12 October 2023
EMA/CHMP/487504/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Agamree

International non-proprietary name: Vamorolone

Procedure No. EMEA/H/C/005679/0000

Note

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

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List of abbreviations

6MWT	6-Minute Walk Test
(11β-)HSD	(11β-)hydroxysteroid dehydrogenase
ACTH	Adrenocorticotropic hormone
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALP	Alkaline phosphatase
$AUC_{0\text{-}24h}$	Area under the drug concentration versus time curve from 0 to 24 hours
$AUC_{0\text{-}last}$	Area under the drug concentration to the last measurable concentration
$AUC_{0\text{-}inf}$	Area under the plasma concentration time curve from time 0 to infinity
BCRP	Breast cancer resistance protein
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
(D)(S)BP	(Systolic) (Diastolic) blood pressure
BSEP	Bile salt export pump
CI	Confidence interval
CINRG-DNHS	Cooperative International Neuromuscular Research Group – Duchenne Natural History Study
C_{max}	Maximum drug concentration
CMQ	Customised MedDRA query
CL/F	Oral clearance
CUP	Compassionate use programme
CYP	Cytochrome P450
DDI	Drug drug interaction
DMD	Duchenne muscular dystrophy
DRF	Dose range finding
DSC	Differential scanning calorimetry
DXA	Dual-energy X-ray absorptiometry
EAE	Experimental autoimmune encephalitis
EAIR	Exposure adjusted incidence rate
EAP	Expanded access programme
ECG	Electrocardiogram
E_{50}	AUC value of vamorolone achieving 50% maximal effect
E_{max}	Maximum effect
ERA	Environmental risk assessment
E-R	Exposure-response
FDA	Food and Drug Administration
FAS	Full analysis set
FOR-DMD	Finding the optimum regimen for DMD
FT-IR	Fourrier transform infrared spectroscopy
FVC	Forced vital capacity
GC	Glucocorticoid
GGT	Gamma-glutamyl transpeptidase

GLDH	Glutamate dehydrogenase
GI	Gastrointestinal
GMSS	Bayley-III Gross Motor scale
(m)GR	(membrane) Glucocorticoid receptor
GRE	Glucocorticoid response element
HbA1c	Hemoglobin A1c
HDL cholesterol	High-density lipoprotein cholesterol
HI	Hepatic impairment
hERG	Human *ether-a-go-go*-related gene
HPA	Hypothalamic-pituitary-adrenal
HP-β CD	Hydroxypropyl-β cyclodextrin
HPLC	High performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IR	Infrared
LDL cholesterol	Low-density lipoprotein cholesterol
LS-BMC	Lumbar spine bone mineral content
LS-BMD	Lumbar spine bone mineral density
LSM	Least squares mean
LTE	Long-term extension
MAD	Multiple ascending dose
MATE	Multidrug and toxin extrusion protein
MCIDs	Minimally clinically important differences
MEC	Molar extinction coefficient
MedDRA	Medical Dictionary for Regulatory Activities
(m)ITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
MR	Mineralocorticoid receptor
MRHD	Maximum recommended human dose
MS	Mass spectrometry
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NMR	Nuclear magnetic resonance
NOAEL	No-observed-adverse-effect level
NSAA	North star ambulatory assessment
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OOS	Out of specification
P1NP	Procollagen 1 N-terminal propeptide
PBO	Placebo
PD	Pharmacodynamic
PDA	Photo diode array
PDN	Prednisone
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia

PK	Pharmacokinetic
PND	Post-natal day
PP	Percentage point; Per protocol
PODCI	Paediatric outcomes data collection instrument
PopK	Population pharmacokinetic(s)
PRED	Prednisone
PT	Preferred term
QBD	Quality by design
QD	Once daily
QMT	Quantitative muscle testing
QTc	QT interval corrected for heart rate
QWBA	Quantitative whole-body autoradiography
RANKL	Receptor activator of nuclear kappa-B ligand
RBC	Red blood cell
REML	Restricted maximum likelihood
RH	Relative humidity
RMM(s)	Risk minimisation measure(s)
RMP	Risk management plan
ROS	Route of synthesis
ROS1	Clinical Formulation
ROS2/	to be marketed formulation
SAD	Single aAscending dose
SAE	Serious adverse event
SCS	Summary of clinical safety
(s-)CTX	(Serum) Type 1 collagen C-telopeptides
SD(s)	Standard deviation (scores)
SE	Standard error
Sgk1	Serum/glucocorticoid regulated kinase 1
SmPC	Summary of product characteristics
SOC	System organ class
TDAR	T cell dependent antibody response
TEAE	Treatment emergent adverse event
TGA	Thermo-fravimetric analysis
t_{max}	Time to maximum drug concentration
$t_{1/2}$	half-life
TSH	Thyroid-stimulating hormone
TTCLIMB(V)	Time to climb 4 steps test (velocity)
TTRW(V)	Time to run/walk 10 metres test (velocity)
TTSTAND(V)	Time to stand (velocity)
UGT	Uridine 5′-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
UV	Ultraviolet
VAM	Vamorolone
V/F	Oral volume of distribution
XR(P)D	X-ray (powder) diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Santhera Pharmaceuticals (Deutschland) GmbH submitted on 29 September 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Agamree, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 June 2020.

Vamorolone was designated as an orphan medicinal product EU/3/14/1309 on 22 August 2014 in the following condition: Treatment of Duchenne muscular dystrophy.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Agamree as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/Agamree

The applicant applied for the following indication: Treatment of Duchenne muscular dystrophy (DMD) in patients aged 2 years and older.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0295/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0295/2022 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's request(s) for consideration

1.5.1. New active Substance status

The applicant requested the active substance vamorolone contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific Advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
22 January 2015	EMA/CHMP/SAWP/47013/2015	André Elferink, Mario Miguel Rosa
17 December 2015	EMA/CHMP/SAWP/819793/2015	Susan Morgan, André Elferink
17 October 2019	EMA/CHMP/SAWP/545127/2019	Karl-Heinz Huemer, Fernando de Andrés Trelles
29 January 2021	EMA/SA/0000047033	André Elferink, Stephan Lehr

The scientific advice and protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- The quality characteristics of drug product and the choice of formulation; the proposed changes in formulation and use of the new formulation for the Phase 2a extension study and Phase 2b study; the justification for not conducting a BE study between the formulation #1 and formulation #2; the proposed justification for new active substance.
- The approach for reproductive, juvenile and chronic toxicology studies; the availability of chronic toxicology data prior to the initiation of the Phase 2a study; the approach for conducting MIST studies; adequacy of non-clinical package for MAA; the approach to perform the carcinogenicity studies post approval.
- Adequacy of the clinical pharmacology studies for MAA.
- The proposed doses, treatment times and extension study for the Phase 2a clinical study; the Phase 2a clinical study design regarding the proposed extension study clinical outcomes and pharmacodynamics biomarker outcomes for dose selection in the Phase 2b study.
- The design of the phase 2b clinical study and in particular the proposed doses, choice of age at treatment, primary clinical outcome measure, time of treatment, sample size; whether the proposed endpoint would be supportive for conditional approval; the proposed efficacy analysis and safety data package for conditional approval; the approach to convert conditional approval to full approval; the analysis approach for the confirmatory study VBP15-004 including estimand, primary, secondary and sensitivity analyses, additional efficacy data from concurrent external controls, and overall safety data including data from concurrent external controls.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Elita Poplavska

The application was received by the EMA on	29 September 2022
The procedure started on	27 October 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 January 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	01 February 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	31 January 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 February 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	15 May 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 June 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	06 July 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	20 July 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	11 September 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	27 September 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Agamree on	12 October 2023
The CHMP adopted a report on similarity of Agamree with TRANSLARNA on (see Appendix on similarity)	12 October 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	12 October 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

In reference to the marketing authorisation application, vamorolone is intended for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older.

2.1.2. Epidemiology

DMD is a severe, progressive paediatric neuromuscular disorder that is ultimately lethal. It 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 approximately 15,000 cases.

2.1.3. 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.

2.1.4. Clinical presentation, diagnosis

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) accompanied with speech and/or global developmental delay. 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 method for diagnosing DMD has not changed during the last decade. 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.

2.1.5. Management

No medical cure exists for DMD, and the disease has a poor prognosis. The main aim of DMD treatment is the modification of the natural course of the disease or prolonging survival. Treatment is centred on glucocorticoid therapy, prevention of contractures, and medical care of cardiomyopathy and respiratory compromise (Shimizu-Motohashi 2019; McMillan 2019). Glucocorticoids should be continued 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 glucocorticoids in younger children, before significant physical decline (Merlini 2012; Lamb 2016). 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. Prednisone is

available and widely used in the US and in the European Union but is not specifically indicated for DMD. Thus, neither prednisone nor deflazacort are approved for the treatment of DMD in Europe.

For a subpopulation of DMD patients, in which mutation created a nonsense stop codon in the dystrophin mRNA resulting in premature termination of translation and, hence, a truncated, non-functional protein, ataluren (Translarna) was granted a conditional marketing authorisation in the EU on 31 July 2014 (EMEA/H/C/2720) for the treatment of patients aged 5 years and above, which has been extended to ambulatory patients aged 2 years and older.

Thus, there is an unmet medical need for mutation-independent treatments similar to glucocorticoids with an acceptable benefit-risk profile.

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 initially proposed by the applicant was:

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

The indication for vamorolone as finally approved by the CHMP is:

"*Treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older*."

The recommended dose of vamorolone in patients 4 years and older 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 once daily.

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

2.3. Type of application and aspects on development

The vamorolone clinical development programme for DMD includes 10 clinical studies: 6 clinical pharmacology studies in healthy subjects and subjects with hepatic impairment (HI), and 4 studies in boys with DMD (a pivotal phase 2b study VBP15-004, a phase 2a open-label study VBP-002, a phase 2 open-label study VBP15-003, and a phase 2 open-label study VBP-LTE).

The quality, pre-clinical and clinical development of vamorolone were discussed within several centralised scientific advice (see above).

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as oral suspension containing 40 mg/ml of vamorolone as active substance.

Other ingredients are: citric acid (monohydrate) (E 330), disodium phosphate (E 339), glycerol (E 422), orange flavour, purified water, sodium benzoate (E 211), sucralose (E 955), xanthan gum (E 415), hydrochloric acid (for pH adjustment).

The product is available in an amber glass bottle containing 100 ml of the suspension as described in section 6.5 of the SmPC. Two 8 ml oral dosage syringes graduated in 0.1 ml increments and a press-in bottle adapter are included.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of vamorolone is (8S,10S,13S,14S,16R,17R)-17-hydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-7,8,12,14,15,16-hexahydro-6H-cyclopenta[a]phenanthren-3-one corresponding to the molecular formula $C_{22}H_{28}O_4$. It has a relative molecular mass of 356.46 g/mol and the following structure:

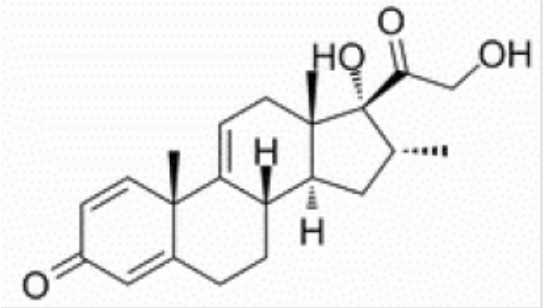


Figure 1: Active substance structure

The chemical structure of vamorolone was elucidated by a combination of elemental analysis, UV, FT-IR, 1H-NMR, 13C-NMR, and MS. The solid state properties of the active substance were measured by XRPD, DSC and TGA.

The active substance is a slightly hygroscopic micronised powder, it has poor aqueous solubility across the physiological pH range.

Vamorolone exhibits stereoisomerism due to the presence of six chiral centres. These centres originate in the starting material and are controlled in the specifications of the starting material and active substance by specific optical rotation.

Only one stable polymorph of vamorolone has been observed. The manufacturing process has been demonstrated to produce the stable polymorphic form. Testing via XRPD during stability studies has shown that micronisation and storage do not impact the polymorphic form. Therefore, the polymorphic form is not tested routinely at release.

2.4.2.2. Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided and was considered satisfactory. Vamorolone is synthesised in seven main steps using well defined starting materials with acceptable specifications.

During the procedure, an MO was raised on the absence of sufficient information on the control strategy and impurity profile of a proposed starting material. This was resolved by the provision of sufficient information on the impurity profile and the justification provided for the associated control strategy in the response. The starting material was therefore considered acceptable.

Reprocessing procedures have been described for certain steps to be performed in case of out of specification results. The manufacturing steps will be repeated and no other solvents or raw materials are used.

Critical process parameters of the manufacturing process of vamorolone have been identified and controls established. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised, including potential mutagenic impurities.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. Changes introduced have been presented in sufficient detail and have been justified. An initial route of synthesis (ROS1) was developed for vamorolone active substance and was used during development for the finished product. It differs from the proposed commercial route of synthesis (ROS2) used. Batches of vamorolone active substance manufactured with the ROS1 synthetic route were used for clinical studies. A commercially suitable route of synthesis ROS2 has been developed. Active substance manufactured by ROS2 was evaluated in the PK study (VBP15-PK-FORM) comparing the proposed to be marketed formulation to the earlier clinical formulations using ROS1.

The active substance is micronised. The particle size of the active substance impacts both the in-vitro dissolution and the in-vivo pharmacokinetics as outlined in study VBP15-PK-FORM. Further information on the pharmacokinetic studies conducted can be found in the clinical section of the report.

The active substance is packaged in bags which comply with EC 10/2011 as amended, and Ph. Eur. requirements. The bags are placed into drums.

2.4.2.3. Specification

The active substance specification includes tests for: appearance, identity (IR), assay (HPLC), related substances (HPLC), residual solvents (Gas Chromatography), water content (Ph. Eur.), residue on ignition (Ph. Eur.), particle size distribution (laser light diffraction), specific optical rotation (Ph. Eur.) and microbiological quality (Ph. Eur.)

Impurities present at higher than the qualification threshold according to ICH Q3A (0.15%) were qualified by toxicological and clinical studies, and appropriate specifications have been set. The limits for un-qualified impurities are set in accordance with ICH Q3A requirements.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The particle size limits for the micronised active substance are set in line with those used in the finished product batches investigated in the PK studies.

Batch analysis data (13 batches, 10 at commercial scale) of the active substance are provided. The analysis includes both micronised and non-micronised active substance produced using the commercial route of synthesis (ROS2). The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from three batches of micronised active substance, one at commercial scale and two at pilot scale from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 24 months (one batch) and 12 months (two batches) under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. In addition to this, supportive stability results of four commercial batches of non-micronised active substance were provided for 24 months at the same conditions. Photostability testing following the ICH Q1B guideline was performed on one batch. Results on stress conditions in both the solid and liquid phase were also provide on one batch. Stress testing conditions included heat, humidity, acidic, neutral, alkaline, light, and oxidation.

The following parameters were tested*:* appearance, assay (HPLC), related substances (HPLC), specific optical rotation (Ph. Eur.), water content (KF), polymorphic form (XRPD), particle size distribution (laser light diffraction) and microbiological quality (Ph. Eur.). The analytical methods used were stability indicating.

At long term and accelerated storage conditions no significant changes are seen in any of the parameters investigated, all results remain within specification.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months in the proposed container. The stability results do not indicate a need for a temperature storage condition, however the applicant's self-imposed storage condition is acceptable. The proposed storage conditions of an active substance do not impact the patient or healthcare professionals.

With respect to ongoing stability studies any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Vamorolone oral suspension is a 40 mg/mL (4.0% w/v) orange flavoured suspension for oral administration.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of the in-house orange flavouring. The composition of the in-house flavouring was suitably described. Excipients were appropriately justified in line with the proposed paediatric patient population. The levels of the preservative selected were suitably justified, the applicant demonstrated that the lowest effective levels for antimicrobial preservation were selected. The list of excipients is included in section 6.1 of the SmPC.

The product was formulated as a multi-dose oral suspension containing 40 mg/mL of vamorolone. The formulation was developed and altered throughout the clinical phases, and an optimised to be marketed formulation was selected based on improved stability, manufacturability, and palatability.

The different clinical formulations demonstrated similar *in vitro*-dissolution profiles. Vamorolone is a BCS Class II compound displaying poor aqueous solubility across the physiological pH range. Only one stable polymorph is known and the active substance manufacturer has been shown to reproducibly manufacture this form. The particle size of the active substance is important to finished product performance (i.e. bioavailability), and micronisation of the active substance also improves physical stability of the product and palatability. The commercial formulation was compared to the earlier clinical formulations in PK studies. Overall the to-be-marketed formulation was considered acceptable, for further information please refer to the clinical section.

It is foreseen that administration via enteral feeding tubes may be relevant for some patients receiving this product. In the course of the assessment the applicant was requested to provide information on the administration via enteral feeding tubes. The applicant indicated that further investigations were required in order to provide this information which would take additional time. A recommendation for further quality development is therefore raised, requesting that these investigations are performed and the outcome of this recorded in the product information (REC1).

A dissolution method was developed, the selected method was demonstrated to be suitably discriminating with respect to particle size of the active substance. Viscosity was also identified as important to ensure dosage uniformity.

The manufacturing process has been developed using elements of QbD such as risk assessment, and potential critical material attributes and critical process parameters were identified.

The primary packaging is an amber glass bottle. The material complies with Ph. Eur. requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. Evidence of relevant CE marks were provided for the oral dosing devices.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site. The process is considered to be a standard manufacturing process.

The manufacturing process and dosage form are considered standard. The applicant has committed to perform process validation on the first three full-scale batches. An acceptable process validation protocol was provided. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. Product specification

The finished product specifications include appropriate tests for this kind of dosage form; appearance (visual & odour), viscosity (Ph. Eur.), re-dispersibility (in-house), pH (Ph. Eur.), identification of active substance (HPLC, PDA), identification of preservative (HPLC), assay of active substance (HPLC), assay of preservative (HPLC), related substance (HPLC), particle size (laser light diffraction), dissolution (USP paddle / HPLC), deliverable volume (USP), uniformity of dosage units (Ph. Eur.) and microbiological quality (Ph. Eur.).

The limits for impurities have been set in line with the relevant ICH guidance, the specification limit for an impurity exceeds the ICH qualification threshold. Sufficient data has been provided to qualify and justify the impurity at the level proposed.

During the procedure, the applicant tightened the dissolution limit and the proposed limit is considered acceptable. It was noted that it may be possible for the limit for dissolution to be set tighter in line with the clinical batch performance. Considering this a recommendation for further quality development to re-evaluate the dissolution limits was noted (REC2).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches using a ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the finished product. Therefore, no specific control measures for nitrosamine impurities are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial sized batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 24 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. In addition to this, data from supportive stability studies on earlier formulations was provided. The applicant initially had not submitted sufficient data to support their request for a 24-month shelf life, as the available time-points were not sufficient to enable an extrapolation of the magnitude requested. A major objection was raised regarding this point, and in response the applicant submitted further data which supported the requested shelf life.

Samples were tested for appearance (visual & odor), viscosity (Ph. Eur.), re-dispersibility (in-house), pH (Ph. Eur.), assay of active substance and the preservative (HPLC), related substances (HPLC), particle size (laser light diffraction), dissolution (in-house), microbiological quality (Ph. Eur.). The analytical procedures used are stability indicating.

The tested parameters are generally stable over time at all testing points and at both long-term as well as accelerated storage conditions. Viscosity values show a decrease over time, but values remain within the validated range. Dissolution data show some variability; however the results indicate no significant trends and no OOS are reported. The results for batch 5149662 were out of specification for the particle size at certain time-points. The OOS results related to issues with the method of analysis used at that

time which was further amended, all results with the amended method are compliant as demonstrated during stability studies.

With respect to ongoing stability studies. In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

Based on available stability data, the proposed shelf-life of 24 months with no specific storage condition as stated in the SmPC (section 6.3) for the un-opened product are acceptable.

In-use stability was investigated on two commercial scale batches at 45, 90, and 140 days, when stored at 2-8°C. With respect to the 140 day time-point, OOS results for assay (decreased values) were observed, therefore it is not possible to set longer in-use shelf life than 90 days. The latest age of the batches available to conduct the testing were from the 14 month time-point. Considering this point the applicant is also recommended to conduct further in-use stability testing with a batch closer to the 24 month time-point, and a relevant commitment by the applicant was provided (REC3). Overall the available data confirm the appropriate shelf life for the opened product is 3 months when stored upright within a refrigerator (2-8°C).

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure, two major objections were raised on the choice of active substance starting material and its impurity control, and on the extent of stability extrapolation to support the claimed finished product shelf life. Further information was provided to justify the proposed control strategy for the starting material of the active substance and further stability data was provided to support the proposed finished product shelf-life. The MOs were considered to be resolved. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, these concern the finished product and relate to the feasibility of administration via enteral feeding tubes, potential re-evaluation of the limit for dissolution in light of further batch data, and performing additional in-use stability testing at the end of shelf life. These points are put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to investigate the feasibility of the administration of the product via enteral feeding tubes in line with the Quality of medicines questions and answers: Part 2, and update the product information based on the outcome of this investigation. It is recommended that the results and updated Product Information be submitted.
2. The applicant is recommended to re-evaluate the proposed dissolution limit for the finished product when results from the process validation batches are available. It is recommended that the results and supporting updated documentation be submitted.
3. The applicant is recommended to perform further in-use stability testing at the end of the shelf life of the finished product. It is recommended that such testing is conducted on at least one batch close to 24 months in age and that the results be submitted.

