23 April 2026
EMADOC-1700519818-2976725
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

AGAMREE

International non-proprietary name: Vamorolone

Procedure No. EMA/VR/0000293535

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

11β-HSD	11β-hydroxysteroid dehydrogenases
AE	Adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
Bayley-III	Bayley Scales of Infant and Toddler Development-III
BMI	Body mass index
C_{max}	Maximum concentration
CK	Creatine kinase
CSR	Clinical study report
CTX	Type 1 collagen C-telopeptides
DBP	Diastolic blood pressure
DCO	Data cut-off
DMD	Duchenne muscular dystrophy
EAP	Expanded Access Programme
ECG	Electrocardiogram
EMA	European Medicines Association
EU	European Union
FDA	Food and Drug Administration
GC	Glucocorticoid
GGT	gamma-glutamyl transpeptidase
GMSS	Gross Motor Scale Score
HbA1c	Hemoglobin A1c (glycated hemoglobin)
HDL	high-density lipoprotein
HSD	11β-hydroxysteroid dehydrogenase
IU	International unit
LDL	Low-density lipoprotein
MR	mineralocorticoid receptor
P1NP	Procollagen 1 N-terminal propeptide
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan
PODCI	Pediatric Outcomes Data Collection Instrument
PPK	Population pharmacokinetics
PK	Pharmacokinetic(s)
PT	Preferred Term
SAE	Serious adverse event
SBP	Systolic blood pressure
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
UK	United Kingdom
ULN	Upper limit of normal
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 Santhera submitted to the European Medicines Agency on 27 August 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of 2 to <4 year olds for AGAMREE, based on final results from study VBP15-006; this is a phase II open-label, multiple dose study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of vamorolone in boys ages 2 to <4 years and 7 to <18 years with Duchenne Muscular Dystrophy (DMD) and an updated paediatric extrapolation report referencing 4 to <7-year-old subjects with DMD from Study VBP15-004, compared to the 2 to <4-year-old population from Study VBP15-006. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder took the opportunity to make some editorial corrections to SmPC.

Information relating to orphan designation

Agamree was designated as an orphan medicinal product EU/3/14/1309 on 21 May 2015. Agamree was designated as an orphan medicinal product in the following indication: treatment of Duchenne muscular dystrophy

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision EMA/PE/0000244420 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMA/PE/0000244420 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Janet Konig

Timetable	Actual dates
Submission date:	27 August 2025
Start of procedure:	13 September 2025
CHMP Rapporteur's preliminary assessment report circulated on:	7 November 2025
PRAC Rapporteur's preliminary assessment report circulated on:	12 November 2025
PRAC RMP advice and assessment overview adopted by PRAC:	27 November 2025
CHMP Rapporteur's updated assessment report circulated on:	5 December 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	11 December 2025
MAH's responses submitted to the CHMP on:	19 February 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	1 April 2026
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	27 March 2026
PRAC RMP advice and assessment overview adopted by PRAC:	10 April 2026
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	16 April 2026
CHMP opinion:	23 April 2026
The CHMP adopted a report on similarity of Agamree Duvyzat on date	23 April 2026

2. Scientific discussion

2.1. Introduction

Disease or condition

Duchenne muscular dystrophy (DMD) is a rare, disabling, progressive and ultimately fatal X-linked recessive neuromuscular disorder caused by mutations in the gene for dystrophin (Emery, 2002). Functional dystrophin is critical for the structural stability of myofibers in skeletal, diaphragm and cardiac muscle and is also of importance for smooth muscles. DMD is characterised by a progressive degeneration of skeletal muscles, with symptoms that manifest early, at around 3 years, causing loss of ambulation before the age of 12, followed by cardiac complications (e.g. dilated cardiomyopathy and arrhythmia) and respiratory disorders, including chronic respiratory failure (Birnkrant et al., 2018). The median life expectancy at birth is around 30 years (Landfelt et al. 2020).

State the claimed therapeutic indication

Vamorolone is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients aged **~~4 years~~ 2 years** and older.

Epidemiology

DMD occurs almost exclusively in males (X-linked recessive disorder) with an estimated male birth prevalence of 1/3,500-1/9,300. The estimated prevalence in the EU is ~ 15,000 cases. The prevalence of symptomatic female carriers is unknown.

Aetiology and pathogenesis

DMD is caused by several types of mutations in the gene for dystrophin located on chromosome Xp21. Most mutations are deletions, duplications and point mutations, which produce a shift in the open reading frame of the dystrophin mRNA leading to the absence of functional dystrophin protein.

Dystrophin is a cytoplasmic protein, which associates with other proteins to form the dystrophin-associated protein complex that connects the actin cytoskeleton with the extracellular matrix. Functional dystrophin is critical for the structural stability of myofibers in skeletal, diaphragm and cardiac muscle and is also of importance for smooth muscles. In DMD, both dystrophin and the dystrophin-associated protein complex proteins are missing, leading to excessive membrane fragility and permeability, dysregulation of calcium homeostasis, oxidative damage. These factors play a crucial role in muscle cell necrosis. During the progression of the disease, the regenerative capacity of the muscles appears to be exhausted, and connective and adipose tissue gradually replaces muscle fibers.

Clinical presentation, diagnosis and stage/prognosis

The onset of DMD occurs in early childhood and initial findings may include delays in reaching developmental milestones such as sitting or standing without assistance, toe walking, unusual gait, difficulty climbing stairs or rising from a sitting position (Gower's sign) and repeated falling leading to an increased incidence of fractures in ambulatory subjects. Weakness is more pronounced in proximal than distal muscles and the lower limb more than the upper limb. Affected boys may show a delay in walking (after 18 months of age). Autism and behavioural problems, such as attention deficit hyperactivity disorder, anxiety, obsessive-compulsive disorder, are relatively common. Untreated children with DMD rarely achieve the ability to run or jump. Loss of independent ambulation occurs between the ages of 6 and 13 years, the average being 9.5 years in non-steroid treated patients. Once ambulation is lost, joint contractures and scoliosis develop rapidly, which leads to an impaired pulmonary function. There is gradual loss of upper limb, trunk, and neck function, severely affecting patient quality of life, as well as that of caregivers and families (Bendixen 2012; Magliano 2014; Uzark 2012). Complications from this loss of ambulation have a major cascading effect, including scoliosis.

Children with DMD have reduced bone density and an increased risk of developing fractures of certain bones, such as hips and spine. Many affected individuals will display mild to moderate degrees of non-progressive intellectual impairment and learning disabilities.

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 of the posterobasal left the ventricular wall. As the disease progresses, fibrosis can spread to the lateral free wall of the left ventricle. With the involvement of the posterior papillary muscle, significant mitral regurgitation can occur. Inter- and intraatrial conduction

abnormalities, possibly involving the AV node, can be seen. Arrhythmias, particularly supraventricular arrhythmias, are also associated with the developing cardiomyopathy (Venugopal, 2022).

Another serious complication associated with DMD is weakness and deterioration of muscles in the rib cage. This can result in an increased susceptibility to respiratory infections (e.g., pneumonia), difficulty coughing, and, ultimately, respiratory failure.

Without physical therapy treatment, leg braces may be needed by the age 8-9 to assist walking in affected individuals. Most affected individuals require a wheelchair between 10 and 12 years of age. Untreated patients die during late teens to early twenties from respiratory failure and or cardiomyopathy.

Achieving a timely and accurate diagnosis of DMD is a crucial aspect of care. Most recent data indicate the mean [median] ages in years of diagnostic milestones as follows: first signs, 2.7 [2.0]; first creatine kinase (CK), 4.6 [4.6]; DNA/muscle biopsy testing, 4.9 [4.8]; and time from first signs to diagnostic confirmation, 2.2 [1.4] (Thomas et al. 2022). The diagnostic process typically begins in early childhood after suggestive signs and symptoms. Diagnosis is suspected on the basis of the clinical picture, family history and laboratory findings (serum creatine kinase (CK) is 100-200 times the normal level). Genetic testing is the gold standard and involves multiplex-ligation dependent probe amplification (MLPA) for detection of deletions and duplications of exon (s) and full gene sequencing for detecting small deletions and duplications and non-sense or point mutations. Given the value of information provided by genetic analysis muscle biopsy is now recommended when genetic analysis in inconclusive. Genetic testing is therefore a critical tool in the accurate diagnosis of DMD.

Management

No medical cure exists for DMD, and the disease has a poor prognosis. Treatment is still centered on corticosteroid therapy, e.g. glucocorticoids, prevention of contractures, and medical care of cardiomyopathy and respiratory compromise (Shimizu-Motohashi 2019; McMillan 2019). Glucocorticoids (GC) should continue after loss of ambulation according to current guideline recommendations (Birkrant et al. 2018) and have been shown to improve strength and motor function, delay loss of ambulation by 2 to 3 years, preserve upper limb and respiratory function, avoid scoliosis surgery, and delay the onset of cardiomyopathy.

Recent studies confirm the benefits of starting treatment with glucocorticoids in younger children, before significant physical decline (Merlini 2012; Lamb 2016, Armstrong 2024).

Complications of corticosteroid therapy must be managed and include weight management, gastric protection, monitoring and treatment of osteoporosis, ophthalmic assessment for cataracts and glaucoma. The two common corticosteroid drugs used to treat individuals with DMD are prednisone and deflazacort. Prednisone is recommended at a dosage of 0.75 mg/kg per day, and deflazacort at 0.9 mg/kg/day.

Deflazacort was approved by the FDA in 2017 for the treatment of DMD in patients aged 5 years and older. In 2019, the indication was extended to include patients 2 years of age and older. Deflazacort is approved for "*treatment of Duchenne muscular dystrophy (DMD) in patients 2 years and older*" in some EU/EEA countries[1]. Prednisone is available and widely used in the US and in the European Union but is not specifically indicated for DMD.

Vamorolone (Agamree), a synthetic corticosteroid analogue, received a marketing authorisation throughout the EU on 14 December 2023 for the treatment of Duchenne muscular dystrophy (DMD) in

[1] HMA/ MRI product index (https://mri.cts-mrp.eu/portal/home?domain=h) referring to DK/H/3029/001-002; Armstrong N et al. The Early Care (0-3 Years) in Duchenne Muscular Dystrophy Meeting Report. Journal of Neuromuscular Diseases 11 (2024) 525-533

patients aged 4 years and older.

On 6 June 2025, givinostat received a conditional marketing authorisation throughout the EU for the treatment of Duchenne muscular dystrophy (DMD) in ambulant patients, aged 6 years and older, and with concomitant corticosteroid treatment. Givinostat is a class I and II histone deacetylase (HDAC) inhibitor which modulates the uncontrolled activity of HDAC in dystrophic muscles, reducing muscle fibre damage, chronic muscular inflammation, fibrosis and fat deposition while promoting the production of new mitochondria.

Thus, there is still an unmet medical need for further treatments.

2.2. About the product

Vamorolone is a synthetic corticosteroid analogue that structurally diverges from other members of the class of glucocorticoid agents. Vamorolone contains a double bond between carbon atoms 9 and 11 of the steroid C-ring. It also lacks the hydroxyl group at carbon 11, which prevents the respective formation of hydrogen bonds at the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). Compared to other glucocorticoid drugs, this different binding of vamorolone is thought to 1) retain the established transcriptional repression at the GR with concomitantly reduced gene trans-activating characteristics and 2) entail MR antagonism contrary to the MR agonistic action of other corticosteroids. In addition, vamorolone is supposed to have membrane stabilizing properties and does not serve as a substrate for 11-β-hydroxysteroid dehydrogenase 1 and 2 (11-β-HSD 1 and 2), whose enzymatic activities have been linked to the adverse effects of standard glucocorticoid therapy (muscle atrophy, bone loss, insulin resistance, hypertension and weight gain).

The indication for vamorolone as claimed by the MAH is:

"*Treatment of Duchenne muscular dystrophy (DMD) in patients aged **2** years and older*."

Posology:

The recommended dose of vamorolone is 6 mg/kg once daily in patients weighing less than 40 kg.

In patients weighing 40 kg and above, the recommended dose of vamorolone is 240 mg (equivalent to 6 ml) once daily.

The daily dose may be down-titrated to 4 mg/kg/day or 2 mg/kg/day based on individual tolerability. Patients should be maintained at the highest tolerated dose within the dose range.

A dosing table (Table 1) is included in the posology section for which additional weight bands have been included as part of this extension of the indication:

Table 1. Dosing table (SmPC section 4.2)

	6 mg/kg/day		4 mg/kg/day		2 mg/kg/day	
Weight (kg)	**Dose in mg**	**Dose in ml**	**Dose in mg**	**Dose in ml**	**Dose in mg**	**Dose in ml**
8-9	48	1.2	32	0.8	16	0.4
10-11	60	1.5	40	1	20	0.5
12-13	72	1.8	48	1.2	24	0.6
14-15	84	2.1	56	1.4	28	0.7
16-17	96	2.4	64	1.6	32	0.8
18-19	108	2.7	72	1.8	36	0.9
20-21	120	3	80	2	40	1
22-23	132	3.3	88	2.2	44	1.1
24-25	144	3.6	96	2.4	48	1.2
26-27	156	3.9	104	2.6	52	1.3
28-29	168	4.2	112	2.8	56	1.4
30-31	180	4.5	120	3	60	1.5
32-33	192	4.8	128	3.2	64	1.6
34-35	204	5.1	136	3.4	68	1.7
36-37	216	5.4	144	3.6	72	1.8
38-39	228	5.7	152	3.8	76	1.9
40 kg and above	240	6	160	4	80	2

The dose of vamorolone must not be decreased abruptly if the treatment has been administered for more than one week (see section 4.4). Dose tapering should be done progressively over weeks, by steps of approximately 20% decrease from the previous dose level. The duration of each tapering step should be adjusted depending on individual tolerability.

2.2.1. The development programme

Study VBP15-006 is included in the Paediatric Investigation Plan (PIP; EMEA-001794-PIP02-16) for vamorolone for DMD (Study 10 of the PIP). The clinical development was done in alignment with the agreed PIP.

2.2.2. General comments on compliance with GCP

The clinical trial VBP15-006 was carried out outside the European Union (Canada) in accordance with the ethical principles that have their origins in the Declaration of Helsinki, the guidelines for current Good Clinical Practice (GCP) International Conference on Harmonization (ICH), the United States (US) Food and Drug Administration (FDA) Code of Federal Regulations (CFR) (21 CFR Parts 50, 54, 56 and 312), and all other applicable local regulatory (e.g., Health Canada, EMA) and ethical requirements.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.1. Ecotoxicity/environmental risk assessment

An ERA Phase I was provided in procedure EMEA/H/C/5679. A Phase II assessment was required because of the endocrine MoA of the active substance. The applicant provided a commitment for a tailored ERA. The MAH confirms that this Phase II ERA is ongoing and is expected to run till Q3 2027.

2.3.2. Discussion and conclusion on non-clinical aspects

With respect to submission of this Type II variation/indication extension for vamorolone, the environmental risk assessment is being covered under the ongoing Phase II ERA.

2.4. Clinical aspects

2.4.1. Introduction

The aim of the provided type II variation is to extend the indication for Vamorolone in DMD patients to patients 2 to <4 years of age. Vamorolone is currently approved for the treatment of DMD in patients aged 4 years and older.

The justification of the extension of the indication to patients 2 to <4 years of age is supported by one phase II study, study VBP15-006 and long-term safety interim results of the Expanded Access programme (EAP), which includes follow up of subjects in the 2 to <4 years group who completed Study VBP15-006. While VBP15-006 also included patients 7 to 18 years of age, this data has not been discussed by the MAH and is also not the focus of this extension of indication variation.

In order to further support the current application in subjects aged 2 to <4 years, the MAH provided an updated paediatric extrapolation report (dated 15 August 2025), aiming at the extrapolation from patients 4 to <7 years of age who have been included in the pivotal study VBP15-004 to confirm the proposed dose selection and the safety profile of vamorolone in subjects aged 2 to <4 years old.

Confirmation of the dose selection relies on PK data from Study VBP15-006. The results of this study were included in a refined population pharmacokinetics (PPK) model to evaluate the dose selection strategy for both the reference and target paediatric populations.

Extrapolation of short-term safety was conducted by comparing exposure and safety data of study VBP15-006 and VBP15-004 up to 12 weeks of treatment. Likewise, extrapolation of long-term exposure and safety was approached by comparing data from the VBP15-EAP and VBP15-004 between Weeks 12 and 48.

The proposed posology in patients 2 to <4 years is the same as in patients 4 years of age and older.

GCP

The Clinical trial VBP15-006 was performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies:

Table 2. Overview of study VBP15-006

Trial No. NCT No. Eudract No.	Trial Design and Objectives	Trial Population	Study Drug Regimen, Schedule, Route	Efficacy Assessments	No. Subjects	No. of Centers Countries
VBP15-006 NCT05185622	Phase 2, multicenter, open-label, multiple dose Primary objective: safety and tolerability Secondary objective: PK Exploratory objective: efficacy, PRO, PD, acceptability	Boys with DMD: • 2 to <4 years of age who were corticosteroid naïve, • 7 to <18 years of age who were corticosteroid treated or corticosteroid untreated	Vamorolone 2.0, and 6.0 mg/kg Orally once daily for 12 weeks	Bayley-III Gross Motor Scale (subjects aged 2 to <4 years), Performance Upper Limb test (subjects aged 7 to <18 years).	54 subjects, including 20 subjects aged 2 to <4 years	5 centers in Canada

DMD=Duchenne Muscular Dystrophy; PD=pharmacodynamics; PK=pharmacokinetics; PRO=patient reported outcome

2.5. Pharmacokinetics

Study VBP15-006

A more detailed description of this study can be found under Clinical efficacy. Only the results of the PK assessment are presented here.

Results

A total of 54 subjects were included in the PK analyses: 20 subjects in the 2 to <4 years group and 34 subjects in the 7 to <18 years group. The assessments were performed after a single dose on Day 1 and after multiple doses in Week 2.

Overall, for each of the age groups (2 to <4 years and 7 to <18 years), the PK data indicate that vamorolone is rapidly absorbed and reaches peak concentration within 2-3 hours post-dose for both dosages.

On Day 1, in the 2 to <4 years group, the geometric mean maximum observed plasma concentration (C_{max}) (geometric standard deviation [SD]) were 246.8 (2.01) ng/mL and 781.7 (1.77) ng/mL, for the 2 and 6 mg/kg dose groups, respectively. Six hours after dosing, the geometric mean concentrations (geometric SD) were 106.1 (1.81) ng/mL and 218.8 (1.99) ng/mL. Following multiple doses in Week 2, pre-dose geometric mean concentration was BLOQ before the next dose, for both dose groups, showing that vamorolone had been cleared from the body between administrations. The geometric mean C_{max} (geometric SD) were 349.3 (2.06) ng/mL and 719.5 (2.23) ng/mL, then the geometric mean concentrations (geometric SD) decreased to 96.7 (2.47) ng/mL and 253.9 (1.48) ng/mL, 6 hours after dosing. This was consistent with the elimination phase that had been previously observed on Day 1. High variability was observed. This must be put in the context of sparse sampling. There was also a low number of subjects in this age group.

For the older group, no notable differences in exposure were observed between the 12 to <18 years subgroup and the 7 to <18 years subgroup, nor between the steroid pretreatment conditions. All

plasma concentration data from the 7 to <18 years subgroup was therefore pooled. On Day 1, the geometric mean Cmax (geometric SD) was of 254.5 (2.04) ng/mL and 922.2 (1.60) ng/mL at 2 and 6 mg/kg, respectively. The geometric mean area under the plasma concentration time curve from time 0 to infinity (AUC0-inf) (geometric SD) had a of 1,253.0 (1.65) ng·h/mL and of 4,119.8 (1.53) ng·h/mL, and the half-life (t1/2) had a mean of 2.4 hours (coefficient of variation [CV]: 40%) and 2.1 hours (CV: 80%) respectively. At Week 2, the geometric mean Cmax (geometric SD) had a of 334.5 (1.67) ng/mL and 765.5 (1.59) ng/mL for 2 and 6 mg/kg respectively. The geometric mean AUC0-inf (geometric SD) was 1,528.6 (1.15) ng·h/mL and 3587.7 (1.72) ng·h/mL respectively. The t1/2 had a mean of 2.3 hours (CV: 42%) and 1.8 hours (CV: 33%) respectively.

The higher dosage (6 mg/kg) consistently resulted in higher mean concentrations compared to the lower dosage (2 mg/kg), demonstrating a dose-dependent PK profile (Table 3).

This PK pattern was maintained in both age and both dose groups across Day 1 and Week 2, indicating reliable and predictable PK for vamorolone after single or multiple doses. No clinically relevant accumulation with once-daily administration dosing of the drug with once-daily administration; given $t_{1/2}$ ~2 h in older children, steady-state is expected within ~1 day (≈5 half-lives), consistent with Week 2 profiles. The PK analysis of vamorolone indicates that the drug exhibits similar exposure profiles at both the 2 mg/kg and 6 mg/kg doses across the two age groups studied (2 to <4 years and 7 to <18 years). These results are also consistent with previously reported PK exposure data in the 4 to <7 years age group (VBP15-002, sequence 0000).

These findings suggest that vamorolone PK is not significantly affected by age within the paediatric population, supporting its potential use across a broad age range in children.

Table 3. Descriptive Statistics of PK Parameters (2 to <4 years), PK Analysis Set

Timepoint Statistic	**2 mg/kg Vamorolone**			**6 mg/kg Vamorolone**		
	T_{max} (h)	**C_{max} (ng/mL)**	**AUC_{0-6} (ng·h/mL)**	**T_{max} (h)**	**C_{max} (ng/mL)**	**AUC_{0-6} (ng·h/mL)**
Day 1						
N	10	10	8	10	10	8
Mean (CV)	2.9 (74)	299.300 (59)	918.880 (49)	2.6 (70)	898.800 (55)	2365.656 (39)
Minimum	1.0	75.000	377.847	1.0	321.000	1234.602
Median	2.0	269.500	974.577	2.0	856.000	2323.279
Maximum	6.0	590.000	1623.691	6.0	1960.000	4065.609
Geom. Mean	2.3	246.8	816.3	2.2	781.7	2216.2
Geom. Mean SD	2.06	2.01	1.72	1.83	1.77	1.47

Week 2						
N	9	9	7	8	8	7
Mean (CV)	2.5 (85)	431.244 (67)	1515.982 (33)	2.4 (63)	935.875 (77)	3055.403 (56)
Minimum	1.0	85.200	1053.803	1.1	206.000	652.422
Median	1.9	343.000	1188.990	2.0	781.000	3023.845
Maximum	6.3	931.000	2321.603	6.0	2450.000	6080.631
Geom. Mean	1.9	349.3	1448.4	2.1	719.5	2571.6
Geom. Mean SD	2.10	2.06	1.38	1.61	2.23	2.02

Source: **Table 14.5.1a**

Absorption and Exposure

In study VBP15-006, vamorolone was rapidly absorbed with a median T_{max} of approximately 2 to 3 hours at 2 and 6 mg/kg followed by fast elimination. Vamorolone demonstrated a dose-dependent PK profile at the therapeutic doses: a higher dosage resulted in higher exposure (C_{max} and AUC), without accumulation of drug with daily administrations. Steady state was achieved after the first administration. These observations were consistent with previous findings in DMD patients the age group 4 to <7 years (study VBP15-002, sequence 00).

Although the same model structure for vamorolone was used in the REP-1-SNT-VAM-PMX-1, the refined PPK (241016_Final_report_Vamorolone_pooled_popPK) using a larger dataset estimated the flip-flop kinetics. However, the exposure metrics (C_{max} and $AUC_{\tau,ss}$) were still comparable for the DMD patients aged from 4 to <7 years of age.

Distribution

In the refined PPK model, the central volume of vamorolone (Vc) was estimated to be 31.9 L, which is five times lower than previous estimates from the model described in REP-1-SNT-VAM-PMX-1.

Elimination

The updated estimated clearance was CL=134 L/h which is 2.3 times faster than the previous estimations. The $t_{1/2}$ were comparable between models.

Intrinsic and Extrinsic Factors

Additional PK analyses on age, race, and hepatic impairment were performed in study VBP15-006 and the PPK.

Effect of Age

In Study VBP15-006, PK parameters were evaluated in DMD patients aged 2 to <4 years and 7 to <18 years. Vamorolone, at 2 mg/kg and 6 mg/kg, showed consistent absorption times, exposure, and variability for the two age groups. These findings were also consistent with previously reported PK exposure data in the 4 to <7 years age subjects (VBP15-002) reported in the initial submission.

In the refined updated PPK, vamorolone exposure ($AUC_{\tau,ss}$ and C_{max}) in DMD patients was simulated for the marketed ROS2 formulation for doses of 2, 4, and 6 mg/kg for the different age groups (≥2 and <4 years of age, ≥4 and <8 years of age, ≥8 and <12 years of age, and ≥12 and <18 years of age).

$AUC_{\tau,ss}$ and C_{max} increased with age because of the increase in weight in the underlying demographic dataset. The geometric mean of $AUC_{\tau,ss}$ was predicted for a dose of 6 mg/kg/day as 3120 ng.hr/mL (28 %CV), 3440 ng.hr/mL (29.5 %CV), 4190 ng.hr/mL (30.4 %CV) and 4700 ng.hr/mL (28.9 %CV) for the respective age groups. For the same dosing scenario C_{max} was predicted as 714 ng/mL (31.2 %CV), 801 ng/mL (32.8 %CV), 980 ng/mL (35 %CV) and 1100 ng/mL (36.5 %CV) for the respective age groups.

Overall, the PPK analysis showed that systemic exposure of vamorolone at 6 mg/kg/day was similar across pediatric age. The PK of vamorolone was consistent across pediatric age groups, and the 6 mg/kg/day dose reliably achieves therapeutic concentrations among all pediatric subpopulations.

Hepatic Impairment

Study VBP15-HI assessed the effect of hepatic impairment on the PK of vamorolone. 8 subjects with normal hepatic function and 8 with moderate hepatic impairment (Child-Pugh B) were considered (sequence 0000, 29Sep2022). Additional assessments were conducted to assess the ability to interpolate the influence of mild hepatic impairment on vamorolone PPK (241016_Final_report_Vamorolone_pooled_popPK). These included investigating the ability of total bilirubin levels to capture hepatic impairment and sub-categorizing hepatically impaired individuals. The assessment of hepatic impairment indicated that age-group adjusted bilirubin was a statistically significant covariate. However, the estimated effect size was not sufficient to adequately predict the observed difference between hepatically impaired and non-impaired adults in the observed data. The model was improved by sub-categorizing data using hepatic impairment categories: healthy, mild-moderate, and moderate-severe. Furthermore, the estimated effect of mild-moderate hepatic impairment on elimination clearance was lower than for moderate-severe impairment. Therefore, the subcategory model was selected as the most appropriate model to describe the observed study data and predict exposure in a population with mild hepatic impairment.

Table 4. Geometric Mean Simulated Vamorolone Exposure Metrics at Steady State for the DMD Reference Population Assuming Hepatic Impairment Mild- Moderate and Moderate-Severe

Exposure variable	Hepatic Impairment Status	Dose (mg/kg/day)	≥2 and <4 years	≥4 and <8 years	≥8 and <12 years	≥12 and <18 years
$AUC_{\tau,ss}$ (ng.h/mL)	Mild-moderate	2	2240 (28.9)	2480 (28.7)	3000 (29)	3290 (31)
	Moderate-severe		3950 (28.8)	4460 (29.1)	5340 (29.7)	5990 (29.3)
	None		1040 (28)	1150 (29.5)	1400 (30.4)	1570 (28.9)
	Mild-moderate	4	4490 (28.9)	4970 (28.7)	5990 (29)	6580 (31)
	Moderate-severe		7910 (28.8)	8910 (29.1)	10700 (29.7)	12000 (29.3)

	None		2080 (28)	2290 (29.5)	2790 (30.4)	3130 (28.9)
	Mild-moderate	6	6730 (28.9)	7450 (28.7)	8990 (29)	9870 (31)
	Moderate-severe		11900 (28.8)	13400 (29.1)	16000 (29.7)	18000 (29.3)
	None		3120 (28)	3440 (29.5)	4190 (30.4)	4700 (28.9)
C_{max} (ng/mL)	Mild-moderate	2	409 (27.1)	475 (29.3)	609 (32)	687 (34.2)
	Moderate-severe		572 (23.5)	703 (23.7)	922 (29.6)	1100 (31.8)
	None		238 (31.2)	267 (32.8)	327 (35)	367 (36.5)
	Mild-moderate	4	817 (27.1)	949 (29.3)	1220 (32)	1370 (34.2)
	Moderate-severe		1140 (23.5)	1410 (23.7)	1840 (29.6)	2190 (31.8)
	None		476 (31.2)	534 (32.8)	653 (35)	735 (36.5)
	Mild-moderate	6	1230 (27.1)	1420 (29.3)	1830 (32)	2060 (34.2)
	Moderate-severe		1720 (23.5)	2110 (23.7)	2760 (29.6)	3290 (31.8)
	None		714 (31.2)	801 (32.8)	980 (35)	1100 (36.5)

Values show the geometric mean (% coefficient of variation). For each age group, N=1000 subjects were simulated, considering sampling from the covariate distributions and from the variability distribution identified in the final model. Values rounded to 3 significant digits.

$AUC_{\tau,ss}$ = area under the concentration time curve during a dosing interval at steady state; C_{max} = maximum observed plasma concentration; DMD = Duchenne muscular dystrophy

Source: 241016_Final_report_Vamorolone_pooled_popPK Table 49

Impact of Race

The effect of race was evaluated in the refined PPK. Most race groups (i.e. Asian, American Indian) were underrepresented in the modelling database considering all studies together. Around 20% of all subjects were black - notably, all subjects of the VBP15-HI study were of black race, whereas only 2 subjects in the VBP15-002 and VBP15-004 studies were of black race. Black race showed a statistically significant impact on first order absorption of vamorolone and was therefore included in the model.

The impact of Asian race on vamorolone PK was also assessed. The Asian covariate was stratified into Chinese (i.e., subject from study SNT-I-VAM-024) and Asian Non-Chinese (i.e., subject from different study than SNT-I-VAM-024). Asian race did no show a statistically significant effect on any of the population PK model parameters.

2.6. Pharmacodynamics

Pharmacodynamics Biomarkers of Adrenal Suppression (Morning Cortisol)

Treatment with vamorolone led to a reduction in morning cortisol in all corticosteroid-untreated subjects over the 12-week treatment period.

- In the 2 to <4 years age group, the median cortisol level decreased from 295 nmol/L at baseline to 127 nmol/L at week 12 in the 2 mg/kg vamorolone group, and from 285.5 nmol/L to 73.0 nmol/L in the 6 mg/kg vamorolone group.
- In the 7 to <18 years corticosteroid untreated group, the median cortisol levels decreased from 205.5 nmol/L at baseline to 95.5 nmol/L at week 12 in the 2 mg/kg vamorolone group, and from 305.0 nmol/L to 62.0 nmol/L in the 6 mg/kg group.

Consistent with adrenal suppression at baseline, subjects on previous steroids treatment showed low morning cortisol at baseline.

- Treatment with 6 mg/kg vamorolone led to a further reduction in median morning cortisol over the 12-week treatment period, from 55.0 nmol/L to below the limit of quantification in the 6 mg/kg vamorolone group.
- At vamorolone 2 mg/kg, the median cortisol levels increased from 74.5 nmol/L at baseline to 96.5 nmol/L at week 12. This is due to some subjects being pretreated with high corticosteroid doses and then low doses of vamorolone, which improved their median cortisol levels slightly, skewing the results.

Pharmacodynamics Biomarkers of Insulin Resistance (Glucose, HbA1c, Insulin)

No increase in fasting insulin from baseline was observed during the 12-week vamorolone treatment in any age group, except for corticosteroid-untreated 7 to <18-year-old in the 6 mg/kg vamorolone group. This group was also the only one to show weight gain in this study. Further study is needed to establish whether these insulin increases are linked to weight gain or the PD effects of the drug. In contrast, subjects with a high body mass index (BMI) who were treated with corticosteroids had higher baseline fasting insulin levels and reduced insulin after switching to vamorolone.

Pharmacodynamics Biomarkers of Bone Turnover (Osteocalcin, P1NP, CTX)

Vamorolone had no effect on serum bone turnover biomarkers (CTX1, osteocalcin or P1NP) in subjects aged 2 to <4 years, regardless of the dose.

There was no evidence for an effect on serum bone turnover markers CTX1, osteocalcin, or P1NP at either dose of vamorolone in untreated with corticosteroid subjects aged 7 to <18 years.

The baseline values for subjects 7 to <18 years who had received previous corticosteroid treatment were low, particularly in the older 6 mg/kg vamorolone group, potentially due to their longer exposure to corticosteroids. Recovery of serum bone turnover biomarkers was observed in both vamorolone dose groups, but a lower proportion of subjects in the older 6 mg/kg group reached normal values after 12 weeks (less than 50%).

2.7. PK modelling

A population PK model was developed and reported in the initial submission. A refined model was designed including more datasets.

The refined PPK model of vamorolone has been further developed in DMD patients 2 to 18 years of age and healthy adults including expanded datasets from VBP15-001, VBP15-002, VBP15-004, VBP15-PK-FORM, VBP15-PK-FORM-002, VBP15-DDI, and VBP15-HI for improved exposure prediction. Final PK data from studies VBP15-006 and SNT-I-VAM-024 (Chinese study) were incorporated into the final

model. The impact of hepatic impairment on vamorolone PK was also assessed by investigating continuous total bilirubin measurements or sub-categorizing hepatically impaired individuals. The selected model described the data accurately as demonstrated by normalized visual predictive checks.

External validation of the model was conducted using emerging data from Study VBP15-006. In the final model update, the completed studies VBP15-006 and SNT-I-VAM-024 were added to the analysis dataset, accounting for relevant covariates.

The final dataset of Study VBP15-006 included patients between ≥2 and <18 years of age with N = 19 patients in the age group of ≥2 and <4 years, N = 9 patients in the age group of ≥4 and <8 years, N = 12 patients in the age group of ≥8 and <12 years, and N = 14 patients in the age group of ≥12 and <18 years.

As expected from the external validation, no changes and adjustments to the structural model were required for the inclusion of study VBP15-006. For the inclusion of Chinese HV from study SNT-I-VAM-024, an additional covariate modelling step was performed. The covariate search led to the inclusion of a fed Chinese HV effect on the absorption parameters zero-order absorption time (Tk0, fixed effect and random effect), lag time (Tlag, fixed effect and random effect), first order absorption rate constant (kabs), and relative bioavailability when compared to fasted ROS1 (Frel). In addition, an effect for fasted Chinese HV on first order absorption rate constant (kabs) compared to fasted Non-Chinese subjects treated with vamorolone led to further improvements in both objective function and BIC and was included in the model.

