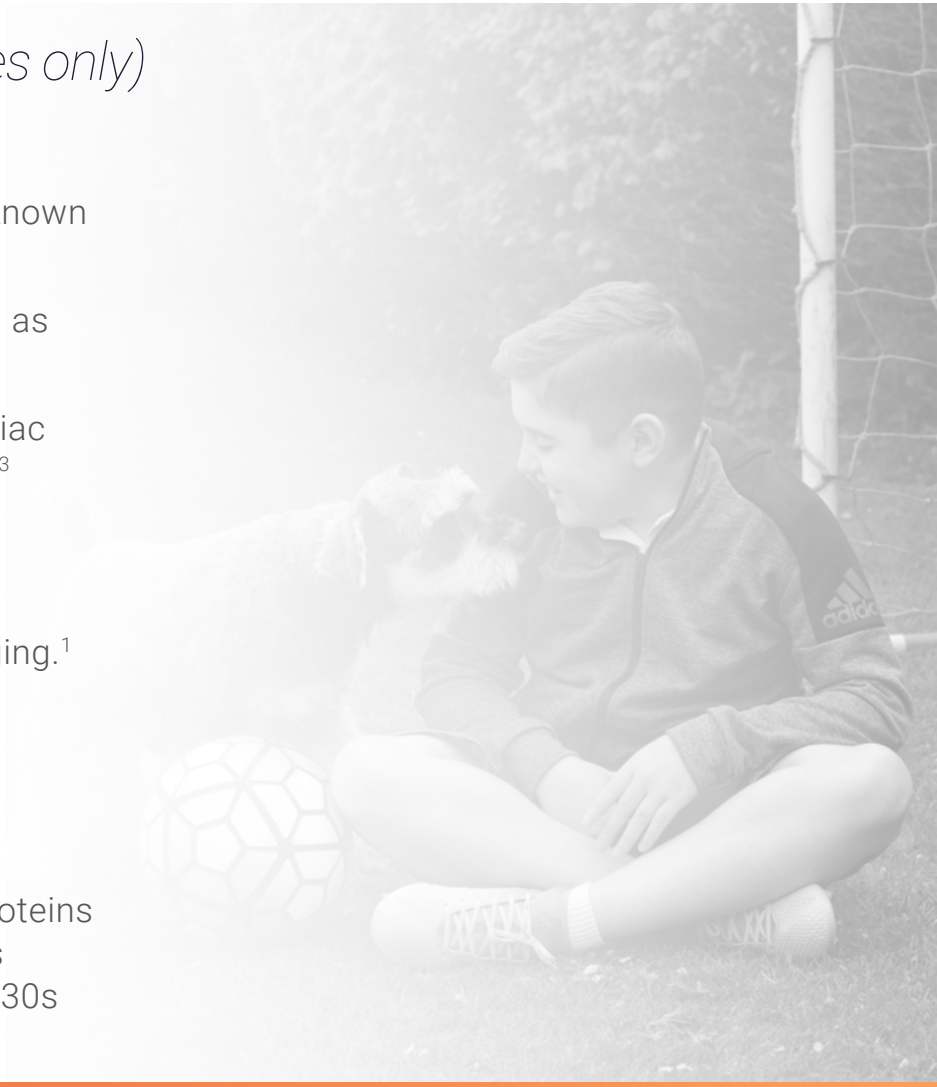
TRANSLARNA TREATMENT

- **Translarna is an approved therapy**: the European Medicines Agency has confirmed a **positive risk–benefit assessment** for patients with nonsense mutation DMD based on Translarna efficacy and safety data over a 48-week treatment period from two randomized, double-blind, placebo-controlled studies.[4]
- **Both clinical trials and real-world data show that Translarna is well tolerated.**[4,5]
- **Translarna helps preserve muscle function and delays loss of ambulation, allowing patients to carry out daily tasks and maintain independence.**[5–8]
- Patients taking Translarna but wishing to be screened for a clinical trial of micro-dystrophin therapy would need to discontinue the approved Translarna treatment for 6 months to be eligible to participate.[9] **This poses a risk, given that every day without Translarna increases the risk of further muscle function loss.**

Translarna restores full-length dystrophin in patients with nonsense mutation DMD and can slow disease progression.[10,11]

1. Will gene therapy for DMD replace the mutated dystrophin gene with a full-length copy?

Background information (for internal learning purposes only)



GENETIC BASIS OF DMD

- The dystrophin gene consists of 79 exons (> 2 Mb) and is the largest known human gene.[12]
- Owing to its large size, the dystrophin gene is prone to mutations such as deletions, duplications, translocations and point mutations.[12]
- In the absence of functional and stable dystrophin in skeletal and cardiac muscle, patients with mutations in the dystrophin gene develop DMD.[13]

INVESTIGATIONAL MICRO-DYSTROPHIN GENE THERAPIES

- Due to the enormous size of the dystrophin gene and the widespread distribution of muscles, gene replacement therapy for DMD is challenging.[1]
- As the full-length dystrophin gene is too large to be included into an adenovirus vector (AAV), micro-dystrophins have been developed to fit inside an AAV.[1,14]
- In BMD, mutations in the dystrophin gene result in shorter versions of dystrophin that are partially and variably functional.[12] These shorter proteins are possibly expressed at lower levels than native dystrophin.[12] BMD is much milder than DMD and can develop in male patients aged in their 30s and 40s.[15]

1. Will gene therapy for DMD replace the mutated dystrophin gene with a full-length copy?

Background information (for internal learning purposes only)

INVESTIGATIONAL MICRO-DYSTROPHIN GENE THERAPIES (CONTINUED)

- Micro-dystrophin gene replacement therapy should not be seen as a cure for DMD, but rather as a way to lessen DMD severity to a level similar to that seen in patients with BMD.[2,3]
- Preliminary findings show that micro-dystrophin gene therapy resulted in improved muscle function that lasted up to 1 year after treatment.[16] However, it is currently unknown whether the expression of the micro-dystrophin genes will translate into clinical efficacy.
- Data from larger cohort studies are required to confirm whether micro-dystrophin gene replacement therapy can help halt the progression of DMD.