2.5. Non-clinical aspects

2.5.1. Introduction

Vamorolone was identified in a screen for corticosteroid analogues with retained anti-inflammatory transrepression activity but reduced transactivation properties at the GR. The 21-aminosteroids (*"lazaroids"*, e.g., tirilazad) and anecortave had served as prototypes for these analogues and contain a double bond between carbon atoms 9 and 11 of the steroid C-ring instead of the 11β-hydroxyl or carbonyl moiety of known members of the glucocorticoid class (Baudy *et al*., 2012).

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Primary pharmacodynamics *in vitro*

Vamorolone was profiled against other corticosteroid candidates by its effective inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kb) inflammatory target genes, which was similar to prednisolone in myoblasts and myotubes *in vitro* (IC_{50} of $2.16\text{-}2.76\times10^{-8}$ M vs. $1.44\text{-}9.91\times10^{-7}$ M, respectively). This anti-inflammatory activity of vamorolone was dependent on nuclear translocation of the GR and consequently abolished in mutant fibroblasts lacking a functional GR. Contrary to prednisolone and dexamethasone, however, the interaction of vamorolone with the GR does not seem to efficiently stimulate GRE-driven transcriptional activation and repression based on lower induction of serum/glucocorticoid regulated kinase 1 (Sgk1) and receptor activator of nuclear kappa-B ligand (RANKL) as well as lesser downregulation of adrenocorticotropic hormone (ACTH) secretion *in vitro*.

X-ray crystallography of the ligand-binding domain of the GR indicates that the structural difference at carbon 11 of the steroid C ring of vamorolone might account for its distinct pharmacodynamic (PD) activity compared to other glucocorticoids. The absence of the hydroxyl group at carbon 11 could also result in the antagonism of vamorolone at the MR, because this hydroxyl group is required for effective hydrogen bond formation with the ligand-binding domain of the MR and therefore present in other

members of the glucocorticoid class that act as MR agonists. In fact, vamorolone was unable to activate the MR like deflazacort in a cellular reporter assay, but rather demonstrated comparable MR antagonist potency like eplerenone.

In cultures of either wildtype myotubes or myoblasts from a patient with limb girdle muscular dystrophy 3B, 1 to 100 µM vamorolone concentration-dependently appeared to alleviate laser- or glass bead-induced experimental membrane damage, while the enhanced intracellular flurorescent dye influx after prednisolone incubation indicated significantly deteriorated damage of myotubes.

Primary pharmacodynamics *in vivo*

Primary PD *in vivo* investigations compared the activity vamorolone with prednisolone, the active metabolite of the glucocorticoid prednisone, in the well-established mdx mouse model of human DMD. Due to the age-dependently different severity of the muscle phenotype of mdx mice, this comparison was performed in mdx mice starting from either post-natal day (PND) 15 for 6 weeks and from adulthood for 4 months. Prednisolone and vamorolone decreased the body weight of young (-18 % vs. -9 to -11%) and at lower magnitude also adult mdx mice indicating a catabolic effect (-10 % vs. -9 %). Owing to the more severe dystrophic phenotype of younger mdx mice, both vamorolone and prednisolone similarly increased grip strength, particularly in the forelimb of these animals, whereas grip strength was not improved after prolonged administration of the two glucocorticoids in older mdx mice. The separate *in vitro* investigation of the *extensor digitorum longus* muscle prepared from vamorolone and prednisolone treated animals did not suggest relevant differences in the functional improvement between the two age groups. Vamorolone also effectively diminished cellular Cathepsin B protease activity in mdx mice, which was comparable to prednisolone at the 30 mg/kg/day vamorolone high dose. The Cathepsin B decrease was less prominent in older mdx mice for both glucocorticoids. Histologically, vamorolone doses ≥15 mg/kg/day effectively reduced diaphragm inflammations in both age groups of mdx mice. A similar reduction was only detected following prednisolone administration of older mdx mice.

Prednisolone further caused degenerations in *gastrocnemius* muscle of young mdx mice and induced cardiac hypertrophy as well as cardiac fibrosis at the two age levels. Vamorolone did not evoke cardiac hypertrophy and mild signs of cardiac fibrosis were restricted to young mdx mice. In addition, vamorolone did not adversely affect bone development of PND 12 wildtype and young mdx mice, which coincides with the lack of relevant *in vitro* induction of the bone resorption marker RANKL. In contrast, prednisolone significantly activated RANKL expression resulting in shortened body and tibia length in the young mdx mice, which was associated with lower trabecular thickness of the animals.

The immunosuppressive activity of vamorolone and prednisolone resulted in dose-dependent and significant reductions of spleen weight and peripheral blood leukocytes counts in young mdx mice. Still, splenocytes were significantly decreased only by prednisolone. Lymphocyte phenotyping unravelled that prednisolone reduced B cells, naïve and regulatory T cells, whereas only high dose vamorolone diminished naïve T cells. These data coincide with the outcome of a T cell dependent antibody response (TDAR) study in mice (see below).

The general anti-inflammatory effect of vamorolone has been substantiated in the experimental autoimmune encephalitis (EAE) model of human multiple sclerosis in mice. Daily doses of either 30 mg/kg vamorolone or 15 mg/kg prednisolone were orally administered one day before EAE induction until study termination on day 20. Vamorolone significantly reduced EAE severity, but not as efficient as prednisolone, which additionally seemed to delay EAE onset. Nevertheless, the number of inflammatory foci in the spinal cord of animals treated with vamorolone or prednisolone was comparable. The low number of just 7 mice per group might have interfered with more meaningful results.

2.5.2.2. Secondary pharmacodynamic studies

Vamorolone only showed significant agonistic activity at the GR and antagonism at the MR *in vitro but* unveiled no relevant affinity to 19 other steroid hormone or other CNS receptors, ion channels, and transporters.

2.5.2.3. Safety pharmacology programme

The impact of vamorolone on vital functions has been evaluated in the core battery of safety pharmacology investigations in adherence to prevailing ICH S7A and B guidelines (CPMP/ICH/539/00; CPMP/ICH/423/02). Vamorolone did not inhibit human ether-a-go-go-related gene (hERG) potassium currents up to the highest concentration of 20 µM *in vitro*. Accordingly, oral vamorolone doses up to 50 mg/kg did not impair cardiovascular and respiratory function in telemetered dogs. Likewise, multiple oral administrations of the same dose in the chronic toxicity study in dogs did not affect electrocardiogram (ECG) parameters but induced reversible mild heart rate increases at the 39-week post dose interval.

Vamorolone did not induce neurobehavioural changes in a functional observation battery in mice, which coincides with results of the 10 weeks juvenile toxicity study in this species that did not indicate any impact on motor activity, auditory startle habituation or the performance in the Morris water maze (see below).

2.5.2.4. Pharmacodynamic drug interactions

No PD drug-drug interaction (DDI) studies have been performed or are deemed necessary.

2.5.3. Pharmacokinetics

The pharmacokinetic (PK) characteristics of vamorolone were evaluated *in vitro* and after single oral or i.v. administration in mice, rats and dogs. These investigations were complemented by toxicokinetic determinations in repeated dose toxicity studies in mice, dogs and monkeys, metabolic profiling and *in vitro* DDI studies.

Vamorolone was quantified in the range of 1.0 - 1,000 ng/ml in plasma of mice, dogs and monkeys by liquid chromatography coupled with tandem mass spectrometry, which was validated in compliance with GLP for use in pivotal toxicology studies.

Vamorolone showed moderate to high permeability in Caco-2 monolayers and artificial membranes *in vitro*. Its solubility was higher in artificial gastric fluids simulating fed compared to fasted state, which has been clinically substantiated (see below and section 4.2 of the Summary of Product Characteristics (SmPC)). For investigations of PK *in vivo* parameter, the poor water solubility of vamorolone necessitated its formulation in either the non-ionic water-dispersible surfactant Labrafil or in a mixture of ethanol, DMSO, PEG400 and hydroxypropyl-β-cyclodextrin (HP-β-CD).

Single oral vamorolone doses of 50 mg/kg in mice and rats or 30 mg/kg in dogs, resulted in relatively fast absorption in mice (time to maximum drug concentration (t_{max}) of 2 h)) with bioavailability of 74.5 %, whereas absorption of the same dose was delayed and oral bioavailability lower in rats (t_{max} of 4 h; F of 47.8 %) and dogs (t_{max} of 6 h; F of 53.2 %). The oral elimination half-life was shortest in mice (~40 min) and prolonged in rats and dogs (~2.3 h). Similarly, mice showed higher clearance than rats and dogs after single i.v. injection of 10 mg/kg vamorolone.

Following multiple oral vamorolone administrations for up to 26 weeks in mice, 39 weeks in dogs and 7 days in monkeys, the t_{max} was confirmed at 1-2 h mice, prolonged to 2-4 h in dogs and seemingly extended to 4-12 h in monkeys, although the low number of monkeys might have precluded reliable determinations. The peak plasma concentrations increased in a roughly dose-proportional manner in all three animal species. Whilst dose proportionality was also apparent for area under the drug concentration versus time curve from 0 to 24 hours (AUC_{0-24h}) in dogs and monkeys, the increase was more than dose-proportional in mice. In all species, maximum drug concentration (C_{max}) and AUC_{0-24h} lacked any obvious sex difference. However, the C_{max} and AUC_{0-24h} based vamorolone exposure clearly dropped in the course of all multiple dose investigations in mice (1.5- to 5.7-- fold lower) and monkeys (1.2- to 2.9-fold lower), particularly at mid and high dose levels. In contrast, AUC_{0-24h} tended to increase over the study duration in dogs (1.2- to 3.2--fold) pointing towards drug accumulation.

Vamorolone demonstrated comparable plasma protein binding in mice (86.7 %), dogs (77-81.1 %) and humans (88.1 %) *in vitro*. The blood/plasma ratio was similar between mice and humans (0.68 vs. 0.87), whereas the distribution of vamorolone into red blood cells was 2-fold lower in mice (0.33) than in humans (0.74).

Vamorolone rapidly and effectively transferred into the brain of mice with maximum plasma/brain ratio of approximately 0.6 at 0.5 h after single oral administration. A subsequent Quantitative Whole Body Autoradiography (QWBA) study revealed wide tissue distribution of ^{14}C-labelled vamorolone in pigmented rats with highest radioactivity levels in the gastrointestinal tract and liver. A slight distribution to melanin-containing pigmented layer of the retina was also detected. Thereafter, radioactivity was eliminated with prolonged half-lives of about 107 h in stomach, 47 h in caecum, 85 h in small and large intestine and 109 h in liver. Low levels of up to 3 % of the total AUC were determined in skeletal muscle, heart and kidney medulla, but were retained in these organs for an extended period as indicated by half-lives of 25.4 days, 16.9 days and 12.4 days, respectively.

Vamorolone unveiled similar *in vitro* metabolic stability when incubated for 1 h with pooled liver microsomes of mice (88.5 %), dogs (92.5 %), monkeys (100.3 %) and humans (82.7 %), which contrasts the poor stability in rats (35 %). Accordingly, minimal to moderate metabolism of vamorolone was found within 4 h in hepatocytes of mice, dogs, monkeys, and humans compared to the extensive metabolic degradation in rats.

In vitro metabolic reactions comprised primarily hydroxylation, hydrogenation, hydroxyl oxidation and glucuronidation. Subsequent high resolution *in vivo* metabolic profiles identified ten circulating metabolites of vamorolone in plasma of mice, dogs, and adult healthy human volunteers. Except the oxidation product M5 and the dehydrogenation metabolite M6 in mice as well as the hydrogenated compound M10 in dogs, all other metabolites were glucuronide conjugates. Four of these glucuronides are major metabolites representing >10 % of the total vamorolone-related AUC in human plasma. However, only the hydrogenated main glucuronide M7 was similarly quantified in dog plasma, whereas the direct O-glucuronide M3 of vamorolone and the hydrogenated major glucuronides M8 and M9 just amounted to <1 % of total drug levels in mice and dogs.

The major human metabolites M3 and M7 were also confirmed in paediatric DMD patients aged 4 to 7 years and amounted to 34.42 % and 37.84 % of the total vamorolone-related exposure. As observed in adult human subjects, the amounts of M3 were higher in young DMD patients than in mice and dogs, while those of M7 were similar between dogs and paediatric patients. Albeit three less prominent human metabolites were additionally determined (<3 % of the drug-related exposure), the hydrogenated major glucuronides M8 and M9 and other minor metabolites of adult human subjects were not found, which might be explained by the shorter sampling period of just 8 h in DMD patients compared to the 24 h time frame in adult subjects.

The excretion of vamorolone was investigated following i.v. bolus injection in bile duct-cannulated albino rats and after oral administration in the mass-balance study in pigmented rats. In line with the extensive turnover of vamorolone in rat liver microsomes *in vitro*, the plasma levels of unchanged vamorolone were low and tiny amounts of the injected i.v. dose were detected in bile (0.04 %) and urine (0.6 %). Likewise, orally administered ^{14}C-labelled vamorolone was predominantly excreted via faeces (~80 %) compared to urine (~10 %) within 24 h.

In PK DDI studies, ≥5 µM vamorolone concentration-dependently induced CYP3A4 and to a lesser extent of CYP2B6, but did not induce CYP1A2, CYP2C8, CYP2C9 and CYP2C19. Vamorolone showed no relevant inhibition of CYP450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5) and minor inhibition of UGT1A1 (uridine 5 diphospho glucuronosyltransferase) (24.4 %) and UGT2B7 (7.65 %) at the highest 50 µM concentration.

Vamorolone was no substrate for the drug transporters BCRP (breast cancer resistance protein), BSEP, (bile salt export pump) P-gp (P-glycoprotein), MATE1 (multidrug and toxin extrusion protein), MATE2-K, OAT1 (organic anion transporting polypeptide), OAT3, OCT2 (organic cation transporter), OATP1B1 (organic anion transporting polypeptide) and OATP1B3. In addition, vamorolone did not reveal any significant inhibition of BCRP, BSEP, MATE-1, P-gp, OAT1, OCT2, OATP1B1 and OATP1B3. Nevertheless, vamorolone inhibited the renal transporters MATE2-K with half maximal inhibitory concentration (IC_{50}) of 12.9 µM and OAT3 with IC_{50} of 19.6 µM.

2.5.4. Toxicology

Vamorolone was evaluated in oral repeated-dose toxicity studies for up to 6 months in mice and 9 months in dogs, while exploratory dose-finding over 7 days was also conducted in Cynomolgus monkeys. Mice were selected as pharmacologically responsive species and because of their similar metabolic profile to humans, whereas dogs were chosen due to the established experience with glucocorticoid effects in this species.

2.5.4.1. Single dose toxicity

Single dose toxicity studies have not been conducted with vamorolone, which coincides with prevailing ICH and European guidance (EMA/CPMP/ICH/286/1995; EMA/CHMP/SWP/81714/2010). Nevertheless, the dose escalations in initial dose-range findings studies indicated that the approximately lethal doses after oral vamorolone administration were >500 mg/kg in mice and monkeys and >750 mg/kg in dogs.

2.5.4.2. Repeat dose toxicity

Repeat-dose toxicity studies revealed a largely consistent profile of various toxicities that were induced in a dose- and time-dependent manner, albeit different species-specific sensitivities towards vamorolone were also eminent. No vamorolone related mortalities were evident. The target organs for vamorolone toxicities comprised the lymphatic system, liver/gall bladder, pancreas, adrenal glands and kidneys, reproductive organs of both sexes, thyroid, salivary glands, skin and skeletal muscle. Long-term vamorolone administration also promoted food consumption and weight gain in mice and dogs. In chronic toxicity studies, no-observed-adverse-effect levels (NOAELs) of 45 mg/kg/day in mice and 2 mg/kg/day in male dogs were established, whereas a NOAEL could not be defined for female dogs given the prominent interference of vamorolone with ovarian cycling (see below).

Lymphatic system

In all toxicity studies in mice and dogs, lymphoid tissues including spleen, thymus and lymph nodes (mesenteric and mandibular lymph nodes as well as gut-associated lymphoid tissue) were generally smaller at vamorolone doses ≥10 mg/kg/day. The decreased size reflected the mild to moderate depletion of lymphocytes within lymphoid tissues and in the circulation at ≥5 mg/kg/day vamorolone in mice and ≥2 mg/kg/day in dogs. After cessation of vamorolone administration, compensatory lymphocyte hyperplasia was observed in thymus and spleen of mice, whereas the lymphoid depletion did not completely reverse in the recovery periods of the 28 days and 39 weeks toxicity studies in dogs.

Liver, gall bladder

Vamorolone doses ≥10 mg/kg/day further increased the liver weight in all toxicity studies in mice and dogs. The liver hypertrophy correlated histologically with mild to moderate centrilobular hepatocyte vacuolation representing glycogen and lipid accumulations, respectively. Concomitantly, triglycerides and cholesterol were reversibly elevated upon long-term dosing of ≥10 mg/kg/day vamorolone in mice and dogs. In the chronic toxicity study in dogs, hypertrophy and vacuolation was additionally observed in the gall bladder mucosa at ≥2 mg/kg/day and in bile duct epithelia at ≥10 mg/kg/day. Moreover, single hepatocellular and focal/subcapsular inflammation/necrosis developed dose- and time-dependently in mice (100 mg/kg/day after 7 days, ≥10-30 mg/kg/day after 28 days and ≥15 mg/kg/day after 26 weeks) but was only detected in the 50 mg/kg/day high dose group of the 39 weeks toxicity study in dogs. The focal inflammation/necrosis might be secondary to the observed hepatocellular hypertrophy and vacuolation. Given the short recovery periods of 14 to 28 days of subchronic and chronic toxicity studies, hepatocellular vacuolation and liver inflammation/necrosis only partially reversed in individual mice and only diminished in severity in dogs.

Hepatic changes were associated with dose- and time-related elevations of liver enzymes in mice and dogs. Long-term administration of 45 mg/kg/day vamorolone in mice induced alanine aminotransferase (ALT; up to +5.3-fold), aspartate aminotransferase (AST; +1.7-fold), alkaline phosphatase (ALP; up to +3-fold) and bilirubin (+1.5-fold). More pronounced increases of liver enzymes were determined following chronic vamorolone doses of 50 mg/kg/day in dogs comprising AP (up to +11.1-fold), ALT (up to +7.7-fold), AST (up to +2.1-fold) and gamma glutamyl transferase (GGT; up to +18.8-fold). The increased liver enzymes partially normalised in the recovery periods in mice and dogs. The liver and gall bladder inflammations also possibly accounted for elevations of inflammatory parameters (neutrophils, monocytes, fibrinogen, albumin, globulin and platelets) after vamorolone doses of ≥10 mg/kg/day in mice and ≥50 mg/kg/day in dogs. Some of these markers were also affected in the dose range finding (DRF) study in monkeys.

Pancreas

Minimal to mild increases of pancreatic islet hypertrophy were detected in several mice administered the 45 mg/kg/day vamorolone high dose in the chronic toxicity study and persisted with lower incidence and severity until the end of the recovery period. Comparable findings were neither identified after shorter vamorolone treatment durations at higher doses in mice, nor in dogs.

Adrenal gland

Repeated vamorolone administration ≥5 mg/kg/day in mice promoted mild to moderate vacuolar degeneration in the X zone of the adrenal cortex and atrophy of the cortical *zona fasciculata*. Following chronic dosing, ceroid pigment deposits were additionally observed. In dogs, bilateral adrenal cortex atrophy in the *zona fasciculata* and *zona reticularis* was evident at ≥2 mg/kg/day, which was adverse at ≥10 mg/kg/day and accompanied by hypertrophy in the *zona glomerulosa*. The adrenal cortical vacuolation, atrophies and ceroid deposits did not completely reverse in the recovery period in mice and dogs, particularly in those groups that had formerly received the respective vamorolone high dose.

However, the minimal to mild hypertrophy in the *zona fasciculata* in mice and in the *zona glomerulosa* in dogs partially compensated for the adrenal cortex atrophy after long-term administrations.

Kidney

Increased kidney weights (up to +51.8 %) with bilateral tubular vacuolation were detected after chronic administration of ≥10 mg/kg/day vamorolone in female and following the 50 mg/kg/day high dose in male dogs. These changes were especially in high dose animals reflected in higher urine volumes (up to +6-fold) with concomitantly decreased serum urea nitrogen (up to -44 %), creatinine (up to -56 %) and chloride (-4 %) and higher potassium (+13 %) and phosphorus (up to +51 %) concentrations. The increased diuresis resulted in the dehydration of high dose animals, resolved in dogs until end of the recovery period at the vamorolone mid dose level, but persisted both histologically and in terms of electrolyte concentrations with lower magnitude in the high dose group. Different electrolyte imbalances were noted at higher vamorolone dosages ≥300 mg/kg/day in the 14 days DRF study in monkeys, but not observed in mice.

Testis, ovary

Vamorolone did not significantly affect sperm motility, caudal epididymis sperm concentrations and relative amounts of abnormal sperm in the chronic toxicity study in mice. Histological examinations of male dogs indicated degenerations of spermatocytes and spermatids within seminiferous testis tubules of the 50 mg/kg/day vamorolone high dose group leading to oligospermia and germ cell debris in the epididymides. The prostate gland of these males was smaller in size (approx. -60 %) and had minimally to moderately reduced secretory product. Upon vamorolone treatment cessation, the spermatocyte/spermatid degenerations partially recovered and remained identifiable in each one male dog of the mid and high dose groups, whereas the diminished prostate glands and exudates did not reverse in high dose animals.

