translarna™
ataluren

Translarna: a guide for healthcare professionals

BECAUSE *EVERY* MOMENT COUNTS

[LOCAL SPECIFIC] Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older. The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing[1]

▼ [LOCAL SPECIFIC] This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. Adverse events should also be reported to PTC Therapeutics at pharmacovigilance@ptcbio.com.

nmDMD, nonsense mutation DMD.

[LOCAL SPECIFIC] Conditional marketing authorisation granted in the European Economic Area is subject to annual reassessment and renewal by the EMA and the European Commission.

The information contained within is intended for healthcare professionals only. Prescribing information can be found on page 17.

PTC THERAPEUTICS™

1 Picture of a real Translarna patient

Contents

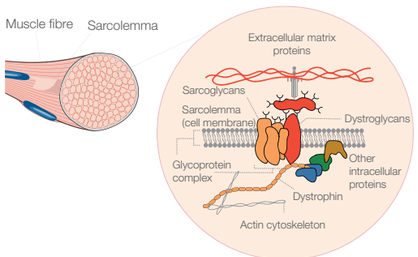
DMD is a rare, severe, progressive, and irreversible muscle-wasting disease[2]

DMD is caused by a mutation in the dystrophin gene, resulting in the absence of functional dystrophin protein[2,3] which provides mechanical stability to muscle cells during contraction[3]

The absence of dystrophin leads to repeated rounds of necrosis and degeneration of skeletal muscles, leading to fibrosis and muscle weakness[2]

- **This results in long-term, irreparable muscle damage, with limited potential to regain muscle function[2,3]**

DMD is a fatal disease, and patients have an average life expectancy of between 21.0 and 39.6 years when provided with ventilatory support[4]



Translarna allows readthrough of a nonsense mutation to enable the production of full-length, functional dystrophin[1]

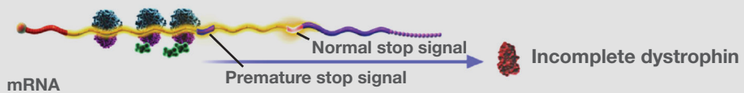
A nonsense mutation in the dystrophin gene leads to a premature stop codon in the mRNA that prevents the creation of full-length, functional dystrophin[1,5]

Translarna binds to the ribosome, allowing readthrough of the premature stop codon to enable production of full-length, functional dystrophin in nmDMD patients[1,6]

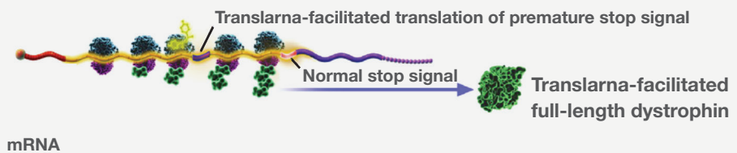
Normal translation of *dystrophin*

Adapted from Haas M, *et al.* 2015[6]

Incomplete translation of *dystrophin* due to a premature stop codon



Translarna readthrough of *dystrophin* premature stop codon



DMD, Duchenne muscular dystrophy; mRNA, messenger ribonucleic acid; nmDMD, nonsense mutation DMD.

Patients from the STRIDE Registry and CINRG DNHS were individually matched using established measures of disease progression[7]

To enable comparison of treatment effect between standard of care (SoC) alone and Translarna + SoC, the results from the STRIDE Registry were compared with propensity score-matched populations from the CINRG DNHS[7]

STRIDE Registry[7]

Translarna Real-World Registry

- Patients received Translarna + SoC; mean (SD) exposure to Translarna was 632 (362.9) days, a total of 313.4 patient-years
- Ongoing, multicentre, observational study of 213 patients
- 53 sites in 11 countries
- Follow-up between March 2015–July 2018

Propensity score matching criteria*†:

Age at first clinical symptoms

Age at first corticosteroid use

Duration of deflazacort use

Duration of other corticosteroid use

The SoC refers to corticosteroids (deflazacort, prednisolone and prednisone) and palliative therapies[7]

CINRG DNHS[7]

Matched Natural History

- Patients included in the present analyses received SoC alone
- A prospective, longitudinal study of >400 patients
- 20 centres in 9 countries
- Follow-up between 2006–2016

CINRG DNHS is the largest natural history study to date in DMD, and represents a real-world control group for comparison with STRIDE[7,8]

Hundreds of patients from around the world were prospectively enrolled in the CINRG DNHS and **followed closely for several years** (median treatment follow-up 1,796 days)[7]