2. How does treatment with Translarna differ from gene replacement therapy with micro-dystrophin?

Initial response

- Translarna specifically targets nonsense mutations, which are found in approximately 10–15% of patients with DMD.[5]
- Translarna enables the insertion of an amino acid at the premature nonsense stop codon, allowing cells to produce full-length functional dystrophin.[17]
- Following stop codon read-through therapy with Translarna, the dystrophin gene is subject to normal regulation with respect to tissue specificity, timing and levels of expression.
- Micro-dystrophin cDNAs are shortened versions of the dystrophin gene which have been developed to fit inside an AAV.
- Even the most functional micro-dystrophins cannot fully restore the function of wild-type (full-length) dystrophin.[1]
- Micro-dystrophin gene replacement therapy should not be seen as a cure for DMD, but rather as a way to lessen DMD severity to a level similar to that seen in patients with BMD.[2,3]

Clarifying questions

- What is your comfort level in considering Translarna as a treatment option for your patients with nonsense mutation DMD?
- How familiar you are with the efficacy, safety and long-term data, and access to Translarna?
- How would you discuss the benefits of Translarna to the families of your patients?

2. How does treatment with Translarna differ from gene replacement therapy with micro-dystrophin?

Key points to communicate

TRANSLARNA TREATMENT

- **Translarna is an approved therapy**; the European Medicines Agency has confirmed a **positive risk–benefit assessment** for patients with nonsense mutation DMD based on efficacy and safety data over a 48-week treatment period from two randomized, double-blind, placebo-controlled studies.[4]
- Translarna is an orally available medication that is administered three times a day.[4]
- **Both clinical trials and real-world data show that Translarna is well tolerated.**[4,5]
- Patients taking Translarna but wishing to be screened for a clinical trial of micro-dystrophin therapy would need to discontinue the approved Translarna treatment for 6 months to be eligible to participate.[9] **This poses a risk, given that every day without Translarna treatment increases the risk of further muscle function loss**.

Translarna helps preserve muscle function and delays loss of ambulation, allowing patients to carry out daily tasks and maintain independence.[4-8]

Because DMD is a progressive disease, **early intervention to slow disease progression is essential.** For patients with nonsense mutation DMD, **early treatment with Translarna is currently available.**

2. How does treatment with Translarna differ from gene replacement therapy with micro-dystrophin?

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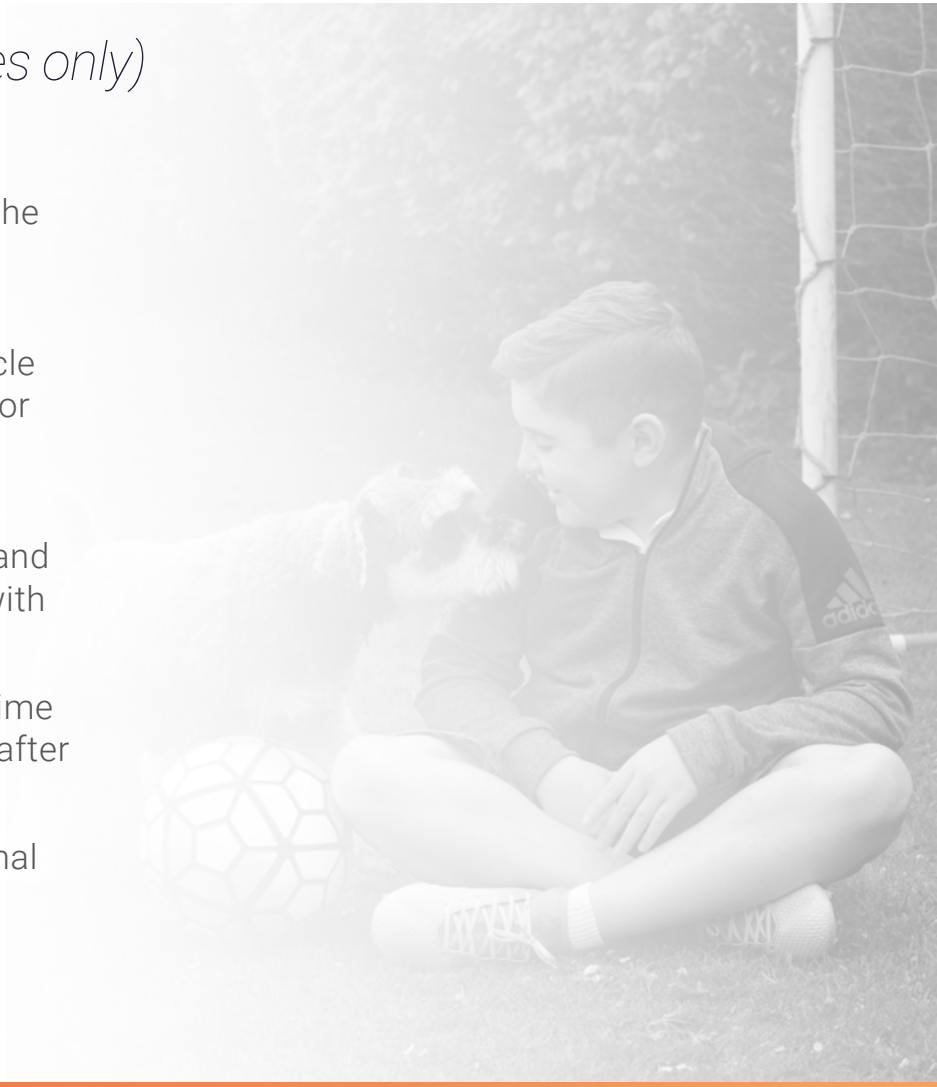

INVESTIGATIONAL MICRO-DYSTROPHIN GENE THERAPIES

- Micro-dystrophins have been developed to fit inside an AAV and even the most functional micro-dystrophins will not be as effective as wild-type (full-length) dystrophin.[1]
- The AAVs carrying the micro-dystrophin gene have an affinity for muscle cells and can be delivered either systemically via intravenous infusion or locally via intramuscular injection.[2]
- Micro-dystrophin gene replacement therapies rely on the regulatory elements that are contained within the AAV. These include promoters and enhancers that drive gene expression in skeletal and cardiac muscle with minimal off-target expression.[18]
- Currently, it seems that micro-dystrophin gene therapy may be a one-time treatment owing to an immune response to the vector that is induced after the first treatment.[3]
- In addition, the durability of micro-dystrophin expression and the optimal timing and dosing of treatment are not yet known.[3]

3. Who is eligible to participate in clinical trials of gene replacement therapy in DMD?

Initial response

- Please note that eligibility for micro-dystrophin gene replacement therapy trials should be discussed with the company conducting the respective clinical trial and only general comments on eligibility should be made.
- It is also important for potential trial participants to remember that clinical trials cannot guarantee beneficial results. In addition to the risk of the investigational therapy not working or causing unwanted side effects, there is a risk of being randomized to the placebo group and not receiving the investigational treatment at all.

