29 April 2025
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for marketing authorisation application

Duvyzat (Givinostat)
Treatment of Duchenne muscular dystrophy
EU/3/12/1009

Sponsor: Italfarmaco S.p.A.

Note

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

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1. Product and administrative information

Product	
Designated active substance(s)	Givinostat
Other name(s)	--
International Non-Proprietary Name	Givinostat
Tradename	Duvyzat
Orphan condition	Treatment of Duchenne muscular dystrophy
Sponsor's details:	Italfarmaco S.p.A. Viale Fulvio Testi 330 20126 Milan MI Italy
Orphan medicinal product designation procedural history	
Sponsor/applicant	Italfarmaco S.p.A.
COMP opinion	11 May 2012
EC decision	4 July 2012
EC registration number	EU/3/12/1009
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Janet Koenig / Ewa Balkowiec Iskra
Applicant	Italfarmaco S.p.A.
Application submission	29 June 2023
Procedure start	17 August 2023
Procedure number	EMA/H/C/006079
Invented name	Duvyzat
Therapeutic indication	Treatment of Duchenne muscular dystrophy (DMD) in ambulant patients, aged 6 years and older, and with concomitant corticosteroid treatment. Further information on Duvyzat can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/duvyzat
CHMP opinion	25 April 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Fernando Mendez Hermida
Sponsor's report submission	10 May 2024
COMP discussion	18-20 March 2025
COMP opinion (adoption via written procedure)	29 April 2025

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2012 was based on the following grounds:

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- Duchenne muscular dystrophy (hereinafter referred to as "the condition") was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made; this was based on several publications on the condition in Europe; this is not more than 5 in 10,000 persons as established in Article 3(1) (a) of Regulation (EC) 141/2000
- the sponsor has provided satisfactory argumentation to establish that the condition is chronically debilitating and life-threatening, mainly due to progressive muscle weakness with loss of function of voluntary muscles. In addition the cardiac muscle is involved. Most children affected by the condition will need a wheel chair before 12 years of age. Respiratory muscles deterioration results in reduced forced vital capacity of the lungs, requiring ventilation support. Death occurs at median age of 25 years, usually due to respiratory or cardiac failure.
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition

The COMP recommends the designation of this medicinal product, containing givinostat, as an orphan medicinal product for the orphan indication: treatment of Duchenne muscular dystrophy.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Duchenne muscular dystrophy (DMD) is a progressive, X-linked recessive, neuromuscular degenerative and fatal disease. It is the most common muscular dystrophy. DM caused by mutations in the dystrophin gene (DYS gene; DMD; locus Xp21.2). Approximately one third of all dystrophin mutations arise from new mutations, and the remaining two-thirds are inherited from a mother who is a carrier of the mutation. The disease primarily affects males. Approximately 10% of female carriers do show disease manifestations, which can include effects on cognitive and/or cardiac function. However, a few cases in female patients do show the same severity as affected males. Affected females with DMD usually have chromosomal rearrangements, and most are assumed to have skewed X-inactivation, which can also cause disease manifestation. Dystrophin is a cytoskeletal protein, which is part of the Dystrophin-Associated Protein Complex (DAPC) located between the extracellular matrix and inner cytoskeleton of muscle fibres. It stiffens muscle fibres, acting as a type of shock absorber by providing resistance against deformation. Mutations can be frameshifting mutations, deletions, or nonsense mutations that result in either nonfunctional or missing dystrophin protein from the DAPC and myofibres. Its deficiency leaves the fibres susceptible to contraction-induced microfissures, which

disrupt calcium homeostasis, ultimately resulting in cellular necrosis. As the disease progresses, muscle fibres are necrotic and are replaced by fibrotic and adipose tissues. The final muscular atrophy and fibrotic tissues are the result of numerous cycles of degeneration and regeneration.

First symptoms are mostly seen before 5 years of age, most commonly before 3 years of age. Loss of ambulation usually occurs between 7 to 11 years of age. The first clinical manifestations of muscle weakness include gait abnormalities and difficulties in climbing stairs and rising from the floor. Progressive pelvic girdle weakness and muscle contractures will further affect ambulation, with subsequent progressive loss of upper limb function. Full-time wheelchair dependency and axial weakness lead to the development of scoliosis and joint contractures in upper and lower limbs. At the advanced stages of the disease, patients have spinal and chest wall deformities. Progressive weakness of respiratory muscles results in a restrictive pulmonary syndrome that evolves into respiratory insufficiency during the late second or third decade. With increasing age, DMD patients typically develop a progressive dilated cardiomyopathy, eventually leading to symptomatic congestive heart failure and an increased risk of cardiac arrhythmia and sudden death. Symptoms of cardiomyopathy (persistent tachycardia and heart failure) can develop in early teens and are present in almost all patients in their twenties. In affected patients, dilated cardiomyopathy is characterised by extensive fibrosis (Venugopal, 2022). Without intervention, cardiac involvement and respiratory complications will result in early mortality in the second or third decade.