In female animals, repeated vamorolone administrations for 28 days reduced ovarian weights at doses ≥30 mg/kg/day in mice and lowered uterus/cervix weight in dogs. Long-term vamorolone doses ≥2 mg/kg/day in the 39 weeks repeat-dose toxicity study in dogs resulted in bilateral absence of *corpora lutea* in the ovaries and other tissues of the reproductive tract of affected females confirmed the anovulation. In addition, mild vacuolation was identified in mammary gland duct epithelia of female dogs of the 50 mg/kg/day high dose group. Upon completion of the recovery phase, *corpora lutea* were still absent in one high dose female suggesting partial reversibility. Hence, a NOAEL could not be established for female dogs in this chronic toxicity study.

Thyroid

The thyroid/parathyroid gland weight was higher in the chronic toxicity study in male dogs at vamorolone doses ≥10 mg/kg/day, which correlated with bilaterally increased colloid within thyroid follicles. In contrast, thyroid/parathyroid gland weights overlapped between vamorolone-treated female dogs and corresponding controls, which hampered to identify an unambiguous difference. The study director hypothesised that surrounding mediastinal adipose tissue could have contributed to the variability in thyroid/parathyroid gland weights. However, mean weights at the end of the treatment phase rather pointed towards a dose-dependent effect, which was more prominent in male dogs (up to +97.5 %). Nevertheless, thyroid/parathyroid weights normalised until the end of the recovery period.

Parotid salivary glands

The parotid salivary glands of male and female dogs administered ≥10 mg/kg/day vamorolone in the chronic toxicity study revealed minimal to moderate increases of multifocal to diffuse cytoplasmic epithelial basophilia. The severity of this finding was reduced at the end of the recovery period but did not completely reverse in affected males and was still visible in one female dog of the 10 mg/kg/day

group. Comparable findings were also detected in juvenile mice, but not in the chronic toxicity study in adult mice.

Skin

Vamorolone doses of 100 mg/kg/day for 28 days and of 45 mg/kg/day for 26 weeks in mice and developed ≥10 mg/kg/day in the chronic toxicity study in dogs caused epidermal collagen thinning and diminished the number of anagen hair follicles resulting in alopecia/hypotrichosis. Decreased anagen follicles recovered incompletely until study termination in most mice that had previously received 15 or 45 mg/kg/day vamorolone doses, but largely resolved in dogs.

Skeletal muscle

Mild skeletal muscle atrophy of the exemplarily investigated *biceps femoris* was evident in dogs treated chronically with 50 mg/kg/day vamorolone, which was characterised by decreased myofibre size due to diminished sarcoplasm. The reduced muscle fibre bundles were separated by adipose tissue. Muscle atrophy was incompletely reversible until the end of the recovery period and remained detectable in each one male and one female dog.

Body weight

Repeated vamorolone doses of ≥10 mg/kg/day for 28 days in mice and at ≥60 mg/kg/day in the exploratory 28 days toxicity study in dogs reduced body weights and/or body weight gain. However, prolonged vamorolone administrations of 45 mg/kg/day for 26 weeks in mice and of ≥10 mg/kg/day for 39 weeks in dogs increased body weights and food consumption (+14 % and +23 % in male and female mice; +13 % to +46 % and +10 % to +21 % in male and female dogs). Upon completion of the recovery period, body weights remained slightly increased in male and female mice (+2 % and +25 % each), which correlated with the food consumption of the animals (-5.5 % in males and +9.3 % in females). The terminal body weights of dogs in the recovery phase were reduced in both sexes (up to -14 %) due to clearly lower food consumption (-54 % in males and -61 % in females, respectively). Hence, alterations in body weight and food consumption tended to reverse, if vamorolone treatment was stopped.

2.5.4.3. Genotoxicity

In vitro, vamorolone was negative for increased reverse mutations in Ames tests in bacteria and for chromosomal aberrations, polyploidy and endoreduplication in mouse lymphoma cells and a micronucleus assay in CHO-K1 cells, respectively. Vamorolone did also not increase the formation of micronuclei in polychromatic erythrocytes of mouse bone marrow *in vivo*.

2.5.4.4. Carcinogenicity

Carcinogenicity studies are planned to be conducted post approval as earlier agreed during scientific advice (EMA/CHMP/SAWP/545127/2019).

2.5.4.5. Reproductive and developmental toxicity

A standard battery of developmental and reproductive toxicology studies was not conducted since vamorolone is intended to treat DMD, which affects almost exclusively male patients.

Juvenile toxicity

Juvenile mice were evaluated for toxicity of vamorolone at dose levels up to 100 mg/kg/day for 8 weeks in an initial DRF study and for 10 weeks in the pivotal investigation. In both studies, vamorolone was orally administered from PND 21 onwards. This corresponds to the intended paediatric DMD patient population of 2 years and older. The main target organs in juvenile mice overlap with those of adult mice, i.e., the liver, spleen, thymus, lymph nodes, and adrenal glands. The findings in the adrenal glands (cortical atrophy), liver (hepatocellular vacuolation, hypertrophy, necrosis and degeneration) and lymphoid organs were considered consistent with the pharmacological activity of vamorolone (i.e., synthetic glucocorticoid/corticosteroid). Vamorolone did not affect neurobehaviour, the histopathology of neuronal tissues as well as specific lymphocyte subtypes in juvenile mice. Toxicokinetic analysis of vamorolone in juvenile mice were also consistent with those obtained in adult mice showing no gender differences, dose-dependently increased C_{max} and AUC-values followed by a 2- to 5-fold decline in AUC-values after multiple dosing.

Different from adult mice, however, minimal to mild mandibulary salivary gland hypertrophy accompanied by significantly decreased mandibular gland weight was detected in juvenile female mice at ≥15 mg/kg vamorolone, which was test-article related. No histopathological changes in mandibular salivary gland were noted upon completion of the recovery period, but decreased salivary gland weights were still present at a lower magnitude.

In males reduced mean tibia and body length were observed at 100 mg/kg and ≥15 mg/kg vamorolone, respectively. In females no effect on body lengths was observed, but tibia length was reduced at ≥30 mg/kg. These findings correlated with lower body weights and were attributed to the slower growth of the animals. Bone mineral density and bone structure as well as biomarkers of bone metabolism have not been investigated in the juvenile mouse toxicity studies.

No effects of vamorolone were observed on sexual maturation, first day of oestrous, oestrous cyclicity, reproductive and fertility indices, sperm evaluations, macroscopic observation, or organ weights in juvenile mice. However, uterine examinations showed marked increases in pre- and post-implantation losses and decreased numbers of viable embryos in the 100 mg/kg dose group compared to controls, albeit these lacked statistical significance. Nonetheless, no comparison with historical control data has been performed.

The NOAEL for the 10 weeks juvenile toxicity study for general toxicity in male and female juvenile mice is proposed to be <15 mg/kg/day based on the findings of adrenal atrophy, mandibulary salivary gland hypertrophy and decreased body lengths. Considering the AUC-levels at this 15 mg/kg/day vamorolone dose, no safety margin with respect to human exposure at the maximum recommended human dose (MRHD) exists.

2.5.4.6. Toxicokinetic data

Safety margins based on the C_{max}- and $AUC_{0\text{-}last}$-related exposure at the respective NOAELs determined in repeat-dose toxicity studies were negligible in adult or juvenile mice or not existent in dogs when compared to corresponding levels in human DMD patients at the MRHD.

2.5.4.7. Local tolerance

Given its administration as oral suspension, the local tolerability of vamorolone has not been investigated in dedicated studies in accordance with the pertinent European guideline (EMA/CHMP/SWP/2145/2000 Rev. 1, Corr. 1*). However, vamorolone showed favourable local tolerance after repeated oral dosing in mice, dogs and monkeys.

2.5.4.8. Other toxicity studies

As expected from the immunosuppressive activity of vamorolone and other glucocorticoids, 100 mg/kg/day vamorolone and prednisolone doses ≥10 mg/kg/day comparably inhibited the TDAR in female mice, while TDAR was completely abolished in male animals.

In accordance with ICH M7 requirements, the two vamorolone epoxides VBP-15-B-2 and VBP-15-B-3 did not indicate any mutagenic risk in a Quantitative structure–activity relationships *in silico* analysis complemented by a bacterial reverse mutation assay.

Vamorolone did not absorb in the range of 290-400 nM and has a molar extinction coefficient (MEC) of approximately 14,800 $l \cdot mol^{-1} \cdot cm^{-1}$.

2.5.5. Ecotoxicity/environmental risk assessment

The environmental risk assessment (ERA) provided for the steroid active substance vamorolone is considered incomplete. Vamorolone is considered as a potential endocrine active substance based on structure, mode of action, and non-clinical mammalian data on development and reproduction. The $PEC_{surfacewater}$ value did not exceed the action limit of 0.01 µg/l. The n-octanol/water distribution coefficient (log Dow) of vamorolone was determined to be <4.5. Thus, no PBT assessment is necessary.

A Phase II environmental risk assessment was not performed by the applicant for vamorolone.

However, the applicant confirmed to conduct the tiered ERA Phase II under a post approval commitment and committed to conduct the proposed studies based on whether vamorolone is readily biodegradable. A detailed letter of commitment has been submitted. According to an updated study schedule of the applicant the final ERA is scheduled to end Q3-2027.

The ERA could not be completed due to outstanding issues and the CHMP agreed that it could be completed during the post-authorisation phase.

Table 1: Summary of main study results

Substance (INN/Invented Name): vamorolone			
CAS-number (if available): 13209-41-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 at 20°C by the shake flask method	log Pow at pH 5: 2.4 log Pow at pH 7: 2.5 log Pow at pH 9: 2.4	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined (prevalence, Fpen = 0.000028)	0.0042	µg/L	>0.01 threshold (N)
Other concerns (e.g. chemical class)		Potentially endocrine active substance	(Y)

2.5.6. Discussion on non-clinical aspects

Pharmacology

Vamorolone shares the effective anti-inflammatory transrepression activity of NF-κB target genes via agonistic interaction with the GR with other members of the pharmaceutical class of corticosteroid agents. In contrast to other corticosteroids like prednisolone or dexamethasone, however, vamorolone revealed diminished transcriptional activation properties of genes, whose expression is driven by the glucocorticoid response element (GRE). Apart from this retained anti-inflammatory (transrepression) and reduced transactivation effects of vamorolone, further characterisation of potential downstream

signalling pathways including the possible role of membrane glucocorticoid receptors (mGRs) has not been investigated so far.

Vamorolone was also found to act as antagonist at the MR *in vitro*, which further contrasts the agonistic properties of other corticosteroids. The basis for the differential pharmacological activities seemingly relies on the molecular structure of vamorolone, which harbours a double bond between carbon atoms 9 and 11 of the steroid C-ring. Consequently, vamorolone lacks a hydroxyl or carbonyl group at carbon 11 of the steroid C-ring that is contained in all other known glucocorticoids.

X-ray crystal structures of the ligand binding domain of the GR complexed with either vamorolone, prednisolone or deacetylated deflazacort suggest that the missing hydroxyl group prevents efficient hydrogen bond formation of vamorolone with Asn564 of the GR, which might account for its preserved transrepression and reduced transactivation properties at the GR (Liu *et al*., 2020). Likewise, the hydroxyl group at carbon 11 of other glucocorticoids is essential for effective hydrogen bonding with Asn770 in the ligand-binding domain of the MR (Rafestin-Oblin *et al*., 2002) and, hence, required for MR agonist activity (Heier *et al*., 2019). As vamorolone lacks the hydroxyl group at carbon 11, it was found to act as MR antagonist *in vitro*.

Contrary to prednisolone, vamorolone concentration-dependently retained and possibly improved plasma membrane integrity of myotubes after experimental damage *in vitro* (Heier *et al*., 2019; Sreetama *et al*., 2018). The applicant hypothesises that the double bond between carbons 9 and 11 of vamorolone lowers its hydrophilicity, which might allow the more favourable orientation of vamorolone within membranes as earlier reported for the membrane-stabilizing properties of tirilazad (Audus *et al*., 1991; Wang *et al*. 1996). It seems noteworthy that vamorolone does not contain the positively charged piperazine moiety of tirilazad, which has been implicated to interact with negative phosphate groups of membrane lipids (Kavanagh and Kam, 2001). In the absence of further data, it remains therefore to be shown whether a similar membrane interaction also applies to vamorolone.

Compared to the vamorolone parent compound, its glucuronide metabolites revealed minimal GR-mediated transrepression and transactivation, which was attributed to steric interference with GR complex formation. However, the identity of the two investigated glucuronides could retrospectively not be clarified. Hence, pharmacological inactivity cannot be reliably concluded for the disproportionate human glucuronides, which are not appreciably formed in mice and dogs (see below). This further reduces the predictive value of the non-clinical toxicology programme, which did not establish any relevant safety margins in terms of human safety. As these limitations are meanwhile reflected in section 5.3 of the proposed SmPC, the issue is not further pursued.

"Proof-of-concept" for the proposed clinical DMD therapy was obtained in the well-established mdx mouse model. As the severity of the dystrophic phenotype of mdx mice depends on the genetic background and the age of these animals, mdx mice were administered vamorolone or prednisolone either from PND 15 for 6 weeks or from adulthood for 4 months. Despite similar molecular weights, oral vamorolone doses between 5 to 30 mg/kg/day were compared with a low 5 mg/kg/day prednisolone dose in mdx mice and in another mouse model of acute lung inflammation, which hampers to reliably evaluate the benefits and side effects of the two corticosteroids. However, 5 mg/kg prednisolone appears to be the maximum feasible oral dose in long-term experiments in mdx mice and avoids the detrimental impact of higher doses (Sali *et al*., 2012). With respect to the clinical translatability of the PD *in vivo* results, the apparent selection of female mdx mice had been questioned. Nevertheless, the efficacy of vamorolone in other inflammatory disease models in male animals and the clinical developmental programme in DMD patients do not suggest sex-specific differences in the PD effects.

Vamorolone and prednisolone similarly improved muscular function and diminished Cathepsin B protease activity, particularly in young mdx mice. Vamorolone also reduced diaphragm inflammations. Considering the lower propensity of vamorolone for GRE-mediated transactivation of muscle atrophy markers, the

known *in vivo* risk for muscle atrophy during long-term therapy with glucocorticoids seems to be lower with vamorolone. Still, the 50 mg/kg/day vamorolone high dose evoked mild skeletal muscle atrophy in dogs of the chronic toxicity study, which incompletely recovered in the rather short treatment cessation period of 4 weeks (see below).

It should be noted that vamorolone did not evoke cardiac hypertrophy in both age groups of mdx mice and mild signs of cardiac fibrosis were restricted to young animals, while prednisolone induced both cardiac hypertrophy and cardiac fibrosis at the two age levels. This seems to be related to the different activity of vamorolone and prednisolone at the MR (antagonist vs. agonist).

In line with the different induction of the bone resorption marker RANKL between vamorolone and prednisolone (see above), the magnitude of the effect of vamorolone on bone development in PND 12 and young mdx mice (body and tibia length, trabecular thickness) was lower than observed with prednisolone. Nevertheless, vamorolone significantly reduced tibia and/or body lengths in juvenile mouse toxicity studies, suggesting that potential growth-retardations by vamorolone cannot be dismissed (see below). Moreover, the potential risk for direct effects on the growth plate and the developing skeleton leading to skeletal fragility cannot be defined yet, because bone mineral density and structure has so far not been analysed.

The missing hydroxyl group at carbon 11 further entails that vamorolone cannot serve as substrate for local and systemic 11β-hydroxysteroid dehydrogenases (11-β-HSD), whose activities have been implicated in the adverse side effects of other glucocorticoid drugs (muscle wasting, bone loss, insulin resistance, hypertension, and weight gain; Morgan *et al.,* 2014; Fenton *et al*., 2019). However, experimental confirmation for the lack of vamorolone metabolism via 11-β-HSD is lacking. In view of the vamorolone effects on muscle and bone in toxicology studies, it remains therefore to be shown, if the absence of 11-β-HSD metabolism translates into a relevant benefit.

The core battery of safety pharmacology studies of vamorolone revealed no inhibition of hERG currents up to 20 µM vamorolone *in vitro*. The applicant claims that this 20 µM concentration translates into a 45-fold safety margin compared to the free vamorolone plasma level of 0.44 µg/ml at the MRHD. However, the documentation of the hERG measurements is rather of exploratory nature and the applicant did not adequately justify the lack of GLP compliance, although the study was conducted in 2010, i.e., after implementation of the pertinent ICH S7A and B guidelines in 2001 and 2005. In addition, the assay was conducted outside the mutual acceptance of data area of the OECD. This limits the scientific reliability of the hERG assay results. Nevertheless, oral vamorolone doses up to 50 mg/kg did not impair cardiovascular and respiratory function in telemetered dogs. Likewise, multiple oral administrations of the same dose in the chronic toxicity study in dogs did not affect ECG parameters, but induced reversible mild heart rate increases at the 39-week post dose interval. The corresponding mean C_{max} of about 1.21 µg/ml vamorolone is slightly below human peak plasma levels at the MRHD of vamorolone (1.31 µg/ml). A minor safety margin might still exist, if the lower plasma protein binding in dogs compared to humans is considered (free fraction of 21 % vs. 12 %). Although, vamorolone did not impact on the QT interval in a clinical single (SAD) and multiple (MAD) ascending dose trial in healthy adult volunteers (study no. VBP15-001), three DMD patients administered vamorolone in clinical phase 2b presented with QTcF >60 msec over baseline and another DMD patients with absolute QTcF >500 msec (study no. VBP015-004). This issue was hence clinically pursued.

Vamorolone did not stimulate neurobehavioural abnormalities in a functional observation battery in mice and in juvenile toxicity studies in this species. However, adversely decreased activity and impaired limb function was noted upon chronic administration of the 50 mg/kg/day vamorolone high dose in dogs, which might be reflective of psychiatric symptoms known from clinical therapy of high glucocorticoid doses (Harris *et al*., 2015).

Pharmacokinetics

Two differently labelled vamorolone substances were used as internal standard during final methodological validations for quantification in mouse plasma and dog plasma and in the mass-balance investigation in rats. Both compounds contained the respective $^{13}CD_3$- and ^{14}C-radiolabels at the same carbon atom, which bares a negligible impact on the respective determinations.

Single oral doses vamorolone were rapidly absorbed (t_{max} of 2 h) with high bioavailability of 74.5 % in mice, while absorption was delayed to 4-6 h and bioavailability lower (~48-53 %) in rats and dogs. Multiple administrations dose-proportionally increased vamorolone exposure (C_{max} and AUC_{0-24h}) in all animal species, but clearly dropped during prolonged administrations in mice and monkeys (1.2- to 5.7-fold lower). Conversely, the vamorolone exposure increased in dogs (1.2- to 3.2-fold) pointing towards accumulation. The reason for the vamorolone decline in mice and monkeys compared to the accumulation in dogs is unknown but was regarded clinically irrelevant as it had not been observed in humans.

Vamorolone showed extensive tissue distribution reaching highest levels in the gastrointestinal tract and liver compared to low (~3 %) but retained levels in skeletal muscle, heart and kidney medulla. The slight binding to melanin-containing retina layers is not of concern (see discussion on the phototoxic potential below). The placental and milk transfer of vamorolone has not been investigated, which is regarded dispensable in view of the envisaged patient population and had been earlier considered by the CHMP during protocol assistance concerning the possibility to waive reproduction toxicity studies.

Vamorolone was metabolically stable in liver microsomes or hepatocytes of mice, dogs, monkeys and humans (88.5-100 %), while it was extensively degraded in rats (35 %). However, the profiling experiments to determine the involvement of hepatic CYPs and UGTs in the hydroxylation, hydrogenation, hydroxyl oxidation and glucuronidation reactions are of limited scientific value, because the submitted study reports do not even meet the standards for documentation of academic research and lack any comprehensible delineation of methodological particulars, results and discussion. Hence, the involvement of particular CYPs and UGTs cannot be reliably concluded from these investigations. This gap in the scientific knowledge has been adequately specified in section 5.2 of the SmPC.

The metabolism of vamorolone has not been completely elucidated *in vivo*. Still, the comparison of animal data with human profiles of paediatric and adult subjects indicates that at least all major metabolites were identified. Overall, ten circulating metabolites of vamorolone were determined in plasma of mice, dogs and adult healthy human volunteers that were sequentially numbered and generated by oxidation, hydrogenation, dehydrogenation, glucuronidation or the combination thereof. Four major glucuronide metabolites were found that amount to >10 % of the total vamorolone-related AUC in human plasma, but only the hydrogenated main glucuronide M7 was similarly quantified in dogs. In contrast, the direct O-glucuronide M3 of vamorolone and the hydrogenated major glucuronides M8 and M9 just amounted to <1 % of total drug levels in mice and dogs. The applicant claims that the three disproportionate human glucuronide metabolites M3, M8 and M9 are pharmacologically inactive and, hence, toxicologically irrelevant. However, these glucuronides were not tested for potential GR activity, so the proposed impact of steric hindrance between the steroid and glucuronide structures, which could potentially further reduce the reactivity of the keto group in the respective metabolites remains unknown. Nevertheless, the applicant clarified that glucuronidation of the three disproportionate human metabolites M3, M8 and M9 occurs at the respective hydroxyl groups resulting in the formation of O-glucuronides, which are usually pharmacologically inactive. As the possible impact on the predictive value of the toxicology programme was considered for section 5.3 of the proposed SmPC, the issue is not further pursued.