Clarifying questions

- What is the reason you are asking about this?
- How many patients with nonsense mutation DMD do you see in your practice and what are your treatment goals for these patients?
- What is your comfort level in considering Translarna as a treatment option for your patients with nonsense mutation DMD?

3. Who is eligible to participate in clinical trials of gene replacement therapy in DMD?

Key points to communicate

TRANSLARNA TREATMENT

- **Both clinical trials and real-world data show that Translarna is well tolerated**.[4,5]
- Because DMD is a progressive disease, **early intervention to slow disease progression is essential**. For patients with nonsense mutation DMD, treatment with Translarna is available for ambulatory patients aged 2 years and older.[4]
- **Continual dosing with Translarna at the appropriate doses and times optimizes patient outcomes**.[4] Therefore, there is a **risk in stopping Translarna treatment, given that every day without Translarna increases the risk of further muscle function loss**.

Translarna helps preserve muscle function and delays loss of ambulation, allowing patients to carry out daily tasks and maintain independence.[4-8]

Patients taking Translarna but wishing to be screened for a clinical trial of micro-dystrophin therapy would need to discontinue the approved Translarna treatment for 6 months to be eligible to participate.[9]

3. Who is eligible to participate in clinical trials of gene replacement therapy in DMD?

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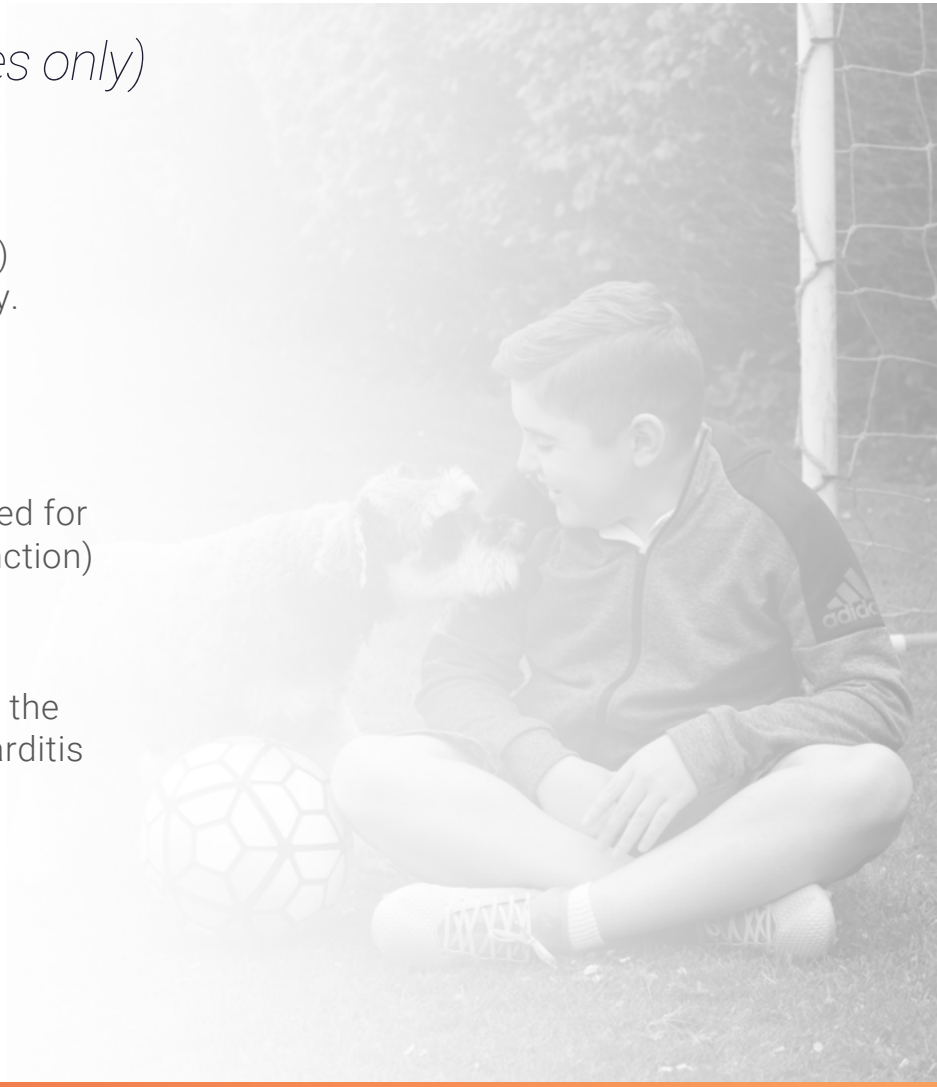
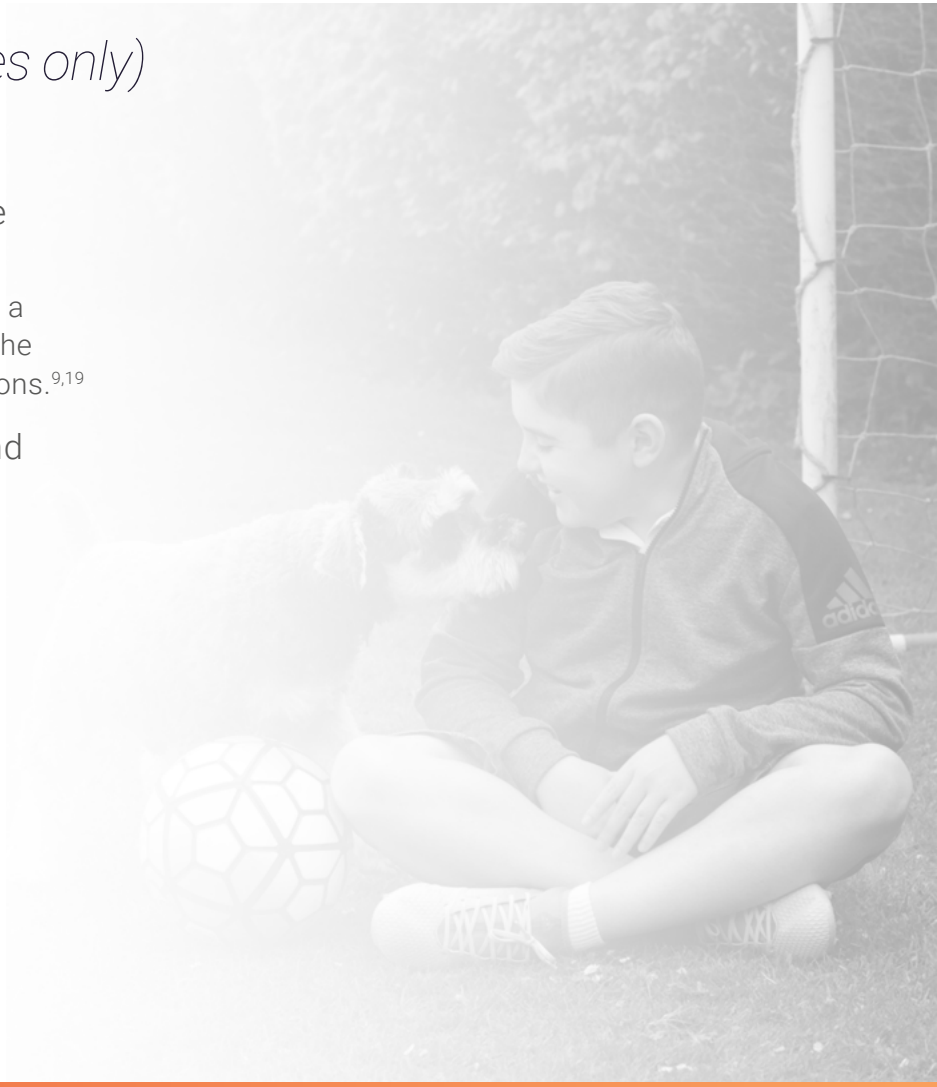