Patients who had previously received investigational drugs in a clinical trial setting were excluded – this means there is **no chance of patient overlap**[7]

Patients from CINRG DNHS were only included in the analysis if they received SoC and were comparable to the STRIDE population, according to **established measures of disease progression**[7]

Propensity score matching allowed patients from STRIDE and CINRG DNHS to be **individually matched on a 1:1 basis**, creating a **real-world control group** to allow the effects of adding Translarna to SoC treatment to be analysed[7]

Why is this comparison valid?*

*Acknowledged limitations of this comparison include the difference in follow-up duration between the two cohorts and that patients were not matched according to mutation type or location[7]. †Propensity score matching is a method to compare two cohorts and eliminate bias when randomisation of patients is not possible.
CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; nmDMD, nonsense mutation Duchenne muscular dystrophy; SD, standard deviation; SoC, standard of care; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

Loss of ambulation is linked to respiratory decline and severely impacts the quality of life of patients and caregivers[9,10]

Loss of ambulation is a key timepoint in the natural disease progression of DMD; after loss of ambulation occurs, **severe respiratory insufficiency is more likely**[9]

Age at loss of ambulation is a predictor of the **timing and rate of pulmonary function decline**[9]

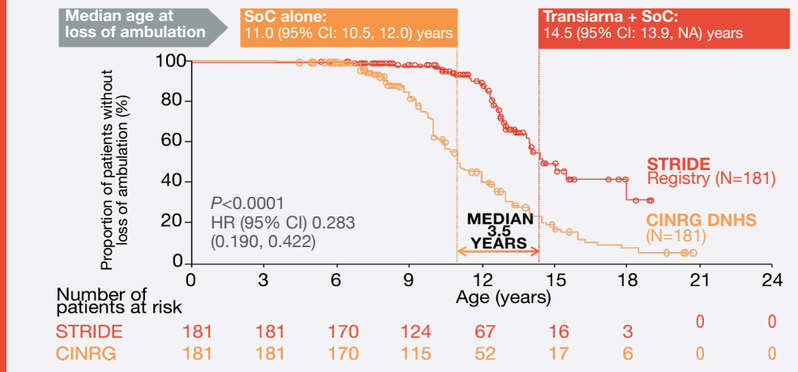
Loss of ambulation is associated with a profound **decline in health-related quality of life and increased burden on caregivers**[10,11]

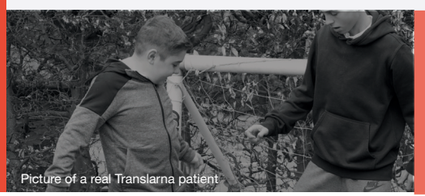
Translarna delayed loss of ambulation in real-world nmDMD patients, allowing patients to keep walking, for longer[7]

Delay to loss of ambulation

3.5 YEARS

Translarna + SoC provided **3.5 years of additional ambulation,** vs SoC alone in real-world DMD patients[7]




Picture of a real Translarna patient

> "We believe it has slowed the progression of the disease down… he walked for, I would say, a good 20 minutes or more yesterday. Without Translarna, I don't think he would be able to do that[12]"

CI, confidence interval; CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; DMD, Duchenne muscular dystrophy; HR, hazard ratio; NA, not available; nmDMD, nonsense mutation DMD; SoC, standard of care; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

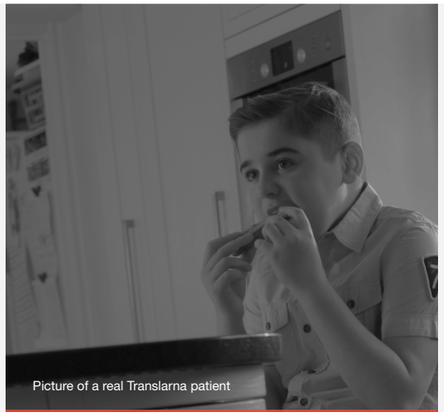
TFTs are validated measures of real-world physical function in DMD[13,14]

In DMD, the **loss of the ability to get up from the floor, climb stairs, or walk are important milestones** for the patient, and closely associated with a decline in health-related quality of life[7,13,14]

Loss of physical function is usually irreversible, and so delaying the loss of motor functions preserves patients' autonomy and ability to carry out daily tasks independently[7]

Decline in the ability to perform TFTs is a **sensitive predictor of loss of function across the next 12 months** in DMD patients[13]