In bile duct-cannulated rats and in the mass-balance study, unchanged vamorolone was only recovered in tiny amounts in plasma and was primarily excreted via faeces (~80 %) within 24 h. The high metabolic

capacity and rapid excretion in rats likely prompted the selection of mice for the toxicology programme of vamorolone.

PK DDI studies only demonstrated significant CYP3A4 induction at ≥15 µM vamorolone. With respect to the unbound clinical C_{max} of 0.44 µM at the MRHD of vamorolone, its potential for clinically relevant CYP3A4 induction seems to be low. No relevant inhibition of CYP enzymes by vamorolone was found. The minor inhibition of UGT1A1 and UGT2B7 by 50 µM vamorolone is regarded clinically irrelevant given its >110-fold lower unbound C_{max} at the MRHD (0.44 µM).

Vamorolone was no substrate for major drug transporters and only inhibited the renal transporters MATE2-K with IC_{50} of 12.9 µM and OAT3 with IC_{50} of 19.6 µM. The pertinent European guideline entails that relevant *in vivo* inhibition of renal transporters can only be excluded if the inhibition constant is higher or equal to 50-times the unbound peak plasma drug concentration (CPMP/EWP/560/95/Rev. 1 Corr. 2). The IC_{50} of MATE2-K is lower than 50x the unbound C_{max} of 0.44 µM vamorolone (22 µM), while that of OAT3 is almost equivalent. Thus, the potential clinical risk for interactions with these renal transporters required further discussion, which was clinically pursued.

Toxicology

The mild to moderate lymphocyte depletions in spleen, thymus and lymph nodes at vamorolone doses ≥5 mg/kg/day in mice and ≥2 mg/kg/day in dogs are related to the primary anti-inflammatory activity of vamorolone as indicated in section 5.1 of the proposed SmPC. The obvious sex difference in the inhibition of the TDAR between male and female mice by 100 mg/kg/day vamorolone compared to ≥10 mg/kg/day prednisolone might be attributable to the distinct interference of androgens and oestrogens with T and B cell responses (Da Silva, 1999).

Vamorolone doses ≥10 mg/kg/day induced partially reversible liver hypertrophy in all toxicity studies in mice and dogs, which correlated with mild to moderate centrilobular hepatocyte vacuolation containing glycogen and lipid accumulations, likely reflects the stimulation of gluconeogenesis as previously reported for prednisone (Fittschen and Bellamy, 1984; Harris *et al*., 2015). Secondary to the observed hepatic hypertrophy and vacuolation, hepatocellular and focal/subcapsular inflammation/necrosis developed dose- and time-dependently at ≥15 mg/kg/day in mice and at 50 mg/kg/day in dogs. Concomitantly, lipid metabolism was altered, inflammatory markers and liver enzymes (ALT, AST, AP and bilirubin) were elevated in mice and dogs. GGT was found to be additionally increased in dogs and had been selected, because it was described as better suited marker for hepatic injury in DMD patients given its preferential liver expression (Rosales *et al*. 2008), whereas the release of AST and AP from dystrophic muscle hampers the reliable interpretation of their blood elevations. Of note, mean levels of GGT and glutamate dehydrogenase, another liver specific enzyme with potential prognostic value in DMD (Schomaker *et al*., 2020), were largely within normal limits in the course of various clinical trials of vamorolone. Nevertheless, glucocorticoid drugs are well-known to damage the liver. Albeit hepatic toxicity is already listed as important potential risk in the risk management plan (RMP), the SmPC includes routine risk minimisation measures in sections 4.2, 4.3 and 4.4.

The applicant interpreted the pancreatic islet hypertrophy in mice of the 45 mg/kg/day high dose group of the chronic toxicity study as pharmacologically-mediated adaptive change. This is agreed given the apparent induction of hepatic gluconeogenesis by vamorolone (see above) and the known potential of glucocorticoids to induce insulin resistance leading to compensatory pancreatic β-cell hyperplasia (Greaves, 2012; Harris *et al*., 2015). The elevated fasting insulin following administration of the MRHD of vamorolone in human DMD patients similarly points towards higher pancreatic islet activity, but no increased incidences of diabetes conditions were noticed. This was followed from a clinical perspective.

The adrenal cortical atrophies in the *zona fasciculata* and *reticularis* observed upon repeated vamorolone dosing ≥5 mg/kg/day in mice and ≥2 mg/kg/day in dogs that relatively spare the *zona glomerulosa*

coincide with existing experience gained with other glucocorticoid agents (Greaves, 2012) and are, hence, ascribable to the suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Excess glucocorticoid administration leads to negative feedback in the pituitary gland resulting in the suppression of ACTH secretion (Rosol *et al*., 2001). This in turn inhibits CYP11A1 and leads to reduced cholesterol metabolism, accumulation of fat vacuoles in the cortical cells, and eventual adrenal cortex atrophy, because ACTH is important for maintaining cortical cell numbers. Impaired adrenal function is a well-established side effect of long-term glucocorticoid administration (Harris *et al*., 2015). As adrenal insufficiency has been also noted in vamorolone-treated DMD patients, a warning has been proposed in section 4.4 of the SmPC, whereas adrenal suppression is listed as undesirable effect in section 4.8. Nevertheless, this issue requires clinical follow-up (see clinical AR).

In contrast, the higher kidney weights with bilateral tubular vacuolation, increased diuresis and dehydration after chronic vamorolone administration ≥10 mg/kg/day in dogs, which persisted with lower severity in dogs of the high dose group at the end of the recovery phase but were not seen in mice are of unlikely clinical significance, because kidney findings developed at lower exposure of dogs compared to DMD patients receiving the MRHD. In addition, kidney function was not impaired during short and long-term clinical vamorolone therapy.

Vamorolone did not significantly affect sperm morphology, motility and viability after long-term treatment of adult and juvenile mice. However, spermatocytes and spermatids were found to degenerate in the testes of male dogs administered 50 mg/kg/day vamorolone in the chronic toxicity study resulting in oligospermia and germ cell debris in the epididymides. Moreover, the prostate gland of these males was smaller and contained less exudate. The sperm degenerations were incompletely and prostate effects not reversible. Nevertheless, the duration of a complete spermatogenic cycle in Beagle dogs of around 60 days was not covered by the rather short recovery period, so reversibility could not be adequately assessed (Soares JM *et al*. 2009). The impairments of male dog fertility were meanwhile highlighted in section 4.6 of the SmPC with more detailed description of the findings in section 5.3.

Vamorolone even more severely impacted on female fertility. Repeated vamorolone doses ≥30 mg/kg/day for 28 days diminished ovarian weights in mice and uterus/cervix weight in dogs, whereas long-term administrations of ≥2 mg/kg/day for 39 weeks in dogs eliminated ovarian *corpora lutea* and induced mild epithelial vacuolation in mammary ducts. As the lack of *corpora lutea* was incompletely reversible, a NOAEL could not be established for female dogs in the chronic toxicity study. However, the impaired female fertility is insignificant for the intended clinical indication DMD, which as an X-linked disease almost exclusively affects boys.

The suppression of male and female fertility by vamorolone is mechanistically related to the known interference of exogenous glucocorticoids with the hypothalamus-pituitary-gonadal axis, which 1) decreases the gonadotropin-releasing hormone secretion by the hypothalamus that leads to 2) the reduced release of luteinizing hormone and follicle-stimulating hormone from the pituitary and subsequently 3) inhibits gonadal gametogenesis. In addition, glucocorticoids also directly suppress steroidogenesis in the testis and ovary (reviewed by Whirledge and Cidlowski, 2010). The androgen biosynthesis can be further impacted by adrenal insufficiency.

The causality for the increased thyroid/parathyroid gland weight by chronic vamorolone doses ≥10 mg/kg/day in male dogs remains to be unravelled, because glucocorticoid agents generally interfere with the hypothalamic–pituitary–thyroid axis resulting in decreased secretion of thyroid-stimulating hormone (TSH) by the pituitary (Wilber and Utiger, 1969). In fact, lower serum TSH levels were found in several dogs administered 180 mg/kg/day vamorolone in the exploratory 28 days repeat-dose toxicity study, although the poor assay sensitivity and low number of study animals (n=2/sex/group) hampered reliable conclusions. Of note, thyroid function was not evaluated during clinical development of

vamorolone, but a warning is proposed in section 4.4 of the SmPC. This issue was therefore clinically discussed.

In the chronic toxicity study in dogs, vamorolone doses ≥10 mg/kg/day induced minimal to moderate increases of multifocal to diffuse cytoplasmic epithelial basophilia with the parotid salivary glands of both sexes. The severity of this finding was reduced at the end of the recovery period but did not completely recover in affected males and remained detectable in one female dog of the 10 mg/kg/day group. These parotid gland findings were associated with excess salivation, which started from weeks 6 to 8 and continued throughout the study and were also noted in vehicle-controls. A causal relationship with the Labrasol/0.5 % carboxymethylcellulose vehicle appears therefore reasonable considering also that this vehicle was not used in other toxicology species.

Vamorolone reduced epidermal collagen of the skin resulting in alopecia/hypotrichosis at doses of 100 mg/kg/day for 28 days and 45 mg/kg/day for 26 weeks in mice as well as at ≥10 mg/kg/day for 39 weeks in individual dogs. Decreased anagen follicles were incompletely reversible in most mice that had previously received ≥15 mg/kg/day vamorolone, while they almost completely resolved in dogs. Compromised skin integrity is a common adverse effect of glucocorticoid drugs (Harris *et al*., 2015), but the incidences of skin and hair alterations were generally low and similar across treatment groups in the clinical programme of vamorolone. Thus, the non-clinical findings do not warrant specific RMMs.

Of note, partially reversible mild skeletal muscle atrophy of the exemplarily investigated *biceps femoris* was found in both sexes of dogs treated with 50 mg/kg/day vamorolone in the chronic toxicity study. This muscular atrophy in dogs contrasts the preservation of skeletal muscle function as well as the protection from muscular inflammation and degeneration by 30 mg/kg/day vamorolone in mdx and PND 12 mice. Thus, non-clinical data cannot unequivocally support the claimed therapeutic benefit of vamorolone in DMD patients.

Despite lower body weights after vamorolone doses of ≥10 mg/kg/day for 28 days in mice and at ≥60 mg/kg/day in the exploratory 28 days toxicity study in dogs, prolonged vamorolone administrations of 45 mg/kg/day for 26 weeks in mice and of ≥10 mg/kg/day for 39 weeks in dogs increased food consumption and, hence, body weights. Upon cessation of vamorolone treatment, body weights tended to lower, but remained slightly elevated in accordance with the food consumption of mice, while they were diminished in dogs. Increased body weights and appetite are frequent adverse events during long-term glucocorticoid therapy (Harris *et al*., 2015), have been observed in the clinical development of vamorolone and are listed in section 4.8 of the proposed SmPC.

Long-term vamorolone dosing ≥2 mg/kg/day in male and at 50 mg/kg/day in female dogs minimally to mildly increased numbers of adipocytes in the bone marrow of the sternum that displaced haematopoietic tissue. No comparable effect was apparently identified during inspection of femur bone marrow and sternal findings normalised in the recovery period. The study director hypothesised a pharmacological relationship of vamorolone with the adipocyte increases, which seems plausible, because long-term glucocorticoid treatment reduces bone mass by contributing to decreased osteogenic at the expense of increased adipogenic differentiation from mesenchymal stem cells (reviewed by Hachemi *et al*., 2018). Although vamorolone did not affect bone length (femur, tibia) in the chronic toxicity studies in mice and dogs, bone development bone was impaired in PND 12, young mdx mice (Damsker *et al*., 2013) and particularly in juvenile mice (see below).

In view of these toxicities, the vamorolone high dose of 45 mg/kg/day was established as NOAEL during chronic treatment of mice, which might be questioned given the incomplete reversibility of hepatic inflammation/necrosis and adrenal atrophies. Following long-term vamorolone administration in dogs, the adversity of adrenal toxicities led to a NOAEL of 2 mg/kg/day in male dogs, whereas no NOAEL could be established for females due to the partially reversible lack of *corpora lutea*. At these NOAELs, both C_{max}- and AUC-based safety margins with respect to the exposure in human DMD patients receiving the

MRHD were negligible in mice or not definable in dogs. This limits the predictive value of the toxicology programme and has meanwhile been considered in section 5.3 of the SmPC.

Vamorolone did not exert a relevant genotoxic potential *in vitro* and *in vivo*. A sufficiently high safety margin can be assumed based on toxicokinetic data of repeat-dose toxicity studies in mice. This been sufficiently summarised in section 5.3 of the proposed SmPC. Accordingly, the applicant plans to defer carcinogenicity studies post-approval as previously agreed with the CHMP (EMA/CHMP/SAWP/545127/2019). However, vamorolone did not induce treatment-related pre-neoplastic lesions in chronic toxicity studies in mice and dogs. It should be also noted that long-term clinical therapy with other glucocorticoids do not suggest a particular carcinogenic hazard of this pharmaceutical class. In view of the recently published ICH S1B(R1) guideline (EMA/774371/2022), it is therefore suggested to reconsider the need for 2-year carcinogenicity studies.

The absence of a standard battery of developmental and reproductive toxicology studies for the MAA is considered acceptable in accordance with the ICH S5 guideline and earlier CHMP protocol assistance (EMA/CHMP/SAWP/545127/2019).

Among toxicities in juvenile mice, which differed from adult counterparts, partially reversible minimal to mild mandibulary salivary gland hypertrophy developed at ≥15 mg/kg vamorolone without any safety margin regarding human exposure at the MRHD. These salivary gland changes have been adequately reflected in section 5.3 of the SmPC. Literature data also suggest a potential effect of vamorolone on salivary gland development in juvenile mice and that juvenile mice may be more vulnerable than adults due to the cellular differentiation of the salivary gland in the postnatal phase. As the human relevance is currently unknown, the applicant agreed to include specific evaluations of salivary glands into the design of a future 10-week juvenile toxicity study in mice aged 5-7 days at study start, in case this study will be conducted to support clinical treatment of younger children.

The reduced mean tibia and body length in males each at 100 mg/kg and ≥15 mg/kg vamorolone and the shortened tibia length at ≥30 mg/kg in females were attributed to the slower growth of the animals, because findings correlated with lower body weights. Nevertheless, the observations rather suggest that vamorolone has the potential to induce growth retardation like other glucocorticoids. The effects on tibia and/or body lengths occurred at the lowest dose group for which no safety margin to human exposure exists. Therefore, these effects should be regarded as clinically relevant and adverse. The findings on tibia and body lengths are adequately reflected in section 5.3 of the SmPC.

Another well-known effect of chronic glucocorticoid administration is the induction of osteoporosis, which has been also reported in children (Ward, 2020). Glucocorticoids have diverse direct effects on the growth plate and developing skeleton leading to skeletal fragility. Unfortunately, no investigations on bone mineral density and bone structure as well as biomarkers of bone metabolism have been performed in the juvenile mouse toxicity studies. According to the latest PDCO opinion for vamorolone (EMEA-001794-PIP02-10-M05), June 2022, however, the applicant plans to conduct a 10-week juvenile toxicity study in CD-1 mice aged 5-7 days at study start and agreed to include measurements of bone mineral density and bone structure and investigations of biomarkers of bone metabolism into the design of this study.

Vamorolone apparently did not affect sexual maturation and fertility in male and female juvenile mice, but markedly increased pre- and post-implantation losses and decreased numbers of viable embryos were observed at 100 mg/kg vamorolone. Variabilities in the respective study designs precluded the comparison with historical control data from the contract laboratory. However, the comparison with historical controls from previous pre-/postnatal development studies indicated general concordance in the numbers of viable foetuses, which resolved further concerns.

The major findings from the juvenile toxicity studies in mice were included into section 5.3 of the SmPC.

Vamorolone did not absorb in the range of 290-400 nM and its MEC is substantially above the 1000 $l \cdot mol^{-1} \cdot cm^{-1}$ threshold for photoreactive compounds of the ICH S10 guideline (EMA/CHMP/ICH/752211/2012). Although vamorolone could be traced at low levels in eye and skin of rats in the QWBA study, no ophthalmological abnormalities were detected in repeat-dose toxicity studies with vamorolone for up to 26 weeks in mice, 39 weeks in dogs and 7 days in monkeys. During clinical development, vamorolone did not induce cataracts and intraocular pressure even normalised after switching from prednisone to vamorolone. Moreover, skin changes were generally similar between human treatment groups. As Vamorolone shows close structural relationship with other glucocorticoids, which are topically and systemically used for therapy of acute dermal photosensitivity reactions (Khandpur *et al*., 2017), a significant phototoxic potential of vamorolone is regarded unlikely and further investigations are not deemed necessary.

The quantitative structure-activity relationship (SAR) *in silico* analyses of the two drug substance impurities VBP-15-B-2 and VBP-15-B-3 using expert rule- and statistical-based MultiCASE Ultra and the expert rule-based Derek Nexus software did not identify any genotoxic potential.

The impurity profile of vamorolone includes potentially 16β-vamorolone, vamorolone acetate and keto-vamorolone, which have been qualified at 1.8- to 6.2-fold multiples in the chronic toxicity study in mice.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of vamorolone to the environment.

The applicant commits to perform the following studies as follow-up measures:

The applicant confirms its commitment in conducting the tiered ERA Phase II in the context of a post approval commitment and commits to conducting the studies proposed by CHMP, based on whether vamorolone is readily biodegradable.

- The biodegradability studies for vamorolone shall take place in Q1-2024, and results will be submitted by end Q1-2025.
- Aerobic and Anaerobic Transformation in Aquatic Sediment System (OECD TG 308) study is planned to start in Q1-2025 and results will be submitted by end Q3-2025.
- Literature review daphnia reproduction is planned for Q1-2025 which includes a CHMP request to waive daphnia reproduction if daphnia are less sensitive than fish.
- The applicant starts to conduct a daphnia reproduction study (OECD TG 211) if daphnia are more sensitive than fish by Q1-2025 with final results to be submitted by end Q3-2025.
- Medaka Extended One Generation Reproduction Test (chronic fish full life-cycle study) (OECD TG 240) study is planned to start Q1-2025 and the results will be submitted by end Q3-2027.

2.5.7. Conclusion on the non-clinical aspects

All but one of the "Other concerns" raised in the non-clinical assessment have been resolved. Comments on the product information have adequately been addressed. From a non-clinical point of view, marketing authorisation can be considered.

The CHMP considers the following measures necessary to address the non-clinical issues:

The applicant confirms its commitment in conducting the tiered ERA Phase II in the context of a post approval commitment and commits to conducting the studies proposed by CHMP, based on whether vamorolone is readily biodegradable.