INVESTIGATIONAL MICRO-DYSTROPHIN GENE THERAPIES

- Paediatric male patients (typically between 4 and 7 years of age) with a genetic diagnosis of DMD (i.e. confirmed dystrophin gene mutations) may be able to participate in clinical trials of gene replacement therapy.
- Comorbidities (e.g. autoimmune diseases), ongoing severe infections, kidney or liver dysfunction and the presence of neutralizing antibodies against the viral vector used may make patients ineligible.
- Participants in gene therapy clinical trials are generally closely evaluated for efficacy (i.e. transgene expression, protein localization and muscle function) and safety (i.e. adverse events including immunological responses).[18]
- Safety concerns were raised in September 2021 regarding one of the micro-dystrophin trials after three serious adverse events attributed to the study drug resulted in muscle weakness. Two of these involved myocarditis (inflammation of the heart tissue).[9,19]

3. Who is eligible to participate in clinical trials of gene replacement therapy in DMD?

Background information (for internal learning purposes only)



INVESTIGATIONAL MICRO-DYSTROPHIN GENE THERAPIES (CONTINUED)

- The criteria for participation in one phase 3 micro-dystrophin trial were revised following the safety concerns.
  - Patients with either a mutation affecting any exon between exon 9 and exon 13 or a deletion that affects both exons 29 and 30 are no longer be able to participate in the trial. It is estimated that 15% of patients with DMD have these mutations or deletions.[9,19]
- Data from larger cohort studies are required to confirm the efficacy and safety of micro-dystrophin gene replacement therapy.

4. Can patients with AAV antibodies receive DMD gene replacement therapy?

Initial response

- Please note that eligibility for micro-dystrophin gene replacement therapy trials should be discussed with the company conducting the respective clinical trial and only general comments on eligibility should be made.

Clarifying questions

- What is the reason you are asking about this?
- How many patients with nonsense mutation DMD do you see in your practice and what are your treatment goals for these patients?
- What is your comfort level in considering Translarna as a treatment option for your patients with nonsense mutation DMD?