Translarna preserved physical function in real-world nmDMD patients, enabling them to be more active and independent[7]



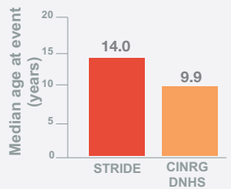
Picture of a real Translarna patient

"I'm letting him do things that I wouldn't have let him do before he started on **Translarna, because I can see there are benefits**[12]"

Patients treated with Translarna + SoC were on average

4.1 years older

than patients receiving SoC alone when their **time to stand from supine** worsened to ≥10 seconds[7]



(median age 14.0 vs 9.9 years; HR 0.290; *P*=0.0008)

Patients treated with Translarna were, on average, older

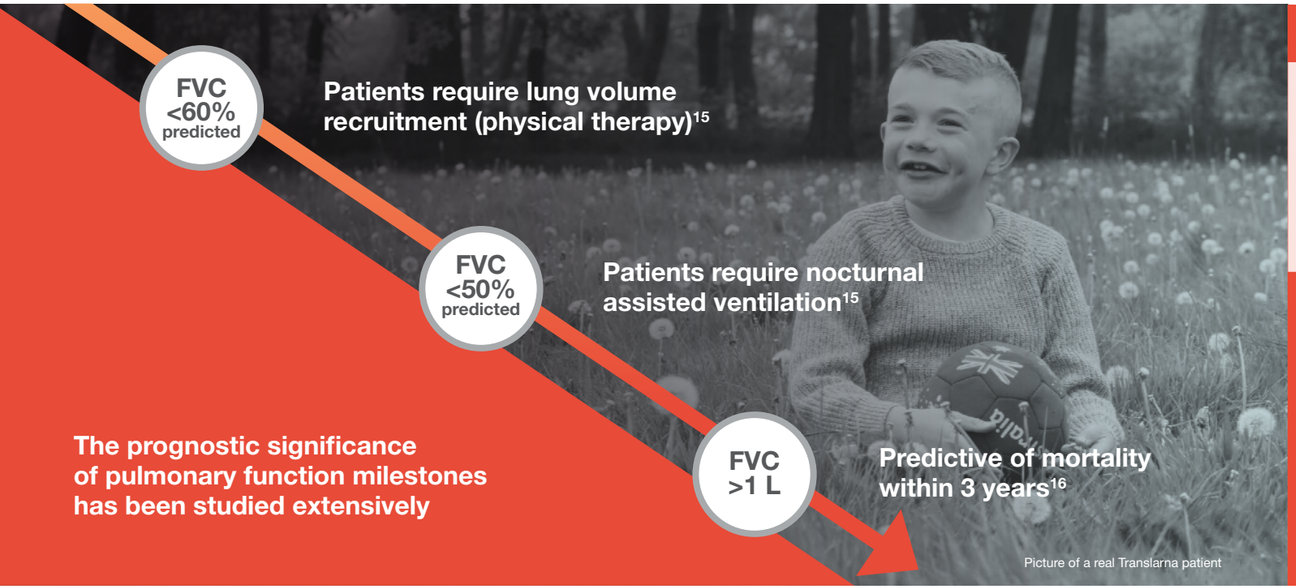
than patients receiving SoC alone when their **time to climb four stairs** worsened to ≥10 seconds[7]

STRIDE not reached **VS** **CINRG DNHS** 13.2

(median age NR vs 13.2 years; HR 0.385; *P*=0.0195)

CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; DMD, Duchenne muscular dystrophy; HR, hazard ratio; nmDMD, nonsense mutation DMD; NR, not reached; SoC, standard of care; STRIDE, Strategic Targeting of Registries and International Database of Excellence; TFT, timed function test.

Pulmonary function is a clinically relevant endpoint with a direct link to mortality[15,16]



The prognostic significance of pulmonary function milestones has been studied extensively

Translarna could delay loss of pulmonary function in nmDMD patients*[7]

Data from the STRIDE Registry suggest that **Translarna treatment delays three important milestones** of pulmonary function decline vs SoC alone[7]

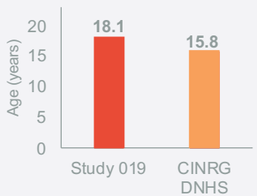
1. FVC <60% predicted
2. FVC <50% predicted
3. FVC <1 L

Proportion of patients whose predicted FVC worsened to <50%[7]

The analysis showed that 32.1% of SoC patients from CINRG DNHS had an FVC of <50%, **compared with only 2.2%** of nmDMD patients receiving Translarna in addition to SoC

Recent data from the **019 trial** (NCT01557400) support this†, suggesting that Translarna could **delay pulmonary function decline by 2.3 years**[17]

Median age at worsening of FVC to <60% predicted



P=0.0180

†Data shown is from a ***post hoc*** analysis which evaluated whether patients with nmDMD who received Translarna plus standard of care for up to 240 weeks in study 019 experienced a difference in pulmonary function decline compared to propensity-score matched patients with DMD who received SoC alone in CINRG DNHS

*Study authors note that there is a trend towards delayed worsening of pulmonary functions but that due to short duration of follow-up and low number of events, it is premature to draw firm conclusions from these results

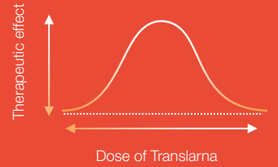
CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; FVC, forced vital capacity; nmDMD, nonsense mutation Duchenne muscular dystrophy; SoC, standard of care; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

Continual dosing with Translarna at the right dose and right time optimises patient outcomes[1,5]

Start Translarna Promptly

In a *post hoc* analysis of data from a phase 3 trial, a subset of patients who were started on Translarna at study initiation experienced **slower decline in walking ability,** compared with patients who were started on placebo and then switched to Translarna*[18]

Dose Translarna Continually



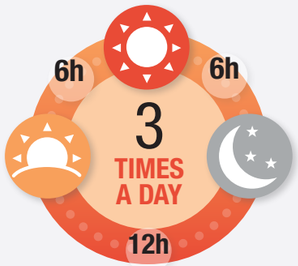
Due to Translarna's hypothesised bell-shaped dose-response curve, it's important that patients **don't miss a dose,** as this might cause plasma concentrations of Translarna to fall to sub-therapeutic levels[1,5,19]

Correct dosing of Translarna ensures optimal therapeutic benefit[1,5,19]

Translarna is an oral therapy that should be mixed with liquid (water, milk, fruit juice; at least 30 mL per sachet) or semi-solid food (yoghurt or apple sauce; at least 3 tablespoons per sachet)[1]

- For patients with body weight ≥12 kg, the licensed dose is 40 mg/kg per day: 10 mg/kg in the morning, 10 mg/kg at midday and 20 mg/kg in the evening[1]
- As little as a 1 kg change in body weight may mean a dose adjustment is required – this is why body weight should be measured at every clinic visit[1]

Maintaining a steady, effective level of dosing is needed for readthrough activity and therapeutic efficacy – incorrect dosing can hinder this[5,20]



*Patients were aged 7–16 years and had a baseline six minute walk distance of ≥300 to <400 m. Numerical advantage, not significant.
Please refer to the table in Section 4.2 of the Translarna Summary of Product Characteristics for recommended dosing by body weight range.

Data from clinical trials and real-world use show that Translarna is a well-tolerated therapy[1,7]

The most frequent adverse reactions in the two placebo-controlled studies in patients aged ≥5 years were vomiting, diarrhoea, nausea, headache, upper abdominal pain and flatulence. The majority of adverse reactions were mild or moderate in severity. One Translarna patient discontinued due to constipation, and one placebo patient discontinued due to loss of ambulation[1]

Safety data from 28 weeks of therapy showed a similar safety profile of Translarna in patients aged ≥2 to <5 years as compared with patients aged ≥5 years.[1] A higher frequency of malaise, pyrexia, ear infection, and rash were reported in patients aged ≥2 to <5 years, compared with patients 5 years of age and older. However, these conditions are reported more frequently in younger children in general[1]

Safety data from the STRIDE registry were consistent with the known safety profile of Translarna[7]

[LOCAL SPECIFIC] Monitoring and other information

Changes in lipid profile

Changes in lipid profile (increased triglycerides and cholesterol) were reported in some patients in clinical trials; it is therefore recommended that total cholesterol, LDL, HDL and triglycerides are monitored on an annual basis in patients receiving Translarna, or more frequently as needed based on the patient's clinical status

Hypertension with use of concomitant systemic corticosteroids

Hypertension was reported with use of concomitant systemic corticosteroids in some patients in clinical trials; it is therefore recommended that resting systolic and diastolic blood pressure are monitored every 6 months in patients receiving Translarna concomitantly with corticosteroids, or more frequently as needed based on the patient's clinical status

Renal impairment

Treatment of patients with severe renal impairment (eGFR <30 ml/min) or end-stage renal disease is not recommended. Patients with severe renal impairment or end-stage renal disease should be treated with Translarna only if the anticipated clinical benefit outweighs the potential risk, and should be closely monitored for possible metabolite toxicity and decrease in efficacy. A lower Translarna dose should be considered. Treatment should not be initiated in previously untreated patients with eGFR <30 mL/min

Renal function monitoring

Serum creatinine, BUN, and cystatin C should be monitored every 6 to 12 months in nmDMD patients receiving ataluren, or more frequently as needed based on the patient's clinical status

Potential interactions with other medicinal products

Caution should be exercised when Translarna is co-administered with medicinal products that are inducers of UGT1A9 or substrates of OAT1 or OAT3

Aminoglycosides

Aminoglycosides have been shown to reduce the readthrough activity of Translarna in vitro. In addition, Translarna was found to increase the nephrotoxicity of intravenous aminoglycosides. The co-administration of these agents with Translarna should be avoided, and concomitant use of intravenous aminoglycosides is a contraindication. The mechanism by which Translarna increases the nephrotoxicity of intravenous aminoglycosides is not known; therefore, concomitant use of other nephrotoxic medicinal products with Translarna is not recommended. If this is unavoidable (eg, vancomycin to treat MRSA), careful monitoring of renal function is advised.

Patients received Translarna 10/10/20 mg/kg/day or 20/20/40 mg/kg/day in the two placebo-controlled trials.
BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MRSA, methicillin-resistant *Staphylococcus aureus*; nmDMD, nonsense mutation Duchenne muscular dystrophy; STRIDE, strategic targeting of registries and international database of excellence.

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[LOCAL SPECIFIC] Abbreviated Prescribing Information Indication: Translarna™ (active ingredient: ataluren) is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene (nmDMD), in ambulatory patients aged 2 years and older. The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing. **Posology and administration**: Translarna is available as granules for oral suspension in sachets of 125 mg, 250 mg or 1000 mg. The recommended dose is 10 mg/kg body weight in the morning, 10 mg/kg body weight at midday, and 20 mg/kg body weight in the evening (for a total daily dose of 40 mg/kg body weight). Patients should not take a double or extra dose if a dose is missed. It is important to administer the correct dose. Increasing the dose above the recommended dose may be associated with reduced effectiveness. Treatment of patients with severe renal impairment (eGFR <30 ml/min) or end-stage renal disease is not recommended. The safety and efficacy of Translarna in children <12kg and aged 6 months to 2 years have not yet been established. Treatment with Translarna should only be initiated by specialist physicians with experience in the management of DMD. **Ingredients**: Active ingredient: ataluren. **Excipients**: polydextrose (E1200), macrogol, poloxamer, mannitol (E421), crospovidone, hydroxyethyl cellulose, artificial vanilla flavour (maltodextrin, artificial flavours and propylene glycol), silica, colloidal anhydrous (E551), magnesium stearate. **Contraindications**: Patients with hypersensitivity to the active substance or to any of the excipients; concomitant use of intravenous aminoglycosides. **Special warnings and precautions for use**: Patients who do not have a nonsense mutation should not receive Translarna. Patients with severe renal impairment or end-stage renal disease should be treated with ataluren only if the anticipated clinical benefit outweighs the potential risk, and should be closely monitored for possible metabolite toxicity and decrease in efficacy. A lower ataluren dose should be considered. Treatment should not be initiated in previously untreated patients with eGFR <30 ml/min. It is recommended that total cholesterol, LDL, HDL, triglycerides be measured annually, and serum creatinine, BUN, cystatin C be measured every 6 to 12 months. Resting systolic and diastolic blood pressure should be monitored every 6 months in patients receiving Translarna concomitantly with corticosteroids. All clinical measures and/or laboratory testing may be conducted more frequently as needed based on clinical status. See precaution for use with other medicines in next “interactions” section.

Interactions: Translarna should not be co-administered with intravenous aminoglycosides, and concomitant use of other nephrotoxic agents is not recommended. Caution should be exercised when Translarna is co-administered with medicinal products that are inducers of UGT1A9, or substrates of OAT1, OAT3 or OATP1B3 and when co-administered with adefovir. Based on in vitro studies Translarna is not expected to be an inducer of P450 isoenzymes. **Fertility, pregnancy and lactation**:: It is recommended to avoid the use of Translarna in pregnancy. Breast-feeding should be discontinued during treatment with Translarna. Non-clinical data revealed no hazard for humans based on standard male and female fertility study in rats. **Effects on ability to drive and use machines:** Patients who experience dizziness should use caution when driving, cycling or using machines. **Adverse reactions**: Adverse reactions reported in clinical trials of paediatric nmDMD patients treated at the recommended dose of 10-, 10-, 20mg/kg/day according to frequency: Very common (≥1/10): vomiting. Common (≥1/100 to <1/10): decreased appetite, hypertriglyceridemia, headache, hypertension, cough, epistaxis, nausea, upper abdominal pain, flatulence, abdominal discomfort, constipation, rash erythematous, pain in extremity, musculoskeletal chest pain, haematuria, enuresis, pyrexia, weight decreased. Events with unknown frequency due to low numbers: increased blood urea nitrogen, cholesterol, creatinine, cystatin C, triglycerides. A higher frequency of malaise (7.1%), pyrexia (42.9%), ear infection (28.6%), and rash (21.4%) were reported in patients aged 2-5 years compared with patients 5 years of age and older. **Marketing Authorisation number and holder**: EU/1/13/902/001-002-003. PTC Therapeutics International Limited, 5th Floor, 3 Grand Canal Plaza, Grand Canal Street Upper, Dublin 4, Ireland. Please consult the SmPC before prescribing. **Date of Preparatio**n: August 2020.

▼ **[LOCAL SPECIFIC] This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. Adverse events should also be reported to PTC at pharmacovigilance@ptcbio.com**

References: 1. Translarna EU Summary of Product Characteristics. **2.** Blake DJ, et al. *Physiol Rev.* 2002;82:291–329. **3.** Pytel P and Anthony DC. Peripheral nerve and skeletal muscle. In: Kumar K, et al. eds. Robbins and Cotran Pathologic Basis of Disease, 9th Edition. Philadelphia, USA: Elsevier Saunders; 2015. **4.** Landfeldt E, et al. *Eur J Epidemiol.* 2020;35:643–653. **5.** Bushby K, et al. *Muscle Nerve.* 2014;50:477–487. **6.** Haas M, et al. *Neuromuscul Disord.* 2015;25:5–13. **7.** Mercuri E, et al. *J Comp Eff Res.* 2020;9:341–360. **8.** Duchenne Natural History. Available from: https://cinrgresearch.org/duchenne-natural-history/ [Accessed March 2021]. **9.** Humbertclaude V, et al. *Eur J Paediatr Neurol.* 2012;16:149–160. **10.** Landfeldt E, et al. *Dev Med Child Neurol.* 2016;58:508–515. **11.** Landfeldt E, et al. *Dev Med Child Neurol.* 2018;60:987–996. **12.** Quote from a parent of a boy with nmDMD. **13.** Arora H, et al. *Muscle Nerve.* 2018;58:631–638. **14.** McDonald CM, et al. *J Child Neurol.* 2010;25:1130–1144. **15.** Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:347–361. **16.** Philips MF, et al. *Am J Respir Crit Care Med.* 2001;164:2191–2194. **17.** McDonald CM, et al. Poster presented at the 25th International Congress of the World Muscle Society (WMS), September 28 – October 2, 2020. **18.** Trifillis P, et al. *Neuromuscular Dis.* 2018;28:S13. **19.** Peltz SW, et al. *Annu Rev Med.* 2013;64:407–425. **20.** Hirawat S, et al. *J Clin Pharmacol.* 2007;47:430–444. **21.** PTC, Data on file.

The totality of evidence consistently demonstrates the efficacy of Translarna in nmDMD in clinical trials and the real world[1,7,17]

- To date, it's estimated that over 1,600 patients have received Translarna in a clinical trial setting*[21]
- When added to SoC, Translarna provided 3.5 years of additional ambulation vs SoC alone in real-world DMD patients in the STRIDE registry[7]
- Translarna could delay loss of pulmonary function[7,17]
- Data from clinical trials and real-world use show that Translarna is a well-tolerated therapy[1,7]

DMD, Duchenne muscular dystrophy; nmDMD, nonsense mutation DMD; SoC, standard of care; STRIDE, Strategic Targeting of Registries and International Database of Excellence.
*As of 31 July, 2020.

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This material has been developed and funded by PTC Therapeutics
Date of preparation: March 2021 | GL-TRNS-0272