The approved therapeutic indication "*Duvyzat is indicated for the treatment of Duchenne muscular dystrophy (DMD) in ambulant patients, aged 6 years and older, and with concomitant corticosteroid treatment*" falls within the scope of the designated orphan condition "treatment of Duchenne muscular dystrophy".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The COMP has previously accepted the condition is life-threatening and chronically debilitating due to progressive weakness occurring throughout the proximal musculature affecting the muscles of the hips, thighs, pelvic area and shoulders and eventually affecting all voluntary muscles. This is followed by dilated cardiomyopathy and cardiac output decrease, leading to terminal respiratory or cardiac failure often by late adolescence. Patients rarely live beyond the age of 30 years.

This view is maintained by the COMP.

Number of people affected or at risk

The sponsor proposes a prevalence estimate of 0.22 in 10,000 male persons in the EU for Duchenne muscular dystrophy in Europe. At the time of the original orphan designation (29 February 2012), the prevalence of Duchenne muscular dystrophy in the European Union was estimated to be approximately 0.5 in 10,000 persons.

For the orphan maintenance report, the sponsor performed the calculation of prevalence, based on systematic search of peer-reviewed published literature. No significantly new data of DMD prevalence in Europe was identified as compared to the original orphan application. In the absence of relevant new data on DMD prevalence in Europe, in agreement with EMA/COMP/436/01 Guideline of 20 June 2019,

the prevalence was calculated using an indirect method, based on the functional relationship between incidence (I) and mean duration (D), commonly expressed as P = I x D.

Data on DMD birth prevalence have been collected in 11 European countries including articles published since 1983 until 2020 (see Table 1).

Table 1. Summary of literature review for the prevalence of DMD in EU countries

Author, Year of publication	**Country**	**Population**	**Study years**	**Birth prevalence/ 100,000 live male births**
Dellamonica et al, 1983	France	Blood samples of 158,000 newborns obtained 4 to 8 days postnatally	1978	16.9
Leth et al, 1985	Denmark	445 patients with progressive muscular dystrophy alive January 1st 1965	1965–1975	22.2
Tangsrud et al, 1989	Southern Norway	All boys with a known history of Duchenne muscle dystrophy born during the period 1968– 1977	1968–1977	25.3
Van Essen et al, 1992	The Netherlands	All males with DMD both born and diagnosed in the period 1961–1982 in the Netherlands	1961–1982	23.7
Merlini et al, 1992	Italy	Children born between 1970 and 1989	1970–1982	25.8
Peterlin et al, 1997	Slovenia	DMD cases diagnosed in the period 1969–1984	1969–1984	13.8
Drousiotou et al, 1998	Cyprus	30,014 newborn males screened for DMD	1992–1997	16.7
Jeppesen et al, 2003	Denmark	Danish live born males from 1972 to 2001	1992–1996	18.8
Talkop et al, 2003	Estonia	All patients with DMD born and diagnosed in the period 1977– 1999 in Estonia	1986–1990	17.7
Moat et al, 2013	Wales	Blood spots collected routinely as part of the Wales newborn screening program	1990-2011	19.5
Wahlgren et al, 2022	Sweden	All patients with DMD born and diagnosed in the period 1970–2019	1970–2019	13.8

It was calculated a mean birth prevalence of 19.5, ranging from 13.8 (lowest rate by Peterlin et al., 1997 and Wahlgren et al., 2022) to 25.8 (highest by Merlini et al., 1992) per 100,000 male births.

This result is in line with the meta-analysis done by Crisafulli et al, (Crisafulli et al, 2020) where the pooled global DMD birth prevalence was 19.8 (95% CI:16.6–23.6) per 100,000 live male births.

Figures on the live birth male population within Europe is not available for the last year (2023), therefore yearly birth rate was estimated from 2022. Taking into consideration the yearly birth rate of approximately 2.0 million male births in 2022 (Eurostat 2022), up to 390 cases of DMD per year in the EU are estimated in this way. If up to 390 DMD-affected male patients per year exist, dividing by the total male population for Europe which in 2023 was 219,353,139 (Eurostat 2023), yearly incidence

rate is approximately 0.02/10,000 males in the EU and 0.01/10,000 total EU population (assuming a total EU population of 448.7Mio as per Eurostat 2023)

Broomfield et al reported a full overview of mortality across the lifetime of a patient with DMD, thus providing a representative estimate of life expectancy for this patient population. A systematic review of the published literature on mortality in DMD up to July 2020 was undertaken, specifically focusing on publications in which Kaplan-Meier (KM) survival curves with age as a timescale were presented (Broomfield et al, 2021). Of 1,177 articles identified, 14 publications met the inclusion criteria and provided data on 2,283 patients, of whom 1,049 had died. Median life expectancy was 22.0 years (95% confidence interval [CI] 21.2, 22.4) (Broomfield et al, 2021).

Based on the functional relationship (P = I x D) between incidence (I) and mean duration (D), if yearly incidence rate (0.01/10,000) is multiplied by the assumed duration of 22 years, a prevalence estimate of approximately 0.22 /10,000 persons is proposed.

The COMP considered the proposed prevalence calculation and final estimate of 0.22 in 10,000 persons acceptable and in line with previously accepted values in this condition.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

At the time of orphan maintenance review, satisfactory methods are determined by the authorized indication of a medicinal product, as per the summary of product characteristics (SmPC). Duvyzat is indicated for the treatment of DMD in ambulant patients from 6 years of age, in combination with corticosteroid treatment. Notably, only authorized medicinal products indicated for the treatment of the target patient population can be considered satisfactory methods.

Authorized medicinal products for the treatment of DMD in the EU/EEA include Agamree and Deflazacort (only nationally approved in five EU/EEA countries). Of note, Duvyzat has a novel mechanism of action as compared to these therapies; it is a histone deacetylase (HDAC) which has been shown to reduce muscle fibre damage, chronic muscular inflammation, fibrosis, fat deposition, and to promote mitochondrial biogenesis.

Agamree (vamorolone), is a synthetic corticosteroid that binds to the same target receptors as the corticosteroid class (glucocorticoid receptor, mineralocorticoid receptor) and the WHO has assigned Vamorolone an ATC-code in the class of corticosteroids (glucocorticoids). The approved therapeutic indication is: "AGAMREE is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older". The target patient population of Duvyzat is fully included in the broader population for which Agamree is authorized. Therefore, Agamree is considered a satisfactory method for establishing the significant benefit of Duvyzat, for the purpose of this procedure.

Deflazacort is a classic corticosteroid which is recommended for the treatment of DMD by international treatment guidelines (Birnkrant et al., 2018) and has historically been used off-label in the EU. However, deflazacort was recently approved (early 2024) for "treatment of Duchenne muscular dystrophy (DMD) in patients 2 years and older" in five EU/EEA countries via the so-called mutual recognition procedure. Denmark served as the Reference Member State (RMS), with Finland, Norway, Sweden, and the Netherlands as Concerned Member States (CMS) (DK/H/3029/001 and /002, MAH:

Vital Pharma Nordic). The target patient population of Duvyzat is fully included in the broader population for which deflazacort is authorized. Therefore, deflazacort is considered a satisfactory method for establishing the significant benefit of Duvyzat, for the purpose of this procedure.

In conclusion, Agamree and deflazacort are considered satisfactory methods for establishing the significant benefit of Duvyzat.

Significant benefit

The sponsors main argument to support the significant benefit of Duvyzat vis a vis the two satisfactory methods Agamree and deflazacort is that Duvyzat has shown better efficacy when used in combination with corticosteroids as compared to corticosteroids only. This is supported by data from the sponsors pivotal study in which all patients received Duvyzat in combination with background corticosteroid therapy, about 80% of patients receiving deflazacort (about 17% of patients received prednisone). Even though no patient in the pivotal nor any other clinical study with Duvyzat received Agamree as background therapy, the sponsor emphasizes that it belongs to the same pharmacological class of corticosteroids and that there is no evidence that Agamree is more effective, safer or otherwise a major contribution to patient care, as compared with prednisone. In support of this argument, the sponsor refers to the European Public Assessment Report (EPAR) of Agamree. Furthermore, the sponsor refers to the For-DMD study, which did not show a significant difference between daily regimens of prednisone and deflazacort (Guglieri et. al., 2022).

Significant benefit of Duvyzat over deflazacort

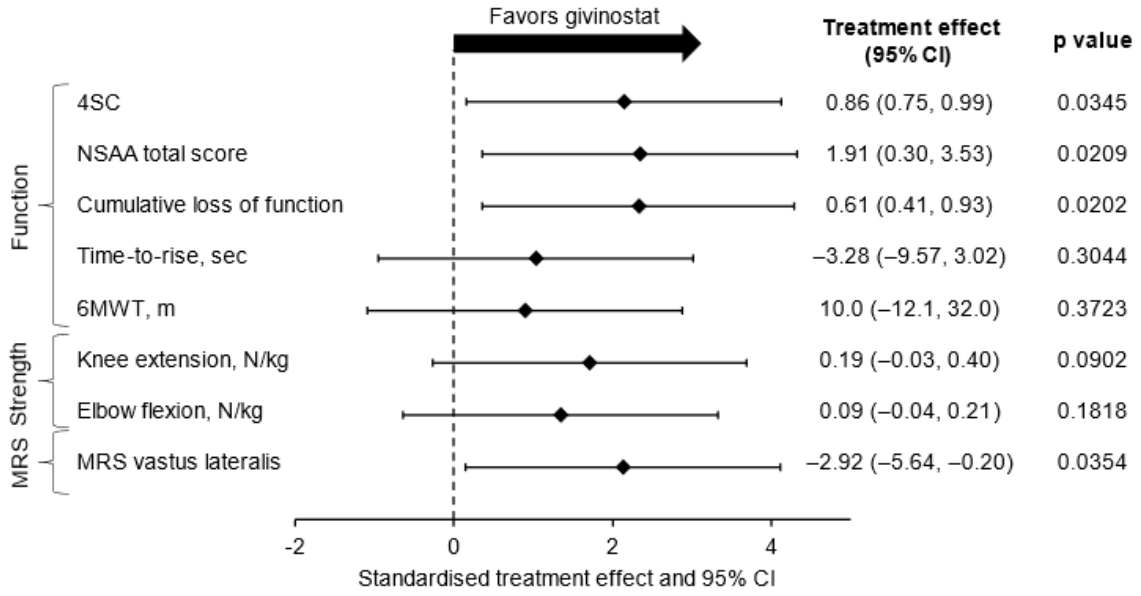
The main evidence of efficacy is derived from a single phase 3, 2:1 randomised, double-blind, parallel group, placebo-controlled study (EPIDYS or Study 48) of 18 months treatment duration to assess the efficacy and safety of givinostat, in ambulant boys with Duchenne muscular dystrophy (DMD). Patients were recruited into 2 groups (Group A: n=120, and Group B: n=59), depending on their baseline percentage of fat fraction present in the vastus lateralis muscles (VL MFF) of the thigh measured with magnetic resonance spectroscopy (MRS). Group A was considered the target patient population in which the primary endpoint was assessed. These patients had to have a baseline VL MFF in the range > 5% and ≤ 30%. The study included boys between 6 and 16 years of age on stable corticosteroid treatment (16.7% prednisone, 79.2% deflazacort and 4.2% another type of corticosteroid; 83.3% of patients received daily and 16.7% received intermittent corticosteroid regimens). Included subjects had to be able at screening to complete two 4-stairs climb (4SC) assessments ≤ 8 seconds (mean), be able to complete the time to rise from floor test between ≥ 3 and < 10 seconds and had manual muscle testing of quadriceps of grade ≥ 3. Givinostat (10 mg/mL) or placebo was administered as an oral suspension twice daily. The primary objective of the study was to establish the effects of givinostat versus placebo to slow disease progression in ambulant DMD patients. The primary endpoint was a single timed-function test, i.e. mean change from baseline in time to 4SC at 18 months, and aimed to demonstrate superiority of givinostat over placebo. Key secondary functional endpoints included Mean change in time to rise from floor (TTR), Mean change in the 6MWT distance, Mean change in the North Star Ambulatory Assessment (NSAA) score, Cumulative loss of function on the NSAA score and Mean change of muscle strength evaluated by knee extension and elbow flexion as measured by hand-held myometry (HHM). Furthermore, Mean change in vastus lateralis muscles fat fraction (VL MFF) was a key secondary endpoint. Results from the study were as follows:

The sponsor reports that their pivotal study met its primary endpoint in the prespecified primary population (Target Population, Group A): givinostat significantly (p=0.0345) reduced the decline in 4SC compared to placebo. The geometric least squares mean (GLS mean) (log scale SE) was 1.27 (0.040) and 1.48 (0.058) for givinostat and placebo, respectively, with a GLS mean ratio (95% CI) of

0.86 (0.071). This represents a 14% less increase in the time to climb 4 stairs at month 18 in favour of givinostat when compared to placebo. In order to translate the treatment effect to seconds, a supportive analysis showed that the mean time of 4SC increased by 1.25 seconds in the givinostat group vs 3.03 seconds in the placebo group. Thus, the treatment effect (change from baseline, givinostat minus placebo) was -1.78 seconds (p=0.0374)

Two additional prespecified analyses complemented the primary analysis of 4SC: shift in grade of functional adaptation and 4SC velocity. In the first analysis 23 (31.5%) patients in the givinostat group showed a reduction in grades for functional adaptation of 4SC, while this occurred in 16 (45.7%) patients treated with placebo. The second analysis provided an estimate of the difference in 4SC velocity between givinostat and placebo of 0.03 task/second (95% CI: 0.00, 0.07) which is nominally statistically significant with a p-value of 0.0285. These results support the primary analysis of 4SC. Moreover, the difference of 1.78 seconds in 4SC change from baseline between givinostat and placebo is considered clinically meaningful by the sponsor, based on published literature (Yost et al, 2005, Wyrwich et al, 1999, Duong et al, 2021). Non-log transformed data on 4SC velocity (task/seconds) still resulted in treatment effects within the same range as minimal clinically important differences (MCID) from published literature. The sponsor further notes that the results of the primary endpoint are supported by a series of secondary endpoints assessing functional efficacy, including total score and cumulated loss for NSAA, TTR, and 6MWT (Figure 1).

Figure 1. Study 48: Forest Plot of Primary and Key Secondary Efficacy Endpoints of Givinostat Versus Placebo (Target population)§



§Givinostat or placebo were administered in addition to a stable dose of corticosteroids throughout the study. 4SC = time to climb 4 standard stairs; 6MWT = 6-minute Walk Test; NSAA = North Star Ambulatory Assessment; Cumulative Loss of Function of the NSAA; MRS vastus lateralis = fat fraction in vastus lateralis muscle. For cumulative loss of function of the NSAA, estimates are obtained from a negative binomial regression. Direction of interpretation has been fixed accordingly.

Overall, the results of the secondary endpoints assessing function support the results of the primary endpoint, with all outcomes favouring givinostat vs placebo (Figure 1). Using the pre-specified Hochberg procedure, no secondary endpoint reached formal statistical significance.

The COMP took note of the discussion on the pre-specified primary analysis at the CHMP. Additional statistical analyses (permutation-based analysis, probability densities and a Bayesian analysis) indicate that even under the conservative jump-to-reference multiple imputation condition, the probability of observing the positive results seen with givinostat on the primary and key secondary endpoints would unlikely be due to chance alone. Overall, the effect sizes for givinostat were considered small but consistently showed a smaller deterioration compared to placebo after 18 months.

The COMP concluded that the clinical efficacy data from the sponsors pivotal study established the significant benefit of Duvyzat over deflazacort. In ambulant DMD patients, treatment with Duvyzat on top of glucocorticoid therapies showed an attenuation of motor function decline as compared to treatment with glucocorticoids in ambulant Duchenne muscular dystrophy patients. All patients had received Duvyzat in combination with background corticosteroid therapy, about 80% of which received deflazacort. Furthermore, more than 80% of patients in the sponsors pivotal efficacy study received a daily corticosteroid regimen, which has shown to be the most effective regimen in the recent FOR-DMD study (Guglieri et. al., 2022).

Significant benefit of Duvyzat over Agamree

No efficacy data of Duvyzat in combination with Agamree as background therapy is available in the target patient population. The sponsor argues that Agamree belongs to the same pharmacological class (corticosteroids/glucocorticoids) as deflazacort and prednisone and clinical evidence is not suggestive of Agamree being more effective, safer or otherwise a major contribution to patient care compared with prednisone. Furthermore, the sponsor points out that the For-DMD study by Guglieri et. al. demonstrated that there was no significant difference between daily regimens of prednisone and deflazacort (Guglieri et. al., 2022). Therefore, the efficacy of Duvyzat is not expected to differ whether it is used in patients on background therapy with the conventional corticosteroids deflazacort and prednisone or in patients on background therapy with Agamree.

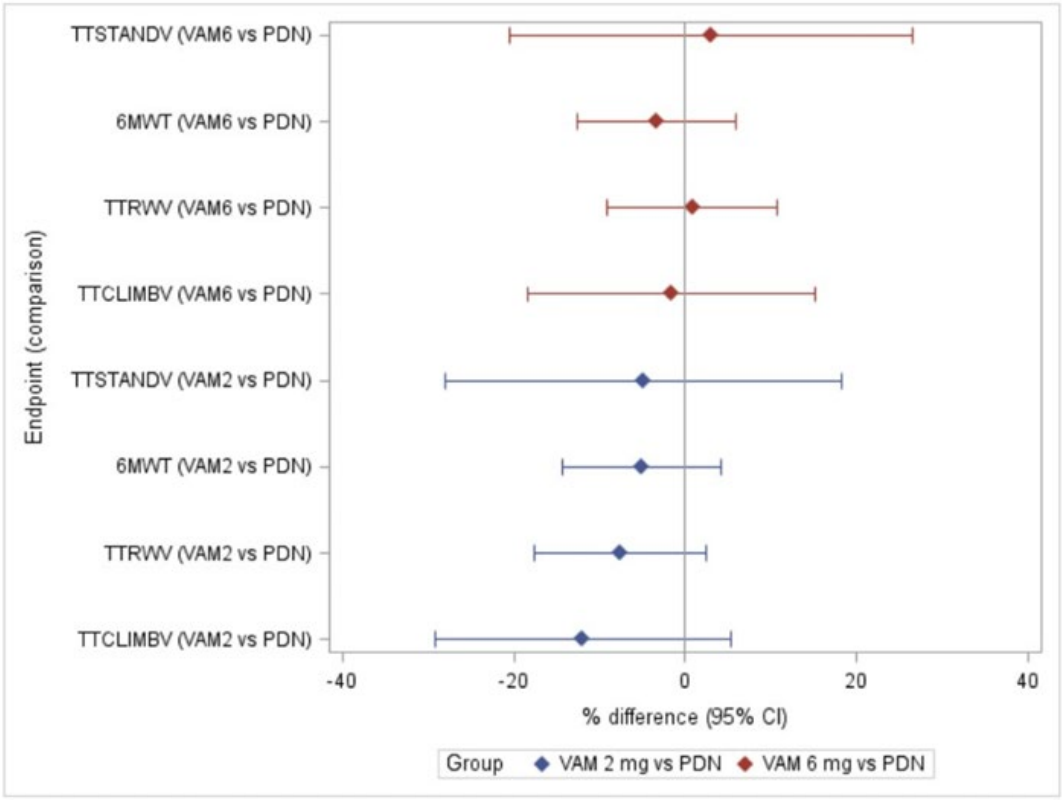
In support of an assumed similar safety and efficacy of Agamree and prednisone, the sponsor describes the analyses conducted for the purpose of licensing by the MAH of Agamree. These analyses are also reflected in the EPAR of Agamree. The pivotal phase 2b study (VBP15-004) with Agamree was a randomised, double-blind, placebo-controlled study and included also a prednisone treatment arm. The study included two sequential 24-week periods. In period 1, a total of 120 glucocorticoid-naïve patients were randomly allocated to receive vamorolone 2.0 or 6.0 mg/kg once daily, placebo, or prednisone 0.75 mg/kg/day, in a 2:2:1:1:1:1 ratio with subjects in the prednisone and placebo groups were randomised into two groups each (resulting in 30 patients per treatment group). In period 2 patients previously treated with prednisone or placebo were switched to vamorolone 2.0 or 6.0 mg/kg and subjects who had received vamorolone in Period 1 continued treatment on their vamorolone dose.

The primary endpoint was the change from baseline in time to stand velocity (TTSTAND) velocity for vamorolone (6mg/kg) versus placebo at 24-weeks in ambulant boys ages 4 to <7 years with DMD. Secondary objectives included an efficacy comparison between vamorolone (2+6mg/kg) vs daily prednisone over 24 weeks in ambulant boys ages 4 to <7 years with DMD. Furthermore, efficacy and safety were also evaluated following the switch from prednisone in Period 1 to vamorolone in Period 2. Hierarchical testing of a number of secondary endpoints against placebo prevented a formal statistical testing of the 6-minute walk test (6MWT) distance of vamorolone against prednisone.

The improvements seen with vamorolone 6mg/kg/day in time to stand velocity (TTSTANDV), Time to run/walk 10 Meters Test velocity (TTRWV), and Time to climb 4 steps test velocity (TTCLIMBV) were almost comparable to those seen with prednisolone at week 24, while for the 6MWT and the North Star Ambulatory Assessment (NSAA) score (data not shown) prednisone provided better results. The

improvements seen with vamorolone 2 mg/kg were overall slightly smaller than those seen with prednisone, when evaluated globally (Figure 2).

Figure 2. Comparisons between vamorolone and prednisone in timed tests, analysed as percentual changes from baseline (mITT-1 population)



Test data are standardised by using the percentual change from baseline as the endpoint. The percentile changes are calculated as (value at visit – baseline value) / baseline value x 100%. All the percentual change values from the four tests are entered to a single statistical model (MMRM) A model comparable to the one presented in FDA-analysis is used, but in addition to the fixed factors included in the original MMRM, the parameter (TTSTAND, TTRW, TTCLIMB or 6MWT) and all 2- and 3-level interaction terms between treatment group, visit and parameter are added. The model uses the Kronecker product covariance structure. Accordingly, the covariance structure is set as type=un@un in the REPEATED statement of the MIXED procedure. TTSTANDV= 1 / TTSTAND and is expressed as rises/sec; TTRWV =1 / TTRW and is expressed as meters/sec; TTCLIMBV=1 / TTCLIMB and is expressed as tasks/sec TTSTANDV=time to stand velocity; 6MWT=6-minute walk test; TTRWV=Time to run/walk 10 Meters Test velocity; TTCLIMBV=Time to climb 4 steps test velocity; VAM2=vamorolone 2 mg/kg; VAM6=vamorolone 6mg/kg PDN=Prednisone.

Overall, the treatment effects achieved under prednisone were maintained until week 48 when subjects were switched from prednisone treatment to vamorolone 6 mg/kg at Week 24. When subjects switched from prednisone to vamorolone 6 mg/kg, the mean TTSTAND velocity, TTRW velocity and NSAA score only slightly decreased and TTCLIMB velocity minimally increased. There was also small decline in the 6MWT distance while subjects, who continuously were treated with vamorolone 6m/kg still improved until Week 48. When subjects switched from prednisone to vamorolone 2 mg/kg, the mean TTSTAND and TTCLIMB velocity decreased more than the 6MWTD and TTRW velocity. No mean changes were seen for the NSAA score.

A comparison of the safety of vamorolone and prednisone was possible only during the initial 24-week period. The overall incidence of TEAEs in this period was lowest in the placebo group, followed by vamorolone 2 mg/kg, prednisone, and vamorolone 6 mg/kg (79.3%, 83.3%, 83.9%, and 89.3%). TEAEs of special interest were similarly recorded in the vamorolone 6 mg/kg and prednisone group (78.6% and 77.4%). The incidence and type of TEAEs reported by > 2% of subjects in any vamorolone

group and at a higher incidence that placebo was very similar when compared with the prednisone group. TEAEs reported for ≥ 10% of subjects in the vamorolone 2-6 mg/kg group included Cushingoid appearance, vomiting and pyrexia. This was similar in the prednisone group for Cushingoid appearance but less frequent for vomiting and pyrexia.

In conclusion, there was no evidence of neither a better efficacy nor a better safety profile for vamorolone 6mg/kg when compared to prednisone 0.75 mg/kg. Comparing vamorolone 2 mg/kg with prednisone 0.75 mg/kg there seemed to be a slightly lower efficacy in several of the domains measured. The recommended dose of Agamree is 6 mg/kg once daily but may be down-titrated to 4 mg/kg/day or 2 mg/kg/day based on individual tolerability, according to the SmPC.

To provide a comparison of efficacy and safety of vamorolone administered orally at daily doses of 2 and 6 mg/kg with corticosteroids over a 48-week treatment period, outcomes of vamorolone treated subjects in VBP15-004 were compared with the outcomes of prednisone- and deflazacort-treated boys from the FOR-DMD study. Imbalances between the different patient populations were noted between the vamorolone groups and the matched prednisone and deflazacort groups, with subjects in the vamorolone groups having worse values at baseline; in particular, 6MWT distance was longer for the prednisone group in FOR-DMD compared with the deflazacort in FOR-DMD and vamorolone groups in VBP15-004. TTSTAND velocity had increased in the vamorolone 6 mg/kg, prednisone, and deflazacort groups at Months 6 and 12. The increases were similar for the vamorolone 6 mg/kg group (LSM change 0.05 and 0.04 at Months 6 and 12), deflazacort group (LSM changes 0.05 and 0.04 at Months 6 and 12, respectively), and the prednisone group (LSM changes were 0.04 and 0.04 at Months 6 and 12, respectively); the vamorolone 2 mg/kg group showed minimal change (LSM changes 0.02 and -0.00). The sponsor concluded that improvements in motor function with vamorolone 6 mg/kg were overall similar to those seen with prednisone at Week 24, except for the 6MWT and the NSAA score for which prednisone provided better results. The improvements seen with vamorolone 2 mg/kg were overall slightly smaller than those seen with prednisone.

Overall, the efficacy and safety results of study VBP15-004 as well as the external comparison with prospectively collected data derived from the FOR-DMD study did not demonstrate either an improved efficacy, nor a better safety profile for vamorolone 6 mg/kg when compared to daily administration of prednisolone 0.75 mg/kg and deflazacort 0.90 mg/kg. Therefore, there is no evidence of a clinically relevant advantage of vamorolone over prednisone or deflazacort.

Comparative efficacy between prednisolone and deflazacort (Study FOR-DMD):

The FOR-DMD study (Guglieri-m-et-al-2022) was a double-blind, parallel-group randomized clinical trial including 196 boys aged 4 to 7 years with Duchenne muscular dystrophy who had not previously been treated with corticosteroids. Participants were randomized to daily prednisone (0.75 mg/kg) (n = 65), daily deflazacort (0.90 mg/kg) (n = 65), or intermittent prednisone (0.75 mg/kg for 10 days on and then 10 days off) (n = 66). The global primary outcome comprised 3 end points: rise from the floor velocity (in rise/seconds), forced vital capacity (in litres), and participant or parent global satisfaction with treatment measured by the Treatment Satisfaction Questionnaire for Medication (TSQM; score range, 0 to 100), each averaged across all study visits after baseline. Overall, both daily prednisone and daily deflazacort were more effective than intermittent prednisone for the primary outcome ($P < .001$ for daily prednisone vs intermittent prednisone using a global test; $P = .017$ for daily deflazacort vs intermittent prednisone using a global test) and the daily regimens did not differ significantly ($P = .38$ for daily prednisone vs daily deflazacort using a global test). Reported adverse events were similar in the three treatment groups.

In conclusion, in this large study in 196 boys with DMD in the age group 4 to 7 years treatment with daily prednisone or daily deflazacort, compared with intermittent prednisone alternating 10 days on and 10 days off, resulted in significant improvement over 3 years in a composite outcome comprising measures of motor function, pulmonary function, and satisfaction with treatment. There was no significant difference between the 2 daily corticosteroid regimens, prednisone and deflazacort. Neither was there a difference in safety parameters.

Overall COMP conclusion

Based on the data provided by the sponsor, clinically relevant differences in efficacy are not expected whether Duvyzat is used in patients on background therapy with the conventional corticosteroids deflazacort (or prednisone) or in patients on background therapy with Agamree. The claim that Duvyzat is of significant benefit to ambulant patients with DMD, as defined in the granted therapeutic indication, is therefore considered established. Treatment with Duvyzat on top of glucocorticoid therapies showed an attenuation of motor function decline as compared to treatment with glucocorticoids in ambulant Duchenne muscular dystrophy patients. The Committee considered that this constitutes a clinically relevant advantage.

The COMP adopted a positive opinion.

4. COMP position adopted on 29 April 2025

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of Duchenne muscular dystrophy (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to progressive muscle weakness affecting voluntary and involuntary muscles leading to loss of ambulation, scoliosis and joint contractures, progressive cardiac and respiratory failure and short life expectancy;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the claim that Duvyzat is of significant benefit to those affected by the orphan condition, as defined in the granted therapeutic indication, is established. Treatment with Duvyzat on top of glucocorticoid therapies showed an attenuation of motor function decline as compared to treatment with glucocorticoids in ambulant Duchenne muscular dystrophy patients. The Committee considered that this constitutes a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Duvyzat, givinostat for treatment of Duchenne muscular dystrophy (EU/3/12/1009) is not removed from the Community Register of Orphan Medicinal Products.