4. Can patients with AAV antibodies receive DMD gene replacement therapy?

Key points to communicate

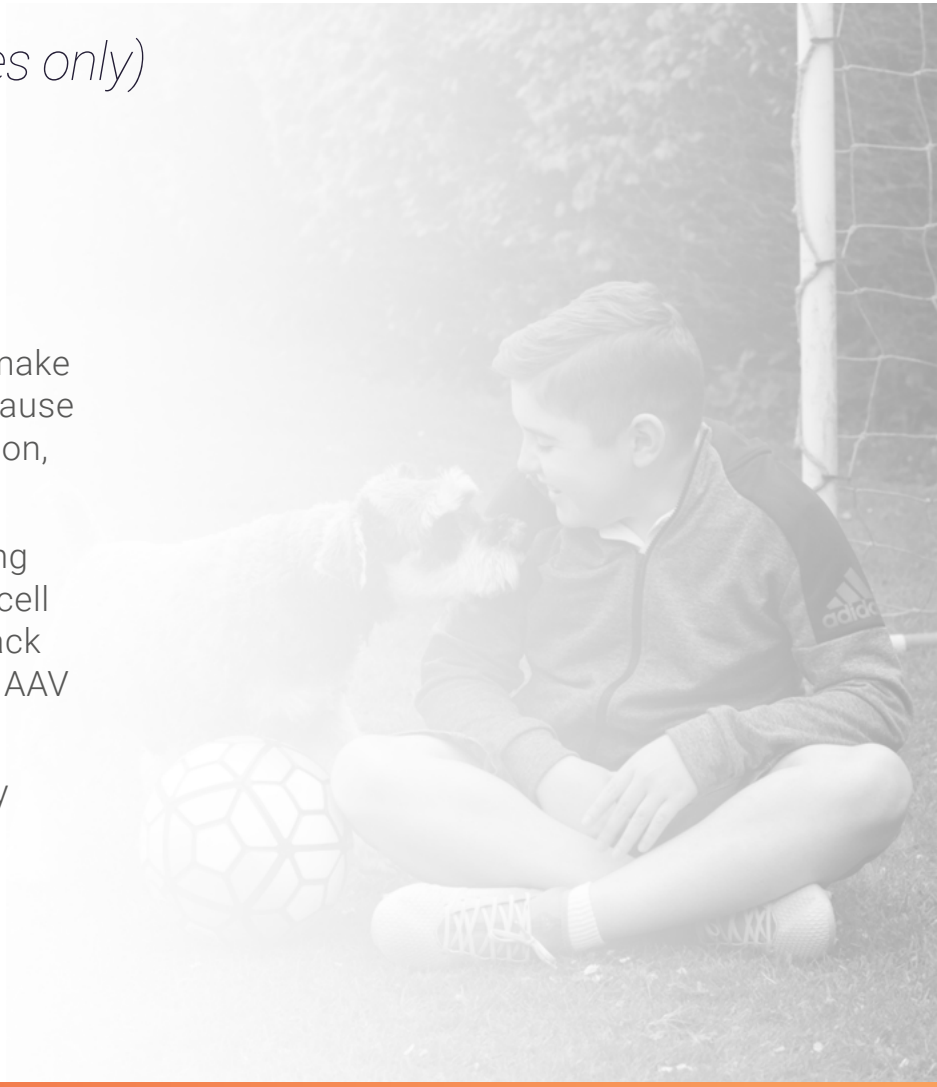
TRANSLARNA TREATMENT

- The European Medicines Agency has confirmed a **positive risk–benefit assessment** for patients with nonsense mutation DMD based on efficacy and safety data over a 48-week treatment period from two randomized, double-blind, placebo-controlled studies.[4]
- **Translarna helps preserve muscle function and delays loss of ambulation, allowing patients to carry out daily tasks and maintain independence**.[4-8]
- **Both clinical trials and real-world data show that Translarna is well tolerated**.[4,5]

Translarna is an approved therapy that does not rely on use of an AAV vector. Translarna treatment can therefore be initiated without delay or consideration of AAV antibody status once the diagnosis of nonsense mutation DMD has been confirmed.

4. Can patients with AAV antibodies receive DMD gene replacement therapy?

Background information (for internal learning purposes only)



AAV ANTIBODIES LIMIT USE OF MICRO-DYSTROPHIN GENE THERAPIES

- People who have been exposed to an AAV most likely have antibodies against that virus. These antibodies are typically long-lived and stay in the body to protect from future re-infection with the same virus.
- The presence of high levels of pre-existing anti-AAV antibodies could make a patient ineligible for micro-dystrophin gene replacement therapy because the antibodies will recognize the vector and promote its rapid elimination, diminishing the efficacy of the treatment.[20]
- The use of AAV vectors in gene therapy has some advantages, including low pathogenicity, broad tropism (i.e. ability to infect a wide variety of cell types) and high levels of transgene expression. However, a key drawback of AAV vectors is the high level of pre-existing immunity against many AAV serotypes in the population.[21]
- Several strategies to overcome the limitations of pre-existing immunity against AAVs are under development.[13,14,18,20]

5. Does gene replacement therapy for DMD help halt the progression of DMD?

Initial response

- The long-term clinical efficacy and safety of micro-dystrophin gene replacement therapy are still unknown.
- Data from larger cohort studies are required to confirm whether gene replacement therapy can help halt the progression of DMD.
- Micro-dystrophin gene replacement therapy should not be seen as a cure for DMD, but rather as a way to lessen DMD severity to a level similar to that seen in patients with BMD.[2,3]

Clarifying questions

- How many patients with nonsense mutation DMD do you see in your practice and what are your treatment goals for these patients?
- What is your comfort level in considering Translarna as a treatment option for your patients with nonsense mutation DMD?

5. Does gene replacement therapy for DMD help halt the progression of DMD?

Key points to communicate

TRANSLARNA TREATMENT

- **Translarna is an approved therapy**; the European Medicines Agency has confirmed a **positive risk–benefit assessment** for patients with nonsense mutation DMD based on efficacy and safety data over a 48-week treatment period from two randomized, double-blind, placebo-controlled studies.[4]
- **Translarna helps preserve muscle function and delays loss of ambulation, allowing patients to carry out daily tasks and maintain independence**.[4-8]
- Patients taking Translarna but wishing to be screened for a clinical trial of micro-dystrophin therapy would need to discontinue the approved Translarna treatment for 6 months to be eligible to participate.[9] **This poses a risk, given that every day without Translarna treatment increases the risk of further muscle function loss**.

Both clinical trials and real-world data show that Translarna is well tolerated.[4,5]

Because DMD is a progressive disease, **early intervention to slow disease progression is essential.**
For patients with nonsense mutation DMD, **early treatment with Translarna is currently available.**

5. Does gene replacement therapy for DMD help halt the progression of DMD?

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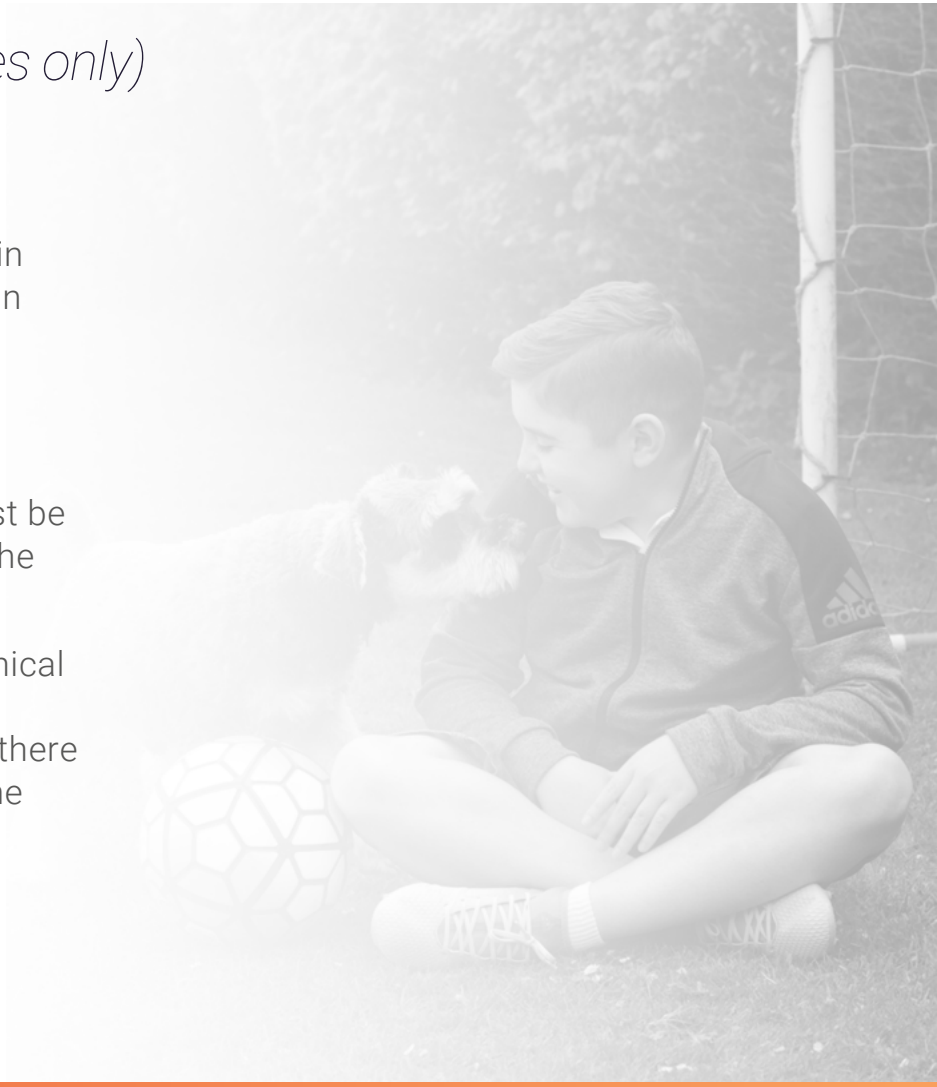