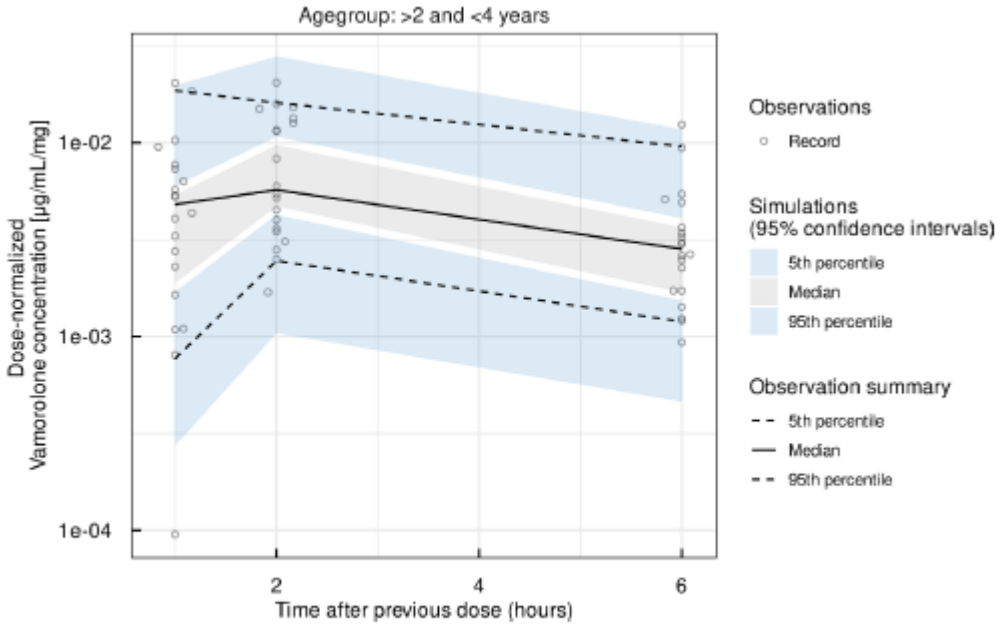
The parameter estimates of the updated model were found to be comparable to the previous estimates, showing that the PK data of the newly included studies were largely consistent with the previously modelled data, except for the following differences in absorption in Chinese HV: Fasted Chinese HV were generally comparable to the previous population, but showed slower absorption. Fed Chinese had longer zero order absorption time (4.65 vs 1.19 h), whereas Tlag was comparable. Relative bioavailability of fed Chinese was higher (Frel = 1.89) than generally for ROS2 (Frel = 1.79 (fed ROS2, Non-Chinese) and 1.78 (fasted ROS2, Non-Chinese)) and the first order absorption rate was 35% higher (kabs = 0.384 1/h vs. 0.284 1/h).

The parameter estimates for the final model are reported in Table 5.

Table 5. Parameter estimates - final model

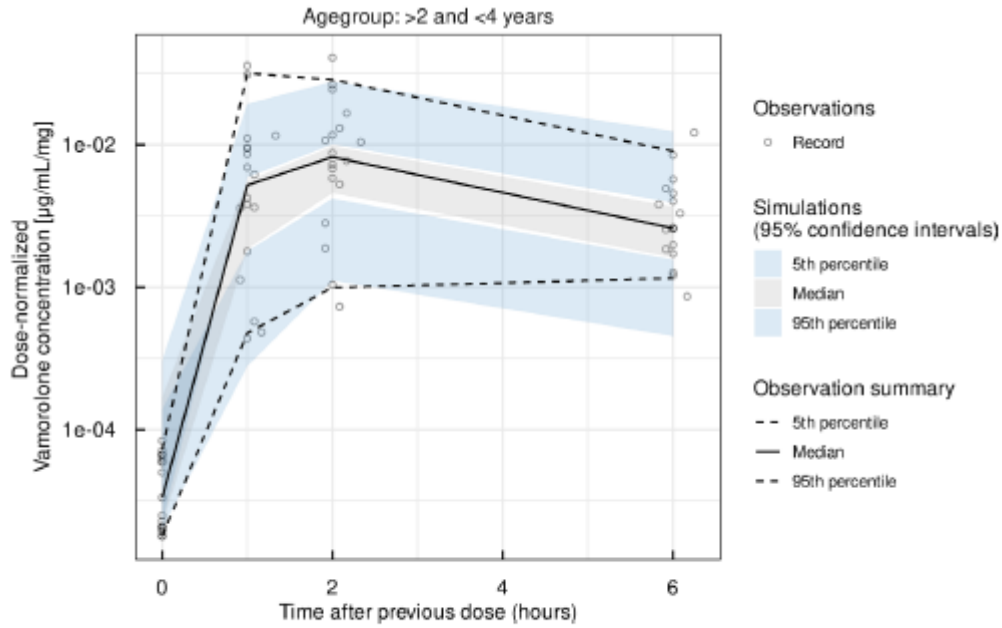
PARAMETER	VALUE	RSE	95% CI	SHRINKAGE	COMMENT
Typical parameters					
Tlag1	0.206	7.73%	[0.1754, 0.2491]	-	Absorption lag time (hours)
Tk0	1.19	7.53%	[1.031, 1.468]	-	Zero-order absorption time (hours)
kabs	0.284	2.86%	[0.2713, 0.2997]	-	First-order absorption rate constant (1/hour)
CL	134	3.15%	[121.4, 140.6]	-	Apparent elimination clearance (L/hour)
Vc	31.9	7%	[20.69, 40.93]	-	Apparent central volume of distribution (L)
Frel	1 (FIX)	-	[1, 1]	-	Relative bioavailability (-)
Tlag2	0.165	51%	[0.08853, 0.2448]	-	Absorption lag time (hours)
Tk02	4.65	11.5%	[3.681, 5.094]	-	Zero-order absorption time (hours)
Inter-individual variability					
omega(Tlag1)	0.447	11.5%	[0.2894, 0.5572]	36.4%	LogNormal
omega(Tk0)	0.743	9.19%	[0.5773, 0.9171]	24.2%	LogNormal
omega(kabs)	0.262	6.2%	[0.229, 0.2913]	22.4%	LogNormal
omega(CL)	0.277	5.29%	[0.2359, 0.3659]	21.5%	LogNormal
omega(Vc)	0.05 (FIX)	-	[0.05, 0.05]	95.8%	LogNormal
omega(Frel)	0 (FIX)	-	[0, 0]	-	LogNormal
omega(Tlag2)	1.28	40.5%	[0.5018, 1.331]	78.4%	LogNormal
omega(Tk02)	0.349	17.9%	[0.1221, 0.6815]	73.8%	LogNormal
Correlation of random effects					
corr(Tlag1,Tk0)	0.397	42.9%	[0.1872, 0.9998]	-	Correlation coefficient
Parameter-Covariate relationships					
beta_BDDICL(DDIITRA_1)	-0.393	30.8%	[-0.4435, -0.3007]	-	Drug interaction Yes on CL

The dose-normalized VPCs for the data from study VBP15-006 with the final model are in alignment with the VPCs prepared using the VBP15-006 data as an external validation (Figure 2, Figure 3). The final model was able to describe both concentration-time profiles on Day 1 and Week 2 and the vamorolone concentration across different age ranges adequately, VPCs for the age group >2 and <4 years are depicted in Figure 1 and Figure 2.



../Output/52_generate_VPC_study006/FIG_VPC_DN_obs_stratAGE1.pdf
T90_Reporting/Scripts/SCRIPT_52_generate_VPC_study006.R
2024-08-08 17:58:56
Page 1

Figure 1. VPC of Study VBP15-006 with the final model - Day 1 profiles



../Output/52_generate_VPC_study006/FIG_VPC_DN_obs_stratAGE2.pdf
T90_Reporting/Scripts/SCRIPT_52_generate_VPC_study006.R
2024-08-08 17:59:32
Page 1

Figure 2. VPC of Study VBP15-006 with the final model - Week 2 profiles

Simulations were conducted to derive AUCtau,SS and Cmax for the clinically relevant range of vamorolone dosing (2, 4 and 6 mg/kg). Geometric mean AUCtau,SS and Cmax with geometric coefficient of variation for the sampled DMD reference population (Race is not black or Chinese, no hepatic impairment) stratified by age group are shown in Table 6 and Table 7).

Larger exposure metrics were predicted for fed than for fasted status with the clinical formulation (ROS1), whilst AUCtau,SS was predicted to be similar between the fasted and fed status for the commercial formulation (ROS2). For both fasted and fed prandial status, larger exposure metrics were predicted for ROS2 than for ROS1. The box plots suggest that the lowest exposure is achieved with the Fasted - ROS1 combination, the Fed - ROS1 results in higher exposure. The largest exposures are suggested with Fasted - ROS2 and Fed ROS1 - 2 combinations, with similar $AUC_{tau,SS}$ values.

Table 6. Baseline age and baseline bodyweight of the subjects in the demographics dataset used for simulation

Age group	N	Mean age in years [SD]	Geom. mean body weight at baseline [CV%]
≥2 and <4 years	19	3.38 (0.365)	15.1 (15.7)
≥4 and <8 years	126	5.11 (1.04)	21 (18.6)
≥8 and <12 years	51	10.2 (0.932)	38.6 (31.6)
≥12 and <18 years	183	14.6 (1.73)	54 (34.2)

Values rounded to 3 significant digits.

N = number of subjects.

../Output/02_explore_demographics/TAB_demographics.txt
T34_Simulations/Scripts/SCRIPT_02_explore_demographics.R
2024-07-29 17:26:33

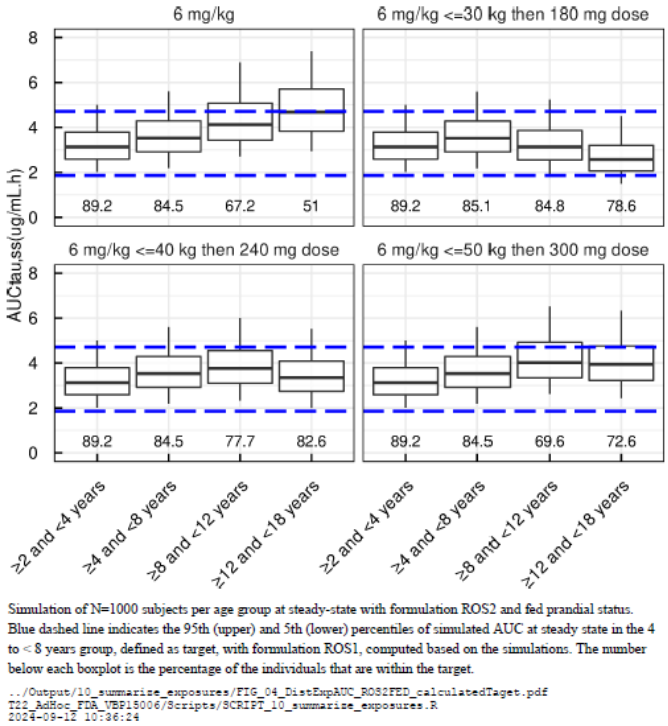
Table 7. Summary of simulated vamorolone exposure metrics at steady state for the DMD reference population

Age group	Exposure variable	Dose [mg/kg/day]	Mean [SD]	Geom. Mean [CV%]	Median [Q5, Q95]
≥2 and <4 years	$AUC_{tau,ss}$(ug/mL.h)	2	1.08 (0.297)	1.04 (28)	1.04 [0.662, 1.64]
		4	2.16 (0.593)	2.08 (28)	2.08 [1.32, 3.27]
		6	3.24 (0.89)	3.12 (28)	3.12 [1.99, 4.91]
	C_{max}(ug/mL)	2	0.249 (0.0745)	0.238 (31.2)	0.243 [0.144, 0.385]
		4	0.498 (0.149)	0.476 (31.2)	0.486 [0.287, 0.771]
		6	0.748 (0.223)	0.714 (31.2)	0.729 [0.431, 1.16]
≥4 and <8 years	$AUC_{tau,ss}$(ug/mL.h)	2	1.2 (0.357)	1.15 (29.5)	1.14 [0.727, 1.85]
		4	2.39 (0.713)	2.29 (29.5)	2.29 [1.45, 3.7]
		6	3.59 (1.07)	3.44 (29.5)	3.43 [2.18, 5.55]
	C_{max}(ug/mL)	2	0.281 (0.089)	0.267 (32.8)	0.268 [0.154, 0.443]
		4	0.561 (0.178)	0.534 (32.8)	0.536 [0.308, 0.887]
		6	0.842 (0.267)	0.801 (32.8)	0.803 [0.462, 1.33]
≥8 and <12 years	$AUC_{tau,ss}$(ug/mL.h)	2	1.46 (0.438)	1.4 (30.4)	1.39 [0.841, 2.24]
		4	2.92 (0.877)	2.79 (30.4)	2.78 [1.68, 4.48]
		6	4.37 (1.32)	4.19 (30.4)	4.18 [2.52, 6.72]
	C_{max}(ug/mL)	2	0.346 (0.119)	0.327 (35)	0.331 [0.184, 0.558]
		4	0.692 (0.237)	0.653 (35)	0.662 [0.367, 1.12]
		6	1.04 (0.356)	0.98 (35)	0.993 [0.551, 1.67]
≥12 and <18 years	$AUC_{tau,ss}$(ug/mL.h)	2	1.63 (0.473)	1.57 (28.9)	1.56 [0.973, 2.54]
		4	3.26 (0.947)	3.13 (28.9)	3.11 [1.95, 5.07]
		6	4.89 (1.42)	4.7 (28.9)	4.67 [2.92, 7.61]
	C_{max}(ug/mL)	2	0.391 (0.139)	0.367 (36.5)	0.364 [0.209, 0.655]
		4	0.781 (0.278)	0.735 (36.5)	0.727 [0.417, 1.31]
		6	1.17 (0.417)	1.1 (36.5)	1.09 [0.626, 1.97]

For each age group, N=1000 subjects were simulated, considering sampling from the covariate distributions and from the variability distribution identified in the final model. Values rounded to 3 significant digits.

../Output/22_summarize_exposures/TAB_Exposure_all_ref.txt
T34_Simulations/Scripts/SCRIPT_22_summarize_exposures.R

In order to investigate options for body weight-based dose caps the previous simulations were adjusted in to compare Fed ROS2 formulation to the previous Fed ROS1 formulation for caps at body weights of 30, 40, or 50 kg. A dose cap at 40 kg seems to keep the exposures of most patients in the previous exposure range of the 6 mg/kg dose of Fed ROS1 formulation across all age ranges.



Simulation of N=1000 subjects per age group at steady-state with formulation ROS2 and fed prandial status. Blue dashed line indicates the 95th (upper) and 5th (lower) percentiles of simulated AUC at steady state in the 4 to < 8 years group, defined as target, with formulation ROS1, computed based on the simulations. The number below each boxplot is the percentage of the individuals that are within the target.

../Output/10_summarize_exposures/FIG_04_DistExpAUC_ROS2FED_calculatedTaget.pdf
T22_AdHoc_FDA_VBP15006/Scripts/SCRIPT_10_summarize_exposures.R
2024-09-12 10:36:24

Figure 3. Summary of simulated vamorolone exposure metrics at steady state for 6 mg/kg/day vamorolone dose and ROS2 formulation, stratified by age and dosing regimen

Discussion on clinical pharmacology

After completion of study VBP15-006 and SNT-I-VAM-024, additional patient data was available to refine the previously developed PPK model. Model development was complicated by the different formulations developed, a food effect and a questionable impact of race for Chinese Asians. It was previously noticed that the final formulation (ROS2) led to higher exposures compared to the initial formulation (ROS1). However, it was shown through PPK based simulations that for the age group from 2 to <4 years similar exposures can be expected compared to older age groups. Weight based dosing of 6 mg/kg bodyweight with a cap at 40 kg bodyweight was proposed, which can be agreed. The MAH presented boxplots comparing exposure (AUC, Cmax) between different age groups including predicted and observed individual exposures for 2 mg/kg/day and 6 mg/kg/day. Exposure and variability were highest in subjects 12 to <18 years compared to younger age groups. Overall, exposure distributions could be considered as similar among age groups.

2.8. Conclusions on clinical pharmacology

Overall, updated PK results from study VBP15-006 indicate similar exposure for the age group >2 to <4 years when compared to older children.

3. Clinical efficacy

3.1. Dose response study(ies)

No dedicated dose response study in this population was conducted by the MAH. The proposed posology in the DMD population aged 2 to 4 is the same as in DMD patients aged 4 years and older.

3.2. Main study

In support of the extension of the approved indication to patients 2 to <4 years of age, the MAH conducted one phase 2, open-label, uncontrolled study of 12 weeks treatment duration, study VBP15-006.

Study VBP15-006

A phase II open-label, multiple dose study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of vamorolone in boys ages 2 to <4 years and 7 to <18 years with Duchenne Muscular Dystrophy (DMD)

Methods

This was a Phase II, open-label, multicenter, multiple dose, parallel group, uncontrolled study to evaluate the safety, tolerability, PK, PD, clinical efficacy, behaviour, neuropsychology, and physical functioning of vamorolone administered orally at daily doses of 2 and 6 mg/kg over a treatment period of 12 weeks in steroid-naïve boys ages 2 to <4 years, and in corticosteroid-treated and currently untreated boys ages 7 to <18 years with a diagnosis of DMD.

Eligible DMD patients had to be within the 2 to <4 years age group and steroid naïve (10 subjects each at the 2 and 6 mg/kg dose groups) or within the 7 to <18 years age group (including an additional 12 to <18 years age subgroup) and either untreated with corticosteroids for at least 3 months prior to enrollment (6 subjects each at the 2 and 6 mg/kg dose levels), or treated with standard of care corticosteroids at stable dose for at least 3 months prior to enrollment and expected to continue the same stable dose regimen through the date of the Baseline Day -1 Visit (6 subjects each at the 2 and 6 mg/kg dose levels). Additionally, 10 subjects 12 to <18 years corticosteroid treated were to be enrolled in the 7 to <18 years age group at the 6 mg/kg dose level (introduced by Protocol Amendment 2).

The study comprised a 5-week Screening Period; a 1-day Baseline Period; a 3-month open-label Treatment Period (Weeks 1-12); and a 4-8 week Dose-tapering Period for subjects not transitioning directly to further vamorolone or standard of care corticosteroid treatment at the end of the study. Subjects were enrolled into the study at the Screening Visit.

The first 6 subjects in each age group at the 2 mg/kg dose level served as the PK/safety run-in cohorts. The PK assessments were performed at Day 1 and Week 2, and together with the safety assessment during the first 4 weeks of treatment were the basis to confirm whether the 2 and 6 mg/kg dose levels would be the doses used in the subsequent subjects or whether a dose adjustment would be needed to avoid over or under-exposure in subjects for either of the two age groups. However, a dose adjustment was not implemented.

Corticosteroid-treated subjects in the 7 to <18 years age group had to take their final dose of standard of care corticosteroid therapy for DMD on Baseline Day -1, within 24 hours prior to administration of the first dose of vamorolone study medication.

Eligible subjects were assigned to treatment at the Baseline Day -1 Visit. After completion of Screening and Baseline assessments, and assignment to a dose group for treatment, subjects in both age groups returned to the study clinic on Day 1 for safety, PK, and PD assessments prior to administration of the

first dose of study treatment. Subjects were assessed for safety and tolerability, PK, PD, clinical efficacy, behaviour and neuropsychology, and physical functioning throughout the study.

The following efficacy assessments were performed:

- Bayley-III Gross Motor Scale score (2 to <4 years age group only): at screening, baseline and week 12
- PUL Test (7 to <18 years age group only): at screening, baseline and week 12
- PARS III: at screening and week 12
- PODCI: at screening and week 12
- Ease of study medication administration assessment (2 to <4 years age group only): at weeks 6 and 12
- Study medication acceptability assessment (7 to <18 years age group only): at weeks 6 and 12

The Bayley-III scale is a developmental assessment tool, used in the paediatric population for diagnosing developmental delays in early childhood. It has been reported to demonstrate statistically and clinically meaningful differences between children with developmental delay and typically developing children up to the age of 42 months in all 5 domains of cognition, motor, language, socio-emotional, and adaptive behaviour. The Bayley-III Gross Motor Scale comprises of 72 items that assess developmental functioning and include movement of the limbs and torso, static positioning (e.g., sitting, standing), dynamic movement including locomotion and coordination, balance, and motor planning [Connolly et al, 2014]. In the population of children with normal development, the mean Gross Motor Score is 10, with a standard deviation of 3.

The Pediatric Outcomes Data Collection Instrument (PODCI), a patient-reported outcome was completed by the subject's parent(s)/legal guardian(s) to assess physical functioning in activities of daily living. The PODCI consists of scores on 7 core scales, 4 encompassing physical function and 3 assessing psychological well-being. Physical function core scales include: 1) Upper Extremity and Physical Function, 2) Transfer and Basic Mobility, 3) Sports and Physical Functioning, 4) Pain/Comfort. Psychological well-being core scales include: 1) Happiness, 2) Satisfaction and 3) Expectations

At the end of the 3-month Treatment Period (Week 12), subjects were given the option to receive vamorolone in an expanded access program (EAP), or to transition to standard of care treatment for DMD (could include corticosteroids). Subjects completing Study VBP15-006 and enrolling directly into the EAP or transitioning directly to standard of care corticosteroid treatment did not need to taper their vamorolone dose prior to participation. All subjects who did not transition directly to further vamorolone or standard of care corticosteroid treatment were to enter the Dose-tapering Period during which the dose of study medication was progressively reduced and discontinued.

Study participants

The study was conducted at five qualified study centers in Canada.

Main inclusion criteria:

- Male patients with a centrally confirmed diagnosis of DMD, as defined as:
  - Dystrophin immunofluorescence and/or immunoblot showing complete dystrophin deficiency, and clinical picture consistent with typical DMD, OR

- Identifiable mutation within the DMD gene (deletion/duplication of one or more exons), where reading frame could be predicted as 'out-of-frame,' and clinical picture consistent with typical DMD, OR
- Complete dystrophin gene sequencing showing an alteration (point mutation, duplication, other) that was expected to preclude production of the dystrophin protein (i.e., nonsense mutation, deletion/duplication leading to a downstream stop codon), with a clinical picture consistent with typical DMD

- 2 to <4 or 7 to <18 years of age at time of enrollment in the study
- If 7 to <18 years of age and currently taking standard of care corticosteroids for treatment of DMD, subject had been taking standard of care corticosteroids at stable dose for at least 3 months prior to enrollment in the study and was expected to continue the same stable dose regimen through the date of the Baseline Day -1 Visit. [Note: Inhaled and/or topical corticosteroids were permitted if last use was at least 4 weeks prior to enrollment or if administered at stable dose beginning at least 4 weeks prior to enrollment and anticipated to be used at the stable dose regimen for the duration of the study]
- If 7 to <18 years of age and not currently corticosteroid-treated, subject had not received oral corticosteroids or other oral immunosuppressive agents for at least 3 months prior to enrollment. [Note: Inhaled and/or topical corticosteroids were permitted if last use was at least 4 weeks prior to enrollment or if administered at stable dose beginning at least 4 weeks prior to enrollment and anticipated to be used at the stable dose regimen for the duration of the study]
- Clinical laboratory test results were within the normal range at the Screening Visit, or if abnormal, were not clinically significant in the opinion of the Investigator. [Serum GGT, CK, and total bilirubin all had to be equal or below the upper limit of the normal range (ULN) at the Screening Visit].
- Evidence of chicken pox immunity

Main <u>exclusion criteria:</u>

- Had current or history of major renal or hepatic impairment, diabetes mellitus or immunosuppression, chronic systemic fungal or viral infections or a history of primary hyperaldosteronism
- Had used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), or mexrenone (mexrenoate potassium) within 4 weeks prior to enrollment
- Had evidence of symptomatic cardiomyopathy
- If 2 to <4 years of age, was currently being treated or had received previous treatment with oral corticosteroids or other immunosuppressive agents [Notes: Past transient use of oral corticosteroids or other oral immunosuppressive agents for no longer than 1 month cumulative, with last use at least 3 months prior to enrollment was considered for eligibility on a case-by-case basis, unless discontinued for intolerance. Inhaled and/or topical corticosteroids were permitted if last use was at least 4 weeks prior to enrollment or if administered at stable dose beginning at least 4 weeks prior to enrollment and anticipated to be used at the stable dose regimen for the duration of the study]
- Had received a live attenuated vaccine within 14 days prior to the first dose of study medication
- Had previously been enrolled in the VBP15-006 study or any other vamorolone study

Treatments

The planned vamorolone dose levels were 2 and 6 mg/kg/day. Doses could be adjusted based on PK and safety data from the first 6 subjects per age group to avoid over or under exposure and to achieve a consistent vamorolone AUC across the entire pediatric age range. However, such a dose adjustment was not implemented.

Approximately 10 subjects in the 2 to <4 years age group were planned to be enrolled into the 2 mg/kg treatment group. After the PK and safety were determined in the initial 6 subjects and the doses confirmed, enrollment continued for the 2 mg/kg treatment group and started for the 10 planned subjects of the 2 to <4 years age group into the 6 mg/kg treatment group.

Approximately 12 subjects in the 7 to <18 years age group were planned to be enrolled into the 2 mg/kg treatment groups (6 untreated at entry, 6 corticosteroid-treated at entry). After the PK and safety were determined in the initial 6 subjects and the doses confirmed, enrollment could continue for 2 mg/kg and the 6 mg/kg treatment groups. Protocol Amendment 2 introduced an additional subgroup of 10 subjects aged 12 to <18 years, corticosteroid treated, to receive the 6 mg/kg dose level.

Vamorolone 4.0% wt/vol oral liquid suspension (ROS2) was administered to all subjects once daily for 12 weeks, from Study Day 1 until the Week 12 Visit using a volumetric syringe supplied by the site. Following administration of the dose of study drug suspension, the syringe was to be filled once with water and the water administered by mouth using the volumetric syringe. The subject then had to drink approximately 50 mL (approximately 2 ounces) of water to ensure the full dose had been ingested. The daily dose of study medication was to be taken with breakfast. There were no other food or drink restrictions before or after dosing. At the Day 1, Week 2, and Week 12 study visits, subjects had to arrive at the study clinic and eat breakfast at the study site within 30 minutes prior to administration of the dose of study medication. Any missed or incomplete doses of study medication were to be recorded in the Subject Diary and reported immediately to the site Investigator.

At the end of the 12-week Treatment Period, subjects could receive additional vamorolone treatment in a dose-tapering manner during a 4-8 week Dose-tapering Period prior to discharge from the study, should they not transition directly to further vamorolone or standard of care corticosteroid treatment.

Concomitant medications

Use of either inhaled and/or topical corticosteroids was permitted in both age groups, provided that the dose was stable beginning at least 4 weeks before the first dose of study drug and was anticipated to be stable for the duration of the study. Hydrocortisone (or prednisone) stress dosing was permitted during an illness, injury, or surgical procedure to avoid an adrenal crisis. Vitamin D insufficiency and deficiency were to be treated with high doses of Vitamin D supplement according to local site guidelines. All other concomitant medications, except for those noted below were permitted if clinically indicated. Concomitant medications were to be maintained at the same dose and regimen during the study if possible.

The following medications were not permitted before the first dose of study drug and were prohibited for the duration of the study: Mineralocorticoid receptor agents had to be discontinued at least 4 weeks prior to the first dose of study drug; oral corticosteroids or other oral immunosuppressive agents. Subjects in the 2 to <4 years age group who had received prior treatment with oral immunosuppressive agents were ineligible for study entry; Subjects in the 7 to <18 years age group who were not currently receiving oral corticosteroids or other oral immunosuppressive agents had to have discontinued all such agents at least 3 months prior to enrollment; Subjects in the 7 to <18 years age group who had been receiving standard of care corticosteroids for treatment of DMD for at least 3 months prior to enrollment in the study had to continue the same stable dose regimen through the

date of the Baseline Day-1 Visit; the standard of care corticosteroids were discontinued on Day 1; live attenuated vaccines were not permitted within 14 days before the first dose of study drug and for the duration of the study; Idebenone had to be discontinued at least 4 weeks prior to first dose of study drug; any investigational medications other than vamorolone had to be discontinued at least 3 months before the first dose of study drug; medications indicated for the treatment of DMD, including Exondys51 and Translarna had to be discontinued at least 3 months prior to first dose of study drug; any approved medications or herbal remedies that could impact strength and function (including, but not limited to, Co-enzyme Q10, creatine) had to be discontinued at least 4 weeks before the first dose of study drug. Additionally, vamorolone was to be used with caution with any drug metabolized by cytochrome P450 3A4 (CYP3A4).

Objectives

Primary objective:

- to evaluate the safety and tolerability of vamorolone administered orally at daily doses of 2 and 6 mg/kg over a 3-month treatment period in boys ages 2 to <4 and 7 to <18 years with DMD.

Secondary objectives:

- To evaluate the PK of vamorolone administered orally in boys ages 2 to <4 years and 7 to <18 years with DMD.
- To confirm the vamorolone exposure in boys ages 2 to <4 years and 7 to <18 years with DMD at 2 and 6 mg/kg and to adjust the doses if appropriate to achieve similar vamorolone area under the concentration-time curves (AUCs) across the entire pediatric age range.

Exploratory objectives:

- To compare the efficacy, as measured by the effect on muscle function, of vamorolone administered orally at daily doses of 2 and 6 mg/kg over a 3-month treatment period in boys ages 2 to <4 years and 7 to <18 years with DMD.
- To evaluate the effect of vamorolone administered orally at daily doses of 2 and 6 mg/kg over a 3-month treatment period on behavior and neuropsychology in boys ages 2 to <4 years and 7 to <18 years with DMD.
- To evaluate the effect of vamorolone administered orally at daily doses of 2 and 6 mg/kg over a 3-month treatment period on physical functioning in boys ages 2 to <4 years and 7 to <18 years with DMD.
- To evaluate the ease of administration of vamorolone in boys ages 2 to <4 years with DMD and study medication acceptability of vamorolone in boys ages 7 to <18 years with DMD at daily oral doses of 2 and 6 mg/kg.
- To investigate the effects of vamorolone administered orally at daily doses of 2 and 6 mg/kg over a 3-month treatment period on PD biomarkers of safety and efficacy in boys ages 2 to <4 years and 7 to <18 years with DMD.

Outcomes/endpoints

Safety Endpoints (endpoints related to the primary objective):

Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs); Change from Baseline to Week 12 in height, weight and body mass index (BMI) (absolute, percentile and Z-score);

Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points in vital signs; Cushingoid features; Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points in clinical laboratory values – Hematology and clinical chemistry, Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL]), Vitamin D level; Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points in 12-lead electrocardiogram (ECG); Eye examination for detection of clinically significant abnormalities. Change from baseline to Week 12.

Pharmacokinetic Endpoints (endpoints related to a secondary objective): Pre-dose and post-dose plasma concentration measurements of vamorolone at Day 1 and Week 2; Other PK parameters (including AUCs and other relevant PK parameters) related to the other secondary endpoint.

Endpoints related to exploratory objectives:

Efficacy Endpoints:

• Change from Baseline to Week 12 in Bayley Scales of Infant and Toddler Development-III (Bayley-III) Gross Motor Scale score (2 to <4 years age group only)

• Change from Baseline to Week 12 in Performance of Upper Limb (PUL) scale (7 to <18 years age group only)

Behavior, Neuropsychology and Physical Functioning Endpoints:

• Changes from Baseline to Week 12 for the total score and the subscale scores of the Personal Adjustment and Role Skills scale III (PARS III). Also, the proportion of subjects with abnormal values (Z score ≤-1) at Baseline and Week 12 for each subscale.

• Changes from Baseline to Week 12 for all Pediatric Outcomes Data Collection Instrument (PODCI) scale scores

Acceptability Endpoints:

• Ease of Study Medication Administration Assessment (2 to <4 years age group only)

• Study Medication Acceptability Assessment (7 to <18 years age group only)

Pharmacodynamic Biomarkers of Safety:

• Changes from Baseline in adrenal suppression biomarker (morning cortisol)

• Change from Baseline in bone turnover biomarkers (osteocalcin, serum aminoterminal propeptide of type I collagen [P1NP], serum Type 1 collagen C-telopeptide [CTX1])

• Change from Baseline in insulin resistance biomarkers (Hemoglobin A1c [HbA1c], fasting glucose and insulin)

• Change from Baseline in other exploratory biomarkers for aspects of safety and efficacy (leutinizing hormone [LH], follicle stimulating hormone [FSH], thyroid stimulating hormone [TSH], and free thyroxine [FT4])

Sample size

This was an open-label, parallel group, multiple dose study assessing safety and tolerability of vamorolone as the primary objective. There was no formal sample size calculation.

A total of approximately 20 subjects were planned to be enrolled within the 2 to <4 years age group, as follows:

- Vamorolone 2.0 mg/kg/day (n=10); enrolled first
- Vamorolone 6.0 mg/kg/day (n=10); enrolled after previous dose group

A total of approximately 34 subjects were planned to be enrolled within the 7 to <18 years age group, with 2.0 mg/kg/day groups enrolled first, as follows:

- Vamorolone 2.0 mg/kg/day, steroid untreated at entry (n=6)
- Vamorolone 2.0 mg/kg/day, steroid treated at entry (n=6)
- Vamorolone 6.0 mg/kg/day, steroid untreated at entry (n=6)
- Vamorolone 6.0 mg/kg/day, steroid treated at entry (n=6)
- Vamorolone 6.0 mg/kg/day, 12 to <18 years and steroid treated at entry (n=10; additional group)

Randomisation

Following the signing of the written ICF, subjects were assigned a unique site-specific 6-digit subject identification (ID) number in sequential order of screening into the study. The site notified the Coordinating Center of the newly assigned subject ID number.

Blinding (masking)

According to the clinical study report, page 40, blinding has not been applicable as this was an open label study.

Statistical methods

The statistical methods used in this study are further described in the latest SAP, version 2.0, dated 25 June 2024, an SAP Annex regarding PD biomarkers, dated 27 June 2024 and a SAP DAP [NCA (noncompartmental analysis) PK data analysis plan], dated 03 October 2024.

Analysis sets:

Screened analysis set: All subjects who have consented for the study, including subjects who failed the screening. Unless specified otherwise, the Screened set will be used for subject listings and for the summary of subject disposition

Safety analysis set: All subjects who receive at least one dose of study medication will be included in the Safety set. The Safety set is the primary analysis population for safety assessments. Results will be presented "as treated."

PK set: All subjects who receive at least one dose of vamorolone study medication and have sufficient data for PK analysis.

Statistical analyses were performed using SAS® version 9.4 or later. All measurements were analyzed based upon the type of distribution, and descriptive statistics are presented by treatment group and assessment time point, as appropriate. Descriptive statistics for continuous variables include the number of observations (n), mean, standard deviation (SD), lower quartile (Q1), median, upper quartile (Q3), minimum, and maximum. Standard error of the mean is also provided for summaries of efficacy data, where relevant. Descriptive statistics for categorical variables include absolute counts and relative frequencies (percentages).

Baseline measurement is defined as the last non-missing value prior to the first dose of study drug in the study.

This study does not include any formal statistical testing and therefore no p-values testing statistical hypotheses are presented. Data could be summarized with confidence intervals and for this purpose, two-sided 95% coverage would be used.

The Safety set was used for presentations and analyses of the efficacy parameters. Standard descriptive statistics were used to summarize the clinical efficacy endpoints by dose level within age group. Change from Baseline was presented.

Pharmacokinetic analysis: Pre-dose and post-dose plasma concentration measurements of vamorolone at Day 1 and Week 2 were collected by age group, dose level, and corticosteroid treatment at entry (ages 7 to <18 years only). PK data analyses were performed using the statistical softwares SAS®, and Phoenix™ WinNonlin®.

For each vamorolone dose level and age group, the endpoints were evaluated. Additionally, subjects within the 7 to <18 years age group who were on corticosteroid therapy at the time of assignment to a dose group were evaluated separately from those who were off corticosteroid therapy for at least 3 months prior to assignment to a dose group. Additionally, these subjects were also evaluated separately according to age <12 years or ≥12 years.

Changes to the planned analyses

Version 1.0 of the SAP was finalised on 02 May 2024. Changes from the planned analysis in the protocol that were introduced in the SAP included removal of a modified intent-to-treat analysis set, as it was not deemed relevant by the MAH, and removal of planned mixed model repeated measures and analysis of covariance models as due to the size and duration of the study these statistical models defined in the protocol were not considered suitable by the MAH.

The SAP was amended once more (Version 2.0, 25 Jun 2024) to add new descriptive tables and listings. A summary of missed and incomplete dosing was also generated based on the subject diaries.

A post-hoc analysis was conducted to investigate whether age had an impact on the Bailey results and to investigate the variability in blood pressure measurements.

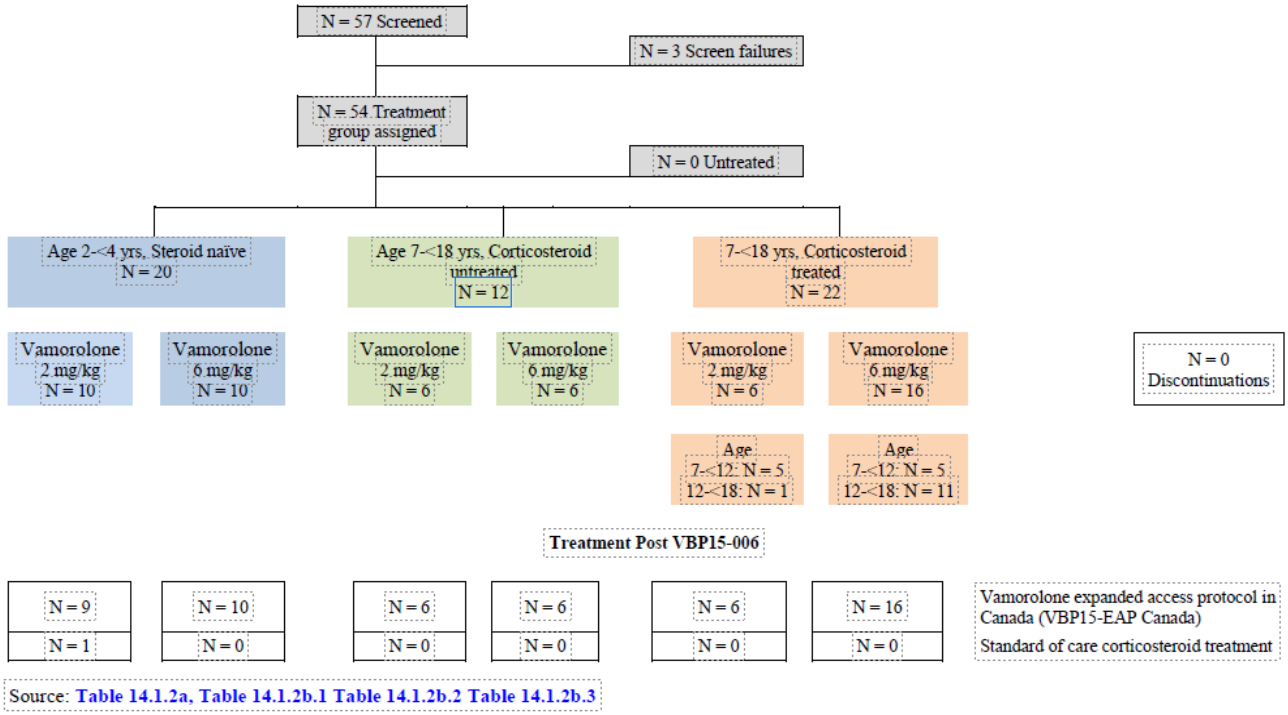
The non-compartmental analysis (NCA) of PK was conducted as a post-hoc analysis, providing deeper insights into the data after the initial study was completed.

Results

Participant flow

Disposition of patients is presented in the figure below:

Figure 4. Participant Flow



A total of 57 subjects were screened. Three subjects did not enter the Treatment Period due to failure to meet the inclusion criteria. Overall, fifty-four subjects were assigned to a treatment group; and were treated with vamorolone as planned per protocol. Twenty subjects aged 2 to <4 years were included and received vamorolone treatment for a duration of 12 weeks in Study VBP15-006: 10 received vamorolone 2 mg/kg and 10 received vamorolone 6 mg/kg.

No subject discontinued the study prematurely. Fifty-three subjects continued vamorolone treatment in the EAP and 1 subject (age 2 to <4 years, 2 mg/kg vamorolone group) transferred to standard of care corticosteroid treatment, thus no subject entered the Dose-tapering Period.

Recruitment

Date first subject enrolled: 21 March 2022 and Date last subject completed: 17 June 2024

Conduct of the study

The original protocol (dated 14 Oct 2021) was amended three times (14 Apr 2022, 09 Feb 2023, and 11 Apr 2023). There were no important changes with a potential impact on the exploratory efficacy results.

Protocol deviations

Overall, 35 subjects (64.8%) had ≥1 protocol deviations reported during the study. The most common deviation was 'data not reported', corresponding to an assessment that was not performed during a visit (resulting in missing ECG, PK, eye exam, physical exam, labs or vital signs), this was reported for 25 subjects (46.3%) in total. Inappropriate consent process was reported in 13.0% of subjects, all protocol deviations were due to delay in re-consenting; no case of missing consent prior to any study procedure was reported.

Overall, 6 subjects (11.1%) entered the study without satisfying entry criteria. 2 subjects violated eligibility criteria: One subject in the 7 to <18 years, corticosteroid untreated, 6 mg/kg vamorolone group was missing his second varicella vaccine and was negative on serology testing and one subject in the 2 to <4 years, 6 mg/kg vamorolone group had previous steroid use for >1 month to treat immune thrombocytopenic purpura (between Day -401 and Day -261). There were 13 deviations impacting "Accuracy and reliability of study data", all consisted of lack of compliance check by weighing study drug bottles at Week 2. Additionally, 2 subjects in the 2 to <4 years, 6 mg/kg vamorolone group had late DMD diagnosis confirmation and 2 subjects in the 7 to <18 years, corticosteroid treated, 6 mg/kg vamorolone group did not have eligibility confirmed by laboratory assessments.

Baseline data

Demographic data and disease characteristics for the intended population (age 2 to <4 years) in the safety set are reported in Table 8 below. Overall, baseline characteristics were generally considered similar across the two dose groups.

In the 2 mg/kg vamorolone group, the median age was 3.3 years (range 2.8 to 4.0 years). Five subjects were White, and 5 subjects were of Asian race. The median age at first signs or symptom identified was 19.0 months (range 12.0 to 30.0 months). All 10 subjects were ambulatory. The most common type of mutation was a deletion, 6 subjects (60.0%).

In the 6 mg/kg vamorolone group, the median age was 3.5 years (range 2.9 to 4.0 years), slightly higher than in the 2.0 mg/kg vamorolone group. Eight subjects were White, 1 subject was of Asian race and 1 subject was of Black or African American race. The median age at first signs or symptoms identified was 12.0 months (range 10.0 to 24.0 months). All 10 subjects were ambulatory. The most common type of mutation was a deletion, 8 subjects (80.0%).

Table 8. Demographic and disease characteristics for age 2 to <4 years steroid naïve subjects

	2 mg/kg N=10	**6 mg/kg N=10**
Age (years)		
Mean (SD)	3.3 (0.45)	3.5 (0.32)
Median (Q1; Q3)	3.3 (3.0 ; 3.8)	3.5 (3.3 ; 3.6)
Min, Max	2.8, 4.0	2.9, 4.0
Race		
Asian	5 (50.0%)	1 (10.0%)
Black or African American	0	1 (10.0%)
White	5 (50.0%)	8 (80.0%)
Age at first signs or symptom identified (months)		
Mean (SD)	20.8 (5.67)	14.2 (4.47)
Median (Q1; Q3)	19.0 (18.0 ; 24.0)	12.0 (12.0 ; 18.0)
Min, Max	12.0, 30.0	10.0, 24.0
Ambulatory status		
Ambulatory	10 (100.0%)	10 (100.0%)
Non-ambulatory	0	0
Type of mutation		
Deletion	6 (60.0%)	8 (80.0%)
Duplication	1 (10.0%)	1 (10.0%)
Indel (small insertion/deletion)	1 (10.0%)	0
Nonsense	2 (20.0%)	0
Splicing	0	1 (10.0%)
Exon 44 skippable?		
No	10 (100.0%)	10 (100.0%)
Yes	0	0
Splice site?		
No	10 (100.0%)	9 (90.0%)
Yes	0	1 (10.0%)
Mutation exons 1 to 7 or 2 dup. or 8 skip?		
No	7 (70.0%)	8 (80.0%)
Yes	3 (30.0%)	2 (20.0%)

Source: VBP15-006 Table 16, Table 17

Numbers analysed

Table 9. Number of subjects (planned and analysed)

Age (years)	Dose (mg/kg)	Corticosteroid-Status at entry	Number of Subjects		
			Planned	Analyzed for Safety	Analyzed for Pharmacokinetics
2 to <4	2	Naïve	10	10	10
2 to <4	6	Naïve	10	10	10
7 to <18	2	Untreated	6	6	6
7 to <18	6	Untreated	6	6	6
7 to <18	2	Treated	6	6	6
7 to <18	6	Treated	16 (including ≥10 age 12 to <18 years)	16 (11 age 12 to <18 years)	16 (11 age 12 to <18 years)

All subjects treated were included in the safety and PK sets.

Outcomes and estimation

Exploratory endpoints:

Change from Baseline to Week 12 in Bayley Scales of Infant and Toddler Development-III (Bayley-III) Gross Motor Scale score

The median Bayley-III GMSS at baseline was 3.50 in the vamorolone 2 mg/kg group and 5.00 in the vamorolone 6 mg/kg group (Table 10). At the end of the study (after 12 weeks of treatment with vamorolone) the median Bayley-III GMSS was 4.00 in the 2 mg/kg group and 8.00 in the 6 mg/kg group. The median change from baseline in the Bayley-III GMSS was '0' in the vamorolone 2 mg/kg group and 2.50 in the vamorolone 6 mg/kg group, showing a marked improvement in the Bayley III GMSS in the vamorolone 6 mg/kg when compared to the 2 mg/kg group. With regard to the mean (SD) change from baseline, the 2 mg/kg vamorolone group showed an improvement of 0.44 (1.130), indicative of a positive trend in the context of a degenerative disease. The mean (SD) change in the vamorolone 6 mg/kg showed a similar magnitude as the median change from baseline, i.e., 2.50 (1.716).

Table 10. Bayley-III Gross Motor Scale for Age 2 to <4 Years Steroid Naïve Subjects

	2 mg/kg N=10	6 mg/kg N=10
Baseline		
n	10	10
Mean (SD)	3.70 (2.214)	5.40 (1.838)
Median (Q1; Q3)	3.50 (2.00 ; 4.00)	5.00 (4.00 ; 6.00)
Min, Max	1.00, 9.00	3.00, 9.00
Week 12		
n	9	10
Mean (SD)	4.22 (2.333)	7.90 (2.558)
Median (Q1; Q3)	4.00 (3.00 ; 4.00)	8.00 (7.00 ; 10.00)
Min, Max	2.00, 9.00	2.00, 11.00
Change from Baseline to Week 12		
n	9	10
Mean (SD)	0.44 (1.130)	2.50 (1.716)
Median (Q1; Q3)	0.00 (0.00 ; 1.00)	2.50 (2.00 ; 4.00)
Min, Max	-1.00, 3.00	-1.00, 5.00

Max = maximum; Min = minimum; Q = quartile; SD = standard deviation
Source: VBP15-006 Table 72

As the median age for the 6 mg/kg vamorolone group (3.5 years) was 2 months higher than for the 2 mg/kg vamorolone group (3.2 years), and taking into account that the Bayley-III scale is validated up to the age of 42 months (or 3.5 years), a post-hoc subgroup analysis was performed to assess the impact of age on the efficacy of vamorolone (reference is made to Ancillary analyses section further in this assessment report).

Patient Reported Outcomes

Behaviour (PARS III): There was no relevant change in the PARS III total score, or in the subscales in none of the included patient groups.

Physical functioning (PODCI): There was no relevant change in the PODCI global functioning score, or in the subscales, in none of the studied treatment arms.

Ease of Treatment Administration Age 2 to <4 Years Steroid Naïve: The majority of caregivers reported that the addition of vamorolone to the morning schedule was easy, and that administration occurred without opposition (Table 11).

Table 11. Ease of Treatment Administration at Week 12 for Age 2 to <4 Years Steroid Naïve Subjects

	Age 2 to <4 Years Steroid Naïve	
	2 mg/kg (N = 10)	6 mg/kg (N = 10)
Ease of Taking Medication		
Cooperatively without opposition	9 (90.0)	9 (90.0)
Cooperatively with some opposition	0	1 (10.0)
With opposition	1 (10.0)	0
Ease of Morning Schedule		
An easy addition to the morning routine	9 (90.0)	9 (90.0)
A manageable addition	1 (10.0)	1 (10.0)

Max = maximum; Min = minimum; NA = not available – no post Baseline data available; SD = standard deviation
Source: Table 14.3.10.3

Efficacy results in patients 7 to <18 years of age:

Medication Acceptability: Age 7 to <18 years

Age 7 to <18 Years Untreated with Corticosteroids at Entry: The majority of subjects were indifferent or liked the smell of the medicine (5/6 subjects [83.3%] in the 2 mg/kg vamorolone group and 4/6 subjects [66.7%] in the 6 mg/kg vamorolone group). In both dose groups, 4/6 subjects (66.7%) were indifferent or liked the taste of the medicine.

Age 7 to <18 Years Treated with Corticosteroids at Entry (and 12 to <18 Years Subgroup Treated with 6 mg/kg): The majority of subjects were indifferent or liked the smell of the medicine (5/6 subjects [83.3%] in the 2 mg/kg vamorolone group and 12/16 subjects [75.0%] in the 6 mg/kg vamorolone group). In the 2 mg/kg vamorolone group, 4/6 subjects (66.7%) were indifferent or liked the taste of the medicine, while the majority 10/16 subjects (62.5%) in the 6 mg/kg vamorolone group did not like it.

Performance of Upper Limb (PUL) Test:

Ages 7 to <18 Years, Untreated with Corticosteroids at Entry: There were no relevant changes from Baseline to Week 12 in the PUL total score in both dose groups.

Age 7 to <18 Years Treated with Corticosteroids at Entry (and 12 to <18 Years Subgroup Treated with 6 mg/kg): There were no relevant changes from Baseline to Week 12 in the PUL total score in both dose groups.

Ancillary analyses

Post-hoc Subgroup Analyses

As the median age was 2.4 months higher for the 6 mg/kg vamorolone group (3 years and 6 months) compared to the 2 mg/kg vamorolone group (3 years and 3.6 months), subgroup analyses were performed to assess the impact of age. Taking into consideration that the Bayley-III scale is validated only up to 3.5 years of age, the effect of vamorolone 2 mg/kg and 6 mg/kg was studied in 2 subgroups; ≤3.5 years versus >3.5 years of age at Week 12.

In subjects ≤3.5 years of age, the median change from baseline in the Bayley-III GMSS was 0.5 in the 2 mg/kg group (n=5) and 2.00 in the 6.0 mg/kg group (n=2), showing a marked improvement in the Bayley III GMSS in the 6 mg/kg as compared to 2 mg/kg group. Older subjects, i.e. subjects >3.5 years of age showed a median change from baseline of 0.00 in the 2 mg/kg group (n=5), and a change of 2.50 from baseline in the 6.0 mg/kg group (n=8).

Table 12. Post-Hoc Analysis of Bayley-III Gross Motor Scale by Age at Week 12, by Vamorolone Dose Group

	Age ≤3.5 years at Week 12		Age >3.5 years at Week 12	
	2 mg/kg N=5	6 mg/kg N=2	2 mg/kg N=5	6 mg/kg N=8
Baseline				
n	5	2	5	8
Mean (SD)	3.40 (1.140)	4.00 (1.414)	4.00 (3.082)	5.75 (1.832)
Median (Q1; Q3)	3.00 (3.00; 4.00)	4.00 (3.00; 5.00)	4.00 (2.00; 4.00)	5.00 (4.50; 7.00)
Min, Max	2.00, 5.00	3.00, 5.00	1.00, 9.00	4.00, 9.00
Week 12				
n	4	2	5	8
Mean (SD)	4.25 (1.893)	6.00 (5.657)	4.20 (2.864)	8.38 (1.598)
Median (Q1; Q3)	3.50 (3.00; 5.50)	6.00 (2.00; 10.00)	4.00 (2.00; 4.00)	8.00 (7.50; 9.50)
Min, Max	3.00, 7.00	2.00, 10.00	2.00, 9.00	6.00, 11.00
Change from Baseline to Week 12				
n	4	2	5	8
Mean (SD)	0.75 (1.708)	2.00 (4.243)	0.20 (0.447)	2.63 (1.061)
Median (Q1; Q3)	0.50 (-0.50; 2.00)	2.00 (-1.00; 5.00)	0.00 (0.00; 0.00)	2.50 (2.00; 3.50)
Min, Max	-1.00, 3.00	-1.00, 5.00	0.00, 1.00	1.00, 4.00

Max = maximum; Min = minimum; Q = quartile; SD = standard deviation
Source: modified from Pediatric Extrapolation Report Addendum Table 9.1

Analysis performed across trials (pooled analyses and meta-analysis)

Comparison of efficacy results from study VBP15-006 were performed with the efficacy results from study VBP15-004 and provided in an updated paediatric extrapolation report (dated 15 August 2025).

In Study VBP15-004, the efficacy endpoints for the 4 to <7-year-old subjects included changes in TTSTAND velocity, 6MWT distance, TTRW velocity, TTCLIMB velocity, and the lower limb NSAA motor function test, while Bayley-III GMSS was used in the 2 to <4-year-old age group in Study VBP15-006. These endpoints were selected based on age-related, validated gross motor assessment tools.

Study VBP15-004 showed clinically meaningful and statistically significant improvements in multiple, independent measurements of lower limb motor function in the 4 to <7-year-old reference population.

Study VBP15-006 showed a dose-dependent improvement in Bayley-III GMSS values in the target population after 12 weeks of treatment, indicating an effect of vamorolone also in younger age groups and supporting the use of the 6 mg/kg/day dose.

Supportive study

Study VBP15-004, a Phase 2b, randomized, double-blind, parallel group, placebo- and active-controlled study with double-blind extension to assess the efficacy and safety of vamorolone in ambulant boys with Duchenne muscular dystrophy (DMD) was the pivotal study in the initial MAA. Reference is made to EMEA/H/C/005679/0000.

It was used for the extrapolation of efficacy by comparing efficacy data of study VBP15-004 to study VBP15-006.

3.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In support of efficacy of vamorolone in DMD patients aged 2 years to <4 years the MAH submitted one phase II study in line with the agreed PIP (EMEA-001794-PIP02-16).

Study VBP15-006 was a Phase 2, multicenter, open-label, study to assess the safety, tolerability and PK of two doses of vamorolone to be used to treat DMD in boys ages 2 to <4 years and 7 to <18 years, and to perform an exploratory evaluation of pharmacodynamics, clinical efficacy, including physical functioning, and behaviour and neuropsychology, over a treatment period of 12 weeks.

No dedicated dose response study in this population was conducted by the MAH. Consistent with the treatment regimen in DMD patients 4 years and older, the proposed starting dose for vamorolone in patients 2 to <4 years of age is 6 mg/kg once daily. The daily dose may be down-titrated to 4 mg/kg/day or 2 mg/kg/day based on individual tolerability. Patients should be maintained at the highest tolerated dose within the dose range. The vamorolone dose levels of 2 and 6 mg/kg/day that were chosen for study VBP15-006 had been shown to be safe and well-tolerated and had demonstrated efficacy in the previous vamorolone DMD study VBP15-004 in boys 4 to <7 years of age.

Steroid-naïve subjects in the 2 to <4 years age group were recruited with a diagnosis of DMD confirmed by genetic testing and/or dystrophin deficiency. In addition, corticosteroid-treated and currently untreated boys ages 7 to <18 years with Duchenne Muscular Dystrophy (DMD) were also included in the study. However, this patient population is not within the scope of this variation procedure.

To ensure safe dosing of vamorolone, the first 6 subjects in each age group at the 2 mg/kg/day dose level served as the PK/safety run-in cohorts. Once the exposure and safety were confirmed at 2 mg/kg/day in these subjects, the subsequent subjects were enrolled at 2 mg/kg/day and 6 mg/kg/day.

Efficacy was an exploratory objective with descriptive statistics in Study VBP15-006 and was measured using the Bayley Scales of Infant and Toddler Development-III (Bayley-III) Gross Motor Scale Score (GMSS) at baseline and Week 12, in subjects aged 2 to 4 years. The effect of both doses of vamorolone, 2 and 6 mg/kg/day, was assessed. Additionally, the PODCI, a patient-reported outcome was completed by the subject's parent(s)/legal guardian(s) to assess physical functioning in activities of daily living. Further assessments comprised behaviour as assessed by the Personal Adjustment and Role skills scale, third edition (PARS III) and Ease of Treatment Administration in this age group.

Efficacy data and additional analyses

Twenty subjects aged 2 to <4 years were included and received vamorolone treatment for a duration of 12 weeks: 10 received vamorolone 2 mg/kg and 10 received vamorolone 6 mg/kg. No subject discontinued the study prematurely. At study completion, 19 subjects transitioned to the EAP, where they continued receiving vamorolone, and 1 subject switched to standard of care corticosteroid treatment.

In the 2 mg/kg vamorolone group, the median age was 3.3 years (range 2.8 to 4.0 years) with the youngest patient being close to 3 years of age. The median age at first signs or symptoms identified was 19.0 months (range 12.0 to 30.0 months). All 10 subjects were ambulatory. The most common type of mutation was deletion (6 [60.0%] subjects). In the 6 mg/kg vamorolone group, the median

age was 3.5 years (range 2.9 to 4.0 years) with the youngest patient also being close to 3 years of age but slightly higher than in the 2.0 mg/kg vamorolone group. Median age at first signs or symptoms identified was 12.0 months (range 10.0 to 24.0 months). All 10 subjects were ambulatory. The most common type of mutation was deletion (8 subjects [80.0%]). The median Bayley-III GMSS at baseline was 3.50 in the vamorolone 2 mg/kg group and 5.00 in the vamorolone 6 mg/kg group. Keeping in mind the degenerative nature of DMD, the score was lower in these DMD patients compared with what would be expected in healthy peers, which represented motor disability in the studied patients even at this early stage of disease (Connolly et al., 2014).

At the end of the study, after 12 weeks of treatment with vamorolone, the median Bayley-III GMSS in the 2 mg/kg group and the 6 mg/kg group was 4.00 and 8.00, respectively. Most subjects (9/10) in the vamorolone 6 mg/kg/day group showed improvements in gross motor function from baseline to Week 12 as demonstrated by an increase in the Bayley-III GMSS score. The median change from baseline in the Bayley-III GMSS in the vamorolone 2 mg/kg group and the vamorolone 6 mg/kg group was '0' and 2.50, respectively, showing improvement in the Bayley III GMSS in the 6 mg/kg group. While the mean (SD) change from baseline in the 2 mg/kg vamorolone group showed an improvement of 0.44 (1.130) and was indicative of a positive trend of efficacy in the context of this degenerative disease, the magnitude of the mean (SD) change from baseline in the vamorolone 6 mg/kg was similar.

As the median age was 2.4 months higher for the 6 mg/kg vamorolone group (3 years and 6 months) compared to the 2 mg/kg vamorolone group (3 years and 3.6 months), a post-hoc subgroup analysis was performed to assess the impact of age on the efficacy results. In this analysis, the effect of vamorolone 2 mg/kg and 6 mg/kg was studied in 2 subgroups, ≤3.5 years versus >3.5 years of age at Week 12, taking into consideration that Bayley-III scale is validated only up to 3.5 years of age. In subjects ≤3.5 years of age, the median change from baseline in Bayley-III score was 0.5 in the 2 mg/kg group and 2.00 in the 6.0 mg/kg, showing improvement in the Bayley III score in the 6 mg/kg as compared to the 2 mg/kg group. Older subjects, i.e. subjects >3.5 years of age showed a median change from baseline in the 2 mg/kg group and the 6.0 mg/kg of 0.00 and 2.50, respectively, indicating that the difference in Bayley-III Gross Motor Scale score across the dose groups was likely not attributed to the difference in age, thus indicating that it is a dose-related difference suggestive of efficacy.

No relevant changes in the PODCI global functioning score or the PARS III or in the subscales was observed in any vamorolone treatment group.

3.4. Conclusions on the clinical efficacy

The descriptive results from this open-label study indicate a dose-dependent effect of vamorolone, with improvements in muscle function observed in the 6 mg/kg day treatment group over the 12-week treatment period. In the 2 mg/kg day group, muscle function remained stable, with trends toward increased Bayley-III Gross Motor Scale Scores (GMSS). Despite methodological limitations, including the open-label design, the small sample size, and the short treatment duration, the overall findings support a dose-dependent effect of vamorolone in steroid-naive children with Duchenne muscular dystrophy (DMD) aged 2 to <4 years (the youngest patients were 2.8 and 2.9 years of age in the vamorolone 2 mg/kg and 6 mg/kg treatment arm, respectively) and substantiate the selection of the 6 mg/kg/day dose for this population.

4. Clinical safety

Introduction

The safety profile of vamorolone 2- 6 mg/kg deriving from 163 paediatric male subjects in four clinical studies in the age range 4 years to <7 years at study entry with 20 patient being treated for ≥30 months is detailed in the Agamree EPAR (EMA/CHMP/487504/2023).

The most relevant data for vamorolone 2 mg/kg and 6 mg/kg (providing direct comparison to placebo and active control prednisone for 24 weeks of treatment) derives from study VBP15-004 (Part 1). Uncontrolled data derived from Part 2 of VBP15-004 (for up to 48 weeks) after the switch of patients from placebo and prednisone to vamorolone, and from studies VBP15-002, -003, and –LTE (up to 30 months). Long-term safety data for vamorolone from clinical trials were thus limited at the time of approval, even though, additional data became available from patients for a total exposure up to 6.7 years from the start of a clinical study (including the ongoing study VBP15-006) with treatment in EAP and CUP programmes. During the original MAA, for patients 2 to <4 years treated with 6 mg/kg, new safety data became available as per the DCO 21 July 2023 indicating that the 6 mg/kg dose in this population led to a higher reporting of some of the dose-related TEAEs, i.e. psychiatric disorders and adrenal suppression as compared to the reference population (50% vs. 0% and 33.3% vs. 10.7%).

Adverse events of special interest defined for vamorolone are the following:

- Behaviour problems: were more frequently reported in the active treatment groups of DMD patients (prednisone > vamorolone 6 mg/kg > vamorolone 2 mg/kg) as compared to placebo and mainly during the first 6 months with no further increase during longer treatment. Behaviour events occurred dose-related for vamorolone and were considered clinically relevant in a single subject on vamorolone 2 mg/kg only (contrasting 22.6% of patients on prednisone). The most frequently reported behavioural problem with vamorolone 6 mg/kg was mild irritability (10.7%), which was also more frequently reported than for prednisone (3.2%). Irritability is an ADR in section 4.8 of the SmPC.
- Bone fractures: were not reported as AESI during the controlled 6 months period of study VBP15-004. Across all studies, 2.1% of subjects on vamorolone 2 mg/kg and 7.1% on 6 mg/kg had bone fractures. The latter group mainly had upper limb fractures and vertebral fractures. A lower limb fracture in a DMD patient may lead to immobilisation, which from transitory may become permanent and thus leading to a non-ambulatory state. There were no treatment-emergent vertebral fractures in either of the vamorolone groups as evidenced by systematic lateral spine X-ray survey up to 6 months, while 4 subjects (10.3%) were found to have had a total of seven vertebral fractures during uncontrolled study VBP15-LTE. Comparison of these data with a matched corticosteroid-treated historical control cohort from the FOR-DMD study showed a lower frequency of vertebral fractures after 30 months of vamorolone compared with both daily prednisone and daily deflazacort (>27%).
- Cataracts/ glaucoma: There were no reports of cataracts or glaucoma in any subject treated with vamorolone for up to 2.5 years.
- Cushingoid features: these included weight gain and typical signs of hypercortisolism, and were most frequently reported during the first 6 months of treatment, dose-dependently with vamorolone (2 mg/kg: 6.7%; 6 mg/kg: 28.6%), mainly mild in severity. The incidence in the prednisone group was lower than in the proposed standard vamorolone dose of 6 mg/kg (22.6%). None of the TEAEs led to discontinuation of vamorolone. Cushingoid features did not increase with longer treatment up to 30 months. The exposure response (ER) analysis showed

a linear relationship with vamorolone $AUC_{T,ss}$ and the risk developing Cushingoid features. The estimated risk of exhibiting Cushingoid features was ≈0.07 at the median $AUC_{T,ss}$ for patients receiving a dose of 2.0 mg/kg/day and ≈0.2 for patients receiving a dose of 6.0 mg/kg/day. Cushingoid is an ADR in section 4.8 of the SmPC.

- Gastrointestinal symptoms: including vomiting, abdominal pain, abdominal pain upper, diarrhoea, and constipation, were among the most frequently reported AESI during the controlled and uncontrolled vamorolone experience and occurred with similar incidences across all treatment groups (25.8% - 30%) in Pool 1. Vomiting was more frequently reported in both vamorolone groups (2 mg/kg: 16.7%; 6 mg/kg: 14.3%) as compared to placebo and prednisone (6.9% and 6.5%). GI symptoms with vamorolone were mild in severity, did not lead to discontinuation and showed evidence for dose-dependency over the long-term treatment. GI disorders are defined ADRs in section 4.8 of the SmPC.
- Hypertension: mean clinical DBP and SPB changes from baseline at Month 6 were higher for vamorolone 6 mg/kg as compared to the other treatment groups. The mean change in DBP and SBP at different time points up to 6 months did not exceed 5 mmHg in the vamorolone 6 mg/kg group. 10.7% of subjects on vamorolone 6 mg/kg had a shift from baseline Stage 1 or lower hypertension to Stage 2 hypertension for DBP vs. only one subject on placebo. Shifts were, however, similar in active groups for SBP. Mean changes in DBP and SBP percentiles (adjusted for change in height and age over time) up to 30 months of uncontrolled treatment remained roughly stable with vamorolone 6 mg/kg.
- Immune suppression: Vamorolone exerts a differential effect on leukocyte subpopulations: lymphocyte counts, monocyte counts, and leukocyte counts dose-dependently increased. Neutrophil counts and immature granulocytes were found less affected by vamorolone up to 6 months as compared to prednisone and mean values were at placebo level. The incidence of infections grouped under the Immune suppression CMQ in Pool 1 was similar across treatment groups (32.1% - 44.8%), but highest in the placebo group and a dose effect could not be observed. The reported events were mild or moderate in severity and in line with seasonal infections and those seen in immunocompetent paediatric patients. A single TEAE in Pool 1 was serious (gastroenteritis viral on vamorolone 2 mg/kg). Infections suggestive of immunosuppression were not reported up to 30 months of treatment.
- Adrenal suppression: vamorolone causes a dose-dependent adrenal suppression. At Month 6, the level of adrenal suppression was highest for vamorolone 6 mg/kg, followed by prednisone and vamorolone 2 mg/kg based on mean (SD) morning cortisol values, and did not substantially change with longer treatment duration up to 30 months. Adrenal suppression was further confirmed by ACTH stimulation testing in study VBP15-004. Switching from prednisone to vamorolone 6 mg/kg (not to vamorolone 2 mg/kg) led to further small decreases in morning cortisol.
- Growth inhibition: vamorolone was not found to inhibit growth based on controlled 6-months data. Median height z-scores slightly increased in the vamorolone 2 and 6 mg/kg (0.07 SD, and 0.11 SD), similar to placebo (0.13 SD), and decreased in the prednisone group at 24 weeks (-0.10 SD). Switching from prednisone after 24 weeks in Period 1 to vamorolone in Period 2 led to an increase in median height z-score up to Week 48. Across all DMD studies, there was a positive change of median height z-score after 3, 6, 12, and 30 months of treatment in both vamorolone groups that remained lower in the 6 mg/kg group. External comparison of median height z-scores in VBP15-004 to the FOR-DMD groups at Month 12 showed positive median changes in height z-scores for both vamorolone groups and negative median changes for the deflazacort and prednisone groups. Comparison over 30 months of

treatment in VBP15-LTE and FOR-DMD revealed stable positive height z-score changes with vamorolone, and gradual decreases with deflazacort and prednisone.

- Skin changes, including hair changes (erythema): in Pool 1 in the combined 2 – 6 mg/kg vamorolone group and placebo were reported for 6.9% of subjects, and in 12.9% of prednisone-treated patients. The most frequently reported TEAE was hypertrichosis. No increased incidence was noted for Pool 3.
- Weight gain (including increased appetite): Treatment with vamorolone in DMD patients was found associated with a dose-dependent increase in body weight and BMI mainly during the first 6 months of treatment, supported by an increase in total body fat mass (higher for vamorolone 6 mg/kg as compared to prednisone). The change in median weight z-score at Month 6 was higher for vamorolone 6 mg/kg than for prednisone and vamorolone 2 mg/kg. In contrast, median BMI changes from baseline were higher for prednisone compared to both vamorolone groups, as were BMI z-score changes. However, clinically relevant changes in BMI z-score (i.e., ≥1.0 SD) after 6 months of treatment were more frequently seen in the vamorolone groups compared to prednisone (6 versus 1 subject(s)). Median changes in BMI dose-dependently increased with longer treatment of up to 30 months, while median changes in z-scores fluctuated. AESIs of weight gain in Pool 1 (24-week data) were more frequently reported with vamorolone 6 mg/kg as compared to 2 mg/kg (17.9% vs. 3.3%) and more frequent than with prednisone (9.7%) and placebo (6.9%) but did not further increase with longer treatment duration. Weight increased and increased appetite are ADRs for vamorolone in section 4.8 of the SmPC.
- Diabetic conditions: Biomarkers of insulin resistance were found differentially affected during clinical vamorolone treatment with fasting glucose and HbA1c nearly unchanged during 6 months of treatment in any group. Fasting insulin was found increased in the prednisone and even more in the 6 mg/kg vamorolone group relative to placebo and vamorolone 2 mg/kg indicating compensatory insulin secretion to maintain euglycaemia. Shifts from normal to high insulin were reported for 50% of patients on vamorolone 6 mg/kg versus 26.9% on prednisone, 18.2% on vamorolone 2 mg/kg, and 0% on placebo. Fasting insulin levels did not increase during longer treatment duration beyond those reported in the controlled study period and mean glucose and HbA1c levels did not change. There were no subjects with hyperglycaemia.

Safety concerns included in the RMP for vamorolone are:

- Important identified risks: none
- Important potential risks: infections due to immunosuppression; hepatotoxicity; acute adrenal insufficiency (adrenal crisis)
- Missing information: Use in patients above 12 years of age; safety on long-term use (in particular regarding bone fractures, weight gain, growth, hyperglycaemia, dyslipidaemia and hypertension)

Presentation of safety data in support of the extension of the indication to paediatric patients from 2 years of age includes the following studies and comparisons (supportive data):

- Safety results from **study VBP15-006**, a Phase 2, open-label, multiple dose study to evaluate the safety, tolerability, PK, pharmacodynamics (PD), clinical efficacy, behaviour and neuropsychology, and physical functioning of vamorolone 2.0 and 6.0 mg/kg administered daily by liquid oral suspension over a treatment period of 12 weeks in steroid-naïve boys ages 2 to <4 years, and GC-treated and currently untreated boys ages 7 to <18 years.

- Safety results from the Expanded access programme **VBP15-EAP**, providing continued access to vamorolone at doses of 2, 4, or 6 mg/kg for subjects who completed study VBP15-006 up to Week 12, inclusive. Subjects could not be included in the EAP if they had an SAE or severe AE related to vamorolone in VBP15-006 that precluded safe use of vamorolone in the EAP. Nineteen out of 20 subjects who completed Study VBP15-006 in the 2-4 years age group were enrolled in the EAP and received vamorolone at 2 mg/kg (1 subject), *and/or* 4 mg/kg (9 subjects), *and/or* 6 mg/kg (15 subjects).
- Paediatric extrapolation report; **comparison of safety between VBP15-006** (target population; including patients aged 2 to <4 years) **and VBP15-004** (reference population; comprising 4 to <7-year-old patients) up to Week 12 → **short-term safety**
- Paediatric extrapolation report; **comparison of safety between VBP15-EAP** (target population; including patients aged 2 to <4 years) **and VBP15-004** from Weeks 12 to 48 (reference population; comprising 4 to <7-year-old patients) → **long-term safety**

Where applicable, the comparison of short- and long-term clinical safety based on the target population (patients aged 2 to <4 years) and the reference population (4 to <7-year-old patients) from the Paediatric Extrapolation Report has been added after presentation of the results of study VBP15-006 and the results from the VBP15-EAP.

The **target population** refers to paediatric patients aged 2 to <4 years (i.e. from study VBP15-006 and VBP15-EAP).

The **reference population** refers to paediatric patients aged 4 to <7 years (i.e. from study VBP15-004).

Patient exposure

Study VBP15-006

Table 13. Duration of vamorolone exposure in age 2 to <4 years steroid naïve subjects

	Age 2 to <4 Years Steroid Naïve	
	2 mg/kg Vamorolone (N = 10)	6 mg/kg Vamorolone (N = 10)
Exposure duration (weeks)		
n	10	10
Mean (SD)	12.5 (0.81)	12.1 (0.41)
Median (Q1 ; Q3)	12.3 (12.0 ; 12.9)	11.9 (11.9 ; 12.6)
Min, Max	11.7, 14.4	11.6, 12.7
Person years	2.40	2.32

Max = maximum; Min = minimum; Q = quartile; SD = standard deviation
Source: Table 14.3.1.1a

Ten subjects aged 2 to <4 years each were exposed to vamorolone 2 mg/kg and 6 mg/kg, respectively. Median duration of exposure was 12.3 weeks in the 2 mg/kg vamorolone group and 11.9 weeks in the 6 mg/kg vamorolone group.

Expanded Access Programme

Table 14. Expanded Access Programme

Exposure	Statistic	2 mg/kg Vamorolone (N=1)	4 mg/kg Vamorolone (N=9)	6 mg/kg Vamorolone (N=15)	Total (N=19)
At least 1 day	n (%)	1	9	15	19
At least 1 months	n (%)	1 (100.0)	9 (100.0)	15 (100.0)	19 (100.0)
At least 3 months	n (%)	1 (100.0)	9 (100.0)	15 (100.0)	19 (100.0)
At least 6 months	n (%)	1 (100.0)	8 (88.9)	15 (100.0)	19 (100.0)
At least 9 months	n (%)	0	7 (77.8)	15 (100.0)	19 (100.0)
At least 12 months	n (%)	0	5 (55.6)	15 (100.0)	19 (100.0)
At least 18 months	n (%)	0	5 (55.6)	10 (66.7)	15 (78.9)
At least 2 years	n (%)	0	4 (44.4)	4 (26.7)	12 (63.2)
Exposure Duration (years)	n	1	9	15	19
	Mean (SD)	0.5 (-)	1.6 (0.98)	1.7 (0.44)	2.2 (0.61)
	Median (Q1 ; Q3)	0.5 (0.5 ; 0.5)	1.7 (0.8 ; 2.6)	1.9 (1.2 ; 2.0)	2.4 (1.9 ; 2.7)
	Min, Max	0.5, 0.5	0.4, 2.7	1.1, 2.4	1.2, 2.9
	Person years	0.54	14.60	25.88	41.03

Source: Extrapolation Report Addendum Table 5.3

All subjects were exposed to vamorolone in the EAP for at least 12 months, and 63.2% for at least 2 years. Vamorolone was administered at the 2 mg/kg dose in 1 subject for 6 months. Vamorolone was administered at the 4 mg/kg dose in 9 subjects for an average of 1.6 years (range: around 5 months to 2 years and 8 months), and at the 6 mg/kg dose in 15 subjects for an average of 1.7 years (range: around 1 year and 1 month to 2 years and 5 months). Median exposure of all doses in total was 2.4 years (range: around 1 year and 4 months to 2 years and 11 months).

Comparison VBP15-006 (target population) versus VBP15-004 (reference population) up to Week 12

Table 15. Duration of Vamorolone Exposure in Studies VBP15-006 and VBP15-004

	Target population VBP15-006		Reference population VBP15-004	
Age group	**2 to <4 years**		**4 to <7 years**	
Vamorolone dose	**2 mg/kg/day (n=10)**	**6 mg/kg/day (n=10)**	**2 mg/kg/day (n=30)**	**6 mg/kg/day (n=28)**
Exposure duration (weeks)				
N	10	10	30	28
Mean (SD)	12.5 (0.81)	12.1 (0.41)	11.8 (1.25)	12.1 (0.5)
Median (Q1; Q3)	12.3 (12.0; 12.9)	11.9 (11.9; 12.6)	11.9 (11.3; 12.3)	12.1 (11.9; 12.4)
Min, Max	11.7, 14.4	11.6, 12.7	6.1, 13.1	11.1, 13.1
Person years	2.40	2.32	6.8	6.5

Max, maximum; Min, minimum; SD, standard deviation; Q1, 1st quartile; Q3, 3rd quartile
Source: VBP15-006 Table 14.3.1.1a, Extrapolation Report Outputs Table 2.1

Comparison VBP15-EAP (target population) versus VBP15-004 (reference population) Week 12 - 48

Table 16. Duration of Vamorolone Exposure for Subjects in the Target (VBP15-EAP) and Reference Populations (VBP15-004)

	Target population VBP15-EAP				Reference population VBP15-004		
Time	**Between first and last visit**				**Between Week 12 and Week 48**		
Age group	**2 to < 4 years**				**4 to < 7 years**		
Vamorolone dose	**2 mg/kg/day (n=1)**	**4 mg/kg/day (n=9)**	**6 mg/kg/day (n=15)**	**Total (n=19)**	**2 mg/kg/day (n=29)**	**6 mg/kg/day (n=28)**	**Total (n=57)**
Exposure, n (%)							
At least 1 day	1	9	15	19	29 (100)	28 (100)	57 (100)
At least 3 months	1 (100.0)	9 (100.0)	15 (100.0)	19 (100.0)	28 (96.6)	28 (100)	56 (98.2)
At least 6 months	1 (100.0)	8 (88.9)	15 (100.0)	19 (100.0)	28 (96.6)	28 (100)	56 (98.2)
At least 12 months	0	5 (55.6)	15 (100.0)	19 (100.0)	–	–	–
At least 2 years	0	4 (44.4)	4 (26.7)	12 (63.2)	–	–	–
Years of exposure[1]							
n	1	9	15	19	29	28	57
Mean (SD)	0.5 (-)	1.6 (0.98)	1.7 (0.44)	2.2 (0.61)	0.7 (0.11)	0.7 (0.04)	0.7 (0.09)
Median (Q1; Q3)	0.5 (0.5; 0.5)	1.7 (0.8; 2.6)	1.9 (1.2; 2.0)	2.4 (1.9; 2.7)	0.7 (0.7; 0.7)	0.7 (0.7; 0.7)	0.7 (0.7; 0.7)
Min, Max	0.5, 0.5	0.4, 2.7	1.1, 2.4	1.2, 2.9	0.1, 0.8	0.6, 0.8	0.1, 0.8
Person years	0.54	14.60	25.88	41.03	20.1	19.5	39.6

[1]Exposures for VBP15-EAP are presented between the time of entry into the EAP and the last visit. Exposures for VBP15-004 are presented from the end of 3 months (Week 12) till the end of the study (Week 48)
EAP, expanded access protocol; f, event count; n, patient count; Q; quartile; SD, standard deviation; TEAE, treatment-emergent adverse event
Source: **Extrapolation Report Outputs Table 5.3; Extrapolation Report Outputs Table 2.2.**

Demographics and baseline characteristics of study population

Study VBP15-006

All 10 subjects in either dose group were ambulatory. In the 2 mg/kg vamorolone group, median age was 3.3 years (range 2.8 to 4.0 years). Median age at first signs or symptom identified was 19.0 months (range 12.0 to 30.0 months). The most common type of mutation was a deletion (6 [60.0%] subjects). In the 6 mg/kg vamorolone group, median age was 3.5 years (range 2.9 to 4.0 years). Median age at first signs or symptoms identified was 12.0 months (range 10.0 to 24.0 months). The most common type of mutation was a deletion (8 [80.0%] subjects).

Expanded Access Programme

The 19 subjects from study VBP15-006, who transitioned into the EAP, were only slightly older (median: 3.6 years).

Comparison VBP15-006 (target population) versus VBP15-004 (reference population) up to Week 12

Target population – see above;

In the 4 to <7-year-old reference population receiving 2 mg/kg vamorolone (n=30), the median age was 5.2 years (4.1 to 7.0 years). Twenty-five subjects were White, four subjects were Asian, and one subject was Black or African American race. In the reference population receiving 6 mg/kg (n=28), median age was 5.5 years (4.1 to 6.8 years), 23 subjects were White, three subjects were Asian, one subject was Black or African American, and race was multiple for one subject.

Adverse events

Study VBP15-006

The incidence and frequency of TEAEs and drug-related TEAEs increased with vamorolone dose (see Table 17).

Table 17. Summary of Treatment-Emergent Adverse Events by Dose Group (Safety Set) – Study VBP15-006

Type of TEAE	**2 mg/kg Vamorolone (N = 10) n (%) ; f (Rate)**	**6 mg/kg Vamorolone (N = 10) n (%) ; f (Rate)**	**Total (N = 20) n (%) ; f (Rate)**
Total number of TEAEs	7 (70.0) ; 18 (7.50)	9 (90.0) ; 39 (16.82)	16 (80.0) ; 57 (12.08)
Drug-related TEAEs	1 (10.0) ; 1 (0.42)	7 (70.0) ; 13 (5.61)	8 (40.0) ; 14 (2.97)
Severe TEAEs	0 ; 0	0 ; 0	0 ; 0
Serious TEAEs	0 ; 0	0 ; 0	0 ; 0
TEAEs leading to withdrawal from study	0 ; 0	0 ; 0	0 ; 0
TEAEs leading to temporary dose interruption	0 ; 0	0 ; 0	0 ; 0
TEAEs leading to death	0 ; 0	0 ; 0	0 ; 0

Rate is calculated as Events per subject per year of exposure. Drug-related TEAEs are those whose causality was labeled as 'Definite', 'Probable', or 'Possible' MedDRA version 25.0 AE = adverse event; f = event count; n = patient count; Source: VBP15-006 CSR, Table 14.3.2.1a

Overall, the most commonly reported TEAEs were from the Gastrointestinal disorders SOC with diarrhoea being the most common PT. The incidence of GI disorders increased with dose, and from the Infections and infestations SOC, with nasopharyngitis being the most commonly reported PT. The latter was expected in the age group concerned. A dose-relationship for the incidence of infections and infestations could not be deduced and none of the infections was considered related to vamorolone (Table 18). An imbalance was observed for the Endocrine disorders SOC, with TEAEs reported in no subjects in the 2 mg/kg group versus 5 (50.0%) subjects in the 6 mg/kg group: five subjects in the 6 mg/kg vamorolone group reported 5 TEAEs of adrenal suppression, based on the Week 12 cortisol values. Additionally, 1 subject in the 6 mg/kg vamorolone group had a TEAE of cortisol decreased. All subjects were asymptomatic and diagnosis was solely based on serum cortisol levels.

Two subjects in the 6 mg/kg vamorolone group reported 4 TEAEs in the SOC Psychiatric disorders, of which 3 TEAEs were considered related to vamorolone.

Table 18. TEAEs by SOC and PT, by Dose Group (Safety Set) – Study VBP15-006

System Organ Class **Preferred Term**	**2 mg/kg Vamorolone (N = 10) n (%) ; f (Rate)**	**6 mg/kg Vamorolone (N = 10) n (%) ; f (Rate)**	**Total (N = 20) n (%) ; f (Rate)**
Blood and lymphatic disorders	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Lymphadenopathy	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Endocrine disorders	0 ; 0	5 (50.0) ; 5 (2.16)	5 (25.0) ; 5 (1.06)
Adrenal suppression	0 ; 0	5 (50.0) ; 5 (2.16)	5 (25.0) ; 5 (1.06)
Gastrointestinal disorders	1 (10.0) ; 2 (0.83)	8 (80.0) ; 11 (4.74)	9 (45.0) ; 13 (2.75)
Diarrhoea	0 ; 0	3 (30.0) ; 3 (1.29)	3 (15.0) ; 3 (0.64)
Abdominal pain upper	0 ; 0	2 (20.0) ; 2 (0.86)	2 (10.0) ; 2 (0.42)
Faeces discoloured	1 (10.0) ; 1 (0.42)	1 (10.0) ; 1 (0.43)	2 (10.0) ; 2 (0.42)
Toothache	0 ; 0	2 (20.0) ; 2 (0.86)	2 (10.0) ; 2 (0.42)
Vomiting	1 (10.0) ; 1 (0.42)	1 (10.0) ; 1 (0.43)	2 (10.0) ; 2 (0.42)
Abdominal pain	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Abnormal faeces	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
General disorders and administration site conditions	1 (10.0) ; 2 (0.83)	3 (30.0) ; 3 (1.29)	4 (20.0) ; 5 (1.06)
Pyrexia	1 (10.0) ; 2 (0.83)	1 (10.0) ; 1 (0.43)	2 (10.0) ; 3 (0.64)
Energy increased	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Fatigue	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Infections and infestations	5 (50.0) ; 9 (3.75)	3 (30.0) ; 4 (1.72)	8 (40.0) ; 13 (2.75)
Nasopharyngitis	4 (40.0) ; 8 (3.33)	3 (30.0) ; 3 (1.29)	7 (35.0) ; 11 (2.33)
COVID-19	1 (10.0) ; 1 (0.42)	0 ; 0	1 (5.0) ; 1 (0.21)
Gastroenteritis viral	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Injury, poisoning and procedural complications	1 (10.0) ; 1 (0.42)	2 (20.0) ; 2 (0.86)	3 (15.0) ; 3 (0.64)
Fall	1 (10.0) ; 1 (0.42)	2 (20.0) ; 2 (0.86)	3 (15.0) ; 3 (0.64)
Investigations	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Cortisol decreased	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Musculoskeletal and connective tissue disorders	0 ; 0	4 (40.0) ; 4 (1.72)	4 (20.0) ; 4 (0.85)
Pain in extremity	0 ; 0	2 (20.0) ; 2 (0.86)	2 (10.0) ; 2 (0.42)
Back pain	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Musculoskeletal stiffness	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Nervous system disorders	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Headache	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Psychiatric disorders	0 ; 0	2 (20.0) ; 4 (1.72)	2 (10.0) ; 4 (0.85)
Aggression	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Compulsive lip biting	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Irritability	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Mood swings	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Respiratory, thoracic and mediastinal disorders	2 (20.0) ; 3 (1.25)	2 (20.0) ; 3 (1.29)	4 (20.0) ; 6 (1.27)

System Organ Class Preferred Term	2 mg/kg Vamorolone (N = 10) n (%) ; f (Rate)	6 mg/kg Vamorolone (N = 10) n (%) ; f (Rate)	Total (N = 20) n (%) ; f (Rate)
Rhinorrhoea	1 (10.0) ; 1 (0.42)	1 (10.0) ; 2 (0.86)	2 (10.0) ; 3 (0.64)
Cough	2 (20.0) ; 2 (0.83)	0 ; 0	2 (10.0) ; 2 (0.42)
Epistaxis	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Skin and subcutaneous tissue disorders	1 (10.0) ; 1 (0.42)	0 ; 0	1 (5.0) ; 1 (0.21)
Urticaria	1 (10.0) ; 1 (0.42)	0 ; 0	1 (5.0) ; 1 (0.21)

Rate is calculated as Events per subject per year of exposure.
AE = adverse event; f = event count; n = patient count
MedDRA version 25.0
Source: VBP15-006 CSR, Table 14.3.2.2a

Most TEAEs were of mild intensity (17/18 in the vamorolone 2 mg/kg group and 36/39 in the vamorolone 6 mg/kg group), the remainder were of moderate intensity; no subject experienced a severe TEAE.

Treatment-related TEAEs

Table 19. TEAEs Related to Vamorolone, by Dose Group (Safety Set)

Preferred term (causality assessment by Investigator)	2 mg/kg Vamorolone (N = 10) n (%) ; f (Rate)	6 mg/kg Vamorolone (N = 10) n (%) ; f (Rate)	Total (N = 20) n (%) ; f (Rate)
Adrenal suppression (definite)	0 ; 0	5 (50.0) ; 5 (2.16)	5 (25.0) ; 5 (1.06)
Abdominal pain (probable)	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Abnormal faeces (possible)	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Diarrhoea (possible)	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Energy increased (possible)	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Cortisol decreased (probable)	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Aggression (possible)	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Irritability (possible)	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Mood swings (possible)	0 ; 0	1 (10.0) ; 1 (0.43)	1 (5.0) ; 1 (0.21)
Urticaria (possible)	1 (10.0) ; 1 (0.42)	0 ; 0	1 (5.0) ; 1 (0.21)

Rate is calculated as Events per subject per year of exposure. Related treatment-emergent adverse events are those with a causality of possible, probable, or definite by the Investigator. f = event count; n = patient count.
Source: extracted from VBP15-006 CSR, Table 14.3.2.4a

Expanded Access Programme

TEAEs were reported more frequently in subjects who received vamorolone 4 mg/kg than 6 mg/kg: 26 events in 6 (66.7%) subjects compared with 18 events in 6 (40.0%) subjects. Drug-related TEAEs, severe TEAEs (1 event of influenza and 1 event of rhabdomyolysis; none was related to vamorolone) and SAEs occurred only with vamorolone 6 mg/kg. No TEAE led to dose modification, interruption, or discontinuation with any vamorolone dose.

Table 20. Summary of TEAEs by Dose at Onset - EAP

Type of TEAE	2 mg/kg Vamorolone (N = 1) n (%) ; f (Rate)	4 mg/kg Vamorolone (N = 9) n (%) ; f (Rate)	6 mg/kg Vamorolone (N = 15) n (%) ; f (Rate)	Total (N = 19) n (%) ; f (Rate)
Total number of TEAEs	0 ; 0	6 (66.7) ; 26 (1.78)	6 (40.0) ; 18 (0.70)	11 (57.9) ; 44 (1.07)
Drug-related TEAEs	0 ; 0	0 ; 0	3 (20.0) ; 3 (0.12)	3 (15.8) ; 3 (0.07)
Severe TEAEs	0 ; 0	0 ; 0	2 (13.3) ; 2 (0.08)	2 (10.5) ; 2 (0.05)
Serious TEAEs	0 ; 0	0 ; 0	1 (6.7) ; 2 (0.08)	1 (5.3) ; 2 (0.05)
TEAEs leading to permanent study treatment discontinuation	0 ; 0	0 ; 0	0 ; 0	0 ; 0
TEAEs leading to drug interruption	0 ; 0	0 ; 0	0 ; 0	0 ; 0
TEAEs leading to dose reduction	0 ; 0	0 ; 0	0 ; 0	0 ; 0
TEAEs leading to dose increase	0 ; 0	0 ; 0	0 ; 0	0 ; 0

Rate is calculated as Events per subject per year of exposure.
Related treatment-emergent adverse events are those with a causality of possible, probable, or definite by the Investigator.
f = event count; n = patient count
Source: Extrapolation Report Addendum Table 6.1

Overall, the most commonly reported TEAEs derived from the Infections and infestations SOC with Nasopharyngitis (4 events) and Gastroenteritis (3 events) being the most common PTs, followed by TEAEs from the General disorders and administration site conditions SOC (pyrexia; 5 events).

Table 21. TEAEs by SOC and PT, by Dose at Onset - EAP

System Organ Class Preferred Term	2 mg/kg Vamorolone (N = 1) n (%) ; f (Rate)	4 mg/kg Vamorolone (N = 9) n (%) ; f (Rate)	6 mg/kg Vamorolone (N = 15) n (%) ; f (Rate)	Total (N = 19) n (%) ; f (Rate)
Total Number of TEAEs	0 ; 0	6 (66.7) ; 26 (1.78)	6 (40.0) ; 18 (0.70)	11 (57.9) ; 44 (1.07)
Ear and labyrinth disorders	0 ; 0	1 (11.1) ; 1 (0.07)	0 ; 0	1 (5.3) ; 1 (0.02)
Ear discomfort	0 ; 0	1 (11.1) ; 1 (0.07)	0 ; 0	1 (5.3) ; 1 (0.02)
Gastrointestinal disorders	0 ; 0	2 (22.2) ; 3 (0.21)	1 (6.7) ; 1 (0.04)	3 (15.8) ; 4 (0.10)
Abdominal discomfort	0 ; 0	1 (11.1) ; 1 (0.07)	0 ; 0	1 (5.3) ; 1 (0.02)
Diarrhoea	0 ; 0	1 (11.1) ; 1 (0.07)	0 ; 0	1 (5.3) ; 1 (0.02)
Dyspepsia	0 ; 0	0 ; 0	1 (6.7) ; 1 (0.04)	1 (5.3) ; 1 (0.02)
Vomiting	0 ; 0	1 (11.1) ; 1 (0.07)	0 ; 0	1 (5.3) ; 1 (0.02)
General disorders and administration site conditions	0 ; 0	4 (44.4) ; 5 (0.34)	0 ; 0	4 (21.1) ; 5 (0.12)
Pyrexia	0 ; 0	4 (44.4) ; 5 (0.34)	0 ; 0	4 (21.1) ; 5 (0.12)
Immune system disorders	0 ; 0	0 ; 0	1 (6.7) ; 1 (0.04)	1 (5.3) ; 1 (0.02)
Hypersensitivity	0 ; 0	0 ; 0	1 (6.7) ; 1 (0.04)	1 (5.3) ; 1 (0.02)
Infections and infestations	0 ; 0	4 (44.4) ; 8 (0.55)	6 (40.0) ; 9 (0.35)	9 (47.4) ; 17 (0.41)
Ear infection	0 ; 0	1 (11.1) ; 2 (0.14)	0 ; 0	1 (5.3) ; 2 (0.05)

System Organ Class Preferred Term	2 mg/kg Vamorolone (N = 1) n (%) ; f (Rate)	4 mg/kg Vamorolone (N = 9) n (%) ; f (Rate)	6 mg/kg Vamorolone (N = 15) n (%) ; f (Rate)	Total (N = 19) n (%) ; f (Rate)
Gastroenteritis	0 ; 0	1 (11.1) ; 1 (0.07)	2 (13.3) ; 2 (0.08)	3 (15.8) ; 3 (0.07)
Influenza	0 ; 0	0 ; 0	1 (6.7) ; 1 (0.04)	1 (5.3) ; 1 (0.02)
Nasopharyngitis	0 ; 0	1 (11.1) ; 1 (0.07)	3 (20.0) ; 3 (0.12)	4 (21.1) ; 4 (0.10)
Otitis media	0 ; 0	1 (11.1) ; 1 (0.07)	0 ; 0	1 (5.3) ; 1 (0.02)
Respiratory tract infection	0 ; 0	1 (11.1) ; 2 (0.14)	0 ; 0	1 (5.3) ; 2 (0.05)
Respiratory tract infection viral	0 ; 0	0 ; 0	1 (6.7) ; 1 (0.04)	1 (5.3) ; 1 (0.02)
Roseola	0 ; 0	0 ; 0	1 (6.7) ; 1 (0.04)	1 (5.3) ; 1 (0.02)
Upper respiratory tract infection	0 ; 0	1 (11.1) ; 1 (0.07)	0 ; 0	1 (5.3) ; 1 (0.02)
Viral infection	0 ; 0	0 ; 0	1 (6.7) ; 1 (0.04)	1 (5.3) ; 1 (0.02)
Injury, poisoning and procedural complications	0 ; 0	1 (11.1) ; 1 (0.07)	2 (13.3) ; 3 (0.12)	3 (15.8) ; 4 (0.10)
Bone contusion	0 ; 0	0 ; 0	1 (6.7) ; 1 (0.04)	1 (5.3) ; 1 (0.02)
Compression fracture	0 ; 0	1 (11.1) ; 1 (0.07)	0 ; 0	1 (5.3) ; 1 (0.02)
Fall	0 ; 0	0 ; 0	1 (6.7) ; 1 (0.04)	1 (5.3) ; 1 (0.02)
Skin laceration	0 ; 0	0 ; 0	1 (6.7) ; 1 (0.04)	1 (5.3) ; 1 (0.02)
Musculoskeletal and connective tissue disorders	0 ; 0	0 ; 0	1 (6.7) ; 2 (0.08)	1 (5.3) ; 2 (0.05)
Rhabdomyolysis	0 ; 0	0 ; 0	1 (6.7) ; 2 (0.08)	1 (5.3) ; 2 (0.05)
Psychiatric disorders	0 ; 0	0 ; 0	1 (6.7) ; 1 (0.04)	1 (5.3) ; 1 (0.02)
Aggression	0 ; 0	0 ; 0	1 (6.7) ; 1 (0.04)	1 (5.3) ; 1 (0.02)
Respiratory, thoracic and mediastinal disorders	0 ; 0	2 (22.2) ; 7 (0.48)	1 (6.7) ; 1 (0.04)	3 (15.8) ; 8 (0.19)
Cough	0 ; 0	2 (22.2) ; 4 (0.27)	1 (6.7) ; 1 (0.04)	3 (15.8) ; 5 (0.12)
Nasal congestion	0 ; 0	2 (22.2) ; 2 (0.14)	0 ; 0	2 (10.5) ; 2 (0.05)
Rhinorrhoea	0 ; 0	1 (11.1) ; 1 (0.07)	0 ; 0	1 (5.3) ; 1 (0.02)
Skin and subcutaneous tissue disorders	0 ; 0	1 (11.1) ; 1 (0.07)	0 ; 0	1 (5.3) ; 1 (0.02)
Rash	0 ; 0	1 (11.1) ; 1 (0.07)	0 ; 0	1 (5.3) ; 1 (0.02)

Rate is calculated as Events per subject per year of exposure.
f = event count; n = patient count. Source: Extrapolation Report Addendum Table 7.1

Drug-related TEAEs were uncommonly reported and occurred exclusively with the 6 mg/kg dose: 1 event of dyspepsia, 1 event of rhabdomyolysis, and 1 event of aggression (SOC: Psychiatric disorders).

Comparison VBP15-006 (target population) versus VBP15-004 (reference population) up to Week 12

Table 22. Overview of TEAEs for Vamorolone at Week 12 in Studies VBP15-006 and VBP15-004

	Target population VBP15-006		Reference population VBP15-004	
Age Group	**2 to <4 years**		**4 to <7 years**	
Vamorolone dose	**2 mg/kg/day (n=10)**	**6 mg/kg/day (n=10)**	**2 mg/kg/day (n=30)**	**6 mg/kg/day (n=28)**
Total exposure (person-years)	2.4	2.32	6.8	6.5
n (%); f (Rate)				
Total number of TEAEs	7 (70.0); 18 (7.50)	9 (90.0); 39 (16.82)	24 (80.0); 56 (8.28)	21 (75.0); 59 (9.07)
Any drug-related TEAEs	1 (10.0); 1 (0.42)	7 (70.0); 13 (5.61)	5 (16.7); 9 (1.33)	12 (42.9); 18 (2.77)
Serious TEAEs	0	0	1 (3.3); 1 (0.15)	0; 0
TEAEs leading to permanent study treatment discontinuation	0	0	0; 0	0; 0
TEAEs leading to temporary dose interruption	0	0	1 (3.3); 1 (0.15)	0; 0

f, event count; n, patient count; TEAE, treatment-emergent adverse event
Source: VBP15-006 CSR Table 32, Table 14.3.21a; Extrapolation Report Outputs Table 3.1

Table 23. Summary of TEAEs Reported by ⩾ 1 Subject by SOC and PT at Week 12 in Studies VBP15-006 and VBP15-004

	Target population VBP15-006		Reference population VBP15-004	
Age Group	**2 to <4 years**		**4 to <7 years**	
Vamorolone dose	**2 mg/kg/day (n=10)**	**6 mg/kg/day (n=10)**	**2 mg/kg/day (n=30)**	**6 mg/kg/day (n=28)**
Total number of TEAEs	7 (70.0); 18 (7.50)	9 (90.0); 39 (16.82)	24 (80.0); 56 (8.28)	21 (75.0); 59 (9.07)
System Organ Class (SOC) Preferred term (PT), n (%); f (Rate)				
Endocrine disorders	**0; 0**	**5 (50.0); 5 (2.16)**	**1 (3.3); 1 (0.15)**	**4 (14.3); 4 (0.62)**
Cushingoid	0; 0	0; 0	0; 0	4 (14.3); 4 (0.62)
Hypothyroidism	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Adrenal suppression	0; 0	5 (50.0); 5 (2.16)	0; 0	0; 0
Ear and labyrinth disorders	**0; 0**	**0; 0**	**0; 0**	**1 (3.6); 2 (0.31)**
Ear pain*	0; 0	0; 0	0; 0	1 (3.6); 2 (0.31)*
Blood and lymphatic system disorders	**0; 0**	**1 (10.0); 1 (0.43)**	**0; 0**	**0; 0**
Lymphadenopathy*	0; 0	1 (10.0); 1 (0.43)*	0; 0	0; 0
Gastrointestinal disorders	**1 (10.0); 2 (0.83)**	**8 (80.0); 11 (4.74)**	**6 (20.0); 9 (1.33)**	**6 (21.4); 8 (1.23)**
Vomiting*	1 (10.0); 1 (0.42)*	1 (10.0); 1 (0.43)*	2 (6.7); 2 (0.3)*	3 (10.7); 3 (0.46)*
Abdominal pain, upper*	0; 0	2 (20.0); 2 (0.86)*	0; 0	2 (7.1); 2 (0.31)*
Abdominal pain*	0; 0	1 (10.0); 1 (0.43)*	1 (3.3); 1 (0.15)*	1 (3.6); 1 (0.15)*
Constipation	0; 0	0; 0	2 (6.7); 2 (0.3)	0; 0
Diarrhoea*	0; 0	3 (30.0); 3 (1.29)*	1 (3.3); 1 (0.15)*	1 (3.6); 1 (0.15)*
Toothache	0; 0	2 (20.0); 2 (0.86)	0; 0	1 (3.6); 1 (0.15)
Dental caries	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0

Gastrooesophageal reflux disease	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Nausea*	0; 0	0; 0	1 (3.3); 1 (0.15) *	0; 0
Abnormal faeces	0; 0	1 (10.0) ; 1 (0.43)	0; 0	0; 0
Faeces discoloured	1 (10.0); 1 (0.42)	1 (10.0); 1 (0.43)	0; 0	0; 0
General disorders and administration site conditions	**1 (10.0); 2 (0.83)**	**3 (30.0); 3 (1.29)**	**4 (13.3); 4 (0.59)**	**1 (3.6); 1 (0.15)**
Influenza like illness*	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15) *
Pyrexia*	1 (10.0); 2 (0.83) *	1 (10.0); 1 (0.43) *	3 (10.0); 3 (0.44) *	0; 0
Application site hypersensitivity	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Energy increased	0; 0	1 (10.0); 1 (0.43)	0; 0	0; 0
Fatigue	0; 0	1 (10.0); 1 (0.43)	0; 0	0; 0
Hepatobiliary disorders	**0; 0**	**0; 0**	**1 (3.3); 1 (0.15)**	**0; 0**
Hyperbilirubinaemia	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Immune system disorders	**0; 0**	**0; 0**	1 (3.3); 1 (0.15)	0; 0
Seasonal allergy	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Infections and infestations*	**5 (50.0); 9 (3.75)**	**3 (30.0); 4 (1.72)**	**9 (30.0); 11 (1.63)**	**7 (25.0); 12 (1.85)**
Upper respiratory tract infection*	0; 0	0; 0	5 (16.7); 5 (0.74) *	1 (3.6); 2 (0.31) *
Nasopharyngitis*	4 (40.0); 8 (3.33) *	3 (30.0); 3 (1.29) *	0; 0	2 (7.1); 5 (0.77) *
Rhinitis*	0; 0	0; 0	1 (3.3); 1 (0.15) *	1 (3.6); 1 (0.15) *
Ear infection*	0; 0	0; 0	1 (3.3); 1 (0.15) *	0; 0
Enterobiasis*	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15) *
Gastroenteritis viral*	0; 0	1 (10.0); 1 (0.43) *	2 (6.7); 2 (0.3) *	0; 0
Pharyngitis*	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15) *
Pharyngitis streptococcal*	0; 0	0; 0	1 (3.3); 1 (0.15) *	0; 0
Respiratory syncytial virus infection*	0; 0	0; 0	1 (3.3); 1 (0.15) *	0; 0
Conjunctivitis*	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15) *
Viral infection*	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15) *
COVID-19*	1 (10.0); 1 (0.42) *	0; 0	0; 0	0; 0
Injury, poisoning and procedural complications	**1 (10.0); 1 (0.42)**	**2 (20.0); 2 (0.86)**	**6 (20.0); 6 (0.89)**	**5 (17.9); 6 (0.92)**
Contusion	0; 0	0; 0	3 (10.0); 3 (0.44)	0; 0
Fall	1 (10.0); 1 (0.42)	2 (20.0); 2 (0.86)	0; 0	3 (10.7); 4 (0.62)
Arthropod bite	0; 0	0; 0	1 (3.3); 1 (0.15)	1 (3.6); 1 (0.15)
Ligament sprain	0; 0	0; 0	1 (3.3); 1 (0.15)	1 (3.6); 1 (0.15)
Tooth injury	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Investigations	**0; 0**	**1 (10.0); 1 (0.43)**	**2 (6.7); 2 (0.3)**	**1 (3.6); 1 (0.15)**
Weight increased	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15)
Ejection fraction decreased	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Serum ferritin decreased	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Cortisol decreased	0; 0	1 (10.0); 1 (0.43)	0; 0	0; 0
Metabolism and nutrition disorders	**0; 0**	**0; 0**	**1 (3.3); 1 (0.15)**	**3 (10.7); 4 (0.62)**
Vitamin D deficiency	0; 0	0; 0	0; 0	2 (7.1); 2 (0.31)
Increased appetite	0; 0	0; 0	1 (3.3); 1 (0.15)	1 (3.6); 1 (0.15)
Dehydration	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15)

Musculoskeletal and connective tissue disorders	**0; 0**	**4 (40.0); 4 (1.72)**	**2 (6.7); 2 (0.3)**	**2 (7.1); 2 (0.31)**
Arthralgia	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15)
Mobility decreased	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15)
Tendinous contracture	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Tendonitis	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Pain in extremity	0; 0	2 (20.0); 2 (0.86)	0; 0	0; 0
Back pain	0; 0	1 (10.0); 1 (0.43)	0; 0	0; 0
Musculoskeletal stiffness	0; 0	1 (10.0); 1 (0.43)	0; 0	0; 0
Nervous system disorders	**0; 0**	**1 (10.0); 1 (0.43)**	**4 (13.3); 4 (0.59)**	**2 (7.1); 2 (0.31)**
Headache	0; 0	1 (10.0); 1 (0.43)	1 (3.3); 1 (0.15)	2 (7.1); 2 (0.31)
Psychomotor hyperactivity	0; 0	0; 0	2 (6.7); 2 (0.3)	0; 0
Poor quality sleep	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Psychiatric disorders	**0; 0**	**2 (20.0); 4 (1.72)**	**1 (3.3); 1 (0.15)**	**4 (14.3); 6 (0.92)**
Aggression	0; 0	1 (10.0); 1 (0.43)	0; 0	1 (3.6); 1 (0.15)
Anxiety	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15)
Compulsive lip biting	0; 0	1 (10.0); 1 (0.43)	0; 0	0; 0
Irritability	0; 0	1 (10.0); 1 (0.43)	0; 0	2 (7.1); 2 (0.31)
Mood swings	0; 0	1 (10.0); 1 (0.43)	0; 0	0; 0
Abnormal behaviour	0; 0	0; 0	1 (3.3); 1 (0.15)	1 (3.6); 1 (0.15)
Sleep disorder	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15)
Renal and urinary disorders	**0; 0**	**0; 0**	**2 (6.7); 2 (0.3)**	**2 (7.1); 3 (0.46)**
Chromaturia	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15)
Urinary incontinence*	0; 0	0; 0	1 (3.3); 1 (0.15) *	1 (3.6); 1 (0.15) *
Micturition urgency*	0; 0	0; 0	1 (3.3); 1 (0.15) *	0; 0
Myoglobinuria	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15)
Reproductive system and breast disorders	**0; 0**	**0; 0**	**1 (3.3); 1 (0.15)**	**1 (3.6); 1 (0.15)**
Penile pain			0; 0	1 (3.6); 1 (0.15)
Penis disorder	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Respiratory, thoracic and mediastinal disorders	**2 (20.0); 3 (1.25)**	**2 (20.0); 3 (1.29)**	**3 (10.0); 6 (0.89)**	**3 (10.7); 4 (0.62)**
Rhinorrhoea*	1 (10.0); 1 (0.42) *	1 (10.0); 2 (0.86) *	1 (3.3); 1 (0.15) *	1 (3.6); 1 (0.15) *
Cough*	2 (20.0); 2 (0.83) *	0; 0	2 (6.7); 4 (0.59) *	1 (3.6); 1 (0.15) *
Nasal congestion*	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15) *
Epistaxis	0; 0	1 (10.0); 1 (0.43)	0; 0	0; 0
Rhinitis allergic	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Asthma	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15)
Skin and subcutaneous tissue disorders	**1 (10.0); 1 (0.42)**	**0; 0**	**3 (10.0); 3 (0.44)**	**1 (3.6); 1 (0.15)**
Erythema	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Rash erythematous	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Skin hyperpigmentation	0; 0	0; 0	1 (3.3); 1 (0.15)	0; 0
Urticaria	1 (10.0); 1 (0.42)	0; 0	0; 0	0; 0

	Target population VBP15-006		Reference population VBP15-004	
Age Group	**2 to <4 years**		**4 to <7 years**	
Vamorolone dose	**2 mg/kg/day (n=10)**	**6 mg/kg/day (n=10)**	**2 mg/kg/day (n=30)**	**6 mg/kg/day (n=28)**
Rash	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15)
Vascular disorders	**0; 0**	**0; 0**	**1 (3.3); 1 (0.15)**	**2 (7.1); 2 (0.31)**
Flushing	0; 0	0; 0	1 (3.3); 1 (0.15)	1 (3.6); 1 (0.15)
Pallor	0; 0	0; 0	0; 0	1 (3.6); 1 (0.15)

Infections and other TEAEs considered related to infections
, event count; n, patient count; PT, preferred term; SOC, system organ class; PT, preferred term; TEAE, treatment-emergent adverse event
Source: VBP15-006 CSR Table 35, Table 14.3.2.2.a; Extrapolation Report Outputs Table 3.2

Treatment-related TEAEs

Target population; see above Table 23.

In the reference population at Week 12, 9 of 56 TEAEs (16.0%) in the 2 mg/kg dose group were considered study drug-related. Drug-related TEAEs were mainly reported in single subjects, except for Psychomotor hyperactivity, which was reported for 2 (6.7%) subjects. Other important related TEAEs seen at this dose were Abnormal behaviour, Poor sleep quality, and Increased appetite, each in 1 subject.

At the 6 mg/kg dose, 18 out of a total of 59 TEAEs (30.5%), were considered study drug related. These were mostly reported for one subject, except for Cushingoid, which was reported for 4 subjects and Irritability, which was reported for 2 subjects. Other important related TEAEs at this dose were Weight increase, Increased appetite, Abnormal behaviour, Aggression, Anxiety, and Sleep disorder, each in 1 subject only. All drug-related TEAEs were considered mild to moderate in severity.

Comparison VBP15-EAP (target population) versus VBP15-004 (reference population) Week 12 - 48

Table 24. Overview of TEAEs by Dose at Onset for Subjects in Target (VBP15-EAP) and Reference Population (VBP15-004)

	Target population VBP15-EAP				Reference population VBP15-004		
Time	**Between first and last visit**				**Between Week 12 and Week 48**		
Age group	**2 to < 4 years**				**4 to < 7 years**		
Vamorolone dose	**2 mg/kg/day (n=1)**	**4 mg/kg/day (n=5)**	**6 mg/kg/day (n=15)**	**Total (n=19)**	**2 mg/kg/day (n=29)**	**6 mg/kg/day (n=28)**	**Total (n=57)**
n (%); f (Rate)							
Total number of TEAEs [1]	0; 0	6 (66.7); 26 (1.78)	6 (40.0); 18 (0.70)	11 (57.9); 44 (1.07)	25 (86.2); 101 (5.03)	24 (85.7); 101 (5.17)	49 (86.0); 202 (5.1)
Any Drug-related TEAEs	0; 0	0; 0	3 (20.0); 3 (0.12)	3 (15.8); 3 (0.07)	8 (27.6); 14 (0.7)	16 (57.1); 31 (1.59)	24 (42.1); 45 (1.14)
Severe TEAEs	0; 0	0; 0	2 (13.3); 2 (0.08)	2 (10.5); 2 (0.05)	–	–	–
Serious TEAEs	0; 0	0; 0	1 (6.7); 2 (0.08)	1 (5.3); 2 (0.05)	0; 0	2 (7.1); 2 (0.1)	2 (3.5); 2 (0.05)
TEAEs leading to permanent study treatment discontinuation (EAP)/withdrawal from study (004)	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
TEAEs leading to drug interruption	0; 0	0; 0	0; 0	0; 0	1 (3.5); 2 (0.1)	3 (10.7); 5 (0.26)	4 (7.0); 7 (0.18)
TEAEs leading to dose reduction	0; 0	0; 0	0; 0	0; 0	NA	NA	NA
TEAEs leading to dose increase	0; 0	0; 0	0; 0	0; 0	NA	NA	NA

[1]TEAEs are presented for the EAP by dose at the onset between the time of entry into the EAP and the last visit. TEAEs for VBP15-004 are presented from the end of 3 months (Week 12) until the end of the study (Week 48). EAP, expanded access protocol; TEAE, treatment-emergent adverse event

Source: **Extrapolation Report Outputs Table 6.1 Extrapolation Report Outputs Table 6.2**

Table 25. TEAEs by SOC and PT Reported by ⩾ 1 Subject in Target (VBP15-EAP) and Reference Population (VBP15-004)

	Target population VBP15-EAP				Reference population VBP15-004		
Time	Between first and last visit				Between Week 12 and Week 48		
Age group	2 to < 4 years				4 to < 7 years		
Vamorolone dose	**2 mg/kg/day (n=1)**	**4 mg/kg/day (n=9)**	**6 mg/kg/day (n=15)**	**Total (n=19)**	**2 mg/kg/day (n=29)**	**6 mg/kg/day (n=28)**	**Total (n=57)**
System organ class (SOC)							
Preferred term (PT), n (%); f (Rate)							
Total Number of TEAEs	0; 0	6 (66.7); 26 (1.78)	6 (40.0); 18 (0.70)	11 (57.9); 44 (1.07)	25 (86.2); 101 (5.03)	24 (85.7); 101 (5.17)	49 (86.0); 202 (5.1)
Ear and labyrinth disorders	**0; 0**	**1 (11.1); 1 (0.07)**	**0; 0**	**1 (5.3); 1 (0.02)**	**1 (3.5); 1 (0.05)**	**0; 0**	**1 (1.8); 1 (0.03)**
Ear discomfort	0; 0	1 (11.1); 1 (0.07)	0; 0	1 (5.3); 1 (0.02)	0; 0	0; 0	0; 0
Motion sickness	0; 0	0; 0	0; 0		1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Gastrointestinal disorders	**0; 0**	**2 (22.2); 3 (0.21)**	**1 (6.7); 1 (0.04)**	**3 (15.8); 4 (0.10)**	**8 (27.6); 18 (0.9)**	**12 (42.9); 23 1.18)**	**20 (35.1); 41 (1.03)**
Abdominal discomfort	0; 0	1 (11.1); 1 (0.07)	0; 0	1 (5.3); 1 (0.02)	0; 0	0; 0	0; 0
Diarrhoea	0; 0	1 (11.1); 1 (0.07)	0; 0	1 (5.3); 1 (0.02)	1 (3.5); 1 (0.05)	4 (14.3); 6 (0.31)	5 (8.8); 7 (0.18)
Dyspepsia	0; 0	0; 0	1 (6.7); 1 (0.04)	1 (5.3); 1 (0.02)	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Vomiting	0; 0	1 (11.1); 1 (0.07)	0; 0	1 (5.3); 1 (0.02)	4 (13.8); 6 (0.3)	3 (10.7); 3 (0.15)	7 (12.3); 9 (0.23)
Constipation	0; 0	0; 0	0; 0	0; 0	2 (6.9); 4 (0.2)	3 (10.7); 4 (0.2)	5 (8.8); 8 (0.2)
Abdominal pain	0; 0	0; 0	0; 0	0; 0	2 (6.9); 2 (0.1)	2 (7.1); 2 (0.1)	4 (7.0); 4 (0.1)
Abdominal pain upper	0; 0	0; 0	0; 0	0; 0	1 (3.5); 2 (0.1)	2 (7.1); 4 (0.2)	3 (5.3); 6 (0.15)
Mouth ulceration	0; 0	0; 0	0; 0	0; 0	0; 0	2 (7.1); 2 (0.1)	2 (3.5); 2 (0.05)
Dental caries	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Gingival pain	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Lip pain	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Toothache	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
General disorders and administration site conditions	**0; 0**	**4 (44.4); 5 (0.34)**	**0; 0**	**4 (21.1); 5 (0.12)**	**6 (20.7); 6 (0.3)**	**3 (10.7); 3 (0.15)**	**9 (15.8); 9 (0.23)**
Pyrexia	0; 0	4 (44.4); 5 (0.34)	0; 0	4 (21.1); 5 (0.12)	5 (17.2); 5 (0.25)	3 (10.7); 3 (0.15)	8 (14.0); 8 (0.2)
Fatigue	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Immune system disorders	**0; 0**	**0; 0**	**1 (6.7); 1 (0.04)**	**1 (5.3); 1 (0.02)**	**1 (3.5); 1 (0.05)**	**1 (3.6); 1 (0.05)**	**2 (3.5); 2 (0.05)**
Allergy to arthropod bite	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Hypersensitivity	0; 0	0; 0	1 (6.7); 1 (0.04)	1 (5.3); 1 (0.02)	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Infections and infestations	**0; 0**	**4 (44.4); 8 (0.55)**	**6 (40.0); 9 (0.35)**	**9 (47.4); 17 (0.41)**	**14 (48.3); 24 (1.19)**	**12 (42.9); 18 (0.92)**	**26 (45.6); 42 (1.06)**
Ear infection	0; 0	1 (11.1); 2 (0.14)	0; 0	1 (5.3); 2 (0.05)	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Gastroenteritis	0; 0	1 (11.1); 1 (0.07)	2 (13.3); 2 (0.08)	3 (15.8); 3 (0.07)	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Influenza	0; 0	0; 0	1 (6.7); 1 (0.04)	1 (5.3); 1 (0.02)	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Nasopharyngitis	0; 0	1 (11.1); 1 (0.07)	3 (20.0); 3 (0.12)	4 (21.1); 4 (0.10)	2 (6.9); 2 (0.1)	3 (10.7); 3 (0.15)	5 (8.8); 5 (0.13)
Otitis media	0; 0	1 (11.1); 1 (0.07)	0; 0	1 (5.3); 1 (0.02)	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Respiratory tract infection	0; 0	1 (11.1); 2 (0.14)	0; 0	1 (5.3); 2 (0.05)	0; 0	0; 0	0; 0
Respiratory tract infection viral	0; 0	0; 0	1 (6.7); 1 (0.04)	1 (5.3); 1 (0.02)	0; 0	0; 0	0; 0
Roseola	0; 0	0; 0	1 (6.7); 1 (0.04)	1 (5.3); 1 (0.02)	0; 0	0; 0	0; 0
Upper respiratory tract infection	0; 0	1 (11.1); 1 (0.07)	0; 0	1 (5.3); 1 (0.02)	7 (24.1); 7 (0.35)	3 (10.7); 6 (0.31)	10 (17.5); 13 (0.33)
Viral infection	0; 0	0; 0	1 (6.7); 1 (0.04)	1 (5.3); 1 (0.02)	0; 0	0; 0	0; 0
Rhinitis	0; 0	0; 0	0; 0	0; 0	2 (6.9); 2 (0.1)	3 (10.7); 4 (0.2)	5 (8.8); 6 (0.15)
Impetigo	0; 0	0; 0	0; 0	0; 0	2 (6.9); 2 (0.1)	0; 0	2 (3.5); 2 (0.05)
Tonsillitis	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	1 (3.6); 1 (0.05)	2 (3.5); 2 (0.05)

Pharyngitis streptococcal	0; 0	0; 0	0; 0	0; 0	1 (3.5); 3 (0.15)	0; 0	1 (1.8); 3 (0.08)
Appendicitis perforated	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Croup infectious	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Enterobiasis	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Gastroenteritis viral	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Laryngitis	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Oral herpes	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Pneumonia	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Injury, poisoning and procedural complications	**0; 0**	**1 (11.1); 1 (0.07)**	**2 (13.3); 3 (0.12)**	**3 (15.8); 4 (0.10)**	**3 (10.3); 5 (0.25)**	**6 (21.4); 9 (0.46)**	**9 (15.8); 14 (0.35)**
Bone contusion	0; 0	0; 0	1 (6.7); 1 (0.04)	1 (5.3); 1 (0.02)	0; 0	0; 0	0; 0
Compression fracture	0; 0	1 (11.1); 1 (0.07)	0; 0	1 (5.3); 1 (0.02)	0; 0	0; 0	0; 0
Fall	0; 0	0; 0	1 (6.7); 1 (0.04)	1 (5.3); 1 (0.02)	2 (6.9); 2 (0.1)	2 (7.1); 2 (0.1)	4 (7.0); 4 (0.1)
Skin laceration	0; 0	0; 0	1 (6.7); 1 (0.04)	1 (5.3); 1 (0.02)	1 (3.5); 1 (0.05)	1 (3.6); 1 (0.05)	2 (3.5); 2 (0.05)
Arthropod bite	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Arthropod sting	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Contusion	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Ear injury	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Limb injury	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Muscle strain	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Spinal compression fracture	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Tooth injury	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Musculoskeletal and connective tissue disorders	**0; 0**	**0; 0**	**1 (6.7); 2 (0.08)**	**1 (5.3); 2 (0.05)**	**4 (13.8); 6 (0.3)**	**7 (25.0); 8 (0.41)**	**11 (19.3); 14 (0.35)**
Rhabdomyolysis	0; 0	0; 0	1 (6.7); 2 (0.08)	1 (5.3); 2 (0.05)	0; 0	0; 0	0; 0
Pain in extremity	0; 0	0; 0	0; 0	0; 0	2 (6.9); 2 (0.1)	3 (10.7); 3 (0.15)	5 (8.8); 5 (0.13)
Back pain	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	2 (7.1); 3 (0.15)	3 (5.3); 4 (0.1)
Arthralgia	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Foot deformity	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Muscle atrophy	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Muscle spasms	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Myalgia	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Psychiatric disorders	**0; 0**	**0; 0**	**1 (6.7); 1 (0.04)**	**1 (5.3); 1 (0.02)**	**3 (10.3); 4 (0.2)**	**5 (17.9); 5 (0.26)**	**8 (14.0); 9 (0.23)**
Aggression	0; 0	0; 0	1 (6.7); 1 (0.04)	1 (5.3); 1 (0.02)	2 (6.9); 2 (0.1)	0; 0	2 (3.5); 2 (0.05)
Abnormal behaviour	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Agitation	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Defiant behaviour	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Emotional distress	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Irritability	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Mood altered	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Stereotypy	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Respiratory, thoracic and mediastinal disorders	**0; 0**	**2 (22.2); 7 (0.48)**	**1 (6.7); 1 (0.04)**	**3 (15.8); 8 (0.19)**	**6 (20.7); 7 (0.35)**	**6 (21.4); 8 (0.41)**	**12 (21.1); 15 (0.38)**
Cough	0; 0	2 (22.2); 4 (0.27)	1 (6.7); 1 (0.04)	3 (15.8); 5 (0.12)	4 (13.8); 4 (0.2)	2 (7.1); 2 (0.1)	6 (10.5); 6 (0.15)
Nasal congestion	0; 0	2 (22.2); 2 (0.14)	0; 0	2 (10.5); 2 (0.05)	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Rhinorrhoea	0; 0	1 (11.1); 1 (0.07)	0; 0	1 (5.3); 1 (0.02)	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Asthma	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 2 (0.1)	1 (1.8); 2 (0.05)
Epistaxis	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)

Nasal mucosal disorder	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Oropharyngeal pain	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Productive cough	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Respiratory tract congestion	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Skin and subcutaneous tissue disorders	**0; 0**	**1 (11.1); 1 (0.07)**	**0; 0**	**1 (5.3); 1 (0.02)**	**4 (13.8); 4 (0.2)**	**6 (21.4); 8 (0.41)**	**10 (17.5); 12 (0.3)**
Rash	0; 0	1 (11.1); 1 (0.07)	0; 0	1 (5.3); 1 (0.02)	2 (6.9); 2 (0.1)	1 (3.6); 1 (0.05)	3 (5.3); 3 (0.08)
Hypertrichosis	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	3 (10.7); 3 (0.15)	4 (7.0); 4 (0.1)
Perioral dermatitis	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 2 (0.1)	1 (1.8); 2 (0.05)
Dry skin	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Eczema	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Pruritus	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Blood and lymphatic system disorders	**0; 0**	**0; 0**	**0; 0**	**0; 0**	**1 (3.5); 1 (0.05)**	**0; 0**	**1 (1.8); 1 (0.03)**
Neutropenia	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Cardiac disorders	**0; 0**	**0; 0**	**0; 0**	**0; 0**	**2 (6.9); 2 (0.1)**	**0; 0**	**2 (3.5); 2 (0.05)**
Left ventricular dilatation	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Left ventricular dysfunction	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Congenital, familial and genetic disorders	**0; 0**	**0; 0**	**0; 0**	**0; 0**	**0; 0**	**1 (3.6); 1 (0.05)**	**1 (1.8); 1 (0.03)**
Talipes	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Endocrine disorders	**0; 0**	**0; 0**	**0; 0**	**0; 0**	**4 (13.8); 4 (0.2)**	**5 (17.9); 5 (0.26)**	**9 (15.8); 9 (0.23)**
Cushingoid	0; 0	0; 0	0; 0	0; 0	4 (13.8); 4 (0.2)	5 (17.9); 5 (0.26)	9 (15.8); 9 (0.23)
Eye disorders	**0; 0**	**0; 0**	**0; 0**	**0; 0**	**1 (3.5); 1 (0.05)**	**0; 0**	**1 (1.8); 1 (0.03)**
Strabismus	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Hepatobiliary disorders	**0; 0**	**0; 0**	**0; 0**	**0; 0**	**0; 0**	**1 (3.6); 2 (0.1)**	**1 (1.8); 2 (0.05)**
Hepatitis acute	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 2 (0.1)	1 (1.8); 2 (0.05)
Investigations	**0; 0**	**0; 0**	**0; 0**	**0; 0**	**7 (24.1); 10 (0.5)**	**4 (14.3); 5 (0.26)**	**11 (19.3); 15 (0.38)**
Weight increased	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	2 (7.1); 2 (0.1)	3 (5.3); 3 (0.08)
Alanine aminotransferase increased	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Blood calcium decreased	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Blood creatine phosphokinase increased	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Blood phosphorus decreased	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Blood pressure increased	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Blood uric acid increased	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Cortisol decreased	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Haematocrit increased	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Haemoglobin increased	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Lymphocyte count increased	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Protein urine present	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Vitamin D decreased	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Metabolism and nutrition disorders	**0; 0**	**0; 0**	**0; 0**	**0; 0**	**2 (6.9); 2 (0.1)**	**3 (10.7); 4 (0.2)**	**5 (8.8); 6 (0.15)**
Vitamin D deficiency	0; 0	0; 0	0; 0	0; 0	2 (6.9); 2 (0.1)	2 (7.1); 3 (0.15)	4 (7.0); 5 (0.13)
Increased appetite	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Nervous system disorders	**0; 0**	**0; 0**	**0; 0**	**0; 0**	**2 (6.9); 2 (0.1)**	**0; 0**	**2 (3.5); 2 (0.05)**
Headache	0; 0	0; 0	0; 0	0; 0	2 (6.9); 2 (0.1)	0; 0	2 (3.5); 2 (0.05)
Renal and urinary disorders	**0; 0**	**0; 0**	**0; 0**	**0; 0**	**3 (10.3); 3 (0.15)**	**1 (3.6); 1 (0.05)**	**4 (7.0); 4 (0.1)**
Chromaturia	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Pollakiuria	0; 0	0; 0	0; 0	0; 0	0; 0	1 (3.6); 1 (0.05)	1 (1.8); 1 (0.03)
Proteinuria	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)
Urinary incontinence	0; 0	0; 0	0; 0	0; 0	1 (3.5); 1 (0.05)	0; 0	1 (1.8); 1 (0.03)

[1]TEAEs are presented for the EAP by dose at the onset between the time of entry into the EAP and the last visit. TEAEs for VBP15-004 are presented from the end of 3 months (Week 12) until the end of the study (Week 48).
EAP, expanded access protocol; f, event count; n, patient count; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event
Source: Extrapolation Report Outputs Table 7.1; Extrapolation Report Outputs Table 7.2

Treatment-related TEAEs

In the target population, drug-related TEAEs were uncommon and occurred exclusively with the 6 mg/kg dose during the EAP. One event each of Dyspepsia, Rhabdomyolysis, and Aggression were the vamorolone-related TEAEs observed during the EAP.

In the reference population, 22.2% of all TEAEs were considered study drug related. There was only 1 event of Cortisol decrease that was definitely related to vamorolone. All other drug-related TEAEs had either a probable or possible association with vamorolone.

The most frequent drug-related TEAEs were Cushingoid with 9 events, occurring more frequently with 6 mg/kg, Abdominal pain upper (4 events), followed by Weight increase (3 events). These were followed by Abdominal pain, Vomiting, and Hypertrichosis (all with 2 events). All other events were reported for 1 subject only. There were 6 Psychiatric disorder events considered possibly related to vamorolone, each seen in 1 (1.8%) subject, including Abnormal behaviour, Agitation, Defiant behaviour, Emotional distress, Irritability and Mood altered.

The most common and prominent drug-related TEAEs during the long-term follow-up were similar to those seen during the short-term safety follow-up and were related to the following SOCs:

- Endocrine disorders (Cortisol decrease being a definitely related TEAE, related to suppression of the HPA axis and Cushingoid features)
- Metabolic and nutritional disorders (Increased appetite and Weight increase)
- Psychiatric disorders (Irritability, Abnormal behaviour, Aggression, Anxiety, Mood swings, and Sleep disorder)
- Gastrointestinal disorders (Diarrhoea, Nausea, and Vomiting)

These adverse events are consistent with the known adverse event profile of vamorolone.

Serious adverse event/deaths/other significant events

Study VBP15-006

No death was reported in Study VBP15-006. None of the patients 2 to <4 years of age reported a SAE or a TEAE leading to treatment or study discontinuation.

Expanded Access Programme

No death was reported in the EAP. A subject experienced 2 SAEs of rhabdomyolysis while receiving vamorolone 6 mg/kg. One event was of moderate intensity and considered related to vamorolone; one event was of severe intensity considered unrelated to vamorolone and related to a viral infection. No subject experienced a TEAE leading to dose interruption or discontinuation.

Comparison VBP15-006 (target population) versus VBP15-004 (reference population) up to Week 12

Target population – see above;

In the reference population 4 to <7 years, one subject receiving 2 mg/kg experienced a SAE of Grade 2 Viral gastroenteritis rated as unrelated to treatment. The study drug was interrupted for two days due to vomiting. The subject received hydrocortisone stress dosing, intravenous fluids and oral ondansetron. The study drug was resumed, and the subject continued in the study without recurrence of the event.

Comparison VBP15-EAP (target population) versus VBP15-004 (reference population) Week 12 - 48

One subject in the target population experienced 2 SAEs of Rhabdomyolysis while receiving vamorolone 6 mg/kg in the EAP. Vamorolone dosing was not interrupted during the SAEs. The first event was considered to be related to vamorolone, the second event was considered as unrelated.

In the reference population, two subjects experienced SAEs between Week 12 and Week 48, one with Appendicitis perforated and one with Asthma. Neither event was considered study drug related.

Analysis of Adverse Events by Organ System or Syndrome

Behavioural Changes/ problems

Study VBP15-006

Two subjects in the 6 mg/kg vamorolone group reported psychiatric disorders: one subject had Grade 1 irritability from Day 1 of dosing (considered possibly related to vamorolone) and then Grade 1 aggression from Day 34 to 37 (considered possibly related to vamorolone); one subject had Grade 1 compulsive lip biting on Day 2 (considered unrelated to vamorolone) and Grade 1 mood swings from Day 6 to 8 (considered possibly related to vamorolone).

Expanded Access Programme

As of the DCO, one subject presented aggressive behaviour (PT: Aggression) that was mild in intensity and considered possibly related to vamorolone 6 mg/kg.

Bone fractures

Study VBP15-006

No events of bone fracture were reported in subjects aged 2 to <4 years and no evidence for an effect of vamorolone on serum bone turnover marker was observed.

Expanded Access Programme

As of the DCO, 1 subject had experienced a compression fracture on right foot while receiving vamorolone 4 mg/kg and 1 subject had experienced bone contusion (reported term: bruised tailbone) while receiving vamorolone 6 mg/kg; both events were considered mild, non-serious and unrelated to vamorolone.

Cataracts and glaucoma

Study VBP15-006 and Expanded Access Programme

No events of cataract or glaucoma were reported in subjects aged 2 to <4 years in study VBP15-006 and up to the DCO in the EAP.

Cushingoid features

Study VBP15-006 and Expanded Access Programme

No events of Cushingoid were reported in subjects aged 2 to <4 years in study VBP15-006 and up to the DCO in the EAP.

Gastrointestinal Symptoms

Study VBP15-006

Gastrointestinal disorders were frequently reported: 2 TEAEs in 1 (10.0%) subject in the vamorolone 2 mg/kg group compared to 11 TEAEs in 8 (80.0%) subjects in the vamorolone 6 mg/kg group. In the 2 mg/kg group, GI symptoms were not considered related to vamorolone; in the vamorolone 6 mg/kg group, abdominal pain, abnormal faces, and diarrhoea were rated related to vamorolone (each 1 case).

Expanded Access Programme

Four TEAEs of GI disorders, all of mild intensity, were reported in 3 (15.8%) subjects: 1 subject experienced abdominal discomfort and diarrhoea in the 4 mg/kg group, 1 subject experienced vomiting in the 4 mg/kg group, and 1 subject experienced dyspepsia in the 6 mg/kg group. Only dyspepsia was rated as related to vamorolone.

Arterial Hypertension

Study VBP15-006 and Expanded Access Programme

No events indicative of hypertension or increased blood pressure were reported in subjects aged 2 to <4 years in study VBP15-006 and up to the DCO in the EAP.

Infections

Study VBP15-006

Infections were frequently reported: 9 TEAEs in 5 (50.0%) subjects in the vamorolone 2 mg/kg group compared to 4 TEAEs in 3 (30.0%) subjects in the vamorolone 6 mg/kg group. However, none of these TEAEs were considered related to vamorolone.

Expanded Access Programme

Infections were frequently reported: 8 TEAEs in 4 (44.4%) subjects while receiving vamorolone 4 mg/kg compared to 9 TEAEs in 6 (40.0%) subjects while receiving vamorolone 6 mg/kg. None was considered related to vamorolone.

Skin and hair changes

Study VBP15-006 and Expanded Access Programme

No observations related to skin and hair changes were reported in study VBP15-006 and up to the DCO in the EAP.

Weight gain

Study VBP15-006

No TEAEs indicative of weight gain were reported. Changes in weight between baseline and Week 12 were small and of unclear clinical relevance.

Expanded Access Programme

No TEAE indicative of weight gain was reported in the EAP as of the DCO.

Weight measurements showed that weight increased over 30 months of follow-up, with a change from first to last measurement in median weight Z-score of 0.44 (0.02; 0.68), indicative of clinically relevant weight gain in a proportion of subjects.

Diabetic condition

Study VBP15-006

No TEAEs indicative of diabetic conditions were reported. No subject had a change in glucose level from low to high or from normal to high between baseline and Week 12, and no subject had results indicative of insulin resistance based on pharmacodynamic biomarkers.

Expanded Access Programme

No TEAE indicative of diabetic conditions was reported in the EAP as of the DCO.

Adrenal suppression

Study VBP15-006

Five subjects in the 6 mg/kg vamorolone group were reported to have a TEAE of Grade 1 adrenal suppression, based on the Week 12 cortisol values, which were available to the investigators. No symptoms consistent with adrenal insufficiency were reported during the study, no action was taken, and all events were ongoing at the end of the study. Additionally, one subject in the 6 mg/kg vamorolone group had a TEAE of Grade 2 cortisol decreased, considered probably related to vamorolone.

Baseline morning cortisol levels were in the normal range, consistent with the fact that subjects had not received prior glucocorticoid treatment. After 12 weeks of treatment with vamorolone 2 mg/kg or 6 mg/kg/, dose-dependent reductions in cortisol levels were observed (Table 26). These changes are in line with the expected inhibitory effect of vamorolone on the hypothalamic-pituitary-adrenal axis.

Table 26. Morning Cortisol Change From Baseline to Week 12 – Study VBP15-006 (Pharmacokinetics Analysis Set)

Change from Baseline to Week 12	**2 mg/kg (N = 10)**	**6 mg/kg (N = 10)**
N	10	8
Mean (SD)	-184.700 (138.2020)	-217.750 (103.9832)
Median (Q1 ; Q3)	-156.000 (-251.000 ; -89.000)	-230.500 (-285.500 ; -132.500)
Min, Max	-464.000, -23.000	-378.000, -67.000

Max = maximum; Min = minimum; Q = quartile; SD = standard deviation
If laboratory value was given as "<X" then "X/2" was used in numerical analyses, for cases with ">X" then "X" was used. Source: extracted from Module 2.7.2, Table 3

Expanded Access Programme

Morning cortisol measurements were not mandated by the EAP protocol. No TEAE indicative of adrenal suppression was reported in the EAP as of the DCO.

Comparison VBP15-006 (target population) versus VBP15-004 (reference population) up to Week 12

Target population – see above;

In the reference population 4 to <7 years, baseline cortisol levels were within the normal range, similar to those of the target population, with median values of 218 nmol/L and 226 nmol/L in the 2 mg/kg and 6 mg/kg groups, respectively. At Week 12, median cortisol levels showed dose-dependent reductions from baseline in the reference population, as expected (Table 27).

Table 27. Morning Cortisol Levels at Baseline, Week 12, and Change at Week 12 for Vamorolone 2 mg/kg and 6 mg/kg in Studies VBP15-006 and VBP15-004

	Target population VBP15-006		Reference population VBP15-004	
Age group	**2 to <4 years**		**4 to <7 years**	
Vamorolone dose	**2 mg/kg/day (n=10)**	**6 mg/kg/day (n=10)**	**2 mg/kg/day (n=30)**	**6 mg/kg/day (n=28)**
Morning Cortisol (nmol/L)[a]				
Baseline, n	10	8	28	27
Median (Q1; Q3)	295.00 (193.00; 364.00)	285.50 (227.50; 351.50)	218 (188; 288)	226 (188; 284)
Week 12, n	10	10	20	25
Median (Q1; Q3)	127.00 (72.00; 171.00)	73.00 (63.00; 80.00)	145 (119; 178)	33 (19; 69)
Median Change (Q1; Q3)	-156.00 (-251.00; -89.00)	-230.50 (-285.50; -132.50)	-81 (-137; -51)	-196 (-253; -144)

CSR, clinical study report; Max, maximum; Min, minimum; SD, standard deviation; Q1, 1st quartile; Q3, 3rd quartile
Values of morning cortisol below the lower limit of quantification were reported as <8 nmol/L.
If laboratory value was given as "<X" then "X/2" was used in numerical analyses, for cases with ">X" then "X" was used.
Source: VBP15-006 Table 14.3.7.1a; VBP15-004 CSR Appendix Table 14.2.5.5.3, Extrapolation Report Outputs Table 14.

Table 28. Morning Cortisol Levels at Baseline and Week 12 for Vamorolone 2 mg/kg and 6 mg/kg in Studies VBP15-006 and VBP15-004

	Target population Study VBP15-006		**Reference population Study VBP15-004**	
	2 mg/kg	**6 mg/kg**	**2 mg/kg**	**6 mg/kg**
Baseline (nmol/L)				
N	10	8	28	27
Median	295.00	285.50	218	226
Min- Max	166- 516	130-455	110-510	116-394
Week 12				
N	10	8	20	25
Median	127.00	73.00	145	33
Min- Max	33-223	17-121	28-207	4-154
n (%) with <100 nmol/L	4 (40.0)	8 (100.0)	3 (15.0)	24 (96.0)

Source: created by the assessor from VBP15-006; App.2 Listing 16.1.3.7.1; Paediatric Extrapolation Report – EAP outputs – Table 14; CSR VBP15-006 – Table 84.

Growth

Study VBP15-006

No TEAEs indicative of stunted growth were reported. Changes in height between baseline and Week 12 were small and of unclear clinical relevance.

Expanded Access Programme

No TEAE indicative of stunted growth was reported in the EAP as of the DCO. Height measurements showed subjects' growth over 30 months of follow-up, with a change from first to last measurement in median (Q1; Q3) height Z-score of 0.10 (-0.38; 0.24). DMD subjects were able to maintain their height Z-scores despite a median exposure of 2.4 (1.9; 2.7) years to vamorolone.

Laboratory findings and vital signs

Laboratory Evaluations

Of note, no clinical laboratory tests were collected specifically under the protocol of the EAP, but clinically significant treatment-emergent abnormal test results obtained as part of clinical care were to be recorded on the designated electronic case report form page for AEs.

Haematology

Study VBP15-006

Haematology changes in white cells, erythrocyte counts and platelets were small and varied at the post-baseline visits. The only shifts observed in > 1 subject post-baseline were for lymphocytes from normal to high in the 6 mg/kg group (4 subjects [40.0%]), and haematocrit from normal to high in the 2 mg/kg and 6 mg/kg groups (2 subjects [20.0%] and 4 subjects [40.0%], respectively). All other shifts were observed in individual subjects. Immature granulocyte counts remained stable. In summary, no relevant changes in median values were observed in any haematology parameter after 12 weeks of treatment with vamorolone at either dose level.

Comparison VBP15-006 (target population) versus VBP15-004 (reference population) up to Week 12

Target population;

In the reference population, eosinophil and neutrophil counts remained stable over the 12-week period, with no clinically meaningful changes observed in either dose group. Small increases in haematocrit and haemoglobin levels were seen in both the 2 mg/kg and 6 mg/kg groups. Additionally, slight increases in lymphocyte, leukocyte, and erythrocyte counts were observed at Week 12. Immature granulocyte counts remained unchanged throughout the observation period.

Table 29. Selected Haematology Median Values at Baseline, Week 12 and Change at Week 12 for in Studies VBP15-006 and VBP15-004

	Target population VBP15-006		Reference population VBP15-004	
Age group	**2 to <4 years**		**4 to <7 years**	
Vamorolone dose	**2 mg/kg/day (n=10)**	**6 mg/kg/day (n=10)**	**2 mg/kg/day (n=30)**	**6 mg/kg/day (n=28)**
Eosinophils (10^9/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	0.185 (0.139; 0.303)	0.141 (0.081; 0.291)	0.15 (0.10; 0.24)	0.21 (0.13; 0.27)
Week 12, n	10	9	21	25
Median (Q1; Q3)	0.155 (0.098; 0.219)	0.148 (0.100; 0.194)	0.15 (0.11; 0.19)	0.16 (0.12; 0.25)
Median Change (Q1; Q3)	-0.096 (-0.134; 0.066)	-0.013 (-0.020; 0.066)	0.00 (-0.07; 0.02)	0.01 (-0.05; 0.03)
Neutrophils (10^9/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	2.123 (1.800; 2.598)	2.959 (2.298; 3.734)	2.33 (1.62; 3.64)	2.70 (1.81; 3.58)
Week 12, n	10	9	21	25
Median (Q1; Q3)	2.313 (1.794; 3.665))	3.518 (2.466; 3.857)	2.19 (1.55; 2.87)	2.31 (1.75; 3.01)
Median Change (Q1; Q3)	-0.275 (-0.382; 1.345)	-0.135 (-0.696; 1.440)	0.08 (-0.31; 0.52)	-0.18 (-1.21; 0.43)
Haematocrit (L/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	0.428 (0.406; 0.435)	0.378 (0.373; 0.407)	0.40 (0.39; 0.43)	0.41 (0.38; 0.42)
Week 12, n	10	9	21	26
Median (Q1; Q3)	0.407 (0.401; 0.446))	0.430 (0.400; 0.442)	0.41 (0.40; 0.43)	0.43 (0.40; 0.45)
Median Change (Q1; Q3)	0.004 (-0.020; 0.012)	0.025 (0.011; 0.066)	0.01 (-0.01; 0.02)	0.02 (0.00; 0.05)
Haemoglobin (g/L)				

Baseline, n	10	10	30	28
Median (Q1; Q3)	127.500 (121.00; 136.00)	123.500 (122.00; 130.00)	128 (119; 137)	128 (121; 133)
Week 12, n	10	9	21	26
Median (Q1; Q3)	130.500 (128.00; 136.00)	131.000 (128.00; 134.00)	129 (122; 135)	135 (126; 140)
Median Change (Q1; Q3)	5.00 (-6.00; 10.00)	5.000 (1.000; 15.000)	1 (-2; 4)	7 (1; 12)
Lymphocytes (10^9/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	4.165 (3.417; 4.462)	4.192 (3.348; 4.776)	3.03 (2.79; 3.68)	2.83 (2.47; 3.32)
Week 12, n	10	9	21	25
Median (Q1; Q3)	4.182 (3.724; 5.016)	4.351 (4.079; 4.868)	3.39 (2.98; 4.56)	4.38 (3.79; 5.18)
Median Change (Q1; Q3)	0.275 (-0.325; 1.035)	0.347 (0.183; 0.841)	0.66 (-0.13; 0.92)	1.29 (1.03; 1.81)
Leukocytes (10^9/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	7.120 (6.520; 8.500)	7.725 (6.760; 9.130)	6.71 (4.96; 7.24)	6.07 (5.17; 7.54)
Week 12, n	10	9	21	26
Median (Q1; Q3)	8.090 (6.330; 9.200)	7.980 (7.940; 9.250)	6.95 (5.70; 8.04)	8.12 (6.22; 9.16)
Median Change (Q1; Q3)	0.240 (-1.230; 1.760)	1.320 (0.320; 1.970)	0.84 (0.12; 1.35)	1.19 (0.23; 2.36)
Erythrocytes (10^{12}/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	4.720 (4.620; 5.030)	4.850 (4.400; 4.950)	4.72 (4.53; 5.03)	4.87 (4.56; 5.25)
Week 12, n	10	9	21	26
Median (Q1; Q3)	5.010 (4.660; 5.110)	4.950 (4.800; 5.330)	4.84 (4.65; 5.16)	5.26 (4.94; 5.47)
Median Change (Q1; Q3)	0.100 (-0.240; 0.230)	0.140 (0.040; 0.490)	0.08 (-0.06; 0.19)	0.31 (0.06; 0.56)
Immature granulocytes (10^9/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	0.018 (0.010; 0.022)	0.020 (0.008; 0.031)	0.02 (0.02 ; 0.02)	0.02 (0.02 ; 0.03)
Week 12, n	10	9	21	25
Median (Q1; Q3)	0.026 (0.019; 0.040)	0.021 (0.008; 0.037)	0.02 (0.02; 0.02)	0.02 (0.02; 0.04)
Median Change (Q1; Q3)	0.004 (-0.010; 0.027)	0.004 (-0.004; 0.024)	0.00 (0.00; 0.00)	0.00 (0.00; 0.02)

Max, maximum; Min, minimum; SD, standard deviation; Q1, 1st quartile; Q3, 3rd quartile
Absolute counts for types of Leukocytes (Monocytes, Neutrophils etc.) were calculated based on fractions from total Leukocyte counts.
If laboratory value was given as "<X" then "X/2" was used in numerical analyses, for cases with ">X" then "X" was used.
Source: VBP15-006 Table 14.3.3.1a; VBP15-004 Table 14.3.8.1, Table 14.3.8.2, Extrapolation Report Outputs Table 10.1, Table 10.2

Clinical Chemistry

Study VBP15-006

There were no clinically relevant changes in the biochemistry parameters.

The vast majority of CK and lactate dehydrogenase results were high as expected. Therefore, changes in CK or lactate dehydrogenase could not be assessed in this population. In addition, many creatinine results were below the lower limit of quantification, making analysis of this parameter impossible.

There was no evidence for an increase in total cholesterol values, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol. Median change from baseline for total cholesterol at Week 12 was -0.100 mmol/L and 0.000 mmol/L for the 2 mg/kg and the 6 mg/kg vamorolone group. Median change from baseline for HDL cholesterol at Week 12 was 0.000 mmol/L and -0.010 mmol/L for the 2 mg/kg and the 6 mg/kg vamorolone group. Median change from baseline for LDL cholesterol at Week 12 was -0.155 mmol/L and -0.100 mmol/L for the 2 mg/kg and the 6 mg/kg vamorolone group.

Changes in triglycerides were of unclear clinical relevance. At baseline, median triglycerides values were higher in the 2 mg/kg than in the 6 mg/kg vamorolone group. Median change from baseline for triglycerides at Week 12 was -0.025 mmol/L and 0.160 mmol/L for the 2 mg/kg and the 6 mg/kg vamorolone group. At Week 12, median triglycerides values were still higher in the 2 mg/kg than in the 6 mg/kg vamorolone group.

At baseline and post-Baseline, ALT and AST values were above 5 x ULN in the vast majority of subjects, in line with muscle dystrophy. No subject presented with an increase of GGT > ULN. Two subjects in the 2 mg/kg group had bilirubin levels between 1 × ULN and 1.5 × ULN: One subject presented with an increase in total bilirubin to 11.6 µmol/L (>1.5 x ULN) at the Week 12 visit, GGT, alkaline phosphatase and ALT were not increased at that visit. There were no cases of Hy's law.

Comparison VBP15-006 (target population) versus VBP15-004 (reference population) up to Week 12

Target population – see above;

In the reference population, small reductions were observed in alkaline phosphatase and amylase levels from baseline to Week 12. Phosphate levels remained stable. There were no relevant changes in total cholesterol, HDL, LDL cholesterol, or triglycerides over 12 weeks of treatment. Vitamin D levels remained relatively stable, with a small increase observed in the 6 mg/kg group (Table 30).

Table 30. Selected Clinical Chemistry Median Values at Baseline, Week 12 and Change at Week 12 in Studies VBP15-006 and VBP15-004

	Target population VBP15-006		**Reference population VBP15-004**	
Age group	**2 to <4 years**		**4 to <7 years**	
Vamorolone dose	**2 mg/kg/day** (n=10)	**6 mg/kg/day** (n=10)	**2 mg/kg/day** (n=30)	**6 mg/kg/day** (n=28)
Alkaline Phosphatase (U/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	151.500 (125.00; 177.00)	135.50 (123.00; 165.00)	127 (106; 154)	116 (104; 128)
Week 12, n	10	10	21	26
Median (Q1; Q3)	142.00 (126.00; 182.00)	110.500 (107.00; 131.00)	123 (103; 148)	109 (95; 130)
Median Change (Q1; Q3)	-7.00 (-18.00; 6.00)	-14.50 (-28.00; -1.00)	-6 (-14; 10)	-4 (-14; 0)
Amylase (U/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	45.00 (35.00; 48.00)	51.000 (38.00; 68.00)	46 (34; 56)	43 (32; 53)
Week 12, n	10	10	21	26
Median (Q1; Q3)	35.500 (32.00; 49.00)	46.000 (32.00; 62.00)	40 (36; 53)	37 (25; 49)
Median Change (Q1; Q3)	-4.00 (-10.00; 0.00)	-8.50 (-13.00; 0.00)	-1 (-4; 2)	-6 (-11; -2)
Phosphate (mmol/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	1.795 (1.650; 2.030)	1.710 (1.680; 1.810)	1.68 (1.62; 1.81)	1.68 (1.58; 1.78)
Week 12, n	9	10	21	24
Median (Q1; Q3)	1.780 (1.680; 1.810)	1.745 (1.650; 1.840)	1.65 (1.62; 1.74)	1.70 (1.64; 1.78)
Median Change (Q1; Q3)	0.00 (-0.190; 0.040)	-0.015 (-0.060; 0.130)	0.00 (-0.09; 0.10)	0.02 (-0.06; 0.10)

Total Cholesterol (mmol/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	4.250 (4.070; 4.530)	3.730 (3.600; 4.170)	3.84 (3.47; 4.38)	4.25 (3.72; 4.68)
Week 12, n	10	10	21	26
Median (Q1; Q3)	4.335 (3.860; 4.690)	3.705 (3.470; 4.250)	4.07 (3.37; 4.61)	4.51 (3.76; 4.90)
Median Change (Q1; Q3)	-0.100 (-0.240; 0.200)	0.000 (-0.290; 0.160)	0.00 (-0.18; 0.51)	0.34 (-0.20; 0.54)
HDL Cholesterol (mmol/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	1.155 (0.850; 1.270)	0.960 (0.850; 1.110)	1.16 (0.93; 1.35)	1.11 (1.00; 1.30)
Week 12, n	10	10	21	26
Median (Q1; Q3)	1.050 (0.880; 1.300)	0.930 (0.850; 1.090)	1.14 (0.91; 1.30)	1.26 (1.09; 1.37)
Median Change (Q1; Q3)	0.00 (-0.050; 0.050)	-0.010 (-0.050; 0.080)	0.05 (-0.11; 0.12)	0.09 (-0.03; 0.33)
LDL Cholesterol (mmol/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	2.510 (2.380; 2.900)	2.460 (2.100; 2.870)	2.13 (1.86; 2.62)	2.37 (2.11; 3.06)
Week 12, n	10	10	21	26
Median (Q1; Q3)	2.550 (2.100; 2.720)	2.205 (1.890; 2.800)	2.38 (1.74; 2.67)	2.56 (1.89; 2.98)
Median Change (Q1; Q3)	-0.155 (-0.280; -0.030)	-0.100 (-0.360; -0.020)	0.03 (-0.25; 0.28)	-0.01 (-0.33; 0.49)
Triglycerides (mmol/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	1.230 (1.010; 1.630)	0.860 (0.680; 1.080)	0.98 (0.88; 1.30)	1.23 (1.11; 1.57)
Week 12, n	10	10	21	26
Median (Q1; Q3)	1.290 (0.970; 1.940)	1.120 (0.960; 1.420)	1.08 (0.81; 1.64)	1.49 (1.15; 1.62)
Median Change (Q1; Q3)	-0.025 (-0.120; 0.200)	0.160 (-0.020; 0.620)	0.11 (-0.14; 0.33)	0.25 (-0.16; 0.61)
25-Hydroxyvitamin D (nmol/L)				
Baseline, n	10	10	27	26
Median (Q1; Q3)	63.500 (45.00; 75.00)	51.000 (45.00; 65.00)	55.0 (45.0; 68.0)	52.0 (40.0; 62.0)
Week 12, n	10	10	16	21
Median (Q1; Q3)	68.500 (45.00; 78.00)	52.000 (45.00; 65.00)	50.0 (35.0; 61.0)	58.0 (50.0; 60.0)
Median Change (Q1; Q3)	1.00 (-3.00; 2.00)	-1.00 (-10.00; 3.00)	0.0 (-15.0; 32.0)	2.0 (-10.0; 18.0)

Max, maximum; Min, minimum; SD, standard deviation; Q1, 1st quartile; Q3, 3rd quartile
Source: VBP15-006 Table 14.3.3.1a; VBP15-004 Table 14.3.8.1, Table 14.3.8.2, Extrapolation Report Outputs Table 10.1, Table 10.2

In line with muscle dystrophy, ALT and AST levels were abnormally high (more than 3 × ULN) at baseline for all subjects rendering assessment of shifts in ALT or AST impossible (Table 31). Changes in ALT and AST in muscle disease are not indicative of changes in liver function.

Two subjects in the 2 mg/kg group had bilirubin levels between 1 × ULN and 1.5 × ULN. In general, there were no clinically relevant changes in median GGT or bilirubin values in either of the dose groups in the target population after 12 weeks of treatment (Table 31).

Table 31. Categorical Analysis of Worst Post-Baseline Value for Liver Function in Studies VBP15-006 and VBP15-004

	Target population VBP15-006		Reference population VBP15-004	
Age group	**2 to <4 years**		**4 to <7 years**	
Vamorolone dose	**2 mg/kg (n=10)**	**6 mg/kg (n=10)**	**2 mg/kg (n=30)**	**6 mg/kg (n=28)**
Variable, n (%) subjects with worst change from baseline				
ALT (>3×ULN)	10 (100.0)	10 (100.0)	25 (83.3)	27 (96.4)
AST (>3×ULN)	10 (100.0)	10 (100.0)	25 (83.3)	27 (96.4)
GGT (>ULN)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bilirubin, total				
>1 to ≤1.5 × ULN	2 (20.0)	0 (0.0)	2 (6.7)	2 (6.7)
>1.5 to ≤2 × ULN	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)
>2 to ≤3 × ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>3 × ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; NA, not available – no post baseline data available; ULN, upper limit of normal range
Source: VBP15-006 Table 14.3.3.3a; Extrapolation Report Outputs Table 4.1

Table 32. Liver Function Clinical Chemistry Median Values at Baseline, Week 12 and Change at Week 12 in Studies VBP15-006 and VBP15-004

	VBP15-006		VBP15-004	
Age group	**2 to <4 years**		**4 to <7 years**	
Vamorolone dose	**2 mg/kg/day (n=10)**	**6 mg/kg/day (n=10)**	**2 mg/kg/day (n=30)**	**6 mg/kg/day (n=28)**
Bilirubin total (µmol/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	3.050 (1.250; 5.00)	2.800 (1.250; 3.800)	3.15 (2.70; 5.30)	3.25 (1.25; 4.80)
Week 12, n	10	10	21	26
Median (Q1; Q3)	3.750 (2.600; 6.00)	2.750 (1.250; 3.100)	3.90 (2.60; 4.60)	3.30 (1.25; 4.40)
Median Change (Q1; Q3)	0.450 (-2.400; 1.850)	0.200 (-1.300; 1.850)	0.00 (-1.45; 0.30)	0.00 (-1.20; 1.35)
Gamma Glutamyl Transferase (U/L)				
Baseline, n	10	10	30	28
Median (Q1; Q3)	5.500 (4.00; 6.00)	5.000 (5.00; 6.00)	6 (5; 7)	6 (5; 9)
Week 12, n	10	10	21	26
Median (Q1; Q3)	4.500 (4.00; 6.00)	5.000 (4.00; 6.00)	6 (5; 7)	8 (6; 11)
Median Change (Q1; Q3)	0.00 (-1.00; 0.00)	-0.500 (-1.00; 0.00)	0 (-1; 1)	1 (0; 2)

Max, maximum; Min, minimum; SD, standard deviation; Q1, 1st quartile; Q3, 3rd quartile
Source: VBP15-006 Table 14.3.3.1a; VBP15-004 Table 14.3.8.1, Table 14.3.8.2, Extrapolation Report Outputs Table 10.1.

Safety Biomarkers (from the paediatric extrapolation report, 2025)

Bone Biomarkers

Comparison VBP15-006 (target population) versus VBP15-004 (reference population) up to Week 12

In the target population, changes in bone biomarkers following 12 weeks of vamorolone treatment varied by dose. For all three biomarkers, the values were within the normal range for most of the subjects.

In the reference population, the values of all three biomarkers were within the normal range for most of the subjects. Osteocalcin levels remained relatively stable in both dose groups. For CTX, both dose groups demonstrated small median increases, and P1NP levels decreased modestly in both dose groups (Table 33).

Table 33. Bone Metabolism Biomarkers, including Osteocalcin, CTX1, and P1NP, at Baseline, Weeks 12 and Change at Week 12 in Studies VBP15-006 and VBP15-004

	Target population VBP15-006		Reference population VBP15-004	
Age group	**2 to <4 years**		**4 to <7 years**	
Vamorolone dose	**2 mg/kg/day (n=10)**	**6 mg/kg/day (n=10)**	**2mg/kg/day (n=30)**	**6 mg/kg/day (n=28)**
Osteocalcin (µg/L)				
Baseline, n	10	10	25	24
Median (Q1; Q3)	63.40 (44.00; 73.00)	46.20 (42.20; 57.40)	59.4 (46.3; 67.9)	58.8 (48.6; 67.5)
Week 12, n	10	9	18	26
Median (Q1; Q3)	53.20 (46.30; 66.10)	56.30 (47.30; 57.60)	58.7 (42.3; 72.7)	55.9 (49.7; 62.4)
Median Change (Q1; Q3)	-4.70 (-10.50; 2.30)	0.20 (-6.20; 12.90)	4.0 (-4.1; 8.5)	0.2 (-9.3; 2.4)
Type I Collagen C-Telopeptides (ng/L)				
Baseline, n	10	10	26	25
Median (Q1; Q3)	1168.00 (860.00; 1378.00)	1029.00 (993.00; 1206.00)	1069	1071
Week 12	10	9	18	26
Median (Q1; Q3)	1183.50 (1039.00; 1300.00)	1254.00 (1122.00; 1436.00)	1145	1105
Median Change (Q1; Q3)	-35.50 (-211.00; 179.00)	228.00 (-150.00; 317.00)	120	49
Procollagen 1 N-Terminal Propeptide (µg/L)				
Baseline, n	10	10	26	25
Median (Q1; Q3)	469.85 (370.40; 627.00)	531.40 (472.90; 562.70)	501.7 (364.7; 653.2)	474.6 (376.3; 590.9)
Week 12, n	10	9	18	26
Median (Q1; Q3)	472.05 (447.60; 511.00)	509.50 (493.90; 570.00)	462.5 (383.0; 559.1)	416.9 (367.1; 501.6)
Median Change (Q1; Q3)	-11.70 (-150.10; 75.30)	30.30 (-89.40; 81.80)	-18.7 (-84.3; 81.5)	-55.7 (-161.0; 8.0)

CTX1, C-terminal peptide fragment of collagen 1; Max, maximum; Min, minimum; P1NP, Procollagen 1 N-terminal propeptide; SD, standard deviation; Q1, 1st quartile; Q3, 3rd quartile. **Source: VBP15-006 Table 14.3.7.1a, VBP15-004 Table 14.2.5.1, Extrapolation Report Outputs Table 15**

Insulin Resistance

Comparison VBP15-006 (target population) versus VBP15-004 (reference population) up to Week 12

In the target population, the fasting glucose values remained within the normal range at baseline and Week 12, with both doses. HbA1c remained stable in both dose groups.

In the reference population, no relevant changes in fasting glucose were observed at either dose. HbA1c data were not available for this population (Table 34).

Table 34. Insulin Resistance Biomarkers: Fasting Glucose (mmol/L), Insulin (pmol/L) and Hemoglobin A1c (%) across studies VBP15-006 and VBP15-004 (amended from Annex to CSR for PIP VBP15-006)

		Study VBP15-006						Study VBP15-003		Study VBP15-004	
		Age 2 to < 4 Years		Age 7 to <18 Years				Age 4 to <7 Years		Age 4 to <7 Years	
		Steroid naive		Corticosteroid Treated		Corticosteroid Untreated		Steroid naive		Steroid naive	
		2.0 mg/kg (N=10)	6.0 mg/kg (N=10)	2.0 mg/kg (N=6)	6.0 mg/kg (N=16)	2.0 mg/kg (N=6)	6.0 mg/kg (N=6)	2.0 mg/kg (N=12)	6.0 mg/kg (N=12)	2.0 mg/kg (N=30)	6.0 mg/kg (N=28)
Glucose											
Baseline	n	10	10	6	16	6	6	12	10	26	27
	Mean	4.77	4.72	4.73	4.79	4.91	5.41	4.96	5.12	4.61	4.63
	SD	0.390	0.538	0.308	0.335	0.215	0.536	0.439	0.455	0.403	0.364
	Min	4.27	3.55	4.44	4.33	4.66	5.00	4.50	4.11	3.89	3.72
	Q1	4.61	4.44	4.44	4.61	4.72	5.00	4.58	4.88	4.39	4.39
	Median	4.72	4.86	4.69	4.77	4.89	5.14	4.83	5.27	4.61	4.72
	Q3	4.77	5.05	4.83	4.91	5.16	5.94	5.38	5.38	4.83	4.88
	Max	5.61	5.33	5.27	5.72	5.16	6.22	5.61	5.77	5.44	5.38
Week 12	n	10	10	6	16	6	6	12	11	19	25
	Mean	4.61	4.48	4.92	4.53	4.85	5.07	4.68	4.80	4.54	4.66
	SD	0.271	0.335	0.523	0.523	0.244	0.701	0.451	0.309	0.387	0.366
	Min	4.33	3.83	4.55	2.94	4.50	4.50	3.94	4.50	3.66	3.94
	Q1	4.44	4.33	4.61	4.33	4.72	4.55	4.30	4.61	4.39	4.44
	Median	4.53	4.47	4.72	4.58	4.86	4.89	4.69	4.72	4.55	4.55
	Q3	4.77	4.72	5.00	4.88	4.94	5.22	4.94	5.11	4.88	5.05
	Max	5.22	5.00	5.94	5.22	5.22	6.38	5.61	5.49	5.16	5.27
Change from Baseline to Week 12	n	10	10	6	16	6	6	12	10	17	24
	Mean	-0.16	-0.24	0.20	-0.25	-0.06	-0.34	-0.28	-0.29	-0.04	0.01
	SD	0.291	0.631	0.573	0.391	0.352	0.382	0.500	0.511	0.374	0.303
	Min	-0.44	-1.17	-0.50	-1.39	-0.44	-0.89	-1.44	-1.00	-0.56	-0.56
	Q1	-0.39	-0.61	-0.11	-0.42	-0.22	-0.55	-0.47	-0.72	-0.38	-0.25
	Median	-0.17	-0.39	0.06	-0.26	-0.20	-0.37	-0.22	-0.33	0.00	0.03
	Q3	-0.05	-0.05	0.56	0.03	0.11	0.00	0.06	0.11	0.28	0.22
	Max	0.50	1.00	1.11	0.28	0.56	0.16	0.39	0.50	0.44	0.72
Insulin											
Baseline	n		9		9	3	6	12	12	27	26
	Mean		18.00		159.44	31.67	45.33	23.61	27.49	28.30	27.19
	SD		7.921		134.355	35.133	18.206	10.750	14.078	18.611	15.041
	Min		2.00		17.00	1.00	28.00	7.64	11.81	1.00	8.00
	Q1		14.00		70.00	1.00	29.00	13.89	19.10	15.00	17.00
	Median		19.00		113.00	24.00	43.00	23.26	25.35	24.00	23.00
	Q3		23.00		178.00	70.00	56.00	33.33	30.90	35.00	33.00
	Max		30.00		415.00	70.00	73.00	38.89	67.36	81.00	74.00
Week 12	n		10		13	5	6	12	11	18	24
	Mean		22.60		129.46	61.60	91.67	27.03	48.42	45.44	59.71
	SD		19.248		108.918	47.711	49.046	15.201	24.483	65.311	40.239
	Min		7.00		28.00	29.00	52.00	5.56	20.83	5.00	14.00
	Q1		10.00		60.00	34.00	61.00	12.50	31.25	17.00	31.00

	Median		17.50		93.00	34.00	82.00	26.39	39.58	29.00	49.00
	Q3		27.00		116.00	69.00	85.00	42.01	63.19	40.00	70.50
	Max		71.00		390.00	142.00	188.00	47.22	104.86	290.00	167.00
Change from Baseline to Week 12	n		9		9	3	6	12	11	17	23
	Mean		6.33		-26.33	0.67	46.33	3.41	20.64	16.00	35.43
	SD		20.518		51.149	33.005	51.926	18.001	15.815	64.775	35.500
	Min		-18.00		-113.00	-36.00	-21.00	-22.92	-0.69	-46.00	-5.00
	Q1		-9.00		-46.00	-36.00	8.00	-11.81	5.56	-6.00	10.00
	Median		4.00		-10.00	10.00	52.00	3.47	22.22	0.00	29.00
	Q3		14.00		0.00	28.00	55.00	15.28	37.50	16.00	44.00
	Max		50.00		45.00	28.00	132.00	34.72	42.36	252.00	125.00
HbA1c											
Baseline	n	9	10	6	14	5	6	12	12	30	28
	Mean	5.21	5.17	5.32	5.18	5.38	5.52	5.19	5.23	5.25	5.30
	SD	0.376	0.231	0.366	0.364	0.259	0.449	0.124	0.231	0.189	0.247
	Min	4.40	4.80	4.60	4.50	5.10	4.90	5.00	5.00	4.90	4.50
	Q1	5.10	5.00	5.30	5.00	5.10	5.40	5.10	5.05	5.20	5.20
	Median	5.20	5.15	5.45	5.10	5.50	5.50	5.20	5.20	5.25	5.30
	Q3	5.50	5.40	5.50	5.30	5.60	5.50	5.30	5.35	5.40	5.50
	Max	5.70	5.50	5.60	5.90	5.60	6.30	5.40	5.80	5.60	5.70
Week 12	n	9	9	5	13	5	6			2	
	Mean	5.26	5.26	5.22	5.06	5.42	5.50			5.25	
	SD	0.416	0.213	0.363	0.345	0.311	0.400			0.071	
	Min	4.40	4.90	4.60	4.60	5.10	5.00			5.20	
	Q1	5.10	5.20	5.20	4.90	5.20	5.30			5.20	
	Median	5.30	5.30	5.40	5.00	5.40	5.45			5.25	
	Q3	5.50	5.30	5.40	5.10	5.50	5.60			5.30	
	Max	5.80	5.70	5.50	5.90	5.90	6.20			5.30	
Change from Baseline to Week 12	n	9	9	5	11	5	6			2	
	Mean	0.08	0.04	-0.04	-0.14	0.00	-0.02			-0.15	
	SD	0.264	0.151	0.114	0.121	0.158	0.098			0.071	
	Min	-0.30	-0.10	-0.20	-0.30	-0.20	-0.10			-0.20	
	Q1	-0.10	-0.10	-0.10	-0.20	-0.10	-0.10			-0.20	
	Median	0.10	0.00	0.00	-0.10	0.00	-0.05			-0.15	
	Q3	0.20	0.20	0.00	-0.10	0.10	0.10			-0.10	
	Max	0.50	0.30	0.10	0.10	0.20	0.10			-0.10	

Vital Signs

Vital signs, ECGs, and eye examination were only performed in Study VBP15-006.

Study VBP15-006

At baseline, diastolic blood pressure (DBP) Z-score was 1.35 (range 0.58 to 2.33) and systolic blood pressure (SBP) Z-score was 1.32 (range -0.67 to 2.33), indicating an increased blood pressure at baseline in this population.

Median change in DBP from baseline to Week 12 was -2.00 mmHg for 2 mg/kg and 3.50 mmHg for the 6 mg/kg vamorolone group, and for SBP it was -2.00 mmHg and 0.00 mmHg, respectively. Median DBP and SBP Z-score change from baseline was between -0.30 and 0.27, thus indicating no clinically relevant change in blood pressure in either group.

A post-hoc analysis comparing the pooled blood pressure measurements taken before vamorolone start with those taken after vamorolone start shows the high variability in readings, without clear trends in both vamorolone groups (Table 35).

Table 35. Blood Pressure Results at Baseline and Week 12 for Age 2 to <4 Years Steroid Naïve Subjects

	2 mg/kg Vamorolone (N = 10)	**6 mg/kg Vamorolone (N = 10)**
Diastolic Blood Pressure (mmHg)		
Baseline		
N	10	10
Mean (SD)	59.90 (4.358)	60.40 (6.004)
Median (Q1 ; Q3)	58.50 (56.00 ; 61.00)	57.50 (56.00 ; 64.00)
Min, Max	56.00, 68.00	54.00, 71.00
Week 12		
N	9	10
Mean (SD)	59.67 (6.042)	62.40 (7.397)
Median (Q1 ; Q3)	58.00 (56.00 ; 64.00)	61.00 (59.00 ; 66.00)
Min, Max	51.00, 71.00	52.00, 78.00
Change from Baseline to Week 12		
N	9	10
Mean (SD)	-0.44 (8.248)	2.00 (8.179)
Median (Q1 ; Q3)	-2.00 (-6.00 ; 6.00)	3.50 (-6.00 ; 9.00)
Min, Max	-12.00, 13.00	-12.00, 11.00
Systolic Blood Pressure (mmHg)		
Baseline		
N	10	10
Mean (SD)	104.50 (12.599)	104.10 (11.030)
Median (Q1 ; Q3)	105.50 (94.00 ; 116.00)	100.50 (95.00 ; 115.00)
Min, Max	82.00, 122.00	89.00, 118.00
Week 12		
N	9	10
Mean (SD)	103.33 (7.176)	101.90 (9.036)
Median (Q1 ; Q3)	103.00 (101.00 ; 106.00)	101.50 (97.00 ; 103.00)
Min, Max	94.00, 119.00	87.00, 121.00
Change from Baseline to Week 12		
N	9	10
Mean (SD)	-2.33 (12.923)	-2.20 (11.233)
Median (Q1 ; Q3)	-2.00 (-12.00 ; 10.00)	0.00 (-13.00 ; 6.00)
Min, Max	-21.00, 12.00	-20.00, 12.00

Max = maximum; Min = minimum; Q = quartile; SD = standard deviation
Source: VBP15-006 CSR Table 50

Comparison VBP15-006 (target population) versus VBP15-004 (reference population) up to Week 12

Target population - see above.

For the reference population, the median change in DBP between baseline and Week 12 was 2.00 mmHg, and in SBP 4.00 mmHg for the 2 mg/kg dose. The changes in Z-score were 0.14 for DBP and 0.33 for SBP, indicating no clinically relevant change in blood pressure.

For the 6 mg/kg dose, the median change in DBP between baseline and Week 12 was -2.00 mmHg, and in SBP 7.00 mmHg. The changes in Z-score were -0.08 for DBP and 0.52 for SDP, indicating no clinically relevant change in blood pressure.

Electrocardiograms

Changes in ECG parameters from VBP15-006 baseline to Week 12 were small and not clinically relevant for either dose group. No subject had a QTcF value > 450 msec at baseline or at Week 12. One subject in the 2 mg/kg dose group had a change in QTcF of 30 to <60 msec (44.79 msec), from a baseline value of 320.40 msec to 365.20 msec at Week 12.

Eye examination

Study VBP15-006

Intraocular pressure (IOP) measurements were only available for 24 of the 40 eyes in the total population at baseline, and for 16 out of 40 eyes (20 subjects) at Week 12. All eyes assessed at Week 12 had intraocular pressure ≤ 21 mmHg. The median change in IOP between baseline and Week 12 was 0 mmHg for the 2 mg/kg and 1.00 mmHg for the 6 mg/kg dose, suggesting no clinically relevant change in IOP.

Comparison VBP15-006 (target population) versus VBP15-004 (reference population) up to Week 12

Height, Weight, and Body Mass Index

Height and weight were assessed both in Study VBP15-006 and in the EAP. Z-scores and percentiles for height, weight and BMI were calculated using the Center for Disease Control standard growth charts for age for normal boys, due to a lack of separate standard growth charts for DMD boys.

Study VBP15-006

At baseline, subjects in the 2 mg/kg vamorolone group were shorter than in the 6 mg/kg vamorolone group. For boys receiving 2 mg/kg vamorolone, the median **height** Z-score at baseline was -0.61 and -0.61 at Week 12, with a median change of -0.04 from baseline to Week 12. For boys receiving 6 mg/kg, the median height Z-scores was -0.45 at baseline and -0.24 at Week 12, with a median change of 0.09 from baseline to Week 12. The change from baseline to Week 12 in height Z-scores at both dose levels was minimal.

Median **weight** Z-score was similar across the vamorolone groups at baseline: For boys receiving 2 mg/kg vamorolone, the median weight Z-score was 0.16 at baseline and -0.02 at Week 12, with a median change of -0.01 from baseline to Week 12. For boys receiving 6mg/kg, the median weight Z-scores was 0.13 at baseline and -0.22 at Week 12, with a median change of 0.13 from baseline to Week 12. The change from baseline to Week 12 in weight Z-scores at both dose levels was minimal.

Median **BMI** Z-score at baseline was higher for the 2 mg/kg than the 6 mg/kg vamorolone group: 0.54 and 0.24, respectively (median percentiles were 70.19 and 59.15, respectively). There was no increase in BMI Z-score from baseline to Week 12.

For height, weight and body mass index, the changes observed from Baseline to Week 12 were small and of unclear clinical relevance.

Expanded Access Programme

The average duration of exposure to vamorolone for all doses for the 19 subjects from enrolment into EAP to the DCO (01 June 2025) was 2.2 years, and the median exposure was 2.4 years (range: 1 year and 4 months to 2 years and 11 months).

The median **height** Z-score at baseline was -0.58 and at the last visit before the DCO was -0.67 representing a change from baseline 0.10, with an interquartile range from -0.38 to 0.24, indicating this change as clinically negligible and therefore not suggestive of suppression of growth, in keeping with the known profile of vamorolone across studies.

The median **weight** Z-score at baseline was -0.37 and at the last visit before the DCO was 0.20. The weight Z-score at baseline and at last visit before DCO was within +1 standard deviation and -1 standard deviation, therefore can be considered normal for age. The change from baseline in the median weight Z-score at the last measurement was 0.44. Considering that 0.5 denotes a clinically relevant change, whilst the median change for weight was slightly under this threshold at 0.44, the upper bound of the interquartile change (0.68) indicates clinically relevant weight gain in a proportion of subjects over an exposure to vamorolone for an average of 2.2 years.

The median **BMI** Z-score at baseline was 0.30 and at the last visit before the DCO was 1.01. The change from baseline in the median BMI Z-score at the last measurement was 0.60, showing that with an exposure to vamorolone for an average of 2.2 years, the increase in BMI was greater than 0.5, which is clinically significant (Table 36).

Table 36. Summary of Anthropology Parameters at Baseline and Last Measurement - EAP

Parameter	**Visit**	**Statistics**	**Total (N = 19)**
Height Z-score	Baseline Measurement	n	19
		Mean (SD)	-0.59 (1.134)
		Median (Q1 ; Q3)	-0.58 (-1.14 ; 0.10)
		Min, Max	-3.53, 1.84
	Last Measurement	n	17
		Mean (SD)	-0.75 (1.135)
		Median (Q1 ; Q3)	-0.67 (-1.04 ; 0.12)
		Min, Max	-3.30, 1.27
	Last Measurement - CBL	n	17
		Mean (SD)	-0.04 (0.539)
		Median (Q1 ; Q3)	0.10 (-0.38 ; 0.24)
		Min, Max	-1.49, 0.89
Weight Z-score	Baseline Measurement	n	19
		Mean (SD)	-0.12 (1.462)
		Median (Q1 ; Q3)	-0.37 (-0.67 ; 1.32)
		Min, Max	-4.41, 1.68
	Last Measurement	n	19
		Mean (SD)	0.27 (1.507)
		Median (Q1 ; Q3)	0.20 (-0.22 ; 1.11)
		Min, Max	-3.96, 2.87
	Last Measurement - CBL	n	19
		Mean (SD)	0.38 (0.621)
		Median (Q1 ; Q3)	0.44 (0.02 ; 0.68)
		Min, Max	-0.79, 1.96

Parameter	Visit	Statistics	Total (N = 19)
Body Mass Index Z-score	Baseline Measurement	n	19
		Mean (SD)	0.39 (1.460)
		Median (Q1 ; Q3)	0.30 (-0.80 ; 1.25)
		Min, Max	-2.19, 2.96
	Last Measurement	n	17
		Mean (SD)	1.03 (1.608)
		Median (Q1 ; Q3)	1.01 (0.29 ; 1.48)
		Min, Max	-2.00, 4.67
	Last Measurement - CBL	n	17
		Mean (SD)	0.61 (0.820)
		Median (Q1 ; Q3)	0.60 (0.07 ; 0.89)
		Min, Max	-0.65, 2.50

Source: modified from Extrapolation Report Addendum Table 8.1

Comparison VBP15-006 (target population) versus VBP15-004 (reference population) up to Week 12

Target population - see above.

In the reference population, for boys receiving 2 mg/kg vamorolone, the median **height** Z-score was -0.74 at baseline and -0.66 at Week 12, with a median change of -0.01 from baseline to Week 12. For boys receiving 6 mg/kg, the median height Z-scores was -1.04 at baseline and -0.80 at Week 12, with a median change of 0.11 from baseline to Week 12. The change from baseline to Week 12 in height Z-scores at both dose levels was minimal (Table 37).

For boys receiving 2 mg/kg, the median **weight** Z-score was -0.27 at baseline and -0.05 at Week 12, with a median change of 0.17 from baseline to Week 12. For boys receiving 6 mg/kg, the median weight Z-score was -0.01 at baseline and 0.03 at Week 12, with a median change of 0.19 from baseline to Week 12. The change from baseline to Week 12 in weight Z-scores at both dose levels was minimal (Table 38).

Table 37. Height Z-score (amended by the assessor from Table 20 of the extrapolation report) for Subjects at Baseline and Change at Week 12 in Studies VBP15-006 and VBP15-004

	Target population VBP15-006		Reference population VBP15-004	
Age Group	**2 to <4 years**		**4 to <7 years**	
Vamorolone dose	**2 mg/kg/day (n=10)**	**6 mg/kg/day (n=10)**	**2 mg/kg/day (n=30)**	**6 mg/kg/day (n=28)**
Height Z-score				
Baseline				
n	10	10	30	28
Mean (SD)	-0.68 (0.553)	-0.63 (1.655)	-0.77 (1.10)	-1.04 (1.05)
Median (Q1; Q3)	-0.61 (-1.11; -0.31)	-0.45 (-1.22; 0.54)	-0.74 (-1.50; -0.20)	-1.04 (-1.81; -0.48)
Min, Max	-1.79, 0.13	-3.99, 1.82	-2.4, 1.4	-3.5,1.0
Week 12				
n	10	10	26	25
Mean (SD)	-0.64 (0.564)	-0.49 (1.509)	-0.907 (1.1108)	-0.681 (1.1453)
Median (Q1; Q3)	-0.61 (-1.14; -0.10)	-0.24 (-1.01; 0.41)	-0.66 (-1.82; -0.22)	-0.80 (-1.41; -0.19)
Min, Max	-1.61, 0.10	-3.53, 1.84	-2.78, 1.15	-2.77, 2.01
Change from Baseline to Week 12				
n	10	10	26	25
Mean (SD)	0.04 (0.361)	0.14 (0.201)	-0.114 (0.5444)	0.284 (0.6976)
Median (Q1; Q3)	-0.04 (-0.15; 0.17)	0.09 (-0.02; 0.28)	-0.01 (-0.09; 0.11)	0.11 (-0.02; 0.27)
Min, Max	-0.58, 0.70	-0.13, 0.46	-2.65, 0.20	-0.37, 2.74

CSR, clinical study report; Max, maximum; Min, minimum; Q, quartile; SD, standard deviation
Source: VBP15-006 CSR Table 41, Table 14.3.4.1.a, VBP15-004 14.3.6.1, 14.3.6.2, Extrapolation Report Outputs Table 11.3, Table 11.4

Table 38. Weight Z-score (amended by the assessor from Table 21 of the extrapolation report) for Subjects at Baseline and Change at Week 12 in Studies VBP15-006 and VBP15-004

	Target population VBP15-006		Reference population VBP15-004	
Age Group	**2 to <4 years**		**4 to <7 years**	
Dose	**2 mg/kg/day (n=10)**	**6 mg/kg/day (n=10)**	**2 mg/kg/day (n=30)**	**6 mg/kg/day (n=28)**
Weight Z-score				
Baseline				
n	10	10	30	28
Mean (SD)	-0.09 (0.924)	-0.16 (1.703)	-0.29 (0.98)	-0.32 (1.02)
Median (Q1; Q3)	0.16 (-0.62; 0.48)	0.13 (-0.15; 1.03)	-0.27 (-0.97; 0.36)	-0.01 (-0.71; 0.35)
Min, Max	-1.90, 1.24	-4.52, 1.17	-2.47, 1.57	-3.07, 1.03
Week 12				
n	10	10	26	25
Mean (SD)	-0.10 (1.017)	-0.11 (1.787)	-0.19 (1.01)	-0.02 (1.02)
Median (Q1; Q3)	-0.02 (-0.64; 0.51)	-0.22 (-0.67; 1.32)	-0.05 (-0.96; 0.52)	0.03 (-0.47; 0.77)
Min, Max	-2.03, 1.68	-4.41, 1.63	-2.46, 1.72	-2.31, 1.81
Change from baseline to Week 12				
n	10	10	26	25
Mean (SD)	-0.01 (0.406)	0.05 (0.430)	0.18 (0.29)	0.27 (0.36)
Median (Q1; Q3)	-0.01. (-0.13; 0.24)	0.13 (-0.33; 0.46)	0.17 (0.01; 0.37)	0.19 (-0.01; 0.53)
Min, Max	-0.96, 0.49	-0.67, 0.53	-0.46, 0.85	-0.17, 1.00

CSR, clinical study report; Max, maximum; Min, minimum; Q, quartile; SD, standard deviation

Comparison VBP15-EAP (target population) versus VBP15-004 (reference population) Week 12 - 48

Target population - see above (EAP).

In the reference population, for 2 mg/kg, the change from baseline in median height Z-score was 0.15, indicating that growth was normal during 48 weeks of treatment with vamorolone.

For 6 mg/kg, the median height Z-score at baseline was 1SD below the mean, indicating that DMD patients are of shorter stature compared to healthy peers at baseline. The change from baseline in median height Z-score at the last measurement was 0.17, indicating that height was not affected negatively with an exposure to vamorolone for 48 weeks, unlike with other steroids (Table 39).

The median weight Z-score for vamorolone 2 mg/kg at baseline and at the last visit was within +1SD and -1SD and can therefore be considered as normal for age. The change from baseline in median weight Z-score at the last measurement was 0.46, indicating that with an exposure to vamorolone for 48 weeks, the weight gain was < 0.5, which is below the level of clinical significance.

The median weight Z-score on vamorolone 6 mg/kg at baseline was -0.01, and 0.44 at the last visit (within +1SD and -1SD), and is therefore considered normal for this age group. The change from baseline in the median weight Z-score at the last measurement was 0.68, indicating a tendency towards weight gain, which is a known AE of vamorolone and this class of drugs (Table 40).

Table 39. Height Z-score (amended by the assessor from Table 39 of the extrapolation report) for Subjects in Target (Study VBP15-EAP) and Reference Population (Study VBP15-004)

	Target population VBP15-EAP	**Reference population VBP15-004**	
Time	**Between first and last measurement**	**Between baseline and Week 48**	
Age group	**2 to < 4 years**	**4 to < 7 years**	
Vamorolone dose	**Total, 2–6 mg/kg/day (n=19)**	**2 mg/kg/day (n=29)**	**6 mg/kg/day (n=28)**
Height Z-score			
Start of EAP (VBP15-EAP)/Baseline (VBP15-004)			
n	19	28	28
Mean (SD)	-0.59 (1.134)	-0.695 (1.0981)	-1.043 (1.0496)
Median (Q1; Q3)	-0.58 (-1.14; 0.10)	-0.66	-1.04
Min, Max	-3.53, 1.84	-2.41, 1.42	-3.47, 1.02
Week 48 (Month 12) (equal duration comparison)			
n	13	27	26
Mean (SD)	-0.96 (1.064)	-0.560 (1.1163)	-0.900 (0.8856)
Median (Q1; Q3)	-0.67 (-1.45; -0.17)	-0.36	-0.79
Min, Max	-3.30, 0.14	-2.48, 1.33	-2.54, 1.31
Change at Week 48 (Month 12)			
n	13	27	26
Mean (SD)	-0.15 (0.565)	0.130 (0.2768)	0.286 (0.3551)
Median (Q1; Q3)	-0.14 (-0.32; 0.12)	0.15	0.17
Min, Max	-1.49, 0.73	-0.53, 0.59	-0.38, 1.37
Last measurement (VBP15-EAP)/Week 48 (VBP15-004)			
n	17	27	26
Mean (SD)	-0.75 (1.135)	-0.560 (1.1163)	-0.900 (0.8856)
Median (Q1; Q3)	-0.67 (-1.04; 0.12)	-0.36	-0.79
Min, Max	-3.30, 1.27	-2.48, 1.33	-2.54, 1.31
Change from baseline to last measurement (VBP15-EAP)/Week 48 (VBP15-004)			
n	17	27	26
Mean (SD)	-0.04 (0.539)	0.130 (0.2768)	0.286 (0.3551)
Median (Q1; Q3)	0.10 (-0.38; 0.24)	0.15	0.17
Min, Max	-1.49, 0.89	-0.53, 0.59	-0.38, 1.37

[1]Height for target population is presented between the time of entry into the EAP and the last measurement, and for the reference population (VBP15-004) from the baseline until the end of the study (Week 48).

Max, maximum; Min, minimum; Q, quartile; SD, standard deviation

Source: Extrapolation Report Outputs Table 8.1; VBP15-004 Table 14.3.7.1, Table 14.3.7.2.

Table 40. Weight Z-score (amended by the assessor from Table 40 of the extrapolation report) for Subjects in Target (Study VBP15-EAP) and Reference Population (Study VBP15-004)

	Target population VBP15-EAP	**Reference population VBP15-004**	
Time	**Between first and last visit**	**Between baseline and Week 48**	
Age group	**2 to < 4 years**	**4 to < 7 years**	
Vamorolone dose	**Total, 2–6 mg/kg/day (n=19)**	**2 mg/kg/day (n=29)**	**6 mg/kg/day (n=28)**
Weight Z-score			
Start of EAP (VBP15-EAP)/Baseline (VBP15-004)			
n	19	28	28
Mean (SD)	-0.12 (1.462)	-0.258 (0.9922)	-0.316 (1.0165)
Median (Q1; Q3)	-0.37 (-0.67; 1.32)	-0.27	-0.01
Min, Max	-4.41, 1.68	-2.47, 1.57	-3.07, 1.03
Week 48 (Month 12) (equal duration comparison)			
n	19	27	26
Mean (SD)	0.05 (1.492)	0.240 (1.0702)	0.468 (1.2068)
Median (Q1; Q3)	-0.07 (-0.87; 1.06)	0.36	0.44
Min, Max	-3.96, 2.36	-1.92, 2.13	-2.28, 2.56
Change at Week 48 (Month 12)			
n	19	27	26
Mean (SD)	0.17 (0.351)	0.517 (0.4500)	0.835 (0.7113)
Median (Q1; Q3)	0.15 (-0.10; 0.44)	0.46	0.68
Min, Max	-0.41, 0.77	-0.29, 1.36	-0.12, 2.49
Last measurement (VBP15-EAP)/Week 48 (VBP15-004)			
n	19	27	26
Mean (SD)	0.27 (1.507)	0.240 (1.0702)	0.468 (1.2068)
Median (Q1; Q3)	0.20 (-0.22; 1.11)	0.36	0.44
Min, Max	-3.96, 2.87	-1.92, 2.13	-2.28, 2.56
Change at last measurement (VBP15-EAP)/Week 48 (VBP15-004)			
n	19	27	26
Mean (SD)	0.38 (0.621)	0.517 (0.4500)	0.835 (0.7113)
Median (Q1; Q3)	0.44 (0.02; 0.68)	0.46	0.68
Min, Max	-0.79, 1.96	-0.29, 1.36	-0.12, 2.49

[1]Weight for target population is presented between the time of entry into the EAP and the last measurement, and for the reference population (VBP15-004) from baseline until the end of the study (Week 48).

EAP, expanded access protocol; Max, maximum; Min, minimum; Q, quartile; SD, standard deviation

Source: Extrapolation Report Outputs Table 8.1; VBP15-004 Table 14.3.7.1, Table 14.3.7.2

Safety in special populations

Intrinsic factors

Intrinsic factors were not evaluated in subjects aged 2 to <4 years in Study VBP15-006. However, a side-by-side comparison of the safety profile of vamorolone was performed **by age** (subjects aged 2 to <4 years in Study VBP15-006 and subjects aged 4 to <7 years in Study VBP15-004) as delineated in the Extrapolation Report. This assessment report considers the results/ comparisons were available and as appropriate in the above sections. The safety profile of vamorolone was overall similar in these two populations, therefore, age does not appear to have a clinically significant impact on vamorolone tolerability.

Extrinsic factors

Not applicable.

Safety related to drug-drug interactions and other interactions

Not applicable: drug interactions have not been evaluated in subjects aged 2 to <4 years included in Study VBP15-006.

Post marketing experience

Not applicable: vamorolone is currently not approved in subjects aged 2 to <4 years.

4.1. Discussion on clinical safety

The safety profile of vamorolone has been characterised in a total of 20 paediatric patients aged 2 to < 4 years based on the reporting of TEAEs, drug-related TEAEs, severe TEAEs, SAEs, TEAEs leading to permanent study treatment discontinuation, and TEAEs resulting in temporary dose interruption or dose reduction, and TEAEs leading to death during study VBP15-006, a Phase 2, open-label, multiple dose study to evaluate safety, tolerability, PK, PD, clinical efficacy, behaviour and neuropsychology, and physical functioning of vamorolone at daily doses of 2 and 6 mg/kg over 12 weeks. Of the 20 patients enrolled, 10 received vamorolone 2 mg/kg and 10 received 6 mg/kg, and they had to be steroid-naïve at treatment start. Study VBP15-006 also included a 7 to <18 years age group cohort (including an additional 12 to <18 years age subgroup), which needed to be either untreated with steroids for at least 3 months prior to enrolment, or treated with standard of care corticosteroids at a stable dose for at least 3 months prior to enrolment and expected to continue the same stable dose through the date of the Baseline Day -1 Visit. However, the letter group of patients 7 to <18 years of age do not fall under the scope of this extension of indication and is hence not discussed.

19 of 20 patients, who completed VBP15-006 without having had a severe or serious TEAE could receive vamorolone in an Expanded Access programme (VBP15-EAP) at doses 2 mg/kg, 4 mg/kg, or 6 mg/kg. Importantly, the EAP protocol does not stipulate specific safety or laboratory assessments but specifies visits according to standard of care for DMD patients with steroid treatment, which hampers interpretability of the collected safety data. The DCO of the ongoing EAP is 1 June 2025. Therefore, safety data for the highest dose of 6 mg/kg are available up to 2.4 years of exposure in the EAP.

A separate Paediatric Extrapolation Report has been created by the MAH (dated 15 August 2025) as part of this extension of indication to compare the short- and long-term safety outcomes in patients 2 to <4 years of age (target population) with those of patients 4 to <7 years of age (reference population). Comparison of short-term safety is based on the 12-weeks data from study VBP15-006

and the first 12 weeks of treatment in study VBP15-004, while comparison of long-term safety in patients 2 to <4 years of age is based on the safety data of these patients collected in the EAP (starting after 12 weeks of treatment in study VBP15-006) and the group of patients 4 to <7 years of age treated in study VBP15-004 between Week 12 and Week 48. The comparison of short-term safety is considered acceptable based on a similar methodology to measure safety outcomes in the two studies -006 and -004. However, the detection of any long-term consequences of vamorolone treatment in the most vulnerable paediatric patients 2 to <4 years of age is limited given that the lack of pre-specified safety assessments in the EAP protocol. Thus, adverse effects and laboratory measures are likely underestimating the safety issues with vamorolone treatment in the very young paediatric population.

Demographics and baseline characteristics of study population

The paediatric population included in the 2 to <4 years age cohort in study VBP15-006 was ambulatory with a median age of 3.3 and 3.5 years in the 2 mg/kg and 6 mg/kg dose group, respectively. However, the youngest patients in the 2 to <4 years cohort treated with 2 mg/kg and 6 mg/kg vamorolone were close to 3 years of age (2.8 years and 2.9 years, respectively), which needs to be considered in the context of the overall efficacy and safety data for the claimed indication. From a clinical safety point of view, although there is no biological reason to assume a different sensitivity towards adverse effects of vamorolone in patients between 2 and 3 years of age and patients between 3 and 4 years of age, this cannot be confirmed based on the available data.

The majority (65%) of the 20 patients included in the 2 to <4 years cohort were White, and 30% were Asian.

Moreover, the long-term safety in the group of paediatric patients 2 to < 4 years of age entering the EAP relates to a median age of 3.6 years at baseline (range 3.2 years to 4.4 years).

Based on the controlled data in the reference population 4 to < 7 years of age, the median age was 5.2 and 5.5 years in the 2 mg/kg and 6 mg/kg dose group, respectively. The majority of patients in study VBP15-004 were White (83%) and 12% were Asian.

Extent of exposure

The median duration of exposure in study VBP15-006 in patients aged 2 to <4 years was comparable for 2 mg/kg and 6 mg/kg, i.e. it was 12.3 weeks and 11.9 weeks, respectively, and it compared similar to the reference population in study VBP15-004 (for the first 12 weeks of treatment) for the two dose groups 2 mg/kg and 6 mg/kg (11.9 weeks and 12.1 weeks, respectively).

In the EAP, only a single patient aged 2 to <4 years received the 2 mg/kg dose. The majority of patients received vamorolone at a dose of 6 mg/kg (15 of 19 patients), followed by 4 mg/kg (9 of 19 patients). The median duration of exposure was 1.9 years and 1.7 years in the 6 mg/kg and 4 mg/kg group, respectively. The majority of patients in the 6 mg/kg group (66.7%) were treated for at least 18 months while 4 of 15 patients received vamorolone for at least 2 years.

Exposure to vamorolone was longer in the target population in the EAP as compared to the reference population (in study VBP15-004) for the highest dose 6 mg/kg with a median of 1.9 years (vs. 0.7 years). No patient received 4 mg/kg in the reference population.

TEAEs, SAEs, and TEAEs leading to permanent treatment discontinuation

During the 12-week treatment period in study VBP15-006, there were no reports of severe TEAEs, SAEs, and TEAEs leading to withdrawal from study, temporary dose reduction or death in paediatric patients aged 2 to <4 years of age. The vast majority of events in both dose groups were mild in

severity. A dose-related increase in TEAEs and drug-related TEAEs was noted in the 2 mg/kg and 6 mg/kg dose group.

TEAEs rated as related to vamorolone in the 6 mg/kg dose group (13 of 39 events overall) were mainly those in line with the known safety profile of vamorolone, i.e. GI disorders, psychiatric disorders, and endocrine disorders. In contrast, only a single event in the 2 mg/kg dose group was rated as related to vamorolone (urticaria).

As expected for this age group of patients, the majority of TEAEs in the 2 mg/kg group were reported from the infections and infestations SOC (mainly nasopharyngitis). In the 6 mg/kg dose group TEAEs were most frequently reported from the GI disorders SOC (in 8 of 10 patients; mainly diarrhoea; three events were rated as related to vamorolone) and the endocrine disorders SOC (in 5 of 10 patients; PT: adrenal suppression, all of them rated as related to vamorolone). Of note, no patient reported diarrhoea and adrenal suppression in the 2 mg/kg group. Psychiatric disorders were solely reported in the 6 mg/kg group (4 events in 2 patients; including aggression, compulsive lip biting, irritability and mood swings; three of them rated as related to vamorolone).

When comparing the overall TEAEs in study VBP15-006 and VBP15-004 based on the 12 week exposure to vamorolone, similar incidences of TEAEs and treatment-related TEAEs were noted in the 2 mg/kg dose groups; however, more patients in the 2 to <4 years of age cohort reported TEAEs and treatment-related TEAEs in the 6 mg/kg dose group as compared to patients aged 4 to <7 years (90% vs. 75% and 70% vs. 43%).

There are some notable findings when common TEAEs up to Week 12 are compared between the target and the reference population, especially in the 6 mg/kg dose group in the target population:

TEAEs from the *Endocrine disorders SOC* were more frequently reported in the 2 to <4-years-old as compared to the 4 to <7-years-old (50% vs. 14.3%), while the only PT reported in the target population was Adrenal suppression. In contrast, adrenal suppression was not reported in the reference population. Upon request, the MAH clarified that this imbalance was caused by rating adrenal suppression in study VBP15-006 as TEAE based on decreased morning cortisol levels, while for patients in study VBP15-004 no TEAE was reported based on laboratory values given that investigators were blinded to laboratory values. Overall, the reduction in morning cortisol appears comparable between the two populations. Although, it is agreed with the MAH that adrenal suppression is a well-expected PD effect of vamorolone in line with other glucocorticoids, it should not be ignored that adrenal suppression in study -006 was captured as a TEAE with definite causal relation to treatment and that this is similarly labelled for other glucocorticoids. Therefore, adrenal suppression is proposed to be added to the paragraph on paediatric population in section 4.8 (SmPC). No patient in the target population was reported with Cushingoid versus 4 patients in the 6 mg/kg group (14.3%) in the reference population.

Moreover, events from the *GI disorders SOC* were also more frequently reported in the 6 mg/kg dose group in the target population as compared to the reference population (80% vs. 21.4%; event rate 4.74 vs. 1.23). According to the MAH, this imbalance relates to a number of PTs under the SOC GI disorders that are related to concomitant infections, which are more frequent in the younger age group. Likewise, the event rate from the psychiatric disorders SOC was slightly higher in the target as compared to the reference population (1.72 vs. 0.92).

When comparing treatment-*related* TEAEs up to Week 12, there was an increased incidence in the 6 mg/kg group in the target population as compared to the reference population (event rate 5.61 vs. 2.77) with the most frequently reported PT being adrenal suppression. Other treatment-related TEAEs in the target and in the reference population occurred in not more than 2 patients and were in line with the known safety profile of vamorolone (GI disorders, psychiatric disorders).

In summary, based on the 12-week comparison, it cannot be fully ruled out that the target population – when being treated with the 6 mg/kg dose - could be slightly more prone to some adverse effects as compared to the reference population, e.g. to adrenal suppression and GI disorders.

In the EAP, no TEAE was reported in the single patient who received 2 mg/kg. TEAEs were more frequently reported in the 4 mg/kg dose group as compared to the 6 mg/kg dose group (67% vs. 40% of patients; event rates: 1.78 vs. 0.70). The overall number of events (26 events in the 4 mg/kg dose group and 18 events in the 6 mg/kg dose group) with exposure duration of up to 2 years contrasts the experience in study VBP15-006 with a much shorter duration of exposure, which can be explained by the lack of prespecified safety data collection in the EAP (visits according to standard of care for DMD patients). No patient in the 4 mg/kg group reported a drug-related, severe or serious TEAE, and no patient reported a TEAE leading to discontinuation, drug interruption, dose reduction or dose increase. The most frequently reported TEAEs in the EAP derived from the infections and infestations SOC and the General disorders and administration site conditions SOC (PT: pyrexia). There were no events in line with endocrine disorders and only a single patient in the 6 mg/kg dose group reported a TEAE in the psychiatric disorders SOC (aggression).

In the 6 mg/kg dose group, 3 patients reported a drug-related TEAE (dyspepsia, rhabdomyolysis, and aggression). Rhabdomyolysis was also rated as severe and reported as a SAE (in one subject). However, DMD patients are per se at an increased risk of rhabdomyolysis (Sauret et al., 2002), questioning a causal relation to vamorolone treatment in this subject.

The comparison for long-term safety (between 12 and 48 weeks of treatment) revealed lower event rates of TEAEs and treatment-related TEAEs in the target population (from the EAP) as compared to the reference population (from study VBP15-004), i.e. 1.07 vs. 5.1 and 0.07 vs. 1.14. There was a lower incidence in almost all SOCs of interest in the target population, including a lower event rate of GI disorders, infections and infestations, psychiatric disorders, and others. However, this is not reassuring of a more benign long-term safety in the youngest patients considering the infrequent collection of AEs and laboratory parameters in the EAP. Therefore, long-term consequences of vamorolone in patients with treatment initiation prior to 4 years of age cannot be firmly assessed.

Only a paucity of TEAEs in the target population were rated as related to vamorolone (i.e. dyspepsia, rhabdomyolysis, and aggression) contrasting the long-term follow-up of the reference population, for whom treatment-related TEAEs were more frequent in the 6 mg/kg group as compared to the 2 mg/kg group. The most frequently reported drug-related TEAEs in the 6 mg/kg group over 48 weeks in the reference population were related to the endocrine system (Cushingoid) and GI disorders. Others were in line with the short-term safety, including psychiatric disorders and weight increase.

Adverse events of special interest:

TEAEs of behavioural problems were only reported in the 6 mg/kg dose group in study VBP15-006. 3 of 4 events (see further above) have been rated as related to vamorolone. A single event of aggression has been reported in the EAP in the 6 mg/kg group (rated as related to vamorolone). As indicated in the Agamree CHMP AR, a warning statement was not considered of clear value given that behavioural problems were not severe or serious, were not considered clinically relevant or required active management or led to discontinuation. Moreover, additional information on behavioural ADRs is provided in section 4.8 of the SmPC.

TEAEs of bone fractures were absent in study VBP15-006, while two events were reported in 2 patients in the EAP (compression fracture and bruised tailbone; both not related). In the RMP, bone fractures have been specified within safety on long-term use as missing information.

TEAEs of gastrointestinal symptoms were frequently reported in study VBP15-006 and dose-related (80% of patients in the 6 mg/kg group), but only events in the 6 mg/kg dose group were rated as related to vamorolone. None of the events was clinically significant. Few events were reported in the EAP.

TEAEs of infections were frequently reported in study VBP15-006 and in the EAP but neither dose-related nor rated as causally related to vamorolone. Infections due to immunosuppression is an important potential risk for vamorolone in the RMP. A class warning regarding a potential increased risk for infections with vamorolone due to immunosuppression is included in section 4.4 of the SmPC.

TEAEs of adrenal suppression were reported in 6 patients in the 6 mg/kg dose group in study VBP15-006 (5 TEAEs of adrenal suppression and 1 TEAE of cortisol decreased), all of them being rated as TEAEs based on decreased morning cortisol values at the Week 12 visit (normal range 66-410 nmol/L). All TEAEs were asymptomatic and rated related to vamorolone. No action was taken, and all events were ongoing at the end of the study. The change (decrease) from baseline values was dose-dependent. Of note, morning cortisol measurement is not mandated during the EAP while no TEAEs in line with adrenal suppression have been reported so far. From the comparison of the target and the reference population, median changes in morning cortisol from baseline to Week 12 appeared higher in the 2 to <4 years-old as compared to the 4 to <7 years-old in both dose groups. This discussion has already been raised during the MAA of vamorolone where it was concluded that the different formulations in the two studies -004 (ROS1) and -006 (ROS2) led to different exposure in patients, specifically, a higher exposure in patients treated with ROS2. This was supported by the fact that the predicted levels of morning cortisol for vamorolone doses 2, 4, and 6 mg/kg based on a new PKPD model did not indicate a differential effect of vamorolone on the HPA axis for patients aged 2 to<4 years and patients 4 to <8 years. Recommendations for management of the risk for adrenal insufficiency after long-term systemic glucocorticoid treatment are provided in sections 4.2 and 4.4 of the SmPC, including the need for dose tapering and the risk of sudden withdrawal of vamorolone, as well as symptoms of adrenal crisis. In order to further raise the awareness and early recognition and treatment of adrenal crisis, section 4.4 includes an advice to a patient alert card for patients treated with vamorolone as an additional risk minimisation measure.

TEAEs of cataracts and glaucoma, Cushingoid, arterial hypertension, skin and hair changes, weight gain, stunted growth, and diabetic condition were not reported in study VBP15-006 and in the EAP.

Clinical laboratory evaluations

No new safety concerns derive from administration of vamorolone in the target paediatric population with regard to haematology and blood chemistry up to Week 12 in study VBP15-006, and the results were generally in line with those in the reference population up to Week 12 in study VBP15-004. No relevant changes were found in median bilirubin and GGT values that would be indicative of liver injury. Hy's law cases have not been reported. As clinical laboratory evaluations have not been mandated by the EAP protocol, no systematic data collection is available in order to describe long-term effects of vamorolone on laboratory parameters.

Biomarkers

Despite not being discussed as part of the clinical summary of safety, biomarkers of bone remodelling (osteoblast- related bone biomarkers: osteocalcin and P1NP; osteoclast – related bone biomarker: CTX) as well as insulin resistance have been reported in the Paediatric Extrapolation Report for the target population (in study VBP15-006) as compared to the reference population (in study VBP15-004) up to Week 12. However, interpretation is hampered by the short duration and the small number of subjects included in the studies leading to high variability. Of note, the bone metabolism in children is complex and differs from that of adults as it reflects both skeletal growth and remodelling.

With regard to insulin resistance, there were no changes in neither dose group for fasting glucose and HbA1c in the target population up to Week 12. HbA1c was not measured at Week 12 in the reference population hampering an adequate comparison.

Vital signs (only in study VBP15-006)

As discussed during the MAA of vamorolone, clinical data are of limited quality to establish an effect of vamorolone on blood pressure and a high variability of measurements was shown based on the results in the reference population (study VBP15-004). This has also been found in the target population. While baseline Z-scores in diastolic and systolic blood pressure were increased in patients 2 to <4 years of age, there was no clinically relevant change in median z-scores at Week 12. There were no clinically relevant changes in ECG parameters and on eye examination (intraocular pressure) up to Week 12.

Height, weight, and BMI (in study VBP15-006 and in the EAP)

Vamorolone in study VBP15-006 led to only small changes in **height** z-scores over the 12-week treatment duration. While baseline height z-scores in both dose groups were negative (-0.61 and -0.45 in the 2 mg/kg and 6 mg/kg dose group, respectively), the median changes at Week 12 were -0.04 and 0.09, respectively, and therefore in line with the reference population of paediatric patients aged 4 to <7 years at Week 12 (median changes -0.01 and 0.11, respectively). As indicated in the original MAA, there seems to be a lack of vamorolone to inhibit growth, which is a well-known adverse outcome of classical glucocorticoids like prednisone. However, the data need to be considered in the context of the uncontrolled study design.

During the EAP, with all patients having a follow-up for at least 1 year up to the DCO and with some patients being treated for up to almost 3 years, data have only been presented for the combined dose levels (i.e. 2 mg/kg - 6 mg/kg). The median change in height z-score from baseline to the last measurement (which was variable) was 0.10 (interquartile range: -0.38 to 0.24). When taking into account data at Week 48 in the EAP, the median change in height z-score from baseline was negative (-0.14; interquartile range: -0.32 to 0.12) contrasting the positive median change in height z-score in the reference population at Week 48 (2 mg/kg: 0.15; 6 mg/kg: 0.17). Upon request, the clinical relevance of the difference regarding the 48-week data in the target versus the reference population has been discussed by the MAH. It is acknowledged that the target and the reference population are not directly comparable regarding age, baseline height z-scores, and timing of assessments during the EAP (not standardised). Nonetheless, growth stunting, defined by a height z-score of -2 SD has neither been reported in the target population nor in the reference population. The observed differences are within expected variability of growth rate in young children.

Treatment with vamorolone is known to be associated with a dose-dependent **increase in weight and BMI**, which was not readily expected given the differential profile of vamorolone on glucocorticoid-like effects. Baseline median weight z-scores were found close to normal in study VBP15-006 and changed marginally at Week 12 (median change in weight z-score -0.01 and 0.13), and therefore not considered clinically relevant. In the EAP, the median change from baseline to the last measurement in weight z-score was 0.44, while the interquartile range exceeds the limit of 0.5, which indicates a clinically relevant change (0.02; **0.68**). However, when compared to the change in median weight z-score in the reference population up to Week 48, the results of the EAP are in full accordance, indicating that significant weight gain is to be expected in a number of patients treated with vamorolone irrespective of age. Reporting of BMI z-scores is generally more appropriate in the DMD population since weight changes need to be corrected for height changes. In study VBP15-006, no increase in BMI z-score was noted in neither dose group up to Week 12. In contrast, a change from baseline in median BMI z-score to the last measurement in the EAP was reported in the combined dose

groups, i.e. 0.60 (0.07; 0.89). The median change in BMI z-score increased from baseline over the 6-monthly measurements in the EAP, and it was similar as compared to the median change in BMI z-score in the reference population over 48 weeks of treatment. A clinically relevant change in BMI z-score is defined as a change of ≥1.0 SD (according to Houwen van Opstal et al, 2022). Upon request, the MAH provided a summary of patients included in study VBP15-006 and in the EAP as well as in the reference population, who presented with clinically relevant change in BMI z-score at 12 weeks and at Week 48. As a result, clinically relevant BMI z-score changes were higher in the reference population as compared to the target population at Week 12 (7.8% vs. 0%) while at Week 48/ Week 60, these changes were found similar for both populations (~21%).

4.2. Conclusions on clinical safety

In support of the extension of the indication of vamorolone to steroid-naïve paediatric patients aged 2 years to < 4 years, the MAH has provided open-label safety data up to 12 weeks in 20 patients deriving from the a completed multiple-dose phase 2 study VBP15-006, for which extrapolation of clinical safety from the reference population (4 to <7 years-old, based on study VBP15-004) to the broader target population is made. Patients 7 to <18 years with and without previous steroid treatment were also included in this study, but these are not within the scope of this procedure. Additional long-term safety data for up to almost 3 years of open-label treatment with vamorolone in 19 paediatric patients, who entered an Extended Access Programme after completion of study VBP15-006 have also been submitted as part of this extension of the indication variation.

The overall safety profile of vamorolone suggests broad qualitative similarities with classical glucocorticoids with distinct quantitative differences in a number of (dose-dependent) safety issues, which might be explained by GR-mediated transrepressive activity while transactivation is reduced. Safety data from study VBP15-006 basically confirm that the safety profile in paediatric patients 2 to <4 years of age is qualitatively in line with that in the older paediatric population 4 to <7 years of age. Based on uncontrolled safety data up to 12 weeks it appears that there is no differential susceptibility of patients 2 to <4 years of age towards bone fractures, cataracts and glaucoma, Cushingoid, arterial hypertension, skin and hair changes, weight gain, stunted growth, and diabetic conditions. However, a higher frequency in the incidence of some events of special interest has been noted in the target population as compared to the reference population during the first 12 weeks of treatment, mainly related to adrenal suppression and gastrointestinal disorders, while the slightly higher incidence in psychiatric disorders is considered negligible.

At present, some uncertainties on the extrapolation of safety from the reference to the target population remain and relate to the following issues:

- The youngest patient in study VBP15-006 was close to 3 years of age. While there is no evidence to assume a different sensitivity towards adverse effects of vamorolone in patients between 2 and 3 years of age and patients between 3 and 4 years of age, this cannot be confirmed because of lack of available data.
- The study design (lack of a comparator) and short duration of study VBP15-006 (12 weeks) does not allow to firmly conclude on the absence of any relevant changes in growth (height z-scores) when starting treatment with vamorolone in patients 2 years of age.
- Interpretation of long-term safety data of the 19 patients aged 2 to < 4 years treated in the EAP is hampered by the fact that no systematic safety data collection/ laboratory measurements have been applied that would enable a fair comparison with the safety data up to 48 weeks from study VBP15-004 (reference population). As a consequence, long-term

adverse events are probably underestimated in the target population relative to the reference population.

In summary, the identified safety issues for vamorolone across the target population are considered manageable alike with the proposed risk minimisation measures in the reference population, i.e. adequate labelling in the product information and routine pharmacovigilance activities. Moreover, an observational PASS study (currently under review) is considered to further characterise and quantify the long-term safety profile of vamorolone.

4.2.1. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

4.3. Risk management plan

The MAH submitted an updated RMP version 2.0 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.2 with the following content:

Safety concerns

Table 41. Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Infections due to immunosuppression Hepatotoxicity Acute adrenal insufficiency (adrenal crisis)
Missing information	Use in patients above 12 years of age Safety on long-term use (in particular regarding bone fractures, weight gain, growth, hyperglycemia, dyslipidemia and hypertension)

Pharmacovigilance plan

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
PASS Planned	Long term safety	Important potential risks: Infections due to immunosuppression Hepatotoxicity, acute adrenal insufficiency (adrenal crisis) Missing information "Safety on long-term use (in particular regarding bone fractures, weight gain, growth, hyperglycemia, dyslipidemia and hypertension)" Missing information "use in patients above 12 years of age"	Final protocol	Q3/2025

Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important potential risk 1: Infections due to immunosuppression	**Routine risk minimisation measures:** SmPC section 4.4 PL section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	An observational PASS currently under review.
Important potential risk 2: Hepatotoxicity	**Routine risk minimisation measures:** SmPC sections 4.2, 4.3 and 4.4 PL sections 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** An observational PASS currently under review
Important potential risk 3: Acute Adrenal insufficiency (adrenal crisis)	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4 and 4.8 PL sections 2 and 4 **Additional risk minimisation measures:** A patient alert card to support early recognition and treatment of adrenal crisis	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** An observational PASS currently under review
Missing information 1: Use in patients above 12 years of age	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • An observational PASS to further characterise and quantify long-term safety profile of AGAMREE

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information 2: Safety on long-term use (in particular regarding bone fractures, weight gain, growth, hyperglycemia, dyslipidemia and hypertension).	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8 PL sections 2 and 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • An observational PASS to further characterise and quantify long-term safety profile of AGAMREE

4.4. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guidelines which were reviewed and accepted by the CHMP.

4.4.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

Duchenne Muscular Dystrophy (DMD) is a rare, disabling, progressive and ultimately fatal X-linked recessive neuromuscular disorder caused by mutations in the gene for dystrophin (Emery, 2002). Functional dystrophin is critical for the structural stability of myofibers in skeletal, diaphragm and cardiac muscle and is also of importance for smooth muscles. The disease primarily affects males with a birth incidence of 1 in 3,600 – 9,300 males (Mah *et al*., 2014). DMD is characterised by a progressive degeneration of skeletal muscles, with symptoms that manifest early, at around 3 years, causing loss of ambulation before the age of 12, followed by cardiac complications (e.g. dilated cardiomyopathy and arrhythmia) and respiratory disorders, including chronic respiratory failure (Birnkrant et al., 2018). The median life expectancy at birth is around 30 years (Landfelt et al. 2020).

Vamorolone is an anti-inflammatory steroid analogue basically aiming at slowing down progressive muscle weakness and delaying associated loss of ambulation.

5.1.2. Available therapies and unmet medical need

There are no approved treatments to cure or stop the *ultimately fatal progression of DMD. For available options in the treatment of DMD reference is made to section 2.1. Deflazacort is approved for "treatment*

of Duchenne muscular dystrophy (DMD) in patients 2 years and older" in some EU/EEA countries only, which is - at present - the only currently available treatment option in paediatric patients aged 2 years and older. Therefore, an unmet medical need still remains.

5.1.3. Main clinical studies

The efficacy of vamorolone in boys with Duchenne muscular dystrophy (DMD) aged 2 to <4 years was supported by Study VBP15-006, a multicentre, open-label Phase II study designed in accordance with the agreed PIP (EMEA-001794-PIP02-16). The study evaluated safety, tolerability, pharmacokinetics, and exploratory efficacy of vamorolone administered orally once daily at 2 mg/kg or 6 mg/kg for 12 weeks.

A total of 20 steroid-naïve subjects (10 per dose group) were enrolled; all were ambulatory boys aged 2–<4 years with a confirmed diagnosis of DMD based on gene analysis and/or a muscle biopsy sample, tested for the presence of dystrophin protein. To ensure safe dosing of vamorolone, the first 6 subjects in each age group at the 2 mg/kg/day dose level served as the PK/safety run-in cohorts. Once the exposure and safety were confirmed at 2 mg/kg/day in these subjects, the subsequent subjects were enrolled at 2 mg/kg/day and 6 mg/kg/day. Efficacy was evaluated exploratory by the Bayley Scales of Infant and Toddler Development-III (Bayley-III) Gross Motor Scale Score (GMSS), a validated developmental tool assessing gross motor performance in young children. Additional exploratory endpoints included the Pediatric Outcomes Data Collection Instrument (PODCI) and behavioural assessments (PARS III).

No randomisation or blinding was applied; all subjects received active treatment and completed the study, while nineteen participants continued in an extension programme. The primary efficacy assessment was descriptive due to the small sample size and the short treatment duration.

5.2. Favourable effects

The proposed posology in 2 to <4 years old steroid naïve DMD subjects is the same as in patients 4 years of age and older. Population PK modelling suggested a comparable exposure for DMD patients aged 2 to <4 years.

Evaluation of efficacy for daily doses of vamorolone 2 and 6 mg/kg over a treatment period of 12 weeks in 2 to <4 years old steroid naïve DMD subjects was based on an exploratory endpoint, the change from baseline in the Bayley-III GMSS at week 12.

While the Bayley-III score at baseline was higher in the 6 mg/kg vamorolone group than in the 2 mg/kg vamorolone group (3.5 vs 5.0, respectively), the difference between the dose groups became larger at Week 12 (4.0 vs 8.0, respectively) with median changes of 0.0 (2 mg/kg) vs 2.5 (6 mg/kg) and mean changes of 0.44 (2 mg/kg) vs 2.5 (6 mg/kg). Improvement was observed in 9/10 subjects at 6 mg/kg. Based on subgroup analyses according to age, improvements in the 6 mg/kg vamorolone treatment arm compared to the 2 mg/kg treatment group could not be explained by the small differences in age between groups.

These efficacy outcomes of vamorolone in steroid naïve DMD patients aged 2 to <4 years of age seem to be consistent with those from patients 4 years and older and in favour of the daily vamorolone 6 mg/kg dose. Results suggest a dose-dependent improvement in motor ability with no clinical progression in the lower dose. Therefore, results are indicative that in patients being in a pre-symptomatic stage or in an early ambulatory stage disease progression might be delayed in case participants start treatment early.

These data support the extrapolation of efficacy of vamorolone from corticosteroid naïve DMD patients included in the pivotal study VBP-004 (4 to <7 years of age) to patients 2 to <4 years of age.

5.3. Uncertainties and limitations about favourable effects

One study has been provided in support of the claimed indication. Due to methodological limitations (including open-label design, small sample size, descriptive statistics and the rather short treatment duration of 12 weeks), results are supportive of a treatment effect but are insufficient for drawing confirmatory conclusions on the efficacy of vamorolone in these young patients.

No relevant changes were observed in the PARS III or PODCI over 12 weeks.

The median age of the subjects included at study entry was 3.3 and 3.5 years with the youngest patient being close to 3 years of age, i.e., 2.8 and 2.9 years of age in the vamorolone 2mg/kg and 6 mg/kg treatment group. Although this limits the representativeness of the youngest subjects for the claimed indication, it is assumed that there are no significant differences in effects of vamorolone in patients between 2 and 3 years of age and patients between 3 and 4 years of age. However, this cannot be confirmed based on the available data.

Population PK Model development was complicated by the different formulations developed, a food effect and a questionable impact of race for Chinese Asians. It was previously noticed that the final formulation (ROS2) led to higher exposures compared to the initial formulation (ROS1). However, it was shown through PPK based simulations that for the age group from 2 to <4 years similar exposures can be expected compared to older age groups. Weight based dosing of 6 mg/kg bodyweight with a cap at 40 kg bodyweight was proposed, which can be agreed.

5.4. Unfavourable effects

Treatment-emergent AEs after administration of vamorolone 2 mg/kg and 6 mg/kg were reported by 70% and 90% of paediatric patients aged 2 to <4 years in the open-label 12-week study VBP15-006, with no severe, or serious AEs, and no TEAEs leading to discontinuations or temporary dose interruption. No death was reported.

TEAEs with vamorolone in the target population were qualitatively in line with those in the reference population. The system organ classes with the highest proportions of subjects reporting TEAEs in descending order in both dose groups combined were gastrointestinal disorders (45%), infections and infestations (40%), endocrine disorders (25%), general disorders and administration site conditions (20%), musculoskeletal and connective tissue disorders (20%), and respiratory, thoracic and mediastinal disorders (20%). The most common TEAEs by PT in both dose groups combined included nasopharyngitis (35%), adrenal suppression (25%), diarrhoea (15%), and fall (15%). Quantitative differences in the reporting of TEAEs in paediatric patients aged 2 to <4 years of age in excess of those in paediatric patients aged 4 to <7 years have been noted for TEAEs reported under the most frequently reported SOCs, mainly for the 6 mg/kg dose, e.g. for gastrointestinal disorders (80% vs. 21.4%), endocrine disorders (50% vs. 14.3%), musculoskeletal and connective tissue disorders (40% vs. 7.1%), and general disorders and administration site conditions (30% vs. 3.6%).

Drug-related TEAEs were more frequently reported in the target population (patients 2 to <4 years of age) as compared to the reference population (patients 4 to <7 years of age; from study VBP15-004), i.e. 70% vs. 42.9% for the 6 mg/kg dose group. In patients aged 2 to <4 years, drug-related TEAEs were mainly those in line with endocrine disorders (adrenal suppression, cortisol decreased), psychiatric disorders (aggression, irritability, mood swings), and GI disorders (diarrhoea, abnormal faeces), and

almost exclusively reported in the 6 mg/kg dose group. In the reference population, drug-related TEAEs were quantitatively similar.

Acute adrenal insufficiency (adrenal crisis) is a potential risk with vamorolone treatment. Based on morning serum cortisol levels, in 6 of 10 subjects from the target population in Study VBP15-006 (all in the 6 mg/kg dose group), Adrenal suppression or cortisol decreased was reported as TEAE. In contrast, no such TEAEs were reported in any dose group in the reference population (Study VBP15-004). However, Cushingoid was not reported as TEAE in study VBP15-006 but in 4 patients from the 6 mg/kg dose group in study VBP15-004. Vamorolone is known to cause a dose-dependent adrenal suppression. In study VBP15-006, at Week 12, the level of adrenal suppression was higher for vamorolone 6 mg/kg than for vamorolone 2 mg/kg based on the median change [Q1; Q3] from baseline in morning cortisol values (-230.5 nmol/L [-285.50; -132.50] vs. -156.00 nmol/L [-251.00; -89.00]). In the reference population (study VBP15-004, at Week 12), the median change [Q1; Q3] from baseline in morning cortisol values was -196 nmol/L [-253; -144] in the 6 mg/kg dose group vs. -81 nmol/L [-137; -51] in the 2 mg/kg dose group.

Treatment with vamorolone in DMD patients is associated with a dose-dependent **increase in body weight and BMI** mainly during the first 6 months of treatment. Weight increased and increased appetite are defined ADRs for vamorolone in section 4.8 of the SmPC. The effect of long-term use on weight gain is missing information in the RMP. No TEAEs of weight increased were reported in the target population in study VBP15-006 and in none of the patients followed-up in the EAP up to the DCO. The change in median weight z-score at Week 12 in study VBP15-006 was not considered clinically relevant, while some patients presented with clinically relevant median change in weight z-score during the follow-up in the EAP, which is found in accordance with the data from the reference population in study VBP15-004. The same trend was observed for median change in BMI z-score.

Growth retardation is a well-known effect of glucocorticoid treatment of children, and this was also observed in juvenile mice following administration of vamorolone. In the reference population studied in VBP15-004, vamorolone was not found to inhibit growth based on controlled 6 months data, and an effect also seemed to be absent based on uncontrolled data up to 30 months when compared to external FOR-DMD study data with conventional GCs. No TEAEs related to stunted growth were reported during short-term or during long-term treatment with vamorolone in patients aged 2 to <4 years of age. There was no clinically relevant median change in height z-scores in the vamorolone 2 and 6 mg/kg group in the target population at Week 12 in line with the reference population. At Week 48, the median change in height z-scores ranged from -0.14 in the EAP (target population) to 0.17 in the 6 mg/kg dose group in study VBP15-004 (reference population).

Behavioural problems were only reported in the vamorolone 6 mg/kg group in the target population (20% of patients) up to 12 weeks in study VBP15-006, and included aggression, irritability, mood swings, and compulsive lip biting. Except for lip biting, all were rated as related to vamorolone. The incidence of psychiatric disorders in the reference population up to Week 12 was similar (14.3% in the 6 mg/kg group). In the EAP, no increased frequency of behavioural problems was noted in the target population. Behavioural problems are already labelled in section 4.8 in the SmPC with irritability being a very common ADR of vamorolone treatment.

Gastrointestinal symptoms, including vomiting, abdominal pain, abdominal pain upper, diarrhoea, and constipation were among the most frequently reported AESI during the controlled and uncontrolled vamorolone clinical studies and occurred with similar incidences across all treatment groups (25.8% - 30%) in the reference population. In the target population, TEAEs from the GI disorders SOC were reported with a higher incidence (80% in the 6 mg/kg group) as compared to the reference population. A minority of these TEAEs were drug-related, and all except one were mild in severity. GI disorders are defined ADRs in section 4.8 of the SmPC.

TEAEs related to cataracts and glaucoma, arterial hypertension, skin and hair changes, and diabetic condition were not reported in patients aged 2 to <4 years in study VBP15-006 and in the EAP. In this context, **safety on long-term use** is specified as missing information in the RMP and includes safety issues which are crucial with long-term treatment, in particular regarding bone fractures, weight gain, growth, hyperglycaemia, dyslipidaemia and hypertension.

5.5. Uncertainties and limitations about unfavourable effects

At present, some uncertainties on the **extrapolation of safety from the reference to the target population** remain and relate to the following issues:

The short-term safety profile of patients aged 2 to <4 years is based on a limited and uncontrolled dataset of 20 patients exposed to vamorolone 2 mg/kg (n=10 patients) and 6 mg/kg (n=10 patients) in study VBP15-006 for 12 weeks only.

Long-term safety for vamorolone in paediatric patients aged 2 to <4 years up to the data cut-off 1 June 2025 from treatment in the Expanded Access Programme is thus limited including data from 19 patients, who entered the EAP from study VBP15-006 with a median duration of exposure of 1.9 years and 1.7 years in the 6 mg/kg and 4 mg/kg group, respectively. Therefore, identified AESI for vamorolone with an impact on long-term safety (i.e. bone health/ fractures, adrenal suppression, weight gain) are difficult to be interpreted for their implications when treatment is started in very young patients 2 to <4 years. Moreover, interpretation of long-term safety data is hampered by the fact that no systematic safety data collection/ laboratory measurements have been applied in the EAP that would enable a fair comparison with the safety data up to 48 weeks from study VBP15-004 (reference population). As a consequence, long-term adverse events are probably underestimated in the target population relative to the reference population.

For patients 2 to <4 years treated in study VBP15-006, the 6 mg/kg dose led to a higher reporting of some dose-related TEAEs, i.e. adrenal suppression and psychiatric disorders as compared to the reference population (50% vs. 0% and 20% vs. 14.3%).

The vast majority of subjects from the target population treated with vamorolone 6 mg/kg had morning cortisol values <100 nmol/L suggestive of clinically relevant adrenal suppression corroborated by the reporting of asymptomatic and mainly mild adrenal suppression TEAEs in this dose group, which could be confirmed by the MAH. Notwithstanding, adrenal suppression was labelled in the paediatric population paragraph in section 4.8 of the SmPC since it was rated a causally related TEAE in study -006 and also to align with other glucocorticoids. Median changes in morning cortisol from baseline to Week 12 were higher in the 2 to <4 years-old as compared to the 4 to <7 years-old in both dose groups, while median morning cortisol at Week 12 was similar in the 2 mg/kg dose group for both ages and it was higher for the 6 mg/kg dose group in patients aged 2 to <4 years as compared to patients aged 4 to <7 years. Nevertheless, the minimum and maximum values observed in the target population at Week 12 were within the range observed in the reference population. As discussed during the original MAA, different formulations were used in the two studies -004 (ROS1 formulation) and -006 (ROS2 formulation; the to-be marketed formulation). Simulations from a new PopPK model predicted a generally higher exposure for the ROS2 formulation compared to the ROS1 formulation across all dosages (~20% increase in AUC), while the predicted levels of morning cortisol for vamorolone doses 2, 4, and 6 mg/kg based on the new PKPD model did not indicate a differential effect of vamorolone on the HPA axis for patients aged 2 to<4 years and patients 4 to <8 years. Uncertainty has also been raised on the time to recovery of the HPA axis following discontinuation of vamorolone treatment and the potential long-term consequences of secondary adrenal insufficiency after glucocorticoid/ vamorolone use. Acute events in line with adrenal insufficiency cannot be excluded in a paediatric patient population that is prone to infections, which could

be a trigger for adrenal crisis. Therefore, the risk of adrenal insufficiency is detailed in the product information, including a warning on use of a steroid emergency card.

Whether the slightly increased incidence in **psychiatric disorders** in the 6 mg/kg dose group in the target population as compared to the reference population indeed reflects a higher susceptibility of the target population as compared to the reference population remains an uncertainty owing to the uncontrolled study setting (in study VBP15-006).

Uncertainties have been raised in the reference population regarding **long-term effects on bone health** Therefore, 'bone fractures' was specified under *safety on long-term use* as missing information in the RMP. This uncertainty likewise applies to patients aged 2 to <4 years. Data on biomarkers of osteoblast and osteoclast activity have only been collected in study VBP15-006, while interpretation is hampered by the short treatment duration and the small number of subjects. No follow-up on bone biomarkers is available from the EAP.

While TEAEs related to diabetic conditions were not reported in patients aged 2 to <4 years, uncertainty remains with regard to long-term effects of vamorolone on **glucose metabolism and insulin resistance.** The diabetogenic potential of vamorolone (*hyperglycaemia*) will be further evaluated in a PASS.

Uncertainties that remain in line with the outcome of the MAA of vamorolone and which are further addressed in the RMP are infections due to immunosuppression and hepatotoxicity (important potential risks), and effects on blood pressure (addressed within safety on long-term use as missing information). However, no such TEAEs have been reported in study VBP15-006 and in the EAP with vamorolone in patients 2 to <4 years of age.

5.6. Effects Table

Table 42. Effects Table for vamorolone for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 2 years and older (efficacy: study VBP15-006; safety: data cut-off of the EAP 1 June 2025)

Effect	Short description	Unit	Vamorolone – Target population	Vamorolone – Reference population	Uncertainties / Strength of evidence	References
Favourable Effects						
Change from Baseline to Week 12 in the Bayley-III) Gross Motor Scale score (2 to <4 years age group only)	Exploratory efficacy endpoint	Change from baseline Mean (SD) Median (Q1;Q3) Min,Max	Vam 2 mg/kg (n=10) 0.44 (1.130) 0.00 (0.00;1.00) -1.00,3.00 Vam 6 mg/kg (n=10) 2.50 (1.716)		Several uncertainties remain due to the open-label study design, the small sample size, the lack of a comparator and the descriptive statistic approach	(1)

Effect	Short description	Unit	Vamorolone – Target population	Vamorolone – Reference population	Uncertainties / Strength of evidence	References
			2.50 (2.00;4.00) -1.00,5.00			
Unfavourable Effects						
Adrenal suppression	Median change (Q1; Q3) in morning cortisol from baseline	nmol/L	6 mg/kg: -230.5 (-285.5; -132.5) 2 mg/kg: -156.0 (-251.0; -89.0)	6 mg/kg: -196 (-253; -144) 2 mg/kg: -81 (-137; -51)	VAM dose-dependently leads to an alteration of the HPA axis with suppression of endogenous cortisol and ACTH in the majority of subjects. Uncertainty: time to recovery of the HPA axis following discontinuation of VAM treatment and the potential long-term consequences of secondary adrenal insufficiency	(1); (2)
	Patients with TEAEs	%	6 mg/kg: 50 2 mg/kg: 0	6 mg/kg: 0 2 mg/kg: 0		
Cushingoid	Patients with TEAEs	%	6 mg/kg: 0 2 mg/kg: 0	6 mg/kg: 14.3 2 mg/kg: 0	See adrenal suppression	(1); (2)
Weight gain/ weight increased	Patients with TEAEs	%	6 mg/kg: 0 2 mg/kg: 0	6 mg/kg: 3.6 2 mg/kg: 0	No clinically relevant changes in median weight Z-scores in the target population during short-term treatment. During long-term treatment, clinically significant weight gain in a number of patients (target and reference population); lack of controlled long-term data	(1); (2); (3)
Growth (height restriction)	Median change in height z-score from baseline		6 mg/kg: 0.09 (-0.02; 0.28) 2 mg/kg: -0.04 (-0.15; 0.17)	6 mg/kg: 0.11 (-0.02; 0.27) 2 mg/kg: -0.01 (-0.09; 0.11)	Uncertainties: Controlled long-term data not available.	(1); (2) ; (3)

Effect	Short description	Unit	Vamorolone – Target population	Vamorolone – Reference population	Uncertainties / Strength of evidence	References
Psychiatric disorders (incl. Irritability, Abnormal behaviour, Aggression, Anxiety, Mood swings, Sleep disorder)	Patients with TEAEs	%	6 mg/kg: 20 2 mg/kg: 0	6 mg/kg: 14.3 2 mg/kg: 3.3	Uncertainty: Event rate higher in the target as compared to the reference population (6 mg/kg dose group: 1.72 vs. 0.92);	(1); (2)
Gastro-intestinal disorders	Patients with TEAEs	%	6 mg/kg: 80 2 mg/kg: 10	6 mg/kg: 21.4 2 mg/kg: 20	Uncertainty: Event rate higher in the target as compared to the reference population (6 mg/kg dose group: 4.74 vs. 1.23); hypothesised to be due to immaturity of GI system or symptoms caused by infections.	(1); (2)

Abbreviations:

Notes: (1) Open-label study VBP15-006, cohort 2 to <4 year old paediatric patients with DMD; (2) Paediatric Extrapolation Report (dated 15 August 2025) – reference population from study VBP15-004 (Week 12 data); (3) Expanded access programme (EAP) (cut-off 01 June 2025);

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Efficacy

The efficacy of vamorolone in the treatment of DMD has already been established in steroid naïve patients aged 4 to 7 years. The MAH is now seeking extension of the indication to paediatric steroid naïve DMD patients 2 to <4 years of age.

The final results of study VBP15-006 now available show that the exploratory efficacy endpoint change from baseline in the Bayley-III GMSS at week 12 indicates a dose-dependent effect of vamorolone on gross motor function, which was observed in the 6 mg/kg day treatment group over the 12-week treatment period. In the 2 mg/kg day group, muscle function remained stable, with trends toward increased Bayley-III Gross Motor Scale Scores (GMSS). However, due to methodological issues, the results should be interpreted with caution and are only considered to be of supportive character.

Overall, the efficacy outcomes of vamorolone in the 2 to <4 years old patient population seem to be consistent with those from older DMD patients. These data support the extrapolation of efficacy of vamorolone from corticosteroid naïve DMD patients ≥4 years and <7 years of age to corticosteroid

naïve DMD patients 2 to <4 years of age. Moreover, based on the same pathomechanism with inflammation being present across all stages of the disease, extrapolation of efficacy of vamorolone from older to younger patients is considered plausible.

Although, data on corticosteroid treatment in boys with DMD are generally limited and scientific knowledge regarding the appropriate treatment duration is still evolving, positive effects of early initiation of corticosteroid treatment have also been described in the youngest patients (with a mean age of 1.7 years) (Armstrong 2024). Considering that the pharmacological mechanism that mediates efficacy of vamorolone in the treatment of DMD is the same as for currently used corticosteroids, extrapolation of these recommendations to vamorolone appears justified. Recently, early corticosteroid treatment of boys with DMD has been recommended because inflammation and muscular degeneration is present from an early stage of the disease. In line with the knowledge about symptom onset and the current treatment recommendations to start treatment early for prolonging function, vamorolone should be a treatment option already below the age of 4 years. A broad indication, including patients from 2 to <4 years of age is therefore considered justified.

Safety

Overall, no new safety issues have been identified with vamorolone in the target population as compared to the reference population in the original MAA. The safety database of vamorolone in patients 2 to <4 years of age is limited due to (1) the small number of patients included, (2) the lack of controlled data, and (3) the limited treatment duration of 12 weeks in study VBP15-006.

Moreover, long-term safety data for the target population 2 to <4 years of age, who transitioned to the EAP cannot compensate for the lack of a clinical long-term study since no systematic safety data collection is conducted in the EAP.

Therefore, while the gap in knowledge with regard to short-term safety of vamorolone in patients 2 to <4 years of age might be addressed by the VBP15-006 safety data, taking into account the uncertainties above, the long-term effects of vamorolone in patients starting treatment at the age of 2 years remain uncertain. This is especially of note since the youngest patient in study VBP15-006, who received the highest dose of 6 mg/kg was close to 3 years of age. Although, there is no biological reason to assume a different sensitivity towards adverse effects of vamorolone in patients between 2 and 3 years of age and patients between 3 and 4 years of age, this cannot be confirmed based on the available data. Therefore, the proposed dose reduction to 4 mg/kg or 2 mg/kg in case of tolerability issues, while patients should continue to receive the highest tolerable dose, is considered a conservative approach in order to minimise safety concerns with vamorolone across all ages.

With the provided short-term data it might be assumed that, based on the same treatment duration in the target and reference population,

- there is no increased risk of severe TEAEs, SAEs, or TEAEs leading to withdrawal from study, temporary dose reduction or death in paediatric patients aged 2 to <4 years as compared to patients 4 to <7 years of age,
- there is an increased incidence in AESI of gastrointestinal disorders as well as infections in the target population as compared to the reference population, with few GI events and no infection TEAEs rated as related to vamorolone. GI disorders and infections are common in very young children and GI disorders are also frequently related to the underlying disease and are therefore not considered a direct consequence of worsened tolerability towards vamorolone in the 2 to <4 years-old as compared to the 4 to <7 years-old,
- the increased reporting of adrenal suppression in study VBP15-006 as TEAE as compared to study VBP15-004 is related to the fact that investigators were not blinded to laboratory values

in study VBP15-006. In addition, the different formulation of the drug product used in studies VBP15-004 (ROS1) and VBP15-006 (ROS2) that led to a slightly higher exposure of vamorolone in patients treated in study VBP15-006 might also have contributed to the more pronounced median morning cortisol changes from baseline.

- the risk for behavioural disorders is dose-related but roughly comparable with the incidences in the reference population,
- height and weight changes in the target population followed the same trajectories as in the reference population, while no firm conclusion can be made based on the short treatment duration.

In contrast, the provided long-term data in paediatric patients 2 to <4 years of age entering an EAP after 12 weeks of treatment with vamorolone in study VBP15-006 are considered to underestimate incidences of adverse events and do therefore not allow an indirect comparison with patients from the reference population with 48 weeks of treatment in study VBP15-004. From these data it cannot be concluded on how vamorolone, when started very early from 2 years of age on, affects

- growth retardation; a growth stunting effect was not observed in the reference population,
- weight gain and increase in BMI; at present it appears that at least some patients might experience clinically significant weight gain/ increase in BMI. Dose reduction seems to mitigate the risk and is also included in section 4.2 of the SmPC. Moreover, dietary measures are recommended for patients at risk,
- bone health; bone turnover markers (while only available from study VBP15-006) do allow to conclude on the risk for future fractures,

as compared to the reference population in study VBP15-004. Moreover, and as indicated during the MAA of vamorolone, the duration of recovery from adrenal insufficiency after treatment cessation remains unknown, which sets patients at risk for acute adrenal crisis during an unknown duration in a worst-case scenario. However, the risk is considered manageable with an adequate withdrawal regimen (for which evidenced-based guidelines are lacking; Bowden et al., 2019), specific warning regarding stress dosing regimens, and raising the awareness for symptoms of adrenal crisis in the product information, e.g. by means of a patient alert card.

The absence of deleterious effects of vamorolone on hypertension, effects on lipid metabolism, and liver impairment during clinical studies with vamorolone needs to be confirmed in the long-term including patients with treatment initiation at 2 years of age. The same applies to the risk for infections due to immunosuppression based on the differential effects of vamorolone on white blood cells, especially neutrophil counts), and the absence of cataracts and glaucoma.

In summary, the long-term effects of vamorolone remain uncertain both in the reference population and in the target population. Therefore, the planned PASS study will shed more light on these safety issues.

5.7.2. Balance of benefits and risks

Efficacy was assessed as exploratory objectives over 12 weeks of treatment in a limited number of corticosteroid naïve DMD patients 2 to < 4 years of age (n = 20). Results indicated a dose-dependent improvement on cross motor function suggestive of a more pronounced effect in favour of the daily vamorolone 6 mg/kg dose compared to the 2 mg/kg dose. Although the youngest patients in this study

were close to 3 years of age no significant differences in effects of vamorolone are assumed in patients between 2 and 3 years of age and patients between 3 and 4 years of age.

The short-term safety of vamorolone in the studied DMD population of patients 2 to <4 years of age does not present with major findings different to the reference population of paediatric patients aged 4 to <7 years that would preclude treatment from a clinical safety perspective. The limited data of 19 patients from the target population treated in the EAP do not raise additional concerns with regard to long-term treatment, which is, however, of limited significance given the evaluation of safety outside a clinical trial in an uncontrolled setting. A PASS study on long-term implications of vamorolone is expected to address the remaining uncertainties across the claimed age range. Adverse drug effects are considered manageable with the monitoring recommendations provided.

Population PK modelling suggested a comparable exposure for DMD patients aged 2 to <4 years. Therefore, extrapolation of efficacy and safety data from the reference DMD study population 4 to <7 years to DMD patients 2 to <4 years is considered acceptable taking into account the provided popPK analysis while the risks appear not unacceptably high.

Based on pathophysiological considerations and recent professional recommendations, vamorolone as anti-inflammatory treatment option should be made available already to patients 2 to < 4 years of age. The benefit/ risk of vamorolone in patients 2 to <4 years of age is positive.

5.7.3. Additional considerations on the benefit-risk balance

5.8. Conclusions

At present, the overall B/R of vamorolone in the extension of indication applied for, i.e. "*treatment of Duchenne muscular dystrophy (DMD) in patients aged 2 years and older*" is positive.

6. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation<s> accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I, IIIB

Extension of indication to include treatment of 2 to <4 year olds for AGAMREE, based on final results from study VBP15-006; this is a phase II open-label, multiple dose study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of vamorolone in boys ages 2 to <4 years and 7 to <18 years with Duchenne Muscular Dystrophy (DMD) and an updated paediatric extrapolation report referencing 4 to <7-year-old subjects with DMD from Study VBP15-004, compared to the 2 to <4-year-old population from Study VBP15-006. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.2 of the RMP has also been approved. In addition, the Marketing authorisation holder took the opportunity to make some editorial corrections to SmPC.

Amendments to the marketing authorisation

In view of the data submitted with the variation amendments to Annex(es) I and IIIB, and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

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

In addition, 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.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Agamree is not similar to Duvyzat within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.