- The biodegradability studies for vamorolone shall take place in Q1-2024, and results will be submitted by end Q1-2025.
- Aerobic and Anaerobic Transformation in Aquatic Sediment System (OECD TG 308) study is planned to start in Q1-2025 and results will be submitted by end Q3-2025.
- Literature review daphnia reproduction is planned for Q1-2025 which includes a CHMP request to waive daphnia reproduction if daphnia are less sensitive than fish.
- The applicant starts to conduct a daphnia reproduction study (OECD TG 211) if daphnia are more sensitive than fish by Q1-2025 with final results to be submitted by end Q3-2025.
- Medaka Extended One Generation Reproduction Test (chronic fish full life-cycle study) (OECD TG 240) study is planned to start Q1-2025 and the results will be submitted by end Q3-2027.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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 vamorolone clinical studies and other supportive studies for the treatment of DMD

Trial No. NCT No. Eudract No.	Study Design and Description	Number of Subjects and Population to be studied	Study Drug Regimen, Schedule, and Route	Study Objectives/ Primary Endpoint	Safety Assessments	No. of Centers Countries
Controlled Studies in DMD						
VBP15-004 NCT03439670 2017-002704-27	**Phase 2b**, randomised, double-blind, parallel group, placebo- and active-controlled; To evaluate the efficacy, safety, tolerability, PD, and PPK of vamorolone vs. placebo and prednisone and to evaluate persistence of effect over a 48-week treatment period. The study comprised the following periods: Treatment Period #1 24 weeks (Weeks 1-24) Transition Period 4 weeks (Weeks 25-28) Treatment Period #2 20 weeks (Weeks 28-48) Dose tapering Period 4 weeks (Weeks 49-52)	121 ambulant boys with DMD between 4 to <7 years of age at study entry, who were corticosteroid naïve	Subjects were allocated to 1 of the 6 treatment groups in a 2:2:1:1:1:1 ratio as follows: 1. Vamorolone 2 mg/kg whole study 2. Vamorolone 6 mg/kg whole study 3. Prednisone 0.75 mg/kg in Treatment Period # 1 then Vamorolone 2 mg/kg in Treatment Period #2 4. Prednisone 0.75 mg/kg in Treatment Period # 1 then Vamorolone 6 mg/kg in Treatment Period #2 5. Placebo in Treatment Period # 1 then Vamorolone 2 mg/kg in Treatment Period #2 6. Placebo in Treatment Period # 1 then Vamorolone 2 mg/kg in Treatment Period #2	PK, PD, efficacy, safety and tolerability Primary endpoint: change from baseline in TTSTAND velocity (rises/sec) for the vamorolone 6 mg/kg group compared to placebo at Week 24	AEs, muscle function, BMI, physical examinations, vital signs, ECG, and clinical laboratory evaluation of hematological and biochemical parameters (blood sample, urine sample)	33 centers: Australia Belgium Canada Czech Republic Greece Israel Netherlands Spain UK US
Uncontrolled Studies in DMD						
VBP15-002 NCT 02760264 2016-004262-26	**Phase 2a**, open-label, MAD study to assess the safety, tolerability, PK, PD, and exploratory efficacy of vamorolone in boys with DMD over a 14-day treatment period, followed by a 14-day post-treatment follow-up period	48 ambulant boys with DMD between 4 to <7 years of age at study entry, who were corticosteroid naïve	VAM 0.25, 0.75, 2.0, and 6.0 mg/kg Orally QD for 14 days	Safety, tolerability, PK, PD and exploratory efficacy Primary objective: safety and tolerability Exploratory objectives: Efficacy: QMT, TTRW, TTSTAND, TTCLIMB, NSAA, 6MWT	See above	11 centers: Australia Canada Israel Sweden US
VBP15-003 NCT02760277 2016-004263-38	**Phase 2**, multicenter, open-label, multiple dose, sequential assignment, 24 weeks extension study to assess the long-term safety and efficacy of vamorolone in boys with DMD	48 ambulant boys with DMD, who completed Study VBP15-002	VAM 0.25, 0.75, 2, and 6 mg/kg/day orally QD for 24 weeks	Long-term safety, tolerability, efficacy and PD Primary objective: Long-term safety, tolerability, efficacy Primary efficacy endpoint: TTSTAND velocity: comparison to an untreated historical control group (CINRG DNHS) for change from baseline to Week 24.	See above	11 centers: Australia Canada Israel Sweden US
VBP15-LTE NCT03038399 2017-003568-10	**Phase 2** open-label, parallel group, multicenter long term, 24 months extension study to assess the long term safety and efficacy of vamorolone in boys with DMD	46 ambulant boys with DMD who completed Study VBP15-003; Maximum age at	VAM up to 6 mg/kg/day orally QD for 24 months. Dose adjustment was allowed between dose levels of 2, 4 and 6 mg/kg/day[1]	Long-term safety, tolerability, efficacy and PD Primary objective: Long-term safety, tolerability, efficacy	See above	11 centers: Australia Canada Israel Sweden US

Trial No. NCT No. Eudract No.	Study Design and Description	Number of Subjects and Population to be studied	Study Drug Regimen, Schedule, and Route	Study Objectives/ Primary Endpoint	Safety Assessments	No. of Centers Countries
		completion was 9.6 years		Primary efficacy endpoint: TTSTAND velocity change from VBP15-002 baseline to VBP15-LTE Month 24.		
External comparison FOR-DMD NCT01603407 EudraCT: 20100237443	**Phase III** randomised, prospective, interventional, double-blind, 36-60 months study, comparing 3 corticosteroid regimens in DMD	196 male subjects with DMD aged ≥ 4 years and < 8 years at study entry	Daily prednisone (0.75 mg/kg): Intermittent prednisone (0.75 mg/kg, 10 days on, 10 days off) Daily deflazacort (0.9 mg/kg).	Comparison of three commonly used corticosteroid regimens in regard to functional outcome and treatment satisfaction Primary endpoint: a three-dimensional (multivariate) outcome of 1) time to rise from floor, from supine to standing, 2) forced vital capacity, and 3) global satisfaction with Treatment Satisfaction Questionnaire for Medication.	AEs, clinical laboratory evaluations, physical examinations, vital signs, ECGs, DXA, and spinal fractures	40 sites: Canada Germany Italy UK USA

[1]Subjects who received 0.25 or 0.75 mg/kg were allowed to escalate the vamorolone dose to the next higher dose level after receiving the current dose level for at least 1 month, with a maximum of 3 dose level escalations, to the maximum of 6.0 mg/kg/day; subjects were allowed to de-escalate vamorolone dose due to intolerability. Subjects whose dose level was decreased from 6.0 mg/kg/day to 2.0 kg/kg/day could have their dose level subsequently increased to 4.0 mg/kg/day per Amendment #1 if they had been on the 2.0 mg/kg/day dose level for at least 1 month and, in the opinion of the investigator, balancing efficacy with safety concerns, they could have benefited from an intermediate higher dose level. LTE=long-term extension; MAD=multiple ascending dose; PBO=placebo; PRED=prednisone; QD=once daily; UK=United Kingdom; US=United States; VAM=vamorolone; AE = adverse event; BMI = body mass index; DMD = Duchenne muscular dystrophy; ECG = electrocardiogram; PD = pharmacodynamics; PK = pharmacokinetics; PPK = population pharmacokinetics; daily; SAE = serious adverse event; QMT = Quantitative Muscle Testing; TTRW = Time to Run/Walk 10 Meters Test; TTSTAND = Time to Stand Test; TTCLIMB = Time to Climb Test; NSAA = North Star Ambulatory Assessment; 6MWT = Six-minute Walk Test

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Summary of pharmacokinetic properties

Vamorolone is well absorbed and distributes quickly into tissues. The major route of elimination is by metabolism with subsequent excretion of metabolites into urine and feces. The PK are linear and vamorolone exposure increases proportionally with either single or multiple doses. Vamorolone does not accumulate with repeated administration.

Analytical methods

In general validations of bioanalytical methods used for analysis of different clinical trials samples have been performed in accordance with the requirements stated in the relevant European guideline. Validations are satisfactory performed covering required parameters (selectivity, precision, accuracy, range, linearity, recovery, dilution integrity, stability).

Modelling

The population PK (popPK) of vamorolone in paediatric DMD patients was adequately described by a one-compartment disposition model with sequential zero-order followed by first order absorption. The elimination of vamorolone was found to be linear and allometric scaling was employed with fixed exponents of 0.75 and 1 for oral clearance (CL/F) and oral volume of distribution (V/F), respectively, to include bodyweight into the model. Patient data was limited to the age from 4 to <7 years, which means that statements regarding paediatric and adolescent patients in other age groups (2 to <4 years and 7 to <18 years) were based on extrapolation and simulation. As the shrinkage in absorption parameters in the paediatric popPK model was high (>29%) individual predicted C_{max} values could not be used for exposure response modelling, which limited the usefulness of the model. Predicting C_{max} precisely in paediatric patients might be relevant for comparing between different formulations used.

The popPK model was updated with PK data from the ongoing study VBP15-006 using the to be Marketed Formulation (ROS2/) 6 mg/kg in patients aged 2 to <4 years (n=2), 7 to <12 years (n=3), and 12 to <18 years (n=1). Although simulations suggest that the youngest age group (2 to <4 years) might show similar exposure compared to patients aged 4 to <7 years, this conclusion is associated with a large degree of uncertainty because of the very low number of cases (n=2).

The popPK model was further updated using data from patients n=16 aged 2 to <4 years and aged 7 to <18 years from ongoing study VBP-006. For the analysis of popPK, data from ongoing study VBP-006 were used for external validation of the model. After validation, VBP-006 data were added to the analysis dataset and the updated final model was used to simulate exposure of different age groups comparing the Clinical Formulation (ROS1) and to be Marketed Formulation (ROS2/). The main difficulty was that the new ROS2 formulation showed higher exposure and was only used in study VBP-006. For the age group 4 to <7 years formulation ROS1 was used. An adjusted dose cap at a weight of 40 kg (at 240 mg for the 6 mg/kg dose and at 160 mg for 4 mg/kg) is supported. The applicant was asked to address the following concerns regarding modelling to ensure that the model is fit for purpose:

To be able to describe the formulation effect properly, effect of food and effect of formulation on bioavailability should not be combined as covariates in the popPK model. As the effect of ROS2 under fed and fasted conditions was similar (0.556 and 0.571 Intiquan 2023a), one single ROS2 formulation effect was estimated not differentiating between fasted and fed conditions. The redefined model was used to simulate the effect of the different formulations on AUC for all age groups in boxplots also

depicting individual data points for AUC. Boxplots were used to compare the AUC for 6 mg/kg, 4 mg/kg, and 2 mg/kg for the ROS2 formulation in patients aged 2 to <4 years to the AUC of 6 mg/kg for the ROS1 formulation in patients aged 4 to <7 years of age (fed status). After refinement of the popPK model, AUC was compared between patients aged 4 to <18 years using 4 mg/kg ROS2 formulation and patients aged 4 to <7 years using 6 mg/kg ROS1 formulation in boxplots also depicting individual data points for AUC to ensure that the exposure is within the target range for dose reduction for different age and weight groups.

Furthermore, body weight was included on volume of distribution using conventional allometric scaling in an updated final model. The current refined model was compared to a model assuming an allometric exponent of body weight effect on volume fixed to 1 and to a modelling estimating the allometric exponent for bodyweight on volume. Forest plots and simulated concentration-time profiles showed an unusually small effect of bodyweight on central volume which might be explained through the flip-flop kinetics of vamorolone.

The popPK model was further used to inform exposure-response modelling for PD effects on morning cortisol and efficacy of vamorolone (North Star Ambulatory Assessment (NSAA), Six-minute Walk Test (6MWT), time to stand (TTSTAND)) which was not accepted (Pharmacodynamics section).

Absorption

In the single dose study in healthy volunteers after oral administration, vamorolone was relatively rapidly absorbed with median t_{max} values ranging from 1.5 to 1.78 hours (range 1.00 to 3.00 hours) across dose groups. After peak plasma concentrations are reached, the decline of vamorolone is generally mono exponential with average half-life (t½) values of ≤1.8 hours for the lower doses up to 1 mg/kg and average t½ values between 2.50 and 4.26 hours at doses from 3 to 20 mg/kg.

Consistent with the short t½ relative to the 24-hour dosing frequency, there was no accumulation and concentration versus time profiles from Day 1 and Day 14 are similar. Median t_{max} values were approximately 3 hours after the lowest dose (1.0 mg/kg/day) on Day 1 and Day 14 and seem to be shorter at the higher doses. Median t_{max} values at doses from 3.0 to 20.0 mg/kg/day ranged from 1 to 2 hours on Day 1 and from 1.25 to 2.5 hours on Day 14.

After oral administration with 8 ounces of whole milk (or its equivalent in fat), the median t_{max} in DMD boys was 2 hours at 2.0 and 6.0 mg/kg. Estimated vamorolone plasma exposures in subjects with DMD given 6.0 mg/kg/day are on average (mean [SD]) 970 ng/mL (270) and 3606 ng.hr/mL (897) for C_{max} and area under the plasma concentration time curve from time 0 to infinity ($AUC_{0\text{-}inf}$), respectively (Day 14).

Bioavailability and food effect

The absolute bioavailability of vamorolone has not been studied as an intravenous formulation for use in humans is not available. Based on the urinary excretion of vamorolone metabolites it can be assumed that the oral bioavailability of vamorolone under fed conditions is at least 56.7% which is consistent with the bioavailability observed in animal species (range 47.8 to 74.5%).

The effect of food (high-fat meal) on the PK of vamorolone administered as the Clinical Formulation ROS1 was initially investigated in study VBP15-001. The geometric mean C_{max} and AUC both increased approximately 2.5-fold when vamorolone Clinical Formulation (ROS1) was administered with a high-fat meal, compared to under fasted conditions. The effect of meal type (low-fat meal and high-fat meal) on the PK of vamorolone after administration of the Clinical Formulation (ROS1) was further evaluated in the relative bioavailability and food effect study VBP15-PK-FORM-002. The results show that a low-fat/low calorie meal had a similar food effect on the Clinical Formulation (ROS1) compared to the high-fat/high calorie meal. The mean vamorolone PK profiles following the two types of meal are essentially

superimposable. The geometric mean C_{max} and median t_{max} are the same after coadministration with low-fat or high-fat meal. $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ are approximately 9% higher with the high-fat meal compared to the low-fat meal, with 90% confidence interval (CI) within the reference range of (80, 125) applied for the evaluation of food effect studies.

The effect of food (low-fat meal and high-fat meal) on the PK of vamorolone after administration of the to be Marketed Formulation (ROS2/) was also evaluated in study VBP15-PK-FORM-002. The results show that the to be Marketed Formulation (ROS2) is much less sensitive to concomitant food intake compared to the Clinical Formulation (ROS1). When the to be Marketed Formulation (ROS2/) is taken fasted, vamorolone is absorbed quickly and reaches t_{max} on average (median) after 1 hour (range 0.5 to 4.0 hours). Concomitant food intake delays the absorption but has little influence on the overall exposure in terms of C_{max} and AUC. For the To be Marketed Formulation (ROS2/), the median (range) t_{max} after a low-fat meal is 2 hours (0.5 to 5.0 hours) and C_{max} is slightly reduced by 4% after a low-fat meal when compared to the fasting condition. After the high-fat meal the t_{max} is similar to the low-fat meal (median 2 hours, range 0.5 to 4 hours) and C_{max} is on average 18% lower than after the fasted condition. The overall exposure in terms of AUC ($AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$) is increased by 14% for the low-fat meal and 13% for the high-fat meal when compared to the fasting administration.

Overall, the updated popPK model shows that the food effect for the ROS2/ "to be marketed" formulation is far less pronounced and intake independent of food is acceptable.

The to be Marketed Formulation (ROS2/) was compared to the Clinical Formulation (ROS1) under fasting conditions in the relative bioavailability study VBP15-PK-FORM and it was shown that the to be Marketed Formulation (ROS2/) shows an improved bioavailability of vamorolone with approximately 2.8-fold higher C_{max} and 1.9-fold higher AUC. When administered with a low-fat meal, the difference between the to be Marketed Formulation (ROS2/) and the Clinical Formulation (ROS1) is 14% for AUC and 35% for C_{max}. When administered with a high-fat meal, the difference between the to be Marketed Formulation (ROS2/) and the Clinical Formulation (ROS1) is 3% to 4% for AUC and 14% for C_{max}.

The differences in vamorolone peak concentrations (35% and 14% higher vamorolone C_{max} with the to be Marketed Formulation compared to the clinical formulation when given with a low-fat or high-fat meal, respectively) is not considered clinically relevant as vamorolone does not cause any acute adverse events (AEs) that would potentially be driven by C_{max}. The ER evaluation of safety revealed no strong association of safety signals with increased plasma levels. As the new to be Marketed formulation is not bioequivalent with the clinical formulation, the applicant provided an updated popPK model using preliminary PK data from ongoing study VBP15-006. For the new formulation, the 6 mg/kg dose significantly exceeds the predefined target exposure range, which could have a potential impact on tolerability. In contrast, exposure levels of the 2 mg/kg appeared to be consistently below the predefined range. However, after further updates to the popPK model it is now expected that the ROS2 formulation has an about 20% increase in overall exposure across all age groups and dose levels.

Distribution

The protein binding of vamorolone in human plasma is approximately 88%. In the blood partition experiment, the blood to plasma ratio was 0.87 and the red blood cell (RBC) to plasma ratio was 0.74. In the human mass balance study using [^{14}C]-vamorolone, radiolabelled vamorolone and its metabolite(s) did not appear to distribute into RBCs or other cellular components of whole blood cells.

Elimination

Metabolism

The *in vivo* metabolism of vamorolone was investigated in plasma, urine, and feces after single administration in samples from a human mass balance study (VBP15-MB) and after repeated

administration (14 days once daily) in plasma samples from the multiple ascending dose study in healthy subjects (VBP15-001) and from the Phase 2a study in DMD patients (VBP15-002).

The major vamorolone metabolite in plasma over 24 hours is the direct glucuronide M5, representing 32.5% of the signal in the sample. The second most abundant metabolite in plasma is M10, which is formed from vamorolone by hydrogenation and glucuronidation and represents 23.3% of the signal in the sample. M10 is further hydrogenated to yield the glucuronides M6 (18.8% of signal) and M8 (20.6% of signal). Vamorolone itself represents 4.4% of signal in plasma over the 24-hour period.

The metabolic pattern in urine confirms the metabolic profile observed in plasma. The four major plasma metabolites M5, M6, M8, and M10 (all glucuronides) are also the major metabolites in urine representing together 36% of dose. Direct excretion of vamorolone into urine is minimal. The major compound related material in feces is vamorolone, representing 55.1% of the sample and 15.4% of dose. The metabolites observed in feces were not identified and seem to represent vamorolone adducts.

While human metabolites are generally well described, the involved enzymes have not been convincingly identified. Therefore, the full potential for DDI has not been sufficiently investigated and requires additional clarification. It was agreed that the applicant can submit the relevant *in vitro* study results within 6 months post approval.

Vamorolone metabolic profiling in plasma from DMD patients showed results that were consistent with the evaluations from healthy adult subjects. The two major metabolites were the direct glucuronide M5 and the hydrogenated glucuronide M10 representing 34.42% and 37.84% of total drug related exposure. In plasma from DMD patients, the intermediate M12 was detected in small amounts, while the further hydrogenated glucuronides M6 and M8 were not observed. It is very likely that this difference compared to the metabolic pattern observed in healthy adults is driven by the difference in PK sampling periods. In patients with DMD only samples up to 8 hours were collected and therefore earlier metabolites (e.g., M12) have a higher relative abundance and can therefore be detected. The collection period in healthy adults was 24 hours and therefore downstream metabolites such as M6 and M8 become more relevant and were observed.

UGT1A3 and UGT2B7 and to a minor extent UGT2B17 were identified as the most likely metabolizing enzymes, although uncertainties still exist due to inadequate non-clinical data. The UGT enzymes involved in the drug metabolism and the potential for drug-drug-metabolism are further investigated in new *in vitro* studies. The applicant has committed to complete the studies within 6 months after approval. With the proposed additional warning provided in the SmPC, this is acceptable. It was further shown that CYP3A4, CYP3A5, CYP2C8, and CYP2C9 can metabolise vamorolone *in vitro*, but it appears that oxidation via CYPs is a minor pathway of vamorolone metabolism *in vivo*.

In addition, the applicant has provided four new *in vitro* study reports. In addition to the requested investigation of inhibition of CYP enzymes by vamorolone metabolite and inhibition of UGT1A3 by parent drug, the inhibition potential on common drug transporters was investigated. Minor inhibition potential was only found at concentrations that are outside the clinically relevant range.

Excretion

Following a single oral dose of [^{14}C]-vamorolone in healthy adult male subjects, approximately 30% of dose is excreted in feces (15.4% unchanged) and 57% of dose is excreted in urine as metabolites (< 1% unchanged). The major metabolites in urine are glucuronides (M5, M6, M8 and M10).

Dose proportionality and time dependencies

In Study VBP15-001 over the single dose range of 0.1 to 20 mg/kg in healthy male adults C_{max} and AUC_{0-inf} increased proportional with dose. Similar results were obtained for the same dose range on Day 1 and Day 14 of them MAD part of that study. In the assessment of the linearity of the vamorolone PK in

subjects with DMD on Day 1 and Day 14 of daily dosing the 95% CI of the slope for C_{max} and $AUC_{0\text{-}inf}$ in plasma did include the value 1.00 indicative of linear relationships across this range of dose levels (0.25 to 6.0 mg/kg).

Vamorolone has an elimination t½ of approximately 2 hours. Consistent with the short t½ relative to the 24-hour dosing frequency, steady state is achieved with the first dose and no accumulation is observed with daily administrations. In healthy adult males, the PK parameters after a single dose of vamorolone under fasting conditions on Day 1 are similar to the PK parameters after 14 days of daily dosing on Day 14. In subjects with DMD, PK profiles on Day 14 compared to PK profiles on Day 1 show slightly higher C_{max} and AUC values but the popPK evaluation did not suggest a change in PK over time.

Special populations

Impaired Hepatic Function

In Study VBP15 HI (N = 16) comparing subjects with moderate hepatic impairment (HI) (Child-Pugh Class B) with healthy matched controls, average C_{max} (geometric mean) was approximately 1.7-fold higher (727 ng/mL in subjects with HI and 439 ng/mL in healthy subjects) and $AUC_{0\text{-}inf}$ was increased by approximately 2.6-fold (4760 hr.ng/mL in subjects with HI and 1800 hr.ng/mL in healthy subjects). CL/F and Vz/F were 41.1 L/h and 230 L, respectively, in subjects with moderate HI compared to 97 L/h and 315 L, respectively, in healthy subjects. The vamorolone $t_{1/2}$ in subjects with moderate HI was on average 3.87 hours compared to 2.25 hours in healthy subjects. The t_{max} was similar in both populations ranging from 2.00 to 4.00 hours.

In paediatric patients with DMD, HI is extremely rare. The applicant provided justification that dose adjustment in moderate but not in mild HI is needed. In patients with moderate HI, the dose should be reduced to 2mg/kg/day for patients up to 40kg and to 80mg for patients with a body weight of 40kg and higher (SmPC Section 4.2). There is no experience with vamorolone in patients with severe HI and administration is contraindicated (SmPC section 4.3).

Influence of Weight

The final popK model was used to predict vamorolone PK at different body weight ranges by simulating 200 hypothetical individuals for each year of age from 2 to 18 years with body weights sampled from the NHANES database. AUC_{ss} and C_{max} were calculated for a dose of 6.0 mg/kg/day with and without caping the dose at certain body weights. For patients weighing up to 40 kg, the 6 mg/kg/day dose provides a consistent exposure in terms of AUC_{ss} with > 80% of patients within the target range defined by the vamorolone exposure observed in 4 to < 7-year-old patients. Applying a dose cap of 240 mg for patients above 40 kg is predicted to provide consistent exposure for paediatric patients up to 70 kg but would potentially lead to underdosing in heavier patients weighing more than that. The proposed dosing algorithm of 6 mg/kg for paediatric patients up to 40 kg and a fixed dose of 240 mg for patients weighing 40 kg is predicted to achieve the most consistent vamorolone exposure within the target region across all paediatric age groups.