INVESTIGATIONAL MICRO-DYSTROPHIN GENE THERAPY

- Preclinical and clinical trials are currently investigating whether the treatment is well tolerated, the AAV vector delivers the micro-dystrophin DNA to muscle, the micro-dystrophin protein is sufficiently expressed in muscle, and whether DMD disease progression is slowed.[18]
- The long-term clinical efficacy and safety of micro-dystrophin gene replacement therapy are still unknown.
- Patients participating in micro-dystrophin gene replacement trials must be followed up for 15 years,[22] this will help to determine the durability of the treatment effect.
- It is also important for potential trial participants to remember that clinical trials cannot guarantee beneficial results. In addition to the risk of the investigational therapy not working or causing unwanted side effects, there is a risk of being randomized to the placebo group and not receiving the investigational treatment at all.

6. How long will the effect of micro-dystrophin gene replacement therapy last?

Initial response

- Clinical trials of gene replacement therapy to treat DMD are still at an early phase; hence, it remains unknown how long the benefits of a single dose of micro-dystrophin will last.

Clarifying questions

- How familiar are you with the efficacy, safety and long-term data, and access to Translarna?
  - If applicable, share with me some successes you have had with your patients taking Translarna.

6. How long will the effect of micro-dystrophin gene replacement therapy last?

Key points to communicate

TRANSLARNA TREATMENT

- **Translarna helps preserve muscle function and delays loss of ambulation, allowing patients to carry out daily tasks and maintain independence**.[4-8]
- Because DMD is a progressive disease, **early intervention to slow disease progression is essential**. For patients with nonsense mutation DMD, **early treatment with Translarna is currently available**.
- Patients taking Translarna but wishing to be screened for a clinical trial of micro-dystrophin therapy would need to discontinue the approved Translarna treatment for 6 months to be eligible to participate.[9] **This poses a risk, given that every day without Translarna treatment increases the risk of further muscle function loss**.

Translarna is an approved therapy; the European Medicines Agency has confirmed a **positive risk–benefit assessment** for patients with nonsense mutation DMD based on efficacy and safety data over a 48-week treatment period from two randomized, double-blind, placebo-controlled studies.[4]

Both clinical trials and real-world data show that Translarna is well tolerated.[4,5]

6. How long will the effect of micro-dystrophin gene replacement therapy last?

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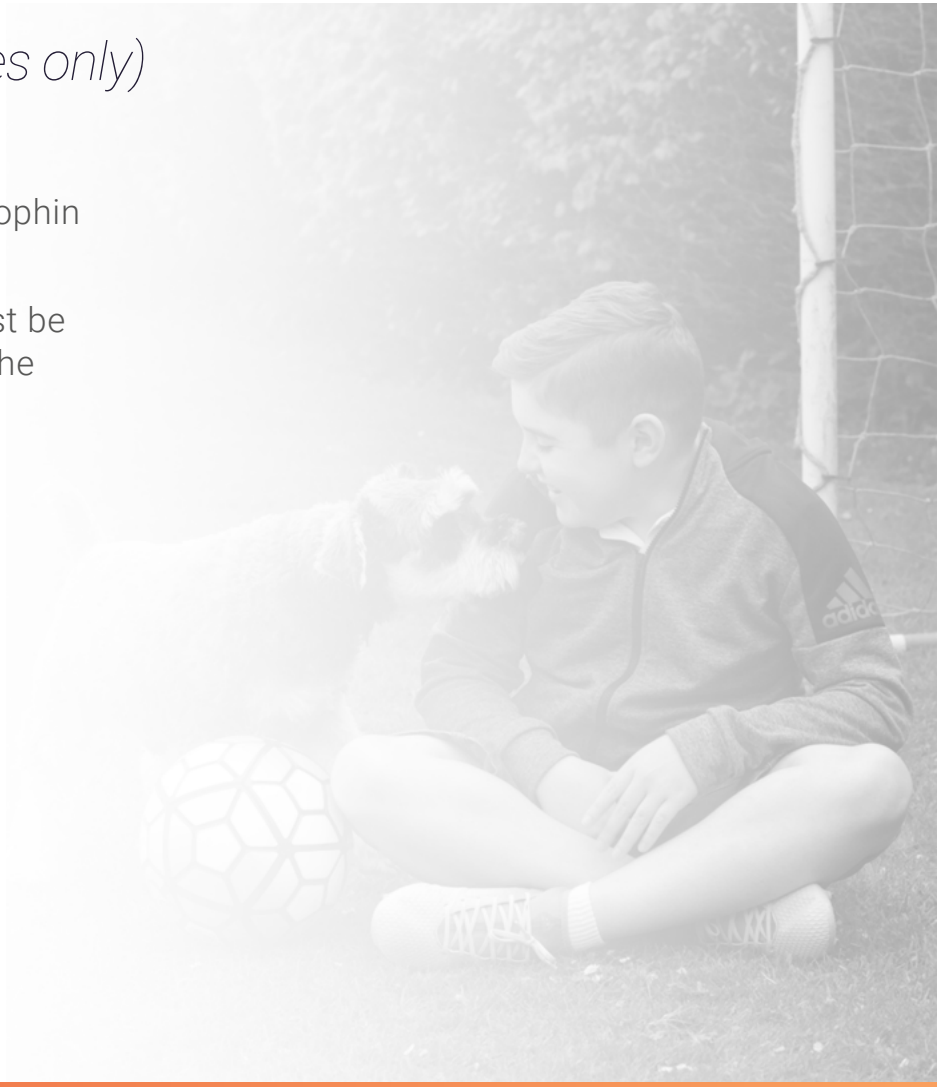


