23 November 2016
EMA/CHMP/738638/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Translarna

International non-proprietary name: ataluren

Procedure No. EMEA/H/C/002720/R/0022

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Assessment Timetable / Steps taken for the assessment

Tick box	Timetable	Planned dates	Actual dates
☒	Start of procedure:	29 February 2016	29 February 2016
☒	CHMP and PRAC Rapporteurs Joint Assessment Report	29 March 2016	06 April 2016
☒	CHMP and PRAC members comments	4 April 2016	4 April 2016
☒	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	7 April 2016	28 April 2016
☒	PRAC endorsed relevant sections of the assessment report	14 April 2016	14 April 2016
☒	Joint AR on responses updated following comments and PRAC discussion (if applicable)	N/A	N/A
☒	CHMP Request for Supplementary Information (RfSI)	28 April 2016	28 April 2016
☒	MAH responses to (RfSI) received on	31 May 2016	31 May 2016
☒	CHMP and PRAC Rapporteurs' joint AR on responses	8 June 2016	9 June 2016
☒	PRAC endorsed relevant sections of the assessment report	9 June 2016	9 June 2016
☒	CHMP members' comments	13 June 2016	13 June 2016
☒	Joint AR on responses updated following comments and PRAC discussion (if applicable)	16 June 2016	N/A
☒	Scientific Advisory Group meeting	16 June 2016	16 June 2016
☒	An Oral explanation took place on	20-23 June 2016	21 June 2016
☒	CHMP 2nd Request for Supplementary Information (RfSI)	23 June 2016	23 June 2016
☒	MAH responses to (RfSI) received on	28 June 2016	28 June 2016
☒	CHMP and PRAC Rapporteurs' joint AR on responses	6 July 2016	8 July 2016
☒	PRAC endorsed relevant sections of the assessment report	7 July 2016	8 July 2016
☒	CHMP members' comments	11 July 2016	11 July 2016
☒	Joint AR on responses updated following comments and PRAC discussion (if applicable)	14 July 2016	N/A
☒	CHMP 3rd Request for Supplementary Information (RfSI)	21 July 2016	21 July 2016
☒	MAH responses to (RfSI) received on	20 September 2016	20 September 2016
☒	CHMP Rapporteur AR on responses	28 September 2016	06 October 2016

Tick box	Timetable	Planned dates	Actual dates
☒	Scientific Advisory Group meeting	29 September 2016	29 September 2016
☒	CHMP members' comments	03 October 2016	03 October 2016
☒	Updated AR on responses following comments	06 October 2016	N/A
☒	An Oral explanation took place on	10-13 October 2016	11 October 2016
☒	CHMP 4th Request for Supplementary Information (RfSI)	13 October 2016	18 October 2016
☒	MAH responses to (RfSI) received on	18 October 2016	19 October 2016
☒	CHMP Rapporteur AR on responses	26 October 2016	28 October 2016
☒	CHMP members' comments	31 October 2016	31 October 2016
☒	Updated AR on responses following comments	3 November 2016	N/A
☒	An Oral explanation took place on	7-10 November 2016	8 November 2016
☒	CHMP opinion adopted on	10 November 2016	23 November 2016

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List of abbreviations and definition of terms

Abbreviation	Term
6MWD	6-min walk distance
6MWT	6-min walk test
ADP	ambulatory decline phase
AE	adverse event
ANCOVA	analysis of covariance
BR	benefit risk
BUN	blood urea nitrogen
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CHMP	committee for medicinal products for human use
CI	confidence interval
CINRG	cooperative international neuromuscular research group
cITT	corrected intent-to-treat
CMA	conditional marketing authorisation
CSR	clinical study report
DMD	duchenne muscular dystrophy
EC	european commission
ECG	electrocardiogram
EU	european union
EMA	european medicines agency
FVC	forced vital capacity
HDL	high density lipoprotein
ITT	intent-to-treat
IV	intravenous
LDL	low density lipoprotein
m	metres
MAH	marketing authorisation holder
MMRM	mix-model repeated-measures
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid

Abbreviation	Term
nmDMD	nonsense mutation duchenne's muscular dystrophy
nmCF	nonserious mutation cystic fibrosis
nmHA/HB	nonsense mutation hemophilia A/B
nmMMA	nonsense mutation methylmalonic acidemia
NSAA	north star ambulation assessment
PBO	placebo
PK	pharmacokinetic
PODCI	paediatric outcomes data collection instrument
RCT	randomised controlled trials
RfSI	request for supplementary information
RMP	risk management plan
RSI	reference safety information
SAE	serious adverse event
SAG	scientific advisory groups
SAP	statistical analysis plan
SAWP	scientific advice working party
SmPC	summary of product characteristic
SOB	specific obligations
TID	three times a day