Pharmacokinetic interaction studies

Vamorolone is eliminated by various routes involving numerous metabolic enzymes. Clinically significant DDIs of vamorolone with enzyme inhibitors or inducers are therefore unlikely. Based on *in vivo* metabolism investigations, glucuronidation was identified as major metabolic pathway for vamorolone.

Further, the applicant has provided four new *in vitro* study reports. In addition to the requested investigation of inhibition of CYP enzymes by vamorolone metabolite and inhibition of UGT1A3 by parent drug the inhibition potential on common drug transporters was investigated. Minor inhibition potential was only found at concentrations that are outside the clinically relevant range.

Since oxidation via CYP3A4 was observed *in vitro*, a DDI study with the strong CYP3A4 inhibitor itraconazole was conducted *in vivo* (VBP15-DDI). The study showed a weak effect of itraconazole on vamorolone PK (1.45-fold increase of vamorolone AUC and no significant effect on C_{max}) and confirmed that metabolism via CYP3A4 is a minor pathway for vamorolone. No dose adjustment is recommended when vamorolone is co-administered with CYP3A4 modulators.

The threshold for a potentially clinically relevant interaction as specified in the EMA guidance for DDI investigations was reached for transporters OAT3 and MATK2-K. The signal is borderline. The applicant decided to not perform a clinical study to evaluate the potential impact of vamorolone on these substrates. As *in vivo* inhibition of OAT3 and MATE2-K cannot be ruled out the issue was further discussed taking into account whether vamorolone is likely to be co-administered with compounds that are substrates for these transporters. Overall, the risk for clinically relevant interaction seems low and no restrictions in the SmPC are required at present.

2.6.2.2. Pharmacodynamics

Mechanism of action

Vamorolone is a novel dissociated steroid that contains a delta 9,11 double bond in its chemical structure and is differentiated from other glucocorticoid/corticosteroid compounds which, in their active form, contain a hydroxyl group in the 11β-position. As a consequence, vamorolone has a unique pharmacological activity profile and acts as selective agonist of the GR, and as antagonist of the MR.

Nonclinical studies have shown that vamorolone maintains transrepression activity (e.g., reduction in the expression of NF-κB mediated inflammatory activity) needed for its anti-inflammatory effect, while reducing the transactivation of GRE mediated transcriptional responses associated with some of the corticosteroid side effects. Furthermore, vamorolone appears to effectively protect cell plasma membranes from physical damage.

Primary and Secondary pharmacology

Primary pharmacology

The SOMAscan assay was utilised to analyze the response to vamorolone of the following pro-inflammatory biomarkers: CD23, MDC, IL22BP, LTa1/b2, IGFBP-2, ITGA1 ITGB1, and MMP-12. Of the seven pre-specified exploratory efficacy biomarkers, all but ITGA1 ITGB1 showed dose-dependently decreased levels with increasing doses of vamorolone from pre-dose to post two weeks of treatment, suggesting an anti-inflammatory effect of vamorolone similar to glucocorticoids. Four of the 7 pro-inflammatory efficacy biomarkers (CD23, IL22BP, MDC, and IGFBP-2) demonstrated a statistically significant dose-dependent decrease.

Secondary pharmacology

Well established PD biomarkers predictive of safety concerns of glucocorticoids were measured in various clinical studies with vamorolone. These biomarkers are related to insulin resistance (fasting glucose and insulin), adrenal suppression (first in morning cortisol and ACTH) and changes in bone turnover (osteocalcin, procollagen 1 N-terminal propeptide (P1NP) for bone formation and Type 1 collagen C-telopeptides (CTX) for bone resorption).

Results should be considered exploratory in nature and interpreted with caution. They might hint at a more favourable side effect profile compared to common glucocorticoids, however ultimately adequate long-term clinical safety data for the relevant age groups are required. Further details can be found as part of the clinical safety assessment on bone health.

Pharmacodynamic interactions and genetic differences in PD response

A general scientific discussion of potential PD interactions with concomitant medication and possible influences of genetic differences on the PD response was provided. The SmPC section 4.5 states that vamorolone to be used with caution in combination with renin-angiotensin-aldosterone system inhibitors and monitoring of potassium levels 1 month after starting a combination between vamorolone and mineralocorticoid receptor antagonists is now suggested.

Relationship between plasma concentration and effect

The exposure-response (ER) relationships for the six-dose responsive inflammatory biomarkers (CD23, MDC, IL22BP, LTa1/b2, IGFBP-2, and MMP-12) were investigated using the PK and SOMAscan data from the VBP15-002 Week 2 visit. AUC was the exposure variable, and a sigmoid Maximum effect (E_{max}) model was applied. Vamorolone showed the highest potency for changes in IGFBP-2, as indicated by the lowest AUC value of vamorolone achieving 50% maximal effect (E_{50}) value.

The order of E_{50} from highest to lowest for the five remaining biomarkers was MDC >IL22BP >CD23 > LTα1/β2 >MMP12. More than 90% of the maximal effect on all biomarkers was observed at AUC ranges achieved with 6 mg/kg daily dosing. IGFBP-2 is the only investigated biomarker showing significant target engagement (>80%) at the 2 mg/kg dose level.

Effects of vamorolone on ECG were investigated in the FIH study in healthy volunteers. Exposure at the highest investigated dose level over 14 days was about twice as high as that in the highest to be expected clinical exposure scenario. Based on these results a waiver for a dedicated QTc study can be granted.

Pharmacodynamic Modelling

ER modelling was used for efficacy endpoints (TTSTAND velocity, 6MWT, Time to Run/Walk 10 Meters Test (TTRW), Time to Climb 4 Steps Test (TTCLIMB) and NSAA), longitudinal evaluation of body mass index (BMI) z-score, and for AEs (cushingoid features and gastrointestinal disorders). These analyses are regarded to be of limited value due to assumptions of the model and uncertainties in the estimated parameters.

ER modelling for different efficacy endpoints (NSAA, 6MWT, TTSTAND) was updated to describe efficacy of the 4 mg/kg dose of the ROS2 formulation in patients 4 to <7 years of age compared to ROS1. It is considered not appropriate to draw conclusions to the age group of 2 to <4 years as no observed data from this age group with the ROS2 formulation was used in model development. The result that no age dependency was observed from 4 to <7 years through the model is not regarded as a meaningful conclusion regarding the age group 2 to <4 years because of the very narrow age range investigated. Furthermore, model development was hampered due to low sample sizes at the estimated EC_{50}, leading to model instabilities which were addressed using a fixed parameter for curvature. Estimated E_{max} values were unexpectedly high. High shrinkage was observed in IIV (up to 99% for all three efficacy endpoints). The efficacy model is not considered appropriate to predict efficacy for the 4 mg/kg dose in DMD patients for the ROS2 formulation across all age groups. TThis is especially relevant for the 2-4 year old patients for whom a 4mg/kg treatment dose was initially proposed.

Furthermore, ER modelling was conducted to predict changes in morning cortisol for different formulations (ROS1 and ROS2) and different doses (2 mg/kg, 4 mg/kg, 6 mg/kg) compared to 0.75 mg/kg prednisone in different age groups. Observed differences between healthy adults and paediatric DMD patients that could not be directly assigned to either study, age, or disease status and only limited patient data was available outside the age range of 4 to <7 years.

2.6.3. Discussion on clinical pharmacology

The PK and PD of vamorolone have been evaluated in six studies in healthy volunteers and in four studies with patients with DMD. Overall, the clinical pharmacology has been well characterised. Initial points for clarification concerned PK data of the To-be Marketed formulation in DMD patients and the updated popPK model, metabolism, and DDI. All issues are considered resolved. In the absence of clinical data for the 2 to 4 year old patients special emphasis was put on the reliability of the popPK model. As no reliable dose-efficacy model could be developed dose justification for this age range was based purely on extrapolation of overall drug exposure from patients aged 4 to 7 years. In the view of the results from the popPK model, the CHMP could not agree on the proposed posology for DMD patients aged 2-4 years. The applicant agreed to restrict the indication to DMD patients aged 4 years and above.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology has been well characterised. With the restriction of the indication to patients aged 4 years and above, it is considered that all concerns on clinical pharmacology have been resolved. The clinical pharmacology in the approved indication has been adequately evaluated.

2.6.5. Clinical efficacy

Primary evidence for efficacy is derived from 1 pivotal phase 2b study, Study VBP15-004. Additional supportive data is provided by dose-finding studies, Study VBP15-002 and VBP15-003 as well as Study VBP15-LTE. Further, efficacy results from Study VBP15-004 at 48 weeks were compared with results of two matched DMD standard of care treatment groups, prednisone and deflazacort from the Finding the Optimum Regimen for DMD study (FOR-DMD).

For a tabulated overview on pivotal placebo-controlled and long-term clinical studies, please refer to section 2.6 of this document.

2.6.5.1. Dose response studies

The doses to be used were established based on pre-clinical data and on the results of the phase I studies (see also Clinical Pharmacology (PK/PD) and non-clinical sections). Based on the provided exposure response modelling, no clear exposure response relationship for the examined clinical endpoints was shown (Reference is made to pharmacodynamics section above).

A Phase IIa Open-Label, Multiple Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Exploratory Efficacy of Vamorolone in Boys with Duchenne Muscular Dystrophy (DMD) (Study VBP15-002)

Study VBP15-002 was conducted from 28 June 2016 to 9 November 2017. It was a first-in patient, proof of concept, multi-center, open-label, multiple ascending dose study evaluating the safety, tolerability, PK, PD, and exploratory efficacy following oral administration of vamorolone 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day and 6.0 mg/kg/day over a 14-day treatment period followed by a 14-day post-treatment follow-up period in boys ages 4-<7 years with DMD. A total of 48 subjects were enrolled in the study. Subjects who completed the 2-week Follow-up Period were eligible to receive vamorolone in an open-label extension study under a separate clinical protocol (VBP15-003) or to receive standard of care treatment (including glucocorticoids) for DMD.

Male corticosteroid naïve subjects, ≥4 - <7 years of age at study entry, diagnosed with DMD by confirmed dystrophin deficiency or identifiable mutation within the DMD gene, who were able to complete TTSTAND without assistance at the study Screening and Baseline Visits were included into the study.

Efficacy was defined as exploratory objective. Exploratory clinical efficacy was assessed by Quantitative Muscle Testing (QMT), TTRW, TTSTAND, TTCLIMB, NSAA, and 6MWT at pre-treatment (Screening and Baseline), Week 2 (Day 13), and the final Week 4 (Day 28) Follow-up Visit.

Efficacy evaluations were based on the safety population, i.e., all subjects who received at least one dose of study medication.

Demographics and baseline characteristics

Overall, demographic and baseline characteristics for the safety population were comparable among the four dose level groups. The mean (±SD) age of subjects in the four dose level groups ranged from 4.7 ± 0.89 to 5.2 ± 1.03 years. Mean (±SD) weight and BMI were similar across the four dose level groups, ranging from 18.53 ± 2.012 to 21.47 ± 3.165 kg and 16.51 ± 1.002 to 17.39 ± 1.071 kg/m2, respectively. Mean (±SD) months since DMD diagnosis ranged from 21.4 ± 14.85 to 28.7 ± 17.26 across the four dose level groups.

Disposition of subjects

Forty-eight (48) subjects were enrolled in the study and received at least one dose of study medication (0.25 mg/kg/day: 12 subjects; 0.75 mg/kg/day: 12 subjects; 2.0 mg/kg/day: 12 subjects; 6.0 mg/kg/day: 12 subjects); all 48 subjects completed the 4-week study.

Exploratory Efficacy Results

Mean changes from baseline to the end of treatment (Week 2) and end of the 2-week off-treatment follow-up period (Week 4) in functional assessments were generally minimal and not dose-related.

A Phase II Open-label, Multicenter Extension Study to Assess the Long-term Safety and Efficacy of Vamorolone in Boys with Duchenne Muscular Dystrophy (DMD) (VBP15-003)

Study VBP15-003 was conducted from 28 July 2016 to 26 April 2018. It was a multi-center, open-label, multiple dose study to evaluate the long-term safety, tolerability, clinical efficacy, and PD of vamorolone at dose levels of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day and 6.0 mg/kg/day administered over a Treatment Period of 24 weeks in boys aged 4-7 years with DMD. Subjects who had previously completed study VBP15-002 were eligible for enrolment. A total of 48 subjects were enrolled in the study.

Subjects received vamorolone throughout the 24-week Treatment Period in this study at the same dose level they received in study VBP15-002. Subjects who elected to discontinue vamorolone treatment at the conclusion of this study at the end of participation in the Treatment Period received vamorolone for an additional 1-4 weeks according to a dose-tapering protocol following the end of the Treatment Period.

Efficacy was defined as secondary objective.

The primary clinical efficacy endpoint was TTSTAND velocity (rises/second): comparison with an untreated historical control group (Cooperative International Neuromuscular Research Group [CINRG] Duchenne Natural History Study [DNHS]) for change from baseline to Week 24. Secondary efficacy endpoints were TTSTAND, TTCLIMB, TTRW, 6MWT, NSAA), and QMT, analysed as change from baseline to each of the on-treatment and post-treatment assessment time points. Efficacy assessments were performed at baseline, Week 12 (±1 w), Week 24 (±1w). Quality of life was assessed by completion of the Paediatric Outcomes Data Collection Instrument (PODCI).

Efficacy evaluations were based on the Full Analysis Set (FAS): all subjects who received at least one dose of study medication in study VBP15-003 and had at least one post-baseline assessment.

Descriptive summaries of variables were provided where appropriate. In general, for continuous variables, the number of non-missing values (n) and the mean, standard deviation (SD), median, minimum, and maximum were tabulated. For categorical variables, the counts and proportions of each value were tabulated. Unless otherwise noted, baseline was defined as the last measurement taken prior to first exposure to study drug (Baseline Visit for VBP15-002).

The comparator group for efficacy consisted of 31 subjects from the CINRG-DNHS study who met all entry criteria of VBP15-003 and remained glucocorticoid-naïve through a 24-week period.

With regard to efficacy, a mixed model for repeated measures (MMRM) adjusted by baseline age was used to compare the vamorolone groups with the external comparator of steroid-naïve subjects from the CINRG-DNHS study. The baseline assessment from study VBP15-002 was used for change from baseline calculations. For within study analyses, change from baseline was analysed using a paired t test.

Demographic data were collected, and baseline characteristics were measured at the time of enrolment in the VBP15-002 core study. Reference is made to study VBP15-002.

Disposition of subjects

48 subjects were enrolled in the study and received at least one dose of study medication (0.25 mg/kg/day: 12 subjects; 0.75 mg/kg/day: 12 subjects; 2.0 mg/kg/day: 12 subjects; 6.0 mg/kg/day: 12 subjects) and were analysed for efficacy; 46 subjects completed the study and were enrolled in the subsequent VBP15-LTE long-term extension study. Two of these 46 subjects participated in the 2- to 5-week Dose-tapering Period prior to enrolling in the VBP15-LTE study.

Efficacy results

Table 3: Efficacy results in Study VBP15-003 (full analysis set)

	Change from Baseline at Week 24				
Endpoint	**VAM 0.25 mg/kg**	**VAM 0.75 mg/kg**	**VAM 2 mg/kg**	**VAM 6 mg/kg**	**CINRG DNHS (steroid-naïve)**
TTSTAND velocity, rises/sec					
N	10	12	12	11	29
Mean	-0.01	0.00	0.05	0.04	0.01
SD	0.066	0.062	0.061	0.045	0.068
p value vs DNHS	0.4062	0.9554	0.0397	0.1048	-
p value vs 0.25 mg/kg	-	0.5067	0.0192	0.0442	-
TTRW 10 meters velocity, meters/sec					
N	12	12	12	11	30
Mean	-0.05	0.06	0.06	0.27	-0.01
SD	0.311	0.210	0.210	0.254	0.256
p value vs DNHS	0.7248	0.3768	0.3500	0.0035	
p value vs 0.25 mg/kg	-	0.082	0.2895	0.0059	
TTCLIMB velocity, task/sec					
N	12	12	12	11	31
Mean	0.00	0.01	0.04	0.05	0.01
SD	0.076	0.066	0.090	0.061	0.062
p value vs DNHS	0.8532	0.6581	0.0811	0.0507	
p value vs 0.25 mg/kg	-	0.6107			
6MWT distance, meters					
N	10	12	10	9	-
Mean	-11.6	18.9	29.2	43.9	-
SD	29.45	41.08	35.91	43.72	-
p value vs 0.25 mg/kg	-	0.0644	0.0153	0.0019	
NSAA total score					
N	12	12	12	11	-
Mean	0.8	1.1	2.3	2.5	-
SD	2.83	2.94	1.78	2.62	-
p value vs 0.25 mg/kg		0.7844	0.3099	0.2157	-

6MWT=6-Minute Walk Test; CINRG DNHS= Duchenne Natural History Study; NSAA=North Star Ambulatory Assessment; TTCLIMB=Time to Climb; TTRW=Time to Run/Walk; TTSTAND=Time to Stand; VAM=vamorolone

QMT: Mean changes from baseline across the four dose level groups generally showed only small improvement compared to baseline scores in elbow extensors, knee flexors, and knee extensors, changes from baseline in QMT of elbow flexors were minimal and not dose related. QMT of knee extensors showed dose-related improvement for change from baseline to Week 24. Changes from baseline to weeks 12 and 24 were minimal (elbow extensors) or not dose-related (elbow extensors and knee flexors). Results for the PODCI showed high variability with no dose-dependent effect.

Efficacy results for TTSTAND, TTRW, and TTCLIMB velocity in the CINRG-DNHS control group were overall comparable to that seen for the lower vamorolone dosages, i.e., 0.25 and 0.75 mg/kg/day although the lowest vamorolone dose of 0.25 mg/kg appears to be worse than the natural history data. Mean improvements from baseline to Week 24 in TTSTAND velocity, TTRW velocity, and TTCLIMB velocity and 6MWT distance were greater for the vamorolone 2 and 6 mg/kg treatment arms when compared with the lower doses of vamorolone and the external untreated CINRG control group, except for TTRW velocity (vamorolone 0.75 and 2 mg/kg provided similar changes). Based on the well accepted minimally clinically

important differences (MCIDs), the effect sizes of the improvements for the vamorolone 2 and 6 mg/kg group in TTSTAND, TTRW and TTCLIMB velocity and 6MWT distance can be considered clinically meaningful (-0.023 rises/sec, -0.212 meters/sec, and 0.035 tasks/sec, for TTSTAND, TTRW, and TTCLIMB velocity, respectively, and 30 meters for 6MWT distance) [Duong et al, 2021; McDonald et al, 2013]. Greater improvements for the vamorolone 6 mg/kg arm in comparison to the vamorolone 2 mg/kg dose were only seen for results on TTRW velocity and 6MWT distance.

A 24-month Phase II Open-label, Multicenter Long-term Extension Study to Assess the Long-term Safety and Efficacy of Vamorolone in Boys with Duchenne Muscular Dystrophy (DMD) (Study VBP15-LTE)

Study VBP15-LTE was conducted from 01 February 2017 to 30 April 2020. It was a multicenter, open-label, multiple dose study evaluating the long-term safety, tolerability, clinical efficacy, and PD of vamorolone at dose levels of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, 4.0 mg/kg/day, and 6.0 mg/kg/day administered over a treatment period of 24 months to young boys with DMD. A total of 46 subjects were enrolled. Subjects who completed the Phase II extension study VBP15-003 Week 24 assessments were eligible for enrolment.

Included subjects were subjects who were diagnosed with DMD by confirmed dystrophin deficiency or identifiable mutation within the DMD gene prior to enrolment into the VBP15-002 core study at age 4-<7 years, who completed the VBP15-002 core and the VBP15-003 extension studies prior to enrolment into VBP15-LTE, and who were not treated at time of enrolment nor had been previously treated with oral glucocorticoids or other oral immunosuppressive agents for longer than 3 months cumulative with last previous use at least 3 months prior to first dose of study medication in VBP15-LTE.

Subjects initially received vamorolone at the same dose level they received in study VBP15-003 (0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, or 6.0 mg/kg/day); subjects were allowed to escalate vamorolone dose to the next higher dose level after receiving their current dose for at least one month, to the maximum of 6.0 mg/kg/day; subjects were allowed to de-escalate vamorolone dose due to intolerability. Subjects whose dose was decreased from 6 mg/kg/day to 2 kg/kg/day could have their dose subsequently increased to 4 mg/kg/day if they had been taking the 2 mg/kg/day dose for at least one month and, in the opinion of the Investigator, balancing efficacy with safety concerns, they could have benefited from an intermediate higher dose. Subjects who transitioned off vamorolone treatment at the end of participation in the Treatment Period (24 months) received vamorolone for an additional 1-4 weeks according to a dose-tapering protocol following the end of the Treatment Period and prior to discharge from the study.

Subjects had been previously treated with vamorolone for 6 months in VBP15-002 (2 weeks treatment) and VBP15-003 (24 weeks 'treatment) and so the combined treatment duration during VBP15-002, VBP15-003, and VBP15-LTE was 30 months.

Efficacy was defined as secondary objective, i.e., to investigate the effects of vamorolone, administered orally at daily doses up to 6 mg/kg over a 24-month Treatment Period, on muscle strength, mobility and functional exercise capacity vs. untreated DMD historical controls.