INVESTIGATIONAL MICRO-DYSTROPHIN GENE THERAPY

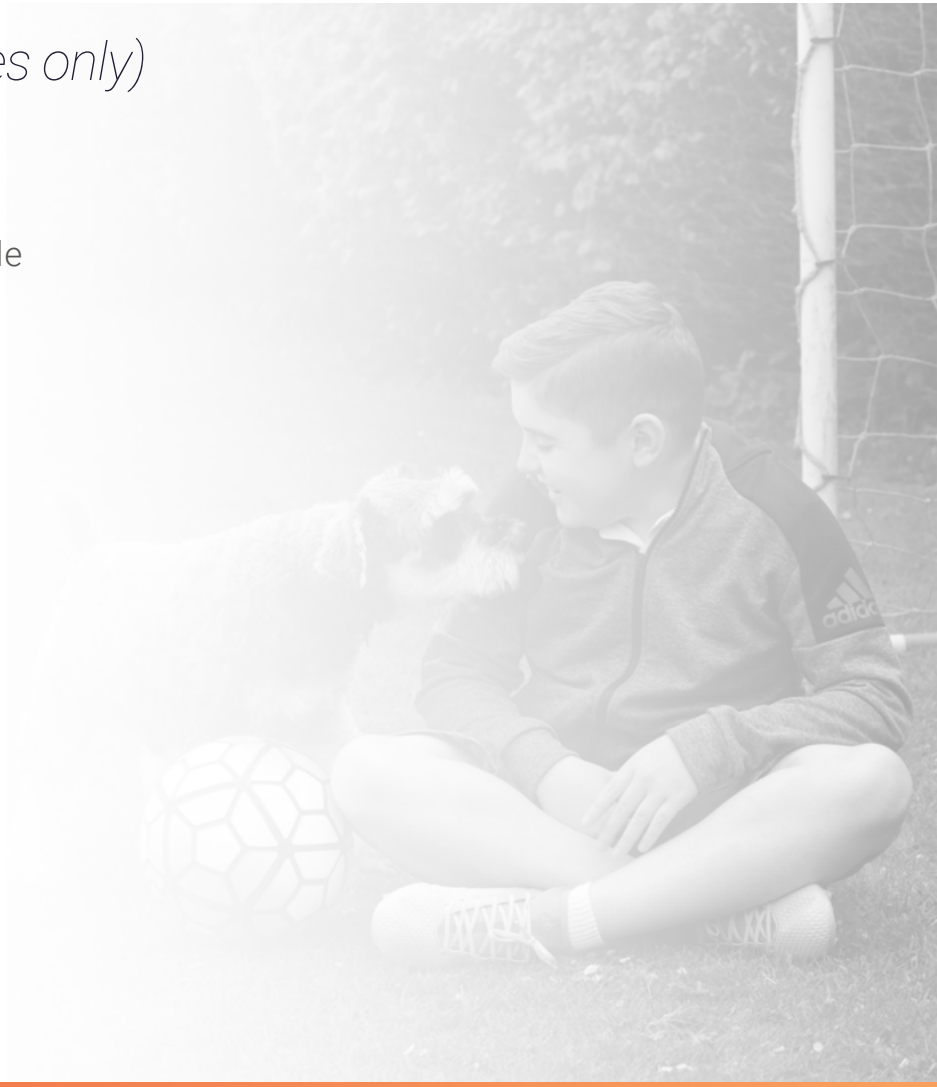
- DMD is a chronic disease, and its treatment requires continuous dystrophin expression.
- Patients participating in micro-dystrophin gene replacement trials must be followed up for 15 years,[22] this will help to determine the durability of the treatment effect.
- Treatment-related factors (e.g. viral vector) and patient-related factors (e.g. immune reactions, severity of the condition) may influence the durability of transgene expression, making it difficult to predict how long the effects of gene therapy will last.[20,23]
- As muscle cells are non-dividing and long-lived, it is possible that a single dose of micro-dystrophin may provide long-lasting or even lifelong clinical benefits.

6. How long will the effect of micro-dystrophin gene replacement therapy last?

Background information (for internal learning purposes only)

INVESTIGATIONAL MICRO-DYSTROPHIN GENE THERAPY (CONTINUED)

- Preliminary findings suggest that systemic micro-dystrophin gene replacement therapy can lead to robust transgene expression in muscle cells and motor function improvement that lasts for up to 1 year.[16]
- Micro-dystrophin gene replacement therapy should not be seen as a cure for DMD, but rather as a way to lessen DMD severity to a level similar to that seen in patients with BMD.[2,3]



7. Can a patient receive several doses of gene therapy for DMD?

Initial response

- Currently, it seems that micro-dystrophin gene therapy may be a one-time treatment owing to an immune response to the vector that is induced after the first treatment.[3]
- The durability of micro-dystrophin expression and the optimal timing and dosing of treatment are not yet known, please discuss the details with the company conducting the respective clinical trial.

Clarifying questions

- What is the reason you are asking about this?
- How would you discuss this with any families of your patients when they ask questions about gene therapy?

7. Can a patient receive several doses of gene therapy for DMD?

Key points to communicate

TRANSLARNA TREATMENT

- Data from clinical trials and real-world use show that Translarna is a well-tolerated therapy.[4,5]
- **Maintaining a steady, effective level of dosing is needed for read-through activity and therapeutic efficacy** – incorrect dosing can hinder this.[24]

The dosing for Translarna has shown long-term efficacy and safety.

8. What is the optimal time to provide micro-dystrophin gene replacement therapy to patients with DMD?

Initial response

- The optimal timing and dosing of micro-dystrophin treatment are not yet known,[3] please discuss the details with the company conducting the respective clinical trial.
- Because muscle damage is mild at the initial stages of the disease, early intervention may be more effective in delaying disease progression than late intervention.[25] Young patients are therefore more likely than older patients to benefit from the treatment.

