הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 05.2013)

תאריך 12.12.2016

שם תכשיר באנגלית ומספר הרישום Translarna 125 34264-00/01

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Translarna 1000 34267-00/01

שם בעל הרישום ___מדיסון פארמה בע"מ_____

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
Potential interactions with other medicinal products Caution should be exercised when ataluren is co-administered with medicinal products that are substrates or inducers of UGT1A9, ~~inhibitors of BCRP~~, or substrates of OAT1, OAT3, or OATP1B3 (see section 4.5).	Potential interactions with other medicinal products Caution should be exercised when ataluren is co-administered with medicinal products that are substrates or inducers of UGT1A9, inhibitors of BCRP, or substrates of OAT1, OAT3, or OATP1B3 (see section 4.5).	**4.4Special warnings and precautions for use**
Effect of other medicinal products on ataluren pharmacokinetics Based on *in vitro* studies, ataluren is a substrate of UGT1A9 ~~and breast cancer resistant protein (BCRP).~~ Caution should be exercised when ataluren is co-administered with medicinal products that are inducers of UGT1A9 (e.g. mycophenolate	*Effect of other medicinal products on ataluren pharmacokinetics* Based on *in vitro* studies, ataluren is a substrate of UGT1A9 and breast cancer resistant protein (BCRP). Caution should be exercised when ataluren is co-administered with medicinal	**4.5Interaction with other medicinal products and other forms of interaction**

mofetil), ~~or inhibitors of BCRP (e.g. cyclosporine).~~	products that are inducers of UGT1A9 (e.g. mycophenolate mofetil), or inhibitors of BCRP (e.g. cyclosporine).	
Summary of the safety profile ~~In clinical trials of~~The safety profile of ataluren is based on pooled data from two randomised, double-blind, 48-week placebo-controlled studies conducted in a total of 232 male patients with Duchenne muscular dystrophy (nmDMD) caused by a nonsense mutation, ~~the most frequent adverse reactions at the recommended dose were nausea, vomiting, and headache. These adverse reactions generally did not require medical intervention, and no patients discontinued ataluren treatment due to any adverse reaction.~~ treated at the recommended dose of 40 mg/kg/day (10, 10, 20 mg/kg; n=172) or at a dose of 80 mg/kg/day (20, 20, 40 mg/kg; n=60), as compared to placebo-treated patients (n=172). The most common adverse reactions in the 2 placebo-controlled studies were vomiting, diarrhoea, nausea, headache, upper abdominal pain, and flatulence, all occurring in ≥5% of all ataluren-treated patients. In both studies, 1/232 (0.43%) patients treated with ataluren discontinued due to an adverse reaction of constipation and 1/172 (0.58%) placebo patients discontinued treatment due to an adverse reaction of disease progression (loss of ambulation). Adverse reactions were generally mild or moderate in severity, and no treatment-related serious adverse events were reported among ataluren-treated patients in these 2 studies.	Summary of the safety profile In clinical trials of patients with Duchenne muscular dystrophy (nmDMD) caused by a nonsense mutation, the most frequent adverse reactions at the recommended dose were nausea, vomiting, and headache. These adverse reactions generally did not require medical intervention, and no patients discontinued ataluren treatment due to any adverse reaction.	**4.8 Undesirable effects**

Tabulated list of adverse reactions

The adverse reactions reported in ~~the clinical trial of predominantly paediatric~~ patients with nmDMD treated ~~at~~ with the recommended daily dose of ~~10-, 10-, 20-~~40 mg/kg/ day ataluren in the 2 placebo-controlled studies are presented in Table 1. Adverse reactions reported in >1 patient in the 40 mg/kg/day group at a frequency greater than that of the placebo group are presented by MedDRA System Organ Class, Preferred Term ~~are classified according to the system organ class of MeDRA~~ and frequency. Frequency groupings are defined to the following convention: very common (≥ 1/10) and common (≥ 1/100 to < 1/10). ~~Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.~~

Table 2. Adverse reactions reported in >1 ataluren-treated patients with nmDMD at a frequency greater than placebo in the 2 placebo-controlled studies (pooled analysis)
~~Table 3. Adverse reactions in Translarna in controlled study of nmDMD~~

System Organ Class	Very common	Common	Frequency not known

Tabulated list of adverse reactions

The adverse reactions reported in the clinical trial of predominantly paediatric patients with nmDMD treated at the recommended dose of 10-, 10-, 20 mg/kg are classified according to the system organ class of MeDRA and frequency. Frequency groupings are defined to the following convention: very common (≥ 1/10) and common (≥ 1/100 to < 1/10). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions in Translarna in controlled study of nmDMD

System Organ Class	Very common	Common	Frequency not known
Metabolism and nutrition disorders		Decreased appetite	Change in lipid profile (increased triglycerides and cholesterol)
Nervous system disorders	Headache	Dizziness	
Vascular disorders		Hypertension	

4.8 Undesirable effects

Metabolism and nutrition disorders		Decreased appetite hypertriglyceridaemia	Change in lipid profile (increased triglycerides and cholesterol)
Nervous system disorders	~~Headache~~	~~Dizziness~~ Headache	
Vascular disorders		Hypertension	
Respiratory, thoracic, and mediastinal disorders		Cough, epistaxis	
Gastrointestinal disorders	~~Nausea~~, Vomiting	Nausea ,~~U~~upper abdominal pain, flatulence, ~~diarrhoea~~, abdominal ~~stomach~~ discomfort, ~~abdominal~~ ~~pain,~~ constipation, ~~regurgitation~~	
Skin and subcutaneous tissue disorders		Rash erythematous ~~Erythema~~	

Respiratory, thoracic, and mediastinal disorders		Cough, epistaxis	
Gastrointestinal disorders	Nausea, Vomiting	,Upper abdominal pain, flatulence, diarrhoea, stomach discomfort, abdominal pain, constipation , regurgitation	
Skin and subcutaneous tissue disorders		Erythema	
Musculoskeletal and connective tissue disorders		Pain in extremity	

Musculoskeletal and connective tissue disorders		Pain in extremity musculoskeletal chest pain	
Renal and urinary disorders		Haematuria, ~~Enuresi~~ enuresis, ~~renal cyst, pollakiuria, urine colour abnormal~~	Change in renal function tests (increased creatinine, blood urea nitrogen, cystatin C)
General disorders and administration site conditions		Pyrexia, ~~fatigue,~~ weight decreased	

Description of selected adverse reactions (laboratory abnormalities)

Serum lipids
During the randomised, placebo-controlledstudies ~~controlled~~ study of nmDMD, mean total cholesterol and triglycerides were normal at baseline and increased, reaching borderline high or high values. Lipid levels shifted from normal at baseline to high (above the upper limit of normal) at Week 48 in slightly higher percentages of patients receiving ataluren compared to those receiving placebo

Renal and urinary disorders		Enuresi , renal cyst, pollakiuria, urine colour abnormal	Change in renal function tests (increased creatinine, blood urea nitrogen, cystatin C)
General disorders and administration site conditions		Pyrexia, fatigue~~,~~ weight decreased	

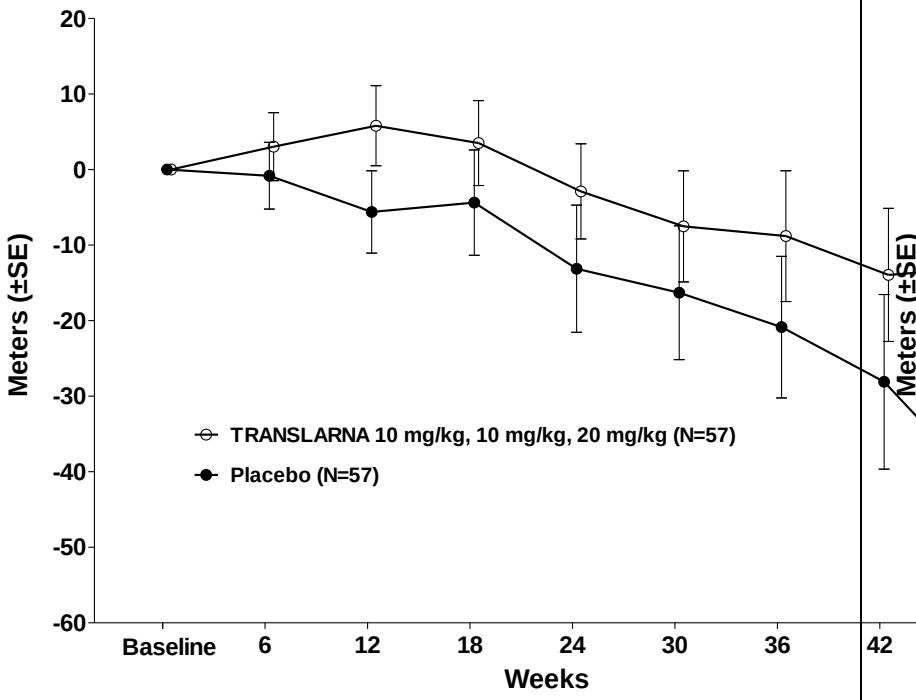
Description of selected adverse reactions

Serum lipids
During the controlled study of nmDMD, mean total cholesterol and triglycerides were normal at baseline and increased, reaching borderline high The values tended to stabilize early in the study and did not increase further with continued treatment.

Renal function tests
During the controlled study of nmDMD, small increases in mean serum creatinine, blood urea nitrogen (BUN), and cystatin C were observed. The values tended to stabilize early in the study and did not increase further with continued treatment.

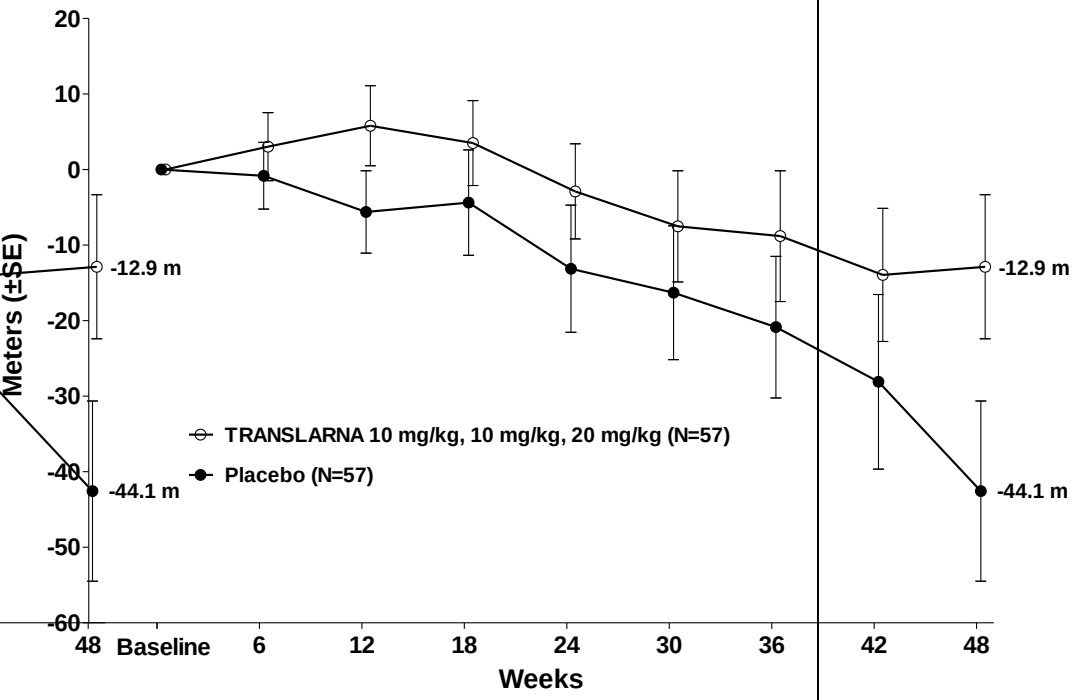
(total cholesterol 15.1% vs. 6.1%, triglycerides 21.1% vs. 13.4%, respectively). The values tended to stabilize early in the study and did not increase further with continued treatment. *Renal function tests* During the randomised, placebo-controlled studies ~~controlled study~~ of nmDMD, small increases in mean serum creatinine, ~~blood urea nitrogen (~~BUN, and cystatin C were observed. The values tended to stabilize early in the study and did not increase further with continued treatment.		
Pharmacotherapeutic group: Other drugs for disorders of the musculo-skeletal system~~{group},~~ ATC code: M09AX03~~not yet assigned~~	Pharmacotherapeutic group: {group}, ATC code: not yet assigned	**5.1Pharmacodynamic properties**
Clinical efficacy and safety The ~~safety and~~ efficacy and safety of Translarna were assessed in a randomized, double-blind, placebo-controlled, trials in nmDMD. The primary efficacy endpoint in both trials was change in 6 Minute Walk Distance (6MWD) at Week 48. Other endpoints included in both trials were time to persistent 10% worsening in 6MWD, change in time to run/walk 10 meters at Week 48, change in time to climb 4 stairs at Week 48, and change in time to descend 4 stairs at Week 48. ~~multicentre nonsense mutation Duchenne muscular dystrophy (nmDMD) study of~~ Study 1 evaluated 174 male patients ages 5 to 20 years. All patients were required to be ~~ambulatory, defined as the ability~~ able to walk ~~for~~ ≥75 meters without the need for assistive devices during a screening 6-~~minute~~ Minute Walk Test (6MWT). Patients were also required to have documented confirmation of the presence of a nonsense mutation in the	Clinical efficacy and safety The safety and efficacy of Translarna were assessed in a randomized, double-blind, placebo-controlled, multicentre nonsense mutation Duchenne muscular dystrophy (nmDMD) study of 174 male patients ages 5 to 20 years. All patients were required to be ambulatory, defined as the ability able to walk for ≥75 meters without the need for assistive devices during a screening 6-minute Walk Test (6MWT). Patients were also required to have documented confirmation of the presence of a nonsense mutation in the dystrophin gene as determined by gene sequencing. The majority of patients in all treatment groups were Caucasian (90%). Patients were randomized in a 1:1:1 ratio and received ataluren or placebo 3 times per day (morning, midday, and evening)for 48 weeks, with 57 receiving placebo, 57 receiving ataluren 10-, 10-, 20-mg/kg, and 60 receiving ataluren (20-, 20-,	**5.1Pharmacodynamic properties**

dystrophin gene as determined by gene sequencing. The majority of patients in all treatment groups were Caucasian (90%). Patients were ~~randomized~~ randomised in a 1:1:1 ratio and received ataluren or placebo 3 times per day (morning, midday, and evening)~~for 48 weeks~~, with 57 receiving ~~placebo, 57 receiving~~ ataluren 40 mg/kg/day (10-, 10-, 20-mg/kg), ~~and~~ 60 receiving ataluren 80 mg/kg/day (20-, 20-, 40 mg/kg) and 57 receiving placebo. ~~173 patients completed the study. The primary efficacy endpoint evaluated the effect of ataluren on ambulation as assessed by the change in distance (6MWD) walked during a 6MWT~~. In Study 1, a ~~The~~ post hoc analysis of the primary endpoint showed that from baseline to Week 48, patients receiving ataluren 40 mg/kg/day ~~10 , 10 , 20 mg/kg~~ had a 12.9 meters mean decline in 6MWD, and patients receiving placebo had a 44.1-meter mean decline in 6MWD (Figure 1). Thus, the mean change in observed 6MWD from baseline to Week 48 was 31.3 meters better in the ataluren ~~10 , 10 , 20-~~ 40 mg/kg/day arm than in the placebo arm (p=0.056). In a statistical based model the estimated mean difference was 31.7 meters (adjusted p=0.0367). There was no difference between ataluren ~~20 , 20 ,~~ ~~40~~80 mg/kg/day and placebo. These results indicate that ataluren ~~10 , 10 , 20~~ 40 mg/kg/day slows the loss of walking ability in nmDMD patients. Figure 1. Mean Change in 6-Minute Walk Distance (Study 1)	40 mg/kg 173 patients completed the study. The primary efficacy endpoint evaluated the effect of ataluren on ambulation as assessed by the change in distance (6MWD) walked during a 6MWT. The post hoc analysis showed that from baseline to Week 48, patients receiving ataluren 10-, 10-, 20-mg/kg had a 12.9 meters mean decline in 6MWD, and patients receiving placebo had a 44.1-meter mean decline in 6MWD (Figure 1). Thus, the mean change in observed 6MWD from baseline to Week 48 was 31.3 meters better in the ataluren 10-, 10-, 20-mg/kg arm than in the placebo arm (p=0.056). In a statistical based model the estimated mean difference was 31.7 meters (adjusted p=0.0367). There was no difference between ataluren 20-, 20-, 40 mg/kg and placebo. These results indicate that ataluren 10-, 10-, 20-mg/kg slows the loss of walking ability in nmDMD patients. Figure 1. Mean Change in 6-Minute Walk Distance (Study 1).	



A post-hoc analysis of time to persistent 10% worsening in 6MWD showed that 26% of patients in the ataluren ~~10-, 10-, 20~~40-mg/kg/day arm had progressed at Week 48 compared to 44% in the placebo group (p=0.0652) (Figure 2). There was no difference between ataluren ~~20-, 20-, 40~~80 mg/kg/day and placebo. These results indicate that fewer patients receiving ataluren 40~~10-, 10-, 20-~~mg/kg/day worsened in 6MWD over 48 weeks.

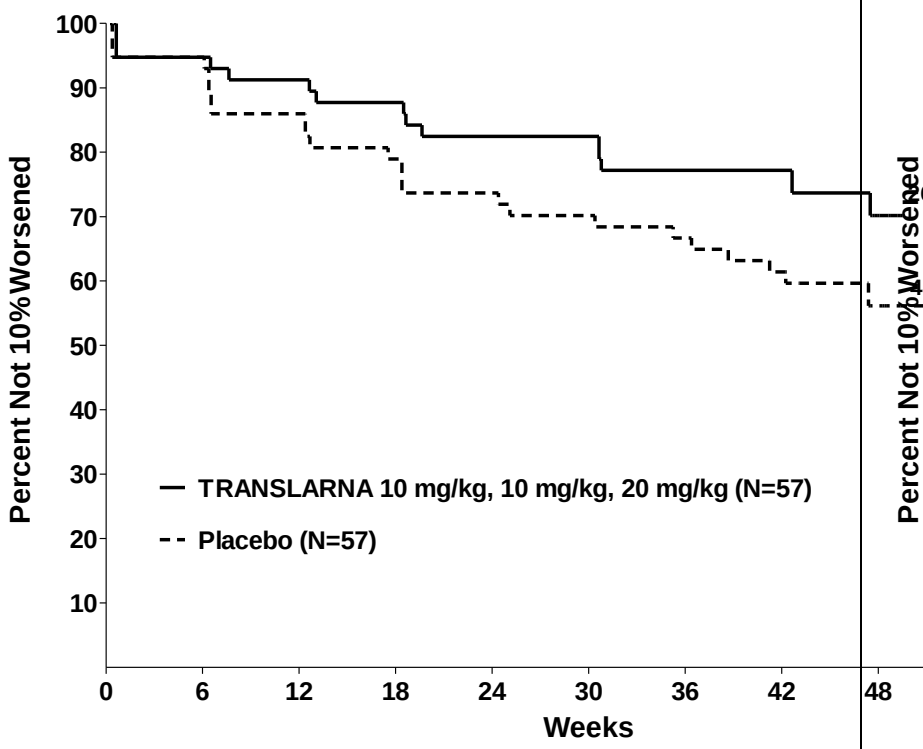
Figure 2. Kaplan-Meier Curve of Time to Persistent 10% 6MWD



A post-hoc analysis of time to persistent 10% worsening in 6MWD showed that 26% of patients in the ataluren 10-, 10-, 20-mg/kg arm had progressed at Week 48 compared to 44% in the placebo group (p=0.0652) (Figure 2). There was no difference between ataluren 20-, 20-, 40 mg/kg and placebo. These results indicate that fewer patients receiving ataluren 10-, 10-, 20-mg/kg worsened in 6MWD over 48 weeks.

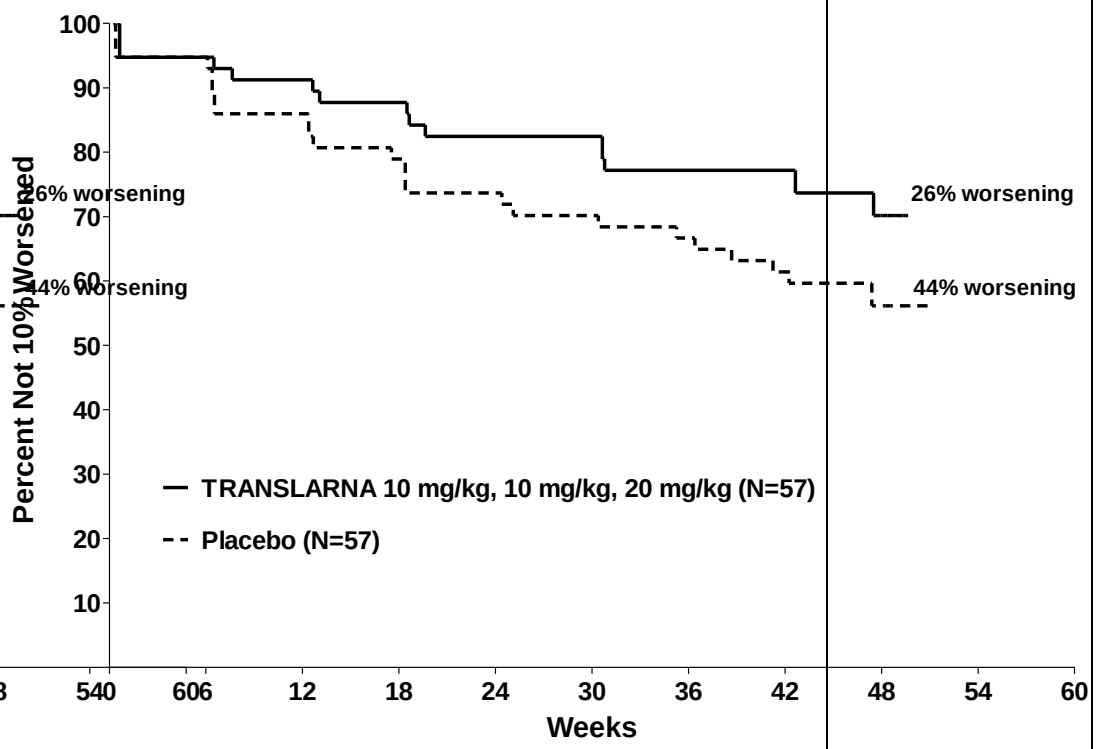
Figure 2. Kaplan-Meier Curve of Time to Persistent 10% 6MWD

Worsening (Study 1)



In timed function tests (TFTs), tests of time to run/walk 10 meters, time to climb 4 stairs, and time to descend 4 stairs, ataluren-treated patients demonstrated smaller increases in the time it takes to run/walk 10 meters, climb 4 stairs, and descend 4 steps, indicating slowing of nmDMD progression relative to placebo.

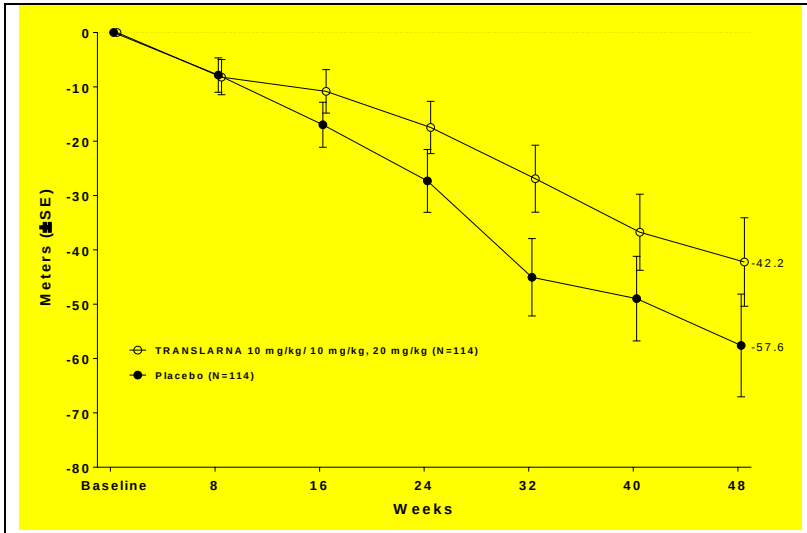
Worsening



In timed function tests (TFTs), tests of time to run/walk 10 meters, time to climb 4 stairs, and time to descend 4 stairs, ataluren-treated patients demonstrated smaller increases in the time it takes to run/walk 10 meters, climb 4 stairs, and descend 4 steps, indicating slowing of nmDMD progression relative to

The mean change in timed function tests from baseline to Week 48 was better in the ataluren ~~10-, 10-, 20~~40-mg/kg/day arm than placebo in time to run/walk 10 meters (better by 1.5seconds), time to climb 4 stairs (better by 2.4 seconds), and time to descend 4 stairs (better by 1.6 seconds), Figure 3.	placebo. The mean change in timed function tests from baseline to Week 48 was better in the ataluren 10-, 10-, 20-mg/kg arm than placebo in time to run/walk 10 meters (better by 1.5seconds), time to climb 4 stairs (better by 2.4 seconds), and time to descend 4 stairs (better by 1.6 seconds), Figure 3.	
In patients with a baseline 6MWD < 350 meters, the mean change in observed 6MWD from baseline to Week 48 was 68 meters better in the ataluren ~~10-, 10-, 20~~ 40-mg/kg/day arm than in the placebo arm (p=0.0053).	In patients with a baseline 6MWD < 350 meters, the mean change in observed 6MWD from baseline to Week 48 was 68 meters better in the ataluren 10-, 10-, 20-mg/kg arm than in the placebo arm (p=0.0053).	
In these patients, the mean change in timed function tests from baseline to Week 48 was better in the ataluren ~~10-, 10-, 20~~ 40-mg/kg/day arm than placebo in time to run/walk 10 meters (better by 3.5 seconds), time to climb 4 stairs (better by 6.4 seconds), and time to descend 4 stairs (better by 5.0 seconds).	In these patients, the mean change in timed function tests from baseline to Week 48 was better in the ataluren 10-, 10-, 20-mg/kg arm than placebo in time to run/walk 10 meters (better by 3.5 seconds), time to climb 4 stairs (better by 6.4 seconds), and time to descend 4 stairs (better by 5.0 seconds).	
Study 2 evaluated 230 male patients, ages 7 to 14 years. All patients were required to be able to walk ≥150 meters and less than 80% predicted without the need for assistive devices during a screening 6MWT. The majority of patients in both treatment groups were Caucasian (76%). Patients were randomised in a 1:1 ratio and received ataluren 40 mg/kg/day (n=115) or placebo (n=115) 3 times per day (morning, midday, and evening).		
Ataluren-treated patients experienced clinical benefit as measured		

by numerically favorable differences versus placebo across the primary and secondary efficacy endpoints. As the primary endpoint (change in 6MWD from baseline to Week 48) did not reach statistical significance ($p \leq 0.05$), all other p-values should be considered nominal. In the ITT population, the difference between the ataluren and placebo arms in mean change in observed 6MWD from baseline to Week 48 was 15.4 meters better in the ataluren 40 mg/kg/day arm than in the placebo arm. In a statistical based model the estimated mean difference was 13.0 meters ($p=0.213$), Figure 4. Separation between ataluren and placebo was maintained from Week 16 through the end of the study. Figure 4. Mean Change in 6-Minute Walk Distance (Study 2)		

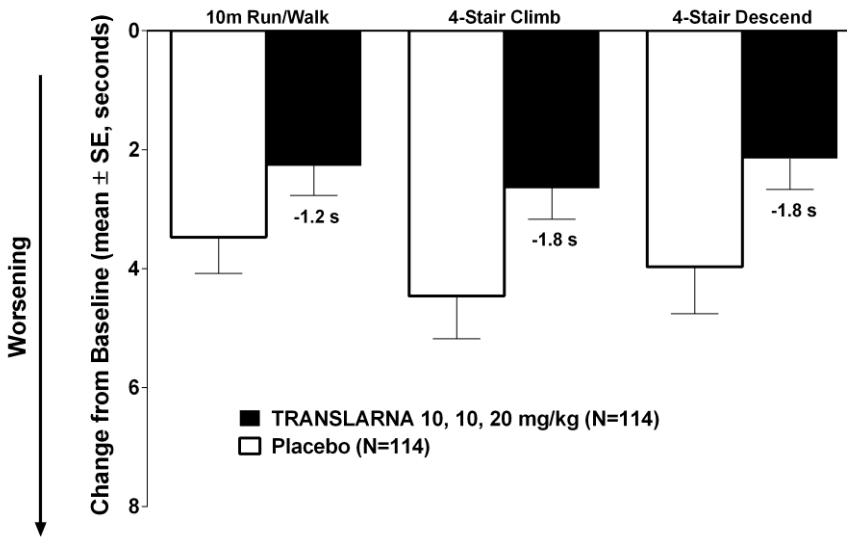


Over 48 weeks, ataluren-treated patients showed less decline in muscle function, as evidenced by smaller increases in the time to run/walk 10 meters, climb 4 steps, and descend 4 steps in the ataluren-treated group relative to placebo. The differences favoring ataluren versus placebo in mean changes in timed function tests at Week 48 in the ITT population reached the threshold for a clinically meaningful difference (changes ~1 to 1.5 seconds).

The mean change in timed function tests from baseline to Week 48 was better in the ataluren 40 mg/kg/day arm than placebo in observed time to run/walk 10 meters (better by 1.2 seconds, p=0.117), time to climb 4 stairs (better by 1.8 seconds, p=0.058), and time to descend 4 stairs (better by 1.8 seconds, p=0.012),

Figure 5.

Figure 5. Mean Change in Timed Function Tests (Study 2)



Time to 10% worsening in 6MWD was defined as the last time that 6MWD was not 10% worse than baseline. In the ITT population, the hazard ratio for ataluren versus placebo was 0.75 (p=0.160), representing a 25% reduction in the risk of 10% 6MWD worsening.

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
1. <u>לפני שימוש בתרופה</u>	• מיקופנולאט מופטיל, פנוברביטל ,ריפמפיצין, ציקלוספורין, אדפוויר, קפטופריל , פורזמיד, מתוטרקסאט, אוסלטמיוויר , אציקלוויר , בומטניד ,ציפרופלוקצסין, פמוטידין , בנזילפניצילין, סיטגליפטין -,פרווסטטין ,רוסווסטטין,אטורווסטטין,פיטווסטטין ,טלמיסרטן,וולסרטן ,אולמסרטן. תכשירים אלה לא נבדקו במתן עם טרנסלרנה, על כן עליך להיות במעקב צמוד של הרופא שלך.	• מיקופנולאט מופטיל, פנוברביטל ,ריפמפיצין, ~~ציקלוספורין~~, אדפוויר, קפטופריל , פורזמיד, מתוטרקסאט, אוסלטמיוויר , אציקלוויר , בומטניד ,ציפרופלוקצסין, פמוטידין , בנזילפניצילין, סיטגליפטין -,פרווסטטין ,רוסווסטטין,אטורווסטטין,פיטווסטטין ,טלמיסרטן,וולסרטן ,אולמסרטן. תכשירים אלה לא נבדקו במתן עם טרנסלרנה, על כן עליך להיות במעקב צמוד של הרופא שלך.
4. <u>תופעות לוואי</u>	כמו בכל תרופה, השימוש ב טרנסלרנה עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. יתכן ולא תסבול מאף אחת מהן. תופעות לוואי המופיעות לעיתים קרובות מאוד (שכיחות של יותר מ- 1:10) : כאב ראש, בחילות, הקאות. תופעות לוואי המופיעות לעיתים קרובות (שכיחות של עד 1:10) : ירידה בתיאבון, ירידה במשקל, סחרחורת, עליה בלחץ הדם, שיעול, דימום מהאף, עצירות, שלשול, גזים, רפלוקס הגורם לתחושה של (צרבת), אי נוחות בבטן, כאבי בטן, פריחה, כאבי זרועות או רגליים, ציסטה בכליה, עליה חריגה בתדירות מתן שתן, כאב בחזה, צבע שתן לא רגיל דם בשתן, חום, עייפות.	כמו בכל תרופה, השימוש ב טרנסלרנה עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. יתכן ולא תסבול מאף אחת מהן. תופעות לוואי המופיעות לעיתים קרובות מאוד (שכיחות של יותר מ- 1:10) : ~~כאב ראש, בחילות~~, הקאות. תופעות לוואי המופיעות לעיתים קרובות (שכיחות של עד 1:10) : ירידה בתיאבון, רמת טריגליצרידים גבוהה בדם, כאב ראש, בחילות, ירידה במשקל, ~~סחרחורת~~, עליה בלחץ הדם, שיעול, דימום מהאף, עצירות, ~~שלשול~~, גזים, ~~רפלוקס הגורם לתחושה של (צרבת)~~, אי נוחות בבטן, כאבי בטן, פריחה, כאבי זרועות או רגליים, ~~ציסטה בכליה, עליה חריגה בתדירות מתן שתן~~, כאב בחזה, ~~צבע שתן לא רגיל~~ דם בשתן, חום, ~~עייפות~~.