Changes in the Planned Analyses

Comparisons with external DMD historical control populations (the untreated DMD historical control population CINRG-DNHS) dataset showed insufficient corticosteroid-naïve subjects (n = 6) with 30-month data to match the VBP15-LTE 24-month assessment time point for efficacy assessments. The study objectives were therefore modified to remove comparisons to the external comparator populations that were not feasible.

As subjects had previously received vamorolone for an additional six months in VBP15-002 (treatment duration: 2 weeks) and VBP15-003 (treatment duration: 24 weeks), the pre-specified analyses which measured changes from baseline used VBP15-002 baseline as baseline. Thus, most pre-specified analyses evaluated the effect of a total of 30 months of vamorolone treatment (VBP15-LTE Month 12 and Month 24 time points reflect 18 months and 30 months, respectively, of total vamorolone treatment).

Efficacy endpoints

Primary (revised)

- TTSTAND velocity (rises/second) change from VBP15-002 baseline to VBP15-LTE Month 24.

Secondary

- TTSTAND velocity (rises/second) change from baseline to Month 12; and TTCLIMB velocity (tasks/sec), TTRW velocity (meters/second), 6MWT total distance travelled, NSAA total score, and QMT knee and elbow extension and flexion, each analysed as change from baseline to Month 12 and Month 24.

Efficacy evaluations were based on the FAS: all subjects who received at least one dose of study medication in VBP15-LTE and had at least one post-baseline assessment in the VBP15-LTE study. Unless otherwise noted, baseline was defined as the last measurement taken prior to first exposure to study drug (baseline Visit for VBP15-002).

Demographics

The age range covered in this study was from 4 years at baseline to up to 9.6 years at the end of the study.

Disposition of subjects

46 subjects were enrolled in the study (11 subjects [0.25 mg/kg/day], 12 subjects [0.75 mg/kg/day], 12 subjects [2.0 mg/kg/day], and 11 subjects [6.0 mg/kg/day]) and all 46 subjects were analysed for efficacy. A total of 41 out of the 46 DMD subjects (89.1%) completed the 24-month treatment period of VBP15-LTE (and therefore the 30-month treatment period of VBP15-002, VBP15-003 and VBP15-LTE combined) through to VBP15-LTE Month 24 (11 subjects [23.9%] at the 2 mg/kg/day dose level, three subjects [6.5%] at the 4mg/kg/day dose level, and 27 subjects [58.7%] at the 6 mg/kg/day dose level). Of the 11 subjects who completed VBP15-LTE at 2 mg/kg/day, five subjects had either started at 2 mg/kg/day or had been up titrated to 2 mg/kg/day and had remained at that dose, and six subjects had been down titrated from 6 mg/kg/day. All three subjects who completed the study at 4 mg/kg/day had been down titrated from 6 mg/kg/day. All 27 subjects who completed the study at 6 mg/kg/day had either started treatment at 6 mg/kg/day or had been up titrated to 6 mg/kg/day.

Efficacy Results:

Table 4: Efficacy in Study VBP15-003 at week 24 and Study VBP15-LTE at 18 months and 30 months (full analysis set and 30-month subset)

	Study VBP15-003		Study VBP15-LTE	
Change from Baseline	**Week 24**		**Month 18**	**Month 30**
	2 mg/kg	**6 mg/kg**	**2 + 6 mg/kg**	**2 + 6 mg/kg**
TTSTAND velocity (rises/sec)				
N	12	11	22	21
Mean (SD)	0.05 (0.06)	0.04 (0.05)	0.04 (0.07)	-0.01 (0.12)
6MWT distance (meters)				
N	10	9	17	15
Mean (SD)	29.2 (35.9)	43.9 (43.7)	62.2 (60.5)	32.0 (92.0)
TTRW velocity (meters/sec)				
N	12	12	23	18
Mean (SD)	0.06 (0.21)	0.27 (0.26)	0.36 (0,31)	0.06 (0.67)
TTCLIMB velocity (tasks/sec)				
N	12	11	23	18
Mean (SD)	0.04 (0.09)	0.05 (0.06)	0.07 (0.08)	0.04 (0.17)

6MWT=6-minute walk test; SD=standard deviation; TTCLIMB=time to climb; TTSTAND=time to stand; TTRW=time to run/walk

Overall, the improvements in TTSTAND, TTRW and TTCLIMB velocity, and 6MWT distance seen with vamorolone 2 and 6 mg/kg at Week 24 in Study VBP15-003 were maintained up to Month 18 in Study VBP15-LTE followed by a gradual decline towards baseline after month 18.

2.6.5.2. Main study

Study VB15-004: 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)

Methods

The study consisted of a screening period (Day -33 to Day -2), a baseline period (Day -1), period 1 (Day 1 to week 24), a 4-week transition period (Week 25 to Week 28) for subjects who received either placebo or prednisone in period 1 (subjects who received vamorolone in period 1 were continued on the same dose of vamorolone during this period), period 2 (Week 28 +1 day to Week 48): all subjects received vamorolone 2.0 or 6.0 mg/kg for 20 weeks, a 4-week dose tapering period (Week 49 to Week 52): subjects who elected not to continue vamorolone treatment had the vamorolone dose progressively reduced and discontinued.

The study included two sequential 24-week periods.

In Period 1, subjects were randomised to 1 of 6 groups in a 2:2:1:1:1:1 ratio: vamorolone 2.0 mg/kg, vamorolone 6.0 mg/kg, 2 groups of placebo and 2 groups of prednisone 0.75 mg/kg/day, with randomisation stratified by age at study entry (<6 years and ≥6 years).

To maintain the double-blind in this treatment period, all subjects received either a matching placebo for vamorolone (i.e., a placebo oral suspension), a matching placebo for prednisone (i.e. a placebo tablet) or both (i.e. placebo oral suspension and placebo tablet).

Following completion of Period 1, all subjects entered a 4-week Transition Period, during which vamorolone or its matching placebo were administered at the same dose as in Period 1, but the dose of prednisone and its matching placebo tablet were tapered to zero. According to the applicant, this tapering

period was designed to re-establish adrenal function, since suppression may have occurred with prednisone in Period 1.

Thereafter, subjects entered Period 2 during which all subjects who previously were treated with either prednisone or placebo were treated with vamorolone 2.0 or 6.0 mg/kg and subjects who had received vamorolone in Period 1 continued treatment on their vamorolone dose.

Table 5: Study VBP15-004 design

	Period #1 [Day 1 to Week 24 (168 days)]		Transition [Week 25 to 28]	Period #2 [Week 29 to 48 (140 days)]		Dose-tapering Period [Week 49 to 53]	Rando. groups
	Treatment (24 weeks)	n		Treatment (20 weeks)	n		
Pre-treatment period [Day -32 to -1]	Vamorolone, 2.0 mg/kg/day	30		Vamorolone, 2.0 mg/kg/day	30		1
	Vamorolone, 6.0 mg/kg/day	30		Vamorolone, 6.0 mg/kg/day	30		2
	Prednisone, 0.75 mg/kg/day	30		Vamorolone, 2.0 mg/kg/day	15		3
				Vamorolone, 6.0 mg/kg/day	15		4
	Placebo	30		Vamorolone, 2.0 mg/kg/day	15		5
				Vamorolone, 6.0 mg/kg/day	15		6

Specific modifications to study conduct were implemented during the COVID-19 pandemic (reference is made to Conduct of the study).

The following efficacy assessments were performed at screening/or baseline and afterwards as follows: TTSTAND assessments were conducted at week 6, 12, 24, 34, 40 and 48. TTCLIMB, TTRW, NSAA, Myometry, 6MWT and ROM assessments were performed at week 12, 24, 40 and 48. TSQM and PODCI were performed at week 24 and week 48, PARS III at week 12, 24 and 48, Ease of Study Medication Administration Assessment at week 2, 12, 24, 30, 40 and 48, Blindedness Assessment at week 24.

The applicant justified the use of the 0.75 mg/kg dose level of prednisone as internal comparator as this is the recommended starting dose for standard-of-care treatment for DMD in the DMD Care Considerations Working Group (Birnkrant et al, 2018). Additionally, it is pointed out, that based on a review by [Matthews et al, 2016] meta-analyses showed that prednisone or prednisolone given at 0.75 mg/kg/day was an effective dose and that a higher dose tested (1.5 mg/kg/day) only showed little evidence of improvement in strength and function measures.

- **Study Participants**

Main inclusion criteria relating to efficacy were: DMD diagnosed subjects with a centrally confirmed diagnosis of DMD defined as any one of the following: Dystrophin immunofluorescence and/or immunoblot showing complete dystrophin deficiency with a clinical picture consistent with typical DMD; Identifiable mutation within the DMD gene, where reading frame was predicted as "out-of-frame" with a clinical picture consistent with typical DMD; Complete dystrophin gene sequencing showed an alteration that precluded production of the dystrophin protein, with a clinical picture consistent with typical DMD; subjects were ≥4 years and <7 years of age at time of enrolment in the study; had a body weight >13.0 kg and ≤39.9 kg at screening,-,were able to walk independently without assistive devices and were able to complete the TTSTAND without assistance in <10 seconds at Screening.

Main exclusion criteria were: being currently being treated or had received previous treatment with oral glucocorticoids or other immunosuppressive agents (past transient use of oral glucocorticoids or other oral immunosuppressive agents for no longer than 1 month cumulative, with last use at least 3 months prior to first dose of study medication, was considered for eligibility on a case by-case basis, unless discontinued for intolerance. Inhaled and/or topical glucocorticoids were permitted if last use was at least

4 weeks prior to first dose of study medication or if administered at a stable dose beginning at least 4 weeks prior to first dose of study medication and anticipated to be used at this dose regimen for the duration of the study); had used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone, prorenone, or mexrenone within 4 weeks prior to the first dose of study medication; had major renal or hepatic impairment, diabetes mellitus, or immunosuppression or a history of any of these conditions including a history of primary hyperaldosteronism; had evidence of symptomatic cardiomyopathy (an asymptomatic cardiac abnormality was not exclusionary) or a chronic systemic fungal or viral infection or a history of these infections; had used idebenone within 4 weeks prior to the first dose of study medication; was taking (or had taken within 3 months prior to the first dose of study medication) any medication indicated for DMD, including Exondys51 and Translarna.

- **Treatments**

Vamorolone 2.0 mg/kg was administered as a 1.33% wt/wt oral, orange-flavoured suspension. Vamorolone 6.0 mg/kg was administered as a 4.0% wt/wt oral, orange-flavoured suspension. Prednisone was supplied as a 5-mg tablet in 15-tablet blister packs packaged in cartons wallets, administered orally.

This was a 'double dummy' design. In Treatment Period 1, each subject received oral doses of either vamorolone or its matching placebo and prednisone or its matching placebo for 24 weeks to maintain the double-blind.

Maintenance of the blind was aided by use of amber bottles and high acceptability for taste for both the vamorolone and placebo suspensions. Subjects in the prednisone and placebo groups received a placebo suspension. The same volume of either vamorolone 2 or 6 mg/kg or its matching placebo were orally administered using a volumetric syringe following a breakfast that included at least 8 g of fat; the dose administered was based on the subject's weight at the previous visit. Following administration of the study drug suspension, the volumetric syringe was filled once with water and the water was orally administered. Additionally, either prednisone 0.75 mg/kg or its matching placebo were administered orally as tablet(s) based on weight bands once daily during Period 1 either immediately before or after vamorolone/placebo administration. The number of prednisone or matching placebo tablets that were administered was based on the subject's weight at the previous visit. Following tablet administration, the subject drank approximately 50 mL (ie, approximately 2 ounces) of water.

During the Transition Period, subjects were continued on the same dose of vamorolone or it´s matching placebo that was administered during Treatment Period 1. However, prednisone (5 mg tablet) or its matching placebo were dose tapered.

During Period 2, all subjects received either vamorolone 2.0 mg/kg or 6.0 mg/kg for 20 weeks as shown in Table 5. Neither the matching placebo for vamorolone nor prednisone nor its matching placebo were administered in Period 2.

No pre-defined early escape clause, e.g., due to AEs or disease progression and no defined rescue medication has been included in the study design due to the lack of any concrete definition accepted in the scientific community for "declining" phase to trigger the initiation of glucocorticoid therapy when the study was designed. However, parents and investigators were allowed to discontinue the subject's participation in the study at any time, should they consider, based on their individual decision, that glucocorticoid treatment should be started and that a delay until the completion of the 24-week period was not acceptable.

Although generally the use of systemic glucocorticoids was not allowed during the study due to their potential impact on study results, there was 1 subject in period 1 in the vamorolone 6 mg/kg treatment arm who received prednisone for 4 days to cover for missing doses of medication, and 2 subjects in the placebo arm and 4 subjects in the vamorolone 2 mg/kg arm who received hydrocortisone for short durations up to 4 days as glucocorticoid supplementation therapy in the context of stress situations to

prevent adrenal crisis. In period 2 systemic corticoids were only used in the continuous vamorolone groups, with 2 subjects in the vamorolone 2 mg/kg treatment arm and 4 subjects in the 6 mg/kg arm with the longest use of hydrocortisone as stress dosing for 6 days. Overall, the treatment with corticosteroids due to adverse events of a small number of patients for a rather short duration is not considered to impact the outcome of the efficacy results.

- **Objectives**

Primary objectives

• To compare the efficacy of vamorolone administered orally at a daily dose of 6.0 mg/kg over a 24-week treatment period versus (vs) placebo in ambulant boys ages 4 to <7 years with DMD

• To evaluate the safety and tolerability of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg in ambulant boys ages 4 to <7 years with DMD

Secondary objectives with regard to efficacy

• To compare the efficacy of vamorolone administered orally at a daily dose of 2.0 mg/kg over a 24-week treatment period versus placebo in ambulant boys ages 4 to <7 years with DMD

• To compare the efficacy of vamorolone administered orally at daily doses of 2.0 mg/kg and 6 mg/kg over a 24-week treatment period vs. daily prednisone 0.75 mg/kg in ambulant boys aged 4 to <7 years with DMD

• To compare the efficacy of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 48-week treatment period in ambulant boys aged 4 to <7 years with DMD vs. untreated DMD historical controls (this objective could not be assessed because of a lack of data for the untreated DMD historical controls)

Although not pre-specified as an objective in the protocol, efficacy and safety were also evaluated following the switch from prednisone in Period 1 to vamorolone in Period 2.

- **Outcomes/endpoints**

Primary efficacy endpoint

- The change from baseline in TTSTAND velocity for the vamorolone 6.0 mg/kg group compared vs placebo at week 24.

Secondary efficacy endpoints (for week 24 tested in a pre-specified hierarchical order)

Change from baseline to week 24 for the following comparisons:

- TTSTAND velocity for the vamorolone 2.0 mg/kg/day vs placebo group
- 6MWT distance for vamorolone 6.0 mg/kg vs placebo
- 6MWT distance for vamorolone 2.0 mg/kg vs placebo
- TTRW velocity for vamorolone 6.0 mg/kg vs placebo
- TTRW velocity for vamorolone 2.0 mg/kg vs placebo
- 6MWT distance for vamorolone 6.0 mg/kg vs prednisone
- 6MWT distance for vamorolone 2.0 mg/kg vs prednisone

Additional secondary efficacy endpoints for week 24 were not tested for multiple comparisons and included the following comparing each of the vamorolone doses versus placebo and each vamorolone

dose versus prednisone: change from baseline in TTCLIMB velocity, change from baseline in NSAA score, change from baseline in knee extension muscle strength, Change from baseline in elbow extension muscle strength.

All the secondary efficacy endpoints were also analysed for the vamorolone groups at week 48, but not in a pre-defined hierarchical order.

- **Sample size**

In consideration of the primary efficacy analysis, comparison of vamorolone 6 mg/kg versus placebo, sample size calculations were performed using data from vamorolone-treated subjects from the VBP15-002/VBP15-003 24-week treatment period. The analysis compared TTSTAND velocity from the combined 2.0 mg/kg and 6.0 mg/kg groups (treatment group) to the combined 0.25 and 0.75 mg/kg groups (pseudo placebo group). The sample size of 30 per treatment group for 2.0 mg/kg, 6.0 mg/kg, prednisone, and placebo (ie, total enrolment of 120 subjects) provided approximately 91% power at alpha level 0.05 to detect a statistically significant difference between 6.0 mg/kg and placebo on TTSTAND velocity at Week 24. Subjects in prednisone and placebo groups were randomised into two groups each (n=15 per group). These groups were pooled for the Period 1 analyses.

- **Randomisation and Blinding (masking)**

Subjects were randomly allocated to treatment to receive vamorolone 2.0 or 6.0 mg/kg, placebo, or prednisone 0.75 mg/kg/day, in a 2:2:1:1:1:1 ratio with subjects in the prednisone and placebo groups were randomised into two groups each. These groups were pooled by initial treatment (prednisone or placebo) for the treatment period 1 analyses. Randomisation was stratified by subject age at study entry (<6 years versus ≥6 years).

- **Statistical methods**

No interim analyses were planned for this study.
Analysis populations

Intent-to-Treat (ITT) Population: All randomised subjects

Modified Intent-to-Treat (mITT)-1 Population: All randomised subjects who received at least one dose of study medication during period 1 and had at least one post-baseline efficacy assessment[1] during Period 1. This was the primary analysis population for efficacy at Week 24 and for the overall study.

Modified Intent-to-Treat (mITT)-2 Population: All randomised subjects who received at least one dose of study medication during period 2 and had at least one post-baseline efficacy assessment[1] during Period 2. This was the primary analysis population for efficacy during period 2.

Per Protocol (PP) Population: Subjects in the mITT Population with no major protocol deviations. Exclusion of subjects from the PP Population will be made on a subject-by-subject basis prior to database soft lock at the end of the 24-week treatment period. The PPP will also exclude some subjects because of missed assessments due to the COVID-19 pandemic. Exclusion of subjects from the PPP will be made on a subject-by-subject basis prior to database hard lock. This was a secondary analysis population for efficacy at Week 24.

Safety-1 and Safety-2 Population: All subjects who received at least one dose of study medication during Period 1 (analysis population for safety at Week 24) and Period 2 (analysis population for safety at Week 48), respectively.

Primary analysis of the primary efficacy endpoint for FDA has been conducted with restricted maximum likelihood (REML) based MMRM using the observed cases (without multiple imputation) on the mITT-1 analysis set. The MMRM includes the TTSTAND velocity values (as changes from baseline) from Weeks

6, 12 and 24 as dependent values. The model includes fixed effects for baseline age (as stratified in randomisation), treatment group (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day or placebo), week (Week 6, 12 or 24) and the treatment-by-week interaction. The baseline TTSTAND velocity will be included as a covariate.

Analysis of the primary efficacy endpoint for EMA used a missing data imputation approach assuming MNAR (missing not at random (Copy-Reference imputation). The estimand of the primary objective for the EMA analysis used a treatment policy strategy regarding the intercurrent event "premature discontinuation" (using a copy-reference approach for missing data imputation), a hypothetical strategy regarding the intercurrent event "COVID-19 pandemic related event" and a composite strategy regarding the intercurrent event "death".

The missing data that have been recorded to be missing due to the COVID-19 pandemic were considered under the assumption of Missing at random (MAR). Missing data due to death or disease progression were imputed as "0".

The following sensitivity analyses were provided by the applicant: (1) Analysis of the primary endpoint for FDA using a REML based MMRM and observed cases. (2) Analyses assessing the impact of COVID-19 (3) Analyses assessing the impact of missing data (4) Primary (EMA) analysis to be repeated in the ITT analysis set (5) Analyses assessing the impact of influential observations.

Analyses of secondary efficacy endpoints at Week 24:

V*amorolone vs. Placebo*

To increase the strength of evidence, the secondary endpoints were tested in a hierarchical order, to maintain the studywise Type I error rate.

The fixed sequential testing process start with the primary endpoint TTSTAND velocity, comparing vamorolone 6.0 mg/kg versus placebo at Week 24. If positive, i.e., there is a statistically significant difference in favour of vamorolone 6 mg/kg, the following comparisons will be performed sequentially:

1. TTSTAND velocity, vamorolone 2.0 mg/kg vs placebo at Week 24
2. 6MWT distance, vamorolone 6.0 mg/kg vs. placebo at Week 24
3. 6MWT distance, vamorolone 2.0 mg/kg vs. placebo at Week 24
4. TTRW velocity, vamorolone 6.0 mg/kg vs. placebo at Week 24
5. TTRW velocity, vamorolone 2.0 mg/kg vs. placebo at Week 24.

Statistical testing of the primary/secondary efficacy endpoints will stop if a p-value >0.05 occurs or if a p-value ≤0.05 occurs in the wrong direction (i.e., control better than vamorolone). In case the fixed sequential testing process stops, the results of the subsequent tests will be reported with nominal p-values, but p-values ≤0.05 in the right direction will not be considered proof of statistical testing success in these subsequent tests.

Vamorolone vs. Prednisone

TTSTAND velocity, 6MWT distance, TTRW velocity, TTCLIMB velocity, NSAA score, and knee and elbow extension muscle strength were compared for each vamorolone dose vs. prednisone at Week 24 using an MMRM model, observed cases (i.e., without multiple imputation) and the mITT-1 analysis set. The MMRM included the response values (as changes from baseline) from Weeks 6, 12, and 24 as dependent values. The model included fixed effects for baseline age (as stratified in randomisation), group (vamorolone 2.0 mg/kg, vamorolone 6.0 mg/kg, or prednisone 0.75 mg/kg), week (Week 6, 12, or 24) and treatment-by-week interaction. The baseline response value was included as a covariate. Within this

model, pairwise comparisons (using LSM contrasts) were made to compare the treatment difference between vamorolone 6.0 mg/kg or 2.0 mg/kg with prednisone. An unstructured covariance structure was applied for MMRM. If this analysis fails to converge, Akaike's information criterion was used to select the best covariance structure from compound symmetry and autoregressive-1 (AR(1)). The denominator degrees of freedom was computed using the Kenward-Roger method.

Formal statistical testing of 6MWT distance for vamorolone 6.0 mg/kg followed by 2.0 mg/kg vs prednisone was only conducted if the pre-specified hierarchical testing order held (ie, p values ≤0.05).

For TTSTAND velocity, 6MWT distance, TTRW velocity and NSAA score, the comparison of efficacy endpoints between the vamorolone groups and prednisone group were focused on a global assessment of efficacy, aiming to show that the efficacy profile of the two vamorolone doses was comparable to prednisone. There was no pre-defined order of the endpoints and for each endpoint, the treatment differences and 95% CIs calculated with MMRM were summarised.

Internal Comparisons of 48-Week Data

Efficacy endpoints at Week 48 were compared between the two dose levels of vamorolone (2.0 mg/kg vs. 6.0 mg/kg) in the set of subjects who were randomised to receive vamorolone in both Period 1 and Period 2. The differences between the doses were estimated with MMRM models similar to the ones used for the Week 24 analyses. Because there was no placebo group up to Week 48, no multiple imputation analyses were conducted, and all analyses were based on observed cases only.

The comparison focused on a global assessment of efficacy without formal statistical hypothesis testing. The following endpoints will be analysed: TTSTAND velocity, 6MWT distance, TTRW velocity, NSAA score.

Results

- **Participant flow**

Table 6: Disposition of subjects by period 1 and period 2 treatment groups (ITT population)

	Vamorolone 2.0 n (%)	Vamorolone 6.0 n (%)	Prednisone 0.75 + Vamorolone 2.0 n (%)	Prednisone 0.75 + Vamorolone 6.0 n (%)	Placebo + Vamorolone 2.0 n (%)	Placebo + Vamorolone 6.0 n (%)	Total n (%)
Number Screened							133
Number of Screen Failures							12
Withdrawal by Parent/Guardian [2]							1 (8.3)
Screen failure [2]							11 (91.7)
Number Randomized	30	30	15	16	15	15	121
Completed Study through Week 24 [1]	28 (93.3)	28 (93.3)	15 (100)	15 (93.8)	14 (93.3)	14 (93.3)	114 (94.2)
Completed Study [1]	28 (93.3)	26 (86.7)	15 (100)	15 (93.8)	14 (93.3)	14 (93.3)	112 (92.6)
Discontinued Study Prior to Week 24 [1]	2 (6.7)	2 (6.7)	0	1 (6.3)	1 (6.7)	1 (6.7)	7 (5.8)
Withdrawal by Parent/Guardian [2]	2 (100)	1 (50.0)	0	0	0	0	3 (42.9)
Withdrawal due to Adverse Event [2]	0	0	0	1 (100)	0	0	1 (14.3)
Withdrawal by Physician Decision [2]	0	1 (50.0)	0	0	0	0	1 (14.3)
Other [2]	0	0	0	0	1 (100)	1 (100)	2 (28.6)
Discontinued Study Prematurely [1]	2 (6.7)	4 (13.3)	0	1 (6.3)	1 (6.7)	1 (6.7)	9 (7.4)
Withdrawal by Parent/Guardian [2]	2 (100)	1 (25.0)	0	0	0	0	3 (33.3)
Withdrawal due to Adverse Event [2]	0	1 (25.0)	0	1 (100)	0	0	2 (22.2)
Withdrawal by Physician Decision [2]	0	1 (25.0)	0	0	0	0	1 (11.1)
Other [2]	0	1 (25.0)	0	0	1 (100)	1 (100)	3 (33.3)

A total of 133 subjects were screened for participation in study VBP15-004 and of these, 121 subjects were randomised: 30 subjects each in the vamorolone 6.0 mg/kg, vamorolone 2.0 mg/kg, and the combined placebo groups and 31 in the combined prednisone groups. 3 subjects (2 in the vamorolone 6.0 mg/kg arm and one randomised to placebo) were not treated and thus excluded from the safety and the mITT analysis populations (the mITT population excluded an additional subject in the placebo group who did not have any post-baseline efficacy assessments). In addition to these 4 subjects, 3 further subjects did not complete the study through week 24: 2 in the vamorolone 2mg/kg treatment arm and one under prednisone treatment.

114 (94.2%) and 112 (92.6%) of the randomised subjects completed period 1 (through week 24) and period 2 (through week 48), respectively. The proportion of subjects who completed the study under vamorolone 2.0 mg, vamorolone 6.0 mg, placebo and prednisone treatment was 93.3%, 86.7%, 93.3% and 96.8%, respectively. One subject in the prednisone group was prematurely discontinued before week 24 because of an adverse event. After week 24 two additional subjects who were initially randomised to vamorolone 6 mg/kg and who received vamorolone throughout the study did not complete the final study: 1 subject was prematurely withdrawn because of an AE and 1 subject withdrew consent.

- **Recruitment**

This study was conducted at 33 centers in 11 countries.

Date first subject enrolled: 29 June 2018 and Date last subject completed: 19 August 2021

- **Conduct of the study**

Changes to the original protocol (dated 15 December 2017) included 4 global protocol amendments. Amendment No 4 (resulting in protocol version 5 with date 28 August 2020) included amongst others the revision of the primary efficacy objective and primary efficacy endpoint to compare vamorolone 6.0 mg/kg vs placebo at Week 24 instead of vamorolone 2 and 6 mg/kg vs placebo at Week 24; the removal of the secondary objective of comparing the efficacy of vamorolone 6.0 mg/kg vs 2.0 mg/kg and addition of a secondary objective of comparing the efficacy of vamorolone 2.0 mg/kg vs placebo at Week 24; to revise the secondary efficacy endpoints for Treatment Period #1; to revise the multiple testing procedures for the efficacy endpoints; to revise the statistical methodology for efficacy and safety analyses.

Additionally, protocol clarification letter #2.1 (27 March 2020) was issued to outline specific modifications that could be made to study conduct due to the COVID-19 pandemic. The key modifications to be made on a visit-, site-, or subject-specific basis were that in cases where on-site study visits are not possible for the completion of scheduled efficacy assessments, the TTSTAND will be conducted remotely by a trained clinical evaluator by videoconferencing interface; remote assessment of TTSTAND must be completed at the Baseline, Week 24, and Week 48 assessment time points. If possible, remote assessment of TTSTAND at Week 12 may also be performed. TTSTAND must be performed per protocol at the on-site Screening visit.

A total of 733 protocol deviations were reported during the study with 82 important protocol deviations that were recorded for 29 subjects in the Safety Population. A total of 271 COVID-19-related protocol deviations were recorded for 81 subjects overall in the Safety Population. A total of 8 important COVID-19-related deviations were reported for 7 subjects overall for the Safety Population.

- **Baseline data**

The majority of subjects in the mITT-1 population were White or Asian and the most common ethnicity was not Hispanic or Latino (82.9%, 10.3% and 95.7% of subjects, respectively). 66 (56.4%) subjects were enrolled in Europe and 51 (43.6%) in the USA. Across the treatment groups, the mean (SD) age

was 5.42 (0.863) years (min 4.0, max 7.0). The mean (SD) height was 108.71 (7.851) cm, the mean (SD) body weight was 19.60 (3.181) kg, and the mean (SD) BMI was 16.49 (1.276) kg/m^2.

Table 7: Disease characteristics at baseline (mITT-1 Population)

	Placebo	Prednisone 0.75 mg/kg	Vamorolone 2 mg/kg	Vamorolone 6 mg/kg	Total
Months Since First DMD Symptoms Noticed					
n	28	31	30	27	116
Mean (SD)	34.1 (16.70)	37.8 (17.25)	38.7 (18.88)	40.7 (17.89)	37.8 (17.63)
Median	28.5	40.0	39.0	40.0	38.0
Min., Max.	5,67	3,65	6,77	7,68	3,77
TTSTAND (seconds)					
n	28	31	30	28	117
Mean (SD)	5.55 (1.93)	4.92 (1.51)	6.07(2.35)	5.97 (1.99)	5.61 (1.99)
Median	5.15	4.40	5.45	5.70	5.00
Min., Max.	2,9; 10.7	2.8; 9.6	3.7; 13.5	3.3; 10.8	2.8; 13.5
TTSTAND velocity (rises/sec)					
n	28	31	30	28	117
Mean (SD)	0.20 (0.06)	0.22 (0.06)	0.18 (0.06)	0.19 (0.06)	0.20 (0.06)
Median	0.19	0.23	0.18	0.18	0.20
Min., Max.	0.1; 0.3	0.1; 0.4	0.1; 0.3	0.1; 0.3	0.1; 0.4
6MWT distance (meters)					
n	24	31	27	26	108
Mean (SD)	354.50 (77.59)	343.32 (55.84)	316.07 (58.43)	312.50 (56.19)	331.57 (63.58)
Median	346.50	350.00	326.00	328.50	338.50
Min., Max.	247.0; 605.0	232.0; 465.0	179.0; 406.0	195.0; 425.0	179.0; 605.0
NSAA total score					
n	28	31	30	28	117
Mean (SD)	18.89 (5.301)	21.16 (5.45)	17.20 (4.66)	18.86 (4.07)	19.05 (5.06)
Median	17.50	20.00	16.50	19.00	18.00
Min., Max.	9.0; 28.0	13.0; 32.0	9.0; 26.0	12.0; 28.0	9.0; 32.0

DMD = Duchenne Muscular Dystrohy; 6MWT=6-minute walk test; SD=standard deviation; TTSTAND=time to stand; NSAA=North Star Ambulatory Assessment.

- **Numbers analysed**

Table 8: Number of subjects by analysis populations

	Placebo (Per1) + VAM 2 mg/kg (Per2)	Placebo (Per1) + VAM 6 mg/kg (Per2)	Prednisone (Per1) + VAM 2 mg/kg (Per2)	Prednisone (Per1) + VAM 6 mg/kg (Per2)	VAM 2 mg/kg (Per1 and Per2)	VAM 6 mg/kg (Per1 and Per2)	Total
mITT Population-1 [1, 2]	14 (93.3)	14 (93.3)	15 (100)	16 (100)	30 (100)	28 (93.3)	117 (96.7)
mITT Population-2 [1, 3]	14 (93.3)	14 (93.3)	15 (100)	15 (93.8)	28 (93.3)	28 (93.3)	114 (94.2)
PP Population [1, 4]	14 (93.3)	14 (93.3)	15 (100)	15 (93.8)	28 (93.3)	27 (90.0)	113 (93.4)
Safety Population-1 [1, 5]	15 (100)	14 (93.3)	15 (100)	16 (100)	30 (100)	28 (93.3)	118 (97.5)
Safety Population 2 [1, 6]	14 (93.3)	14 (93.3)	15 (100)	15 (93.8)	28 (93.3)	28 (93.3)	114 (94.2)

[1] Denominator is based on number of subjects randomised.
[2] All randomised subjects who had at least one dose of study medication and had at least one postbaseline efficacy assessment during Treatment Period 1.
[3] All randomised subjects who had at least one dose of study medication and had at least one postbaseline efficacy assessment during Treatment Period 2.
[4] All exclusions from the PP population were because a TTSTAND assessment at Week 24 was missing.
[5] All subjects who received at least one dose of study medication during Treatment Period 1.
[6] All subjects who completed Treatment Period 1 and received at least one dose of vamorolone during Treatment Period 2.
mITT=modified Intent-to-Treat; Per1=Period 1; Per2=Period 2; PP=per protocol

- **Outcomes and estimation**

Week 24 Results

Primary efficacy endpoint: TTSTAND Velocity - Vamorolone 6 mg/kg versus Placebo

Primary analysis:

Table 9: TTSTAND velocity change from baseline to week 24: vamorolone 6 mg/kg versus placebo (and vamorolone 2 mg/kg versus placebo) (mITT-1 population)

TTSTAND Velocity (rises/sec)	Placebo (N =28)	Vamorolone 6 mg/kg (N= 28)	Vamorolone 2 mg/kg (N = 30)
Baseline[1]			
N	28	28	30
Mean (SD)	0.200 (0.0642)	0.186 (0.0588)	0.184 (0.0546)
Median	0.194	0.176	0.184
Min; Max	0.093:0.345	0.093;0.303	0.074;0.270
Week 24[1]			
N	28	27	29
Mean (SD)	0.193 (0.0918)	0.242 (0.0785)	0.225 (0.0921)
Median	0.192	0.238	0.227
Min; Max	0.000;0.357	0.108;0.476	0.070;0.476
Change from Baseline at Week 24[1]			
N	28	27	29
Mean (SD)	-0.007 (0.0628)	0.054 (0.0666)	0.041 (0.0869)
Median	-0.011	0.041	0.033
Min;Max	-0.120;0.161	-0.082;0.198	-0.092;0.351
FDA Analysis[2]			
LSM (SE) change from baseline	-0.0120 (0.0135)	0.0483 (0.0136)	0.0328 (0.0131)
LSM difference (SE)		0.0603 (0.0188)	0.0449
95% CI		0.0230,0.0976	0.0082:0.0816
p value		0.0018	0.0171
EMA Analysis[3]			
LSM (SE) change from baseline	-0.0121 (0.0134)	0.0464 (0.0135)	0.0309 (0.0130)
LSM difference (SE)		0.0586 (0.0187)	0.0430
95% CI		0.0218;0.0953	0.0069;0.0791
P value		0.0018	0.0196

TTSTAND velocity = 1 / TTSTAND and is expressed as rises/sec. Note that velocity was set to 0 for responses determined to be missing due to disease progression (inability to do the test). Moreover, at the first visit a subject could not perform the test due to disease progression, and at ALL subsequent visits, the raw score was left as missing and velocity was imputed as 0.
[1]Descriptive statistics based on observed cases (without multiple imputation)
[2]REML-based MMRM using observed cases (without multiple imputation)
[3]REML-based MMRM using multiple imputation based the assumption of missing not at random
CI=confidence interval; LSM=least squares mean; mITT=modified Intent-to-Treat; MMRM=mixed model for repeated measures; REML=restricted maximum likelihood; SD=standard deviation; SE=standard error; TTSTAND=time to stand.

In the primary analysis of change from baseline in TTSTAND velocity at week 24, a statistically significant difference was demonstrated when vamorolone 6 mg/kg/day was compared against placebo (p = 0.0018). TTSTAND velocity increased in the vamorolone 6 mg/kg group from 0.186 to 0.242 rises/sec and slightly decreased in the placebo group from 0.200 to 0.193 rises/sec at Week 24. The least squares mean (LSM) difference for vamorolone 6 mg/kg from placebo was 0.0586 rises/sec in the EMA analysis and 0.0603 rises/sec in the primary FDA analysis. The improvement in TTSTAND velocity under

vamorolone 6 mg/kg/day is considered clinically relevant as it is greater than the MCID for TTSTAND of 0.023 rises/sec.

Table 10: Sensitivity analyses for TTSTAND velocity (mITT-1 population)

	LSM (SE) Vamorolone 6 mg/kg vs Placebo	LSM Difference (SE) 95% CI	p value
Impact of the COVID-19 Pandemic			
Primary analysis (EMA)	0.0464 (0.0135) vs -0.0121 (0.0134)	0.0586 (0.0187) 0.0218, 0.0953	0.0018
Missing or delayed due to COVID-19[1]	0.0466 (0.0135) vs -0.0121 (0.0134)	0.0587 (0.0187) 0.0220, 0.0954	0.0017
Alternative assessment method due to COVID-19[2]	0.0459 (0.0137) vs. -0.0140 (0.0140)	0.0599 (0.0193) 0.0220, 0.0977	0.0019
Missing data sensitivity analyses			
Primary analysis (mITT-1; FDA)	0.0483 (0.0136) vs -0.0120 (0.0135)	0.0603 (0.0188) 0.0230, 0.0976	0.0018
Primary analysis (mITT-1; EMA)	0.0464 (0.0135) vs. -0.0121 (0.0134)	0.0586 ((0.0187)) 0.0218, 0.0953	0.0018
All randomized subjects[3]	0.0482 (0.0138) vs. -0.0119 (0.0135)	0.0601 (0.0191) 0.0226, 0.0975	0.0017
All randomized subjects (EMA analysis)	0.0407 (0.0136) vs. -0.0109 (0.0136)	0.0516 (0.0188) 0.0148, 0.0885	0.0060
All randomized subjects with no missing data at baseline[3]	0.0484 (0.0137) vs. -0.0121 (0.0135)	0.0605 (0.0189) 0.0235, 0.0975	0.0014
All randomized subjects with no missing data at baseline and at least 1 postbaseline assessment[3]	0.0483 (0.0136) vs. -0.0121 (0.0135)	0.0603 (0.0188) 0.0234, 0.0972	0.0014
Randomized subjects with no missing data[4]	0.0356 (0.0144) vs. -0.0057 (0.0135)	0.0413 (0.0195) 0.0027, 0.0800	0.0363
Influential observations sensitivity analysis			
Impact of influential observations[5]	0.0454 (0.0124) vs. -0.0121 (0.0122)	0.0575 (0.0171) 0.0236, 0.0913	0.0011

[1] Assessments missing or delayed due to COVID-19 were set as missing and imputed similarly as for the EMA primary analysis.
[2] Assessments that were conducted with alternative assessment methods due to COVID-19 were set as missing and imputed similarly as for the EMA primary analysis.
[3] Missing data imputed based on assumption of missing at random regardless of the reason for missingness.
[4] MMRM based on observed cases.
[5] TTSTAND values < 2.5 seconds imputed as 2.5 seconds; FDA analysis.
CI=Confidence interval; EMA=European Medicines Agency; FDA=Food and Drug Administration; LSM=Least squares mean; mITT= modified intent-to-treat; MAR=missing at random; MMRM=mixed model for repeated measures; MNAR=missing not at random; REML=restricted maximum likelihood; SE=standard error; TTSTAND=time to stand.

Several sensitivity analyses have been performed to confirm the results of the primary analysis. Overall, sensitivity analyses demonstrate that the COVID-19 pandemic, missing data, and influential observations did not affect the results of the primary analysis at Week 24. The primary EMA analysis repeated in the ITT analysis set was also in accordance with the primary EMA analysis (mITT population). Per Protocol Analysis: The LSM change from baseline at week 24 in the vamorolone 6 mg/kg group was comparable to that in the mITT-1 population.

TTSTAND in seconds decreased in the vamorolone 6 mg/kg group and slightly increased in the placebo group at Week 24 with LSM (SE) changes from baseline of -1.0523 (0.3604) and 0.6187 (0.3664), respectively. The LSM difference for vamorolone 6 mg/kg from placebo was -1.67 seconds in favour of vamorolone (p=0.0009). The LSM difference for vamorolone 2 mg/kg against placebo was -0.9 seconds (p = 0.0607).

Secondary Efficacy Endpoints - Pre-specified Hierarchical Testing Order:

First pre-specified secondary endpoint: TTSTAND Velocity - Vamorolone 2 mg/kg versus Placebo

The first secondary efficacy endpoint was met: in the primary analysis (EMA analysis) of change from baseline in TTSTAND velocity at week 24, a statistically significant difference was demonstrated when vamorolone 2 mg/kg/day was compared against placebo (p = 0.0196). TTSTAND velocity increased in the vamorolone 2 mg/kg group from 0.184 to 0.225 rises/sec and slightly decreased in the placebo arm from 0.200 to 0.193 rises/sec at week 24. The LSM difference for vamorolone 2 mg/kg from placebo was 0.0430 rises/sec (EMA analysis) and comparable to the primary FDA analysis. The improvement in

TTSTAND velocity mg/kg/day is considered clinically relevant also for 2 mg/kg as it is greater than the MCID for TTSTAND of 0.023 rises/sec. Sensitivity and supportive analyses for TTSTAND velocity in change from baseline under vamorolone 2 mg/kg compared to placebo confirmed the results of the primary analysis.

Second and third pre-specified secondary endpoints: 6MWT Distance - Vamorolone 6 mg/kg and 2 mg/kg versus Placebo

The second and the third of the pre-specified secondary endpoints were met: in the primary analyses (EMA analysis) of change from baseline in the 6MWT distance at week 24, statistically significant differences were demonstrated for the vamorolone 6 mg/kg and the 2 mg/kg treatment arms when compared against placebo (p=0.0117 and p=0.0112, respectively). While in the vamorolone treatment groups the 6MWT distance increased it showed some decline under placebo. The LSM (SE) change from baseline for placebo, vamorolone 6 mg/kg and 2 mg/kg was -11.37 (10.6082), 24.57 (10.0582) and 24.98 (10.0352), respectively. The LSM difference for vamorolone 6 mg/kg and 2 mg/kg was 35.9 meters and 36.2 meters, respectively, which is compellingly clinically relevant. Provided sensitivity analyses supported the primary analyses, demonstrating that missing data and the analysis method had no impact on the results received.

Fourths and fifths pre-specified secondary endpoint: TTRW Velocity - Vamorolone 6 mg/kg and 2 mg/kg versus Placebo