1. Background information on the renewal

1.1. Conditional marketing authorisation

On 31 July 2014, the European Commission issued a conditional Marketing Authorisation for Translarna based on a positive Opinion adopted by the Committee for Medicinal Products for Human Use (CHMP) on 23 May 2014. This implied that, pursuant to Article 14(7) of Regulation (EC) No 726/2004 and Article 5 of Commission Regulation (EC) No 507/2006, the Marketing Authorisation Holder (MAH) will complete ongoing studies, and conduct new studies as required, as listed in Annex II.E of the marketing authorisation, the so-called Specific Obligations (SOBs), in order to confirm that the benefit-risk (BR) balance is positive and to provide the additional data. These data form the basis of the renewal of the conditional marketing authorisation.

1.2. Annual renewal

A conditional marketing authorisation is valid for one year and may be renewed annually upon request by the MAH. Therefore, pursuant to Article 14 (7) of Regulation (EC) No 726/2004 and Article 6(2) of Commission Regulation (EC) No 507/2006, the MAH, PTC Therapeutics International Limited, submitted to the Agency on 05 February 2016 an application for renewal of the conditional marketing authorisation for Translarna. In accordance with Article 6(4) of Commission Regulation (EC) No 507/2006, the conditional marketing authorisation shall remain valid until a decision is adopted by the Commission in accordance with Article 10 of Regulation (EC) No 726/2004.

Translarna was designated as an orphan medicinal product EU/3/05/278 on 31 May 2005.

EXECUTIVE SUMMARY

On 31 July 2014, the European Commission issued a conditional Marketing Authorisation for Translarna, for the treatment of Duchenne muscular dystrophy (DMD) resulting from a nonsense mutation (nm) in the dystrophin gene, in ambulatory patients aged 5 years and older, based on a positive opinion adopted by the CHMP on 23 May 2014. The Marketing Authorisation Holder (MAH) was obligated to complete ongoing studies, and to conduct (PTC124-GD-020-DMD [referred to as “Study 020” hereafter]) as a SOB, in order to confirm that the benefit-risk balance is positive and to provide additional data. These data form the basis of the renewal of the conditional marketing authorisation.

Study 020 was a multicentre, randomised, double-blind, placebo-controlled, confirmatory study with the 10, 10, 20 mg/kg doses in nmDMD patients. The clinical study report was completed on 09 Dec 2015. Final results were submitted to the European Medicine Agency (EMA) on 07 January 2016 as a separate Type II variation application. These results have been assessed in the parallel variation and also form the basis for this renewal procedure.

This renewal procedure provides the basis for the benefit-risk re-evaluation of Translarna based on the totality of the data including those at the time of the conditional approval, the ones gathered from Study 020, and additional analyses of the data from Study 019 and extension phase of 020 study (020e), provided in response to the list of questions from the CHMP. In order to address the scientific concerns regarding the impact of the Study 020 results on the benefit-risk balance and the possibility to conduct a new study to confirm the benefit-risk balance of the medicinal product, four requests for supplementary information were exceptionally needed to conclude the scientific assessment; these requests are described in detail in this report. Furthermore, three CHMP oral explanations by the MAH, two Scientific Advisory Groups (SAG) Neurology and a Scientific Advice Working Party (SAWP) meetings took place in

the context of this assessment; these are also addressed in this report. Patients' representatives were involved during the oral explanations and the SAG neurology meeting. While the scientific details of the assessment are included in the following sections of this report, the milestones are summarised hereafter.

In June 2016, the CHMP was of the view that efficacy generated in the post-hoc analysis of PTC124-GD-007 DMD (referred as "Study 007" hereafter) had not been confirmed in Study 020, and therefore did not allow to convert to a full marketing authorisation. This also questioned the positive benefit-risk ratio of the product. The company sought to maintain conditional approval with updated SOBs. However, the CHMP was not convinced that the proposal to generate further data was sufficiently robust and the company was invited to propose alternative study designs. Therefore, the CHMP requested that the MAH provides a detailed proposal for generating additional scientifically valid, confirmatory data on the efficacy of ataluren in the indicated population, taking into consideration the experience from the results of the two randomised trials as well as the current knowledge and public data from other trials in DMD.

In July 2016, the CHMP was not convinced that the key design features for the newly proposed randomised controlled trial (RCT) were optimal in terms of sensitivity to detect drug effects and generalizability to the broad target population. In this respect, the MAH was advised to consider applying for protocol assistance at the SAWP to discuss an adequate proposal for a clinical trial which will be able to demonstrate in a nmDMD patient population, a robust and clinically meaningful effect of ataluren. The CHMP requested the MAH to propose a study that should confirm the positive benefit-risk ratio and address the outstanding uncertainties. Related to this, the feasibility to conduct this study (e.g. in terms of proposed measurements and within a reasonable timeframe) should also be documented and discussed.

In October 2016, the revised proposal for the RCT design subsequently submitted by the MAH was extensively discussed by the CHMP taking into account conclusions of the SAWP, a SAG neurology meeting held in September and an Oral Explanation held during the October CHMP meeting. The CHMP was of the view that the lack of robustness of the totality of the data provided so far, together with concerns about some of the key design features of the proposed RCT (to serve as a SOB in the context of the conditional marketing authorisation), did not allow to support the renewal of the conditional marketing authorisation. Therefore, the CHMP requested that the MAH should discuss the benefit-risk of Translarna in the light of all available clinical data, and that the MAH provide a final proposal for a study that will be able to provide comprehensive clinical data on the benefit-risk of Translarna in the current indication and can potentially serve as a SOB in the context of the maintenance of the conditional approval.

In November 2016, the CHMP concluded that the conditional marketing authorisation can be renewed considering that the totality of the clinical data available (including new data and analyses made available by the MAH and presented during the last oral explanation) continued to support the positive benefit-risk of Translarna in the context of a conditional approval. The Committee also took into account the fact that the MAH proposed an updated confirmatory study design, built upon the most current knowledge of the disease and its natural progression, as well as on the data gathered from the previous studies, and considered it appropriate to serve as a SOB to answer the remaining uncertainties in the context of conditional marketing authorisation.

2. Overall conclusions and benefit-risk balance

2.1. Specific Obligations

Compliance of SOB data submitted:

During the period covered by this Annual Re-Assessment: - no new data regarding SOBs were due. - no new data regarding SOBs have emerged.	 ☐ ☐
During the period covered by this Annual Re-Assessment, data on the SOBs have been submitted that overall: - are compliant in terms of adherence to deadlines - are compliant in terms of acceptability of data submitted	Yes No ☒ ☐ ☐

Pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH, PTC Therapeutics International Limited (PTC), committed to complete a multicentre, randomised, double-blind, placebo-controlled, confirmatory study with the 10, 10, 20 mg/kg doses in nmDMD patients (Study 020) as a SOB. The Study 020 clinical study report was completed on 09 Dec 2015. Final results were submitted to the EMA on 07 Jan 2016 as a separate Type II variation application, hereafter referred to as SOB Type II variation (sequence 0040, Procedure No: EMEA/H/C/002720/II/0020).

Overall Conclusions

Based on the totality of the data provided, the Committee recommended the renewal of the conditional marketing authorisation for Translarna, concluding that the MAH demonstrated that the criteria for the renewal of the conditional marketing authorization continued to be met, including a positive benefit-risk balance of the medicinal product and the ability to provide comprehensive clinical data through a well-designed and feasible post-authorisation study.

2.2. Benefit-risk Balance

Benefits

Beneficial effects

The initial conditional marketing authorisation was based on a single Phase II, multicentre, randomised, placebo-controlled study of 48 weeks duration (further referred to as Study 007) in which two dose regimens of ataluren were compared to placebo. In this study, the difference in the mean 6-min walk distance (6MWD) at Week 48 between ataluren low dose (10, 10, 20 mg/kg per day) and placebo in a corrected intent-to-treat (cITT) population was 31.7 metres (95 % confidence interval [CI] 5.1,58.3; nominal p=0.0197, adjusted p=0.0367). In the same population, the percentages of patients with at least 10% worsening in 6MWD at Week 48 were 44% for the placebo group and 26% in the group treated with the lower ataluren dose (nominal p=0.0326, adjusted p=0.0652).

A more pronounced effect was observed in a subset of patients in the “ambulatory decline phase” (ADP) of the disease, defined post-hoc as patients between 7 and 16 years of age, with baseline 6MWD ≥150 m and ≤80% of predicted value. This post-hoc subgroup analysis showed a difference of 49.9 meters (p=0.0096) in 6MWD in favour of the group treated with the lower ataluren dose when compared with the placebo group. Additionally, treatment differences favouring ataluren were observed for each of the timed

function tests evaluated in the study (time to run/walk 10 m, time to climb and descend 4 steps), suggesting positive effects of ataluren on daily activities.

The completion of Study 020 in declining patients was a condition to the initial conditional marketing authorisation. In this study, the observed difference in the mean 6MWD at Week 48 between ataluren and placebo was 15.4 meters and 12.3 meters model-estimated (p=0.213). Although the primary endpoint did not reach statistical significance, a pattern of positive trends in the ITT population favouring ataluren versus placebo was observed across different endpoints, including time to run/walk 10 m, time to climb and descend 4 steps and time to loss of ambulation, which is consistent with slowing of disease progression. The North Star Ambulation Assessment (NSAA) was measured in Study 020 only and showed a positive trend of 1.5 points difference, favouring ataluren in the ITT population (p=0.270), in a population with an average score of 20. The post-hoc analysis of the 17 individual functions of the NSAA showed that on all but 1 item (head lift), the proportion of ataluren treated patients who lost a certain level of ability was lower compared to placebo group. Positive trends were also observed in the Paediatric Outcomes Data Collection Instrument (PODCI) Transfers/Basic Mobility and Sports/Physical Functioning domain scores which assess difficulty in performing routine motor activities in daily life.

The beneficial effects of ataluren in Studies 007 and 020 were more evident in post-hoc defined sub-populations corresponding to those patients with moderate decline. In the subset of patients with a baseline 6MWD test ≥300 m and <400 m, a 49.9 m difference (p=0.0125) in mean change in 6MWD at Week 48 was observed in favour of ataluren (n=32) versus placebo (n=31) in Study 007. Similarly in Study 020, a 47.2 m difference (p=0.007) was observed in favour of ataluren. This larger treatment difference was also observed across time function tests in both Studies 007 and 020. Using another categorisation by functional status at baseline i.e. patients with a baseline 6MWD test ≥300 m and a time to stand from supine >5 seconds to exclude stable patients, larger beneficial effects of ataluren were also noted on the 6MWD test and the time function tests.

Data from ongoing open-label extension studies 019 and 020e provided supportive evidence of preservation of an effect of ataluren on loss of ambulation, walking ability, and functional endpoints.

Uncertainty in the knowledge about the beneficial effects

Both Studies 007 and 020 did not show a statistically significant result according to the analysis on the primary endpoint (6MWD).

In Study 020, with an intended enriched patient population, the outcome on the primary endpoint showed a smaller difference (15.4 m) in favour of ataluren when compared with placebo in the change from baseline to the end of the study at 48 weeks in 6MWD. Similarly to the outcome on the primary endpoint, Study 020 showed smaller differences between ataluren and placebo, when compared with Study 007. Finally, the positive trend observed in Study 007 with respect to the percentages of patients with at least 10% worsening in 6MWD at Week 48 was not demonstrated in Study 020.

The analyses in a ‘mid-range’ population corresponding to those patients with moderate decline were performed post-hoc, albeit before un-blinding according to the MAH for the subgroup ≥300m 6MWD test <400m. Although it can be agreed in principle that stable patients may not show a change within 48 weeks, and that patients characterized by a rapid loss of ambulation due to extensive muscle deterioration may be too unpredictable, the post-hoc definition of the mid-range subgroup. The open label and uncontrolled nature of the ongoing extension studies 019 and 020e limits the interpretation of the effects of ataluren seen in the efficacy outcomes and hence, the results could be considered as supportive only.

Pharmacodynamic confirmation of efficacy based on dystrophin analysis could not be provided by study 007, despite the fact that biopsies were collected. While the technical problems with dystrophin quantification were recognised by the CHMP, the quality of the biopsies supplied was of concern. The GCP inspection identified that several steps were not respected, namely instructions for performing the muscle biopsies and the storage/ shipping logistics. The CHMP concluded that despite the identified weaknesses of the pharmacology data (e.g. on mechanism of action and bell-shaped dose-response hypothesis), the limitations within the nonclinical package could be considered acceptable, if sufficiently compensated by compelling clinical evidence. Considering the limitations of data on clinical efficacy, the CHMP pointed out that the dossier would have benefited from supportive data on pharmacodynamics. Despite these uncertainties no biopsies were collected in study 020 and hence, unfortunately, no further confirmatory data on PD has been provided which could have potentially allowed to further support the claims of the benefit of ataluren.

Risks

Unfavourable effects

The exposure to ataluren has extended to more than 1,000 subjects in clinical trials, including more than 400 nmDMD patients, some of them with up to 5 years of exposure. Study 020 did not show any new safety concerns. Therefore, ataluren remains generally well tolerated in patients with nmDMD, with the most common adverse events being headache and gastrointestinal disorders such as nausea, vomiting, (upper) abdominal pain, flatulence, diarrhoea, stomach discomfort, constipation and regurgitation.

Among the serious adverse events reported, a number of cases were identified of infections. This is of concern in a patient population, which is on long-term corticosteroids treatment.

Another risk, which has been observed in both studies and also in the post marketing exposed subjects, are bone fractures. This is of concern, in particular the lower limb fractures which may accelerate the time to loss of ambulation due to temporary immobilization.

The laboratory data indicated that exposure to ataluren could cause elevation of serum cholesterol and triglycerides. In Study 020 all patients received corticosteroids and in about 17% an increase in total cholesterol, low-density lipoprotein (LDL), and triglycerides values in pathological ranges values was observed. Therefore, ataluren adds an additional risk of change in lipid profile due to corticosteroid treatment. “Changes in the lipid profile” were considered as an important identified risk in the proposed Risk Management Plan.

Of note, elevations of serum creatinine occurred in several patients with nonsense mutation cystic fibrosis (nmCF) treated concomitantly with intravenous aminoglycosides. In all cases, the elevations resolved after discontinuation of the aminoglycosides indicating that co-administration of ataluren and intravenous aminoglycosides may potentiate the nephrotoxic effect of the aminoglycosides. Based on this findings “potentiation of aminoglycoside renal toxicity” was determined as an important identified risk.

There were no deaths in the placebo-controlled study. Three fatal cases were seen in one open-label study, but the fatal outcomes were not considered related to treatment with ataluren.

Uncertainty in the knowledge about the unfavourable effects

Increase in blood pressure including cases of hypertension requiring antihypertensive treatment was observed in subjects treated with ataluren. While this could have been due to the use of corticosteroids administered concomitantly, this issue was considered an uncertainty and captured as a potential risk in the proposed Risk Management Plan.

One 12-year-old boy, exposed to ataluren for a longer period of time, has suffered from a myocardial infarction. Despite uncertainties about the causal relationship of this event and the treatment with ataluren, this case raises a concern about a possible increased risk for cardiac events due to a number of factors. Boys with DMD have a compromised cardiac function related to the development of dilative cardiomyopathy due to underlying disease. Treatment with corticosteroids is related to increased blood pressure and lipid changes, and as ataluren is meant for long-term treatment this may lead to an increased risk for cardiac events.

The cumulative data up to 05 April 2016 provided 16 cardiac SAEs. While most events occurred in patients with a history of cardiac disease, the concern of cardiac safety remains, since this is a realistic risk in the DMD patient population which is known to have cardiac comorbidity.

The preclinical data as well as data from healthy volunteers and DMD patients indicated that exposure to ataluren may lead to an increase in transaminases. These changes seemed to be reversible after exposure to ataluren was stopped but a clear hepatotoxic effect has not been confirmed. The CHMP considered hepatotoxicity as an important potential risk.

From the non-clinical database, the finding of malignant hibernomas in rat raised the concern as to whether occurrence of similar effects could be expected in humans, particularly in the paediatric population where the quantity of the brown adipose tissue is higher. In particular, the CHMP considered that malignant hibernomas could be related to the effects of ataluren on fat tissue metabolism and to effects on plasma lipid parameters, which were observed in rats, dogs and humans. Thus, “hibernomas” were reflected in the proposed risk management plan of ataluren as an important potential risk.

As stated before, the nmCF study data suggested an effect of ataluren on renal abnormalities. Although the mechanism of a potential contribution of ataluren to the reported cases of nephrotoxicity was not known, this signal in the clinical development appeared to reinforce the non-clinical findings seen in mice. Based on the clinical data available, renal toxicity was assumed to occur less likely in DMD patients, but was still perceived as a potential important risk. In their conclusions, the CHMP highlighted that while the evidence did not indicate increased risk for the DMD population, as a precautionary measure, additional wording should be implemented in the Product Information to discourage concomitant use of ataluren and nephrotoxic medicinal products.

Treatment of patients with renal or hepatic impairment is another area of uncertainty, as no specific studies were performed and potential safety concerns are implied by the pharmacokinetics of ataluren. Since renal excretion accounts for ~ 50% of the drug elimination, renal impairment is likely to result in accumulation of ataluren and/or ataluren glucuronide. Similarly, since ataluren is extensively metabolized in liver, hepatic impairment is expected to result in ataluren increased plasma concentrations. The CHMP considered that without clinical data, understanding of both efficacy and safety profile of ataluren in subjects with renal or hepatic impairment remains limited.

The latest data submitted reported also 6 cases of off label use: 1 child < 5 years and 5 non-ambulant patients. This is of concern because such use may happen in cases without a confirmed nonsense mutation.

Benefit-risk balance

Importance of favourable and unfavourable effects

Treatment effect on muscle function is critical to patients (Peay, 2014). Preserving ambulation and delaying the time to wheelchair use is important in the life of young DMD boys, because autonomy is essential for the patients and their families. In this respect measuring the effect of treatment with ataluren by means of the 6 minute walk test (6MWT) can provide relevant information. Notwithstanding

several lines of evidence supporting the clinical relevance of a 30-meter difference in 6MWD, recent natural history studies discuss even smaller differences as being clinically meaningful for DMD patients.

Delaying the time to loss of ambulation and loss of other functions is relevant for these patients since it means longer time with preserved autonomy and better quality of life (QOL). The data on time to loss of ambulation and on the separate NSAA items provide some positive trends whereby these milestones may be delayed in ataluren exposed patients. Ability to climb and descend a short grouping of stairs, ability to run in short bursts or to walk a short distance unaided e.g. to a bathroom, reflect the typical activities important in the lives of DMD patients. Importantly, recent data indicated that timed function tests (TFTs) evaluating these abilities are, similarly to the 6MWD test, predictive of the time for a patient to become non-ambulant (Humbertclaude et al, 2012). Natural history data from the Cooperative International Neuromuscular Group indicated that changes in these parameters are predictive of the likelihood of loss of ambulation over 1 year. Therefore, the outcomes of these measurements are important for the entire understanding of efficacy and this makes the consistent pattern of positive trends across TFTs and studies a relevant finding.

Falls commonly lead to fractures in DMD patients and these injuries may accelerate loss of ambulation. Decreasing the rate of accidental falls and hence the risk of fractures, pain and other trauma would be of benefit to the patients. It remains unclear if the falls and fractures in the ataluren treated patients were related to treatment or because patients in the studies were encouraged to be active and believed to be able to move more. However increased risk of fractures is of special concern in this population and measures should be taken to avoid these.

With respect to decrease in wheel chair use, benefits can be attributed not only in terms of ambulation itself, but also by positive impact on the respiratory function and minimisation of scoliosis. Thus, if sufficiently documented these effects would be considered of high importance. The most commonly reported treatment-related adverse events vomiting, diarrhoea, upper abdominal pain, flatulence, nausea, headache, and decreased appetite were not considered to raise major safety concerns in a seriously debilitating and life-threatening condition such as DMD.

The effect of ataluren on the lipid profile (cholesterol and triglyceride levels) continued to be considered as important, especially in a situation where long-term administration of corticosteroids is expected. The values appeared to stabilize early in a proportion of the subjects, which was considered reassuring, however, there were also patients with high risk levels. This is reflected in the label.

Similarly, the risk of hypertension during concomitant use of corticosteroids and ataluren was seen as clinically relevant, considering that such co-administration would occur in the majority of patients in the clinical practice.

In the context of the age group targeted, the potential risk of hibernoma was considered relevant, due to higher proportion of brown fat tissue in children.

Discussion on the benefit-risk balance

Nonsense mutation DMD is a rare, progressive and fatal disease. There is no cure available and the unmet medical need is therefore considerable.

Translarna received a conditional marketing authorisation in 2014 for the treatment of DMD resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older. According to the MAH, there are approximately 400 patients that fit the current indication in Europe.

The conditional marketing authorisation was granted with an obligation for the MAH to generate additional data post-authorisation in a study (020) targeting ADP patients to provide confirmatory

evidence of efficacy. The hypothesis that the ability to measure a treatment effect would be greater in the ADP patients could not be considered as confirmed by the primary analysis of the data from Study 020 since the study did not meet its primary endpoint. Therefore, a full marketing authorisation cannot be granted on the basis of this new clinical data.

Study 020 results were considered inconclusive, yet they were informative as they contributed to a pattern of numerically positive trends across clinical endpoints reflecting the daily functioning of DMD patients. As patients pointed out during the oral explanations, it can be difficult in the setting of DMD to reconcile data with real life experience and the perceived treatment benefits. Methodological challenges may have contributed to limit the interpretability of Study 020 results. As outlined by external experts from the SAG Neurology, the variability in the results of the endpoints is inherent to the tests themselves. "Noise" in the results is to be expected because many factors influence those measurements (e.g. motivation of the patient, performance of the measuring specialist, conditions while performing the test etc.). In this context, patients' representatives also underlined during the oral explanations that differences on endpoints such as TFTs which appear small and not statistically significant can be life changing for patients.

Although the intended enrichment in Study 020 led to inconclusive results, the MAH divided Study 020 into three subgroups, defined post- hoc according to functional status at baseline: 6MWD <300m (high risk of loss of ambulation), 6MWD ≥300m and <400m (mid-range) and 6MWD ≥400m (stable population). The beneficial effects of ataluren were more evident in the mid-range population across endpoints and Studies 007 and 020. Even though the specific cut-off points on the baseline 6MWD results were considered arbitrary, both CHMP and SAG Neurology agreed that a mid-range population with regards to disease severity would be more suitable to demonstrate an effect from a drug intended to induce production of dystrophin. This is supported by natural history data whereby such patients have started their decline in walking ability, so no learning effects are present, but still have sufficient muscle preserved to expect an effect. In the other two sub-groups, natural history data have shown a tendency for relative stability on the 6MWD in the milder patients with baseline >400 m, and very rapid and unpredictable decline to loss of ambulation in the advanced <300 m group, within the timelines of a potential clinical study duration (e.g. 12-24 months).

Further analyses, including a slope analysis of the 6MWD including data from Studies 020 and 020e up to 72 weeks provided additional support for the argument that a mid-range group is more suitable to demonstrate an effect. In the same dataset, time to loss of ambulation, change in 6MWD, TFTs, and NSAA were performed for the three subgroups. Although extensions studies are open label and uncontrolled, they provide valuable information in particular as the SAG Neurology pointed out that longer trials and observation time would be needed to collect meaningful data in DMD. Placebo and ataluren arms remained stable in the >400 m group with no patients losing ambulation. There were fewer events in the active arm than in the placebo arm in the 300-400 m subgroup, and the effect was carried on after Week 48 when the placebo patients were switched to ataluren. In the <300 m subgroup, there seemed to be some effect in the first 48 weeks which was reduced in the later 48 weeks, despite the switch to ataluren, which supports the assumptions that such a population is not suitable to demonstrate efficacy. Similar observations were made for results on 6MWD and TFTs and NSAA.

Focusing on a mid-range population, the MAH conducted post-hoc analyses in a newly defined subgroup of patients characterised by a baseline 6MWD ≥300m and a time to stand from supine with >5 seconds. Change in 6MWD and functional outcomes were analysed both for Studies 007 and 020 and comparisons were performed between the active arms, the placebo arms and patients from 2 natural history of disease data cohorts (University of Leuven study and the UK North Star Registry). The results observed favoured ataluren.

In view of the methodological challenges limiting the interpretation of Study 020 and the consistent pattern of positive effects across studies and endpoints, the CHMP explored the possibility for an additional scientifically valid, confirmatory study taking into consideration the learnings from the completed randomised trials as well as the current knowledge and public data from other trials in DMD. The design and the feasibility of a randomised controlled clinical study as proposed by the MAH were extensively discussed by the CHMP SAWP, a SAG Neurology meeting as well as in Oral Explanations during CHMP plenary meetings. A randomised, double-blind, clinical trial in patients with nmDMD ≥ 5 years old and baseline 6MWD ≥150 meters, a placebo-controlled treatment period of 18 months, followed by open-label treatment for an additional 18 months and a primary analysis in a pre-defined patient subset using the 6MWD as a primary endpoint was eventually agreed by the CHMP as being feasible and able to generate confirmatory data.

This study differs considerably from the previously conducted Studies 007 and 020. The broader inclusion criteria and the extended follow-up time will allow for a greater understanding of the effect of ataluren for all patient subgroups, including patients who would most likely be stable for up to 2 years (>400m baseline 6MWD). The primary analysis will be a slope analysis on the 6MWD, conducted at the end of the 18 months long placebo controlled phase on a pre-defined patient subset where a treatment effect can be more sensitively measured. A comprehensive set of outcome measures is also included to provide information beyond measurements of ambulation. This will include evaluation of the effects of ataluren on lower-limb muscle function, upper-limb muscle function, patient and/or parent perception of treatment benefit, as well as exploratory measures of the changes observed in muscle composition during the disease course.

During the oral explanation at the CHMP the MAH proposed to conduct a primary pharmacological and functional correlation study in order to provide further data on the activity of ataluren in nmDMD. The new proposal was not considered essential to address the remaining uncertainties on the efficacy of Translarna. The data from such a study could only be viewed as supportive in the context of a conditional marketing authorisation, as the focus would be on the clinical data, derived from the study, as proposed in the above.

Based on the totality of the data provided, the CHMP concluded that the criteria for the renewal of the conditional marketing authorization continued to be met, including a positive benefit-risk balance of the medicinal product and the ability to provide comprehensive clinical data through a well-designed and feasible post-authorisation study. As a condition to this renewal of the conditional marketing authorisation, the MAH must conduct and submit the results of a 2-phase, multicentre, randomised study, including 18-month, placebo-controlled study, followed by a 18-month open-label extension, according to a final protocol agreed by CHMP. This will be monitored on an annual basis as the final study report must be submitted by September 2021.

3. Final Recommendations

Based on the review of the totality of the clinical data available including the final results of the study object of the SOBs, the benefit-risk balance for Translarna in the treatment of DMD resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older, continues to be favourable, and therefore the renewal of the conditional marketing authorisation is recommended, subject to the conditions and obligations as detailed in this assessment report.

Amendments to the marketing authorisation

In view of data submitted as part of the renewal application, amendments to the Annex II of the Product Information are recommended.

The following conditions of the marketing authorisation(s) of medicinal products containing the active substance ataluren are recommended:

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed Risk Management Plan (RMP) presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit-risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a Periodic Safety Update Report (PSUR) and the update of a RMP coincide, they can be submitted at the same time.

SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of ataluren in the treatment of ambulant patients with nmDMD aged 5 years or older, the MAH will conduct and submit the results of a multicentre, randomised, double-blind, 18-month, placebo-controlled study, followed by a 18-month open-label extension, according to an agreed protocol.	Final study report to be submitted Due date: September 2021

4. Appendix – divergent position to CHMP opinion

APPENDIX 1

DIVERGENT POSITION

Divergent position expressed by CHMP members:

The undersigned member(s) of the CHMP did not agree with the CHMP's positive opinion recommending the renewal of the conditional marketing authorization of Translarna (ataluren) indicated in the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older.

The reason for the divergent opinion was as follows:

The conditional marketing authorization of Translarna, granted in 2014, was mainly based on the data from the single phase 2b study (007). Study 007 failed, however, to demonstrate evidence of therapeutic efficacy of Translarna either on the primary endpoint (change in 6MWD) or on secondary efficacy measures. Efficacy claims were based on post hoc subgroup analyses in an acute decline phase (ADP) group of patients. There were concerns that the presented analyses in the post hoc defined subgroup might be data driven. Translarna was granted a marketing authorization after a majority vote in CHMP on the condition that the company should performed a further study in the post hoc defined subgroup and generated additional data to confirm product's efficacy and safety.

The company has now provided the results of this randomized placebo controlled study in 230 ADP DMD patients. The new data failed to confirm that Translarna has an effect in slowing down the progression of the disease as there was no significant difference in the primary and secondary endpoints.

The study 020 showed from a clinical perspective a questionable difference and statistically nonsignificant difference in the change from baseline 6MWD compared with 6MWD at 48 weeks (12.3 meter, p=0.213) in favor of ataluren when compared with placebo. Although a favorable difference for ataluren was reported in 6MWD with at least 10% at week 48 in study 007 in favor of ataluren (44% vs 26%; time to at least 10% worsening nominal p=0.0326, adjusted p=0.0652), this finding was not confirmed in study 020 (45.6% vs 43% ; time to at least 10% worsening p=0.160). Similarly the results on timed function tests in the overall population and in the subgroups showed inconclusive results in both studies with less differences in study 020 when compared with study 007.

In a new subset of the predefined ADP population, characterized by a baseline 6MWD test between 300 and 400 m, a 49.9 m difference (p=0.0125) in mean change in 6MWD at Week 48 was observed favoring ataluren (n=32) when compared with placebo (n=31).

In spite of the findings in this subset of patients it is considered that the results of the confirmatory study 020 did not confirm the hypothesis for efficacy in the ADP population generated in the post hoc analysis of study 007.

It is acknowledged that there is an unmet medical need in patients with DMD and that no major safety concerns were identified with Translarna. However, based on a lack of robust primary and secondary efficacy outcome effects, the uncertainty concerning the target population to be treated, and the unclear mechanism of action of Translarna the available data are, however, not considered robust enough to support a positive benefit/risk balance

In light of all this, the undersigned CHMP members considered that the renewal of a conditional approval is not acceptable, since at least two of the conditions for a CA are not met, namely the B/R is considered negative and the MAH cannot guarantee the generation of additional comprehensive data in an acceptable timeframe.

London, 23 November 2016

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Johann Lodewijk Hillege

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Koenraad Norga

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Aranzazu Sancho-Lopez

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Sol Ruiz

…….
Nikola Moravcova

…….
Ondřej Slanař

…….
Fátima Ventura

Divergent position expressed by Norwegian CHMP member:

The undersigned Norwegian member of the CHMP did not agree with the CHMP's positive opinion recommending the renewal of the conditional marketing authorization of Translarna (ataluren) indicated in the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older.

The reason for the divergent opinion was as follows:

The conditional marketing authorization of Translarna, granted in 2014, was mainly based on the data from the single phase 2b study (007). Study 007 failed, however, to demonstrate evidence of therapeutic efficacy of Translarna either on the primary endpoint (change in 6MWD) or on secondary efficacy measures. Efficacy claims were based on post hoc subgroup analyses in an acute decline phase (ADP) group of patients. There were concerns that the presented analyses in the post hoc defined subgroup might be data driven. Translarna was granted a marketing authorization after a majority vote in CHMP on the condition that the company should performed a further study in the post hoc defined subgroup and generated additional data to confirm product's efficacy and safety.

The company has now provided the results of this randomized placebo controlled study in 230 ADP DMD patients. The new data failed to confirm that Translarna has an effect in slowing down the progression of the disease as there was no significant difference in the primary and secondary endpoints.

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In light of all this, the undersigned CHMP members considered that the renewal of a conditional approval is not acceptable, since at least two of the conditions for a CA are not met, namely the B/R is considered negative and the MAH cannot guarantee the generation of additional comprehensive data in an acceptable timeframe.

London, 23 November 2016

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Karsten Bruins Slot