Clarifying questions

- What is the reason you are asking about this?
- How many patients with nonsense mutation DMD do you see in your practice and what are your treatment goals for these patients?
- How would you discuss this with any families of your patients when they ask questions about gene therapy?

8. What is the optimal time to provide micro-dystrophin gene replacement therapy to patients with DMD?

Key points to communicate

TRANSLARNA TREATMENT

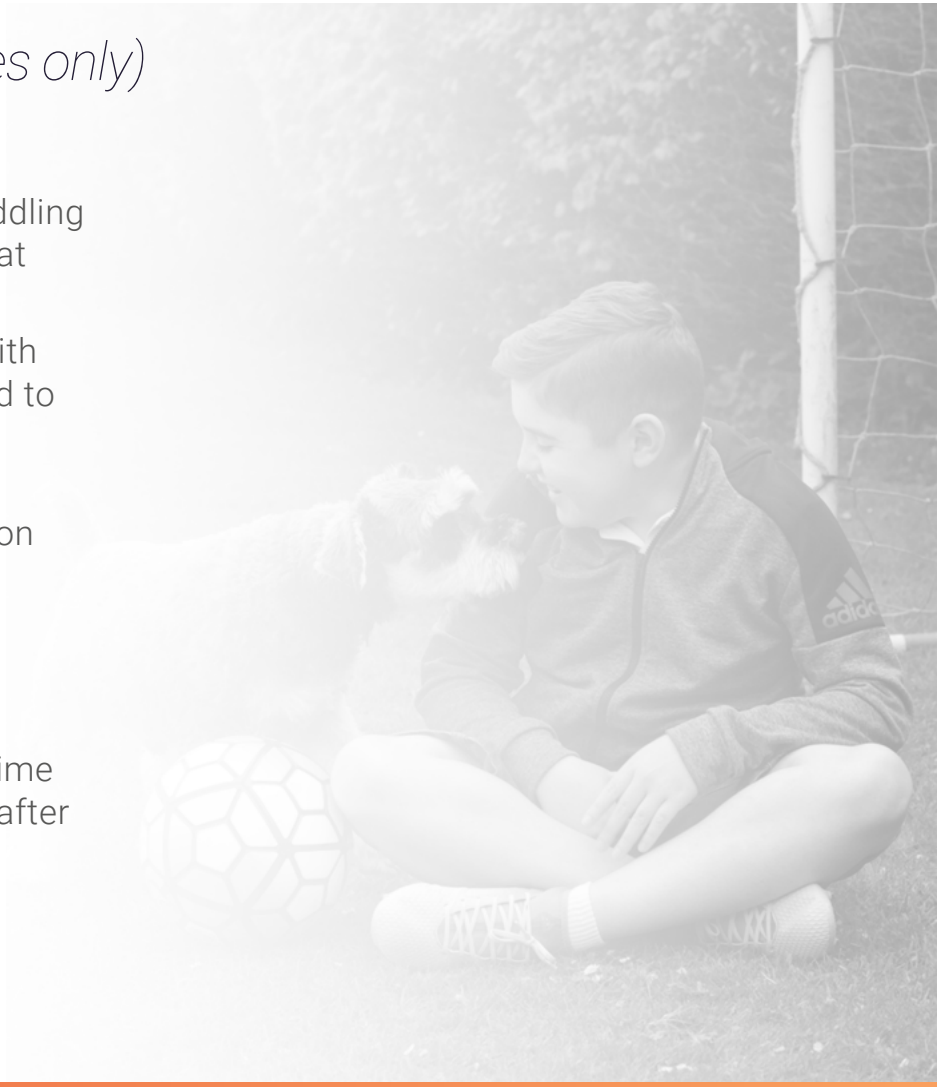
- **Translarna is an approved therapy**; the European Medicines Agency has confirmed a **positive risk–benefit assessment** for patients with nonsense mutation DMD based on efficacy and safety data over a 48-week treatment period from two randomized, double-blind, placebo-controlled studies.[4]
- Both clinical trials and real-world use show that Translarna is well tolerated.[4,5]
- Patients taking Translarna but wishing to be screened for a clinical trial of micro-dystrophin therapy would need to discontinue the approved Translarna treatment for 6 months to be eligible to participate.[9] **This poses a risk, given that every day without Translarna treatment increases the risk of further muscle function loss**.

Translarna helps preserve muscle function and delays loss of ambulation, allowing patients to carry out daily tasks and maintain independence.[4-8]

Because DMD is a progressive disease, **early intervention to slow disease progression is essential**.
For patients with nonsense mutation DMD, **early treatment with Translarna is currently available**.

8. What is the optimal time to provide micro-dystrophin gene replacement therapy to patients with DMD?

Background information (for internal learning purposes only)



POTENTIAL BENEFIT OF EARLY INTERVENTION

- Common symptoms of DMD are difficulties with climbing stairs, a waddling gait and frequent falls. Patients usually present with these symptoms at about 2–3 years of age.[13]
- However, signs and symptoms of DMD may be seen in early infancy with delayed motor milestones such as decreased head control when pulled to sitting and not walking by the age of 18 months.[25]
- Because muscle damage is mild at this initial stage of the disease, early intervention may be more effective in delaying disease progression than late intervention.[25]
- Systemic gene therapy in older patients with DMD poses practical challenges and safety concerns associated with the need for higher doses of the vector.[3]
- Currently, it seems that micro-dystrophin gene therapy may be a one-time treatment owing to an immune response to the vector that is induced after the first treatment.[3]

9. Will patients need to continue standard of care treatment after they receive gene therapy?

Initial response

- Micro-dystrophin gene replacement therapy should not be seen as a cure for DMD, but rather as a way to lessen DMD severity to a level similar to that seen in patients with BMD.[2,3]
- It is still too early to say how long the effects of micro-dystrophin gene replacement therapy will last.[20]
- We don't know yet what level of care will be needed following gene replacement therapy.

Clarifying questions

- What is the reason you are asking about this?
- How many patients with nonsense mutation DMD do you see in your practice and what are your treatment goals for these patients?
- How would you discuss this with any families of your patients when they ask questions about gene therapy?

9. Will patients need to continue standard of care treatment after they receive gene therapy?

Key points to communicate

TRANSLARNA TREATMENT

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Translarna helps preserve muscle function and delays loss of ambulation, allowing patients to carry out daily tasks and maintain independence.[4-8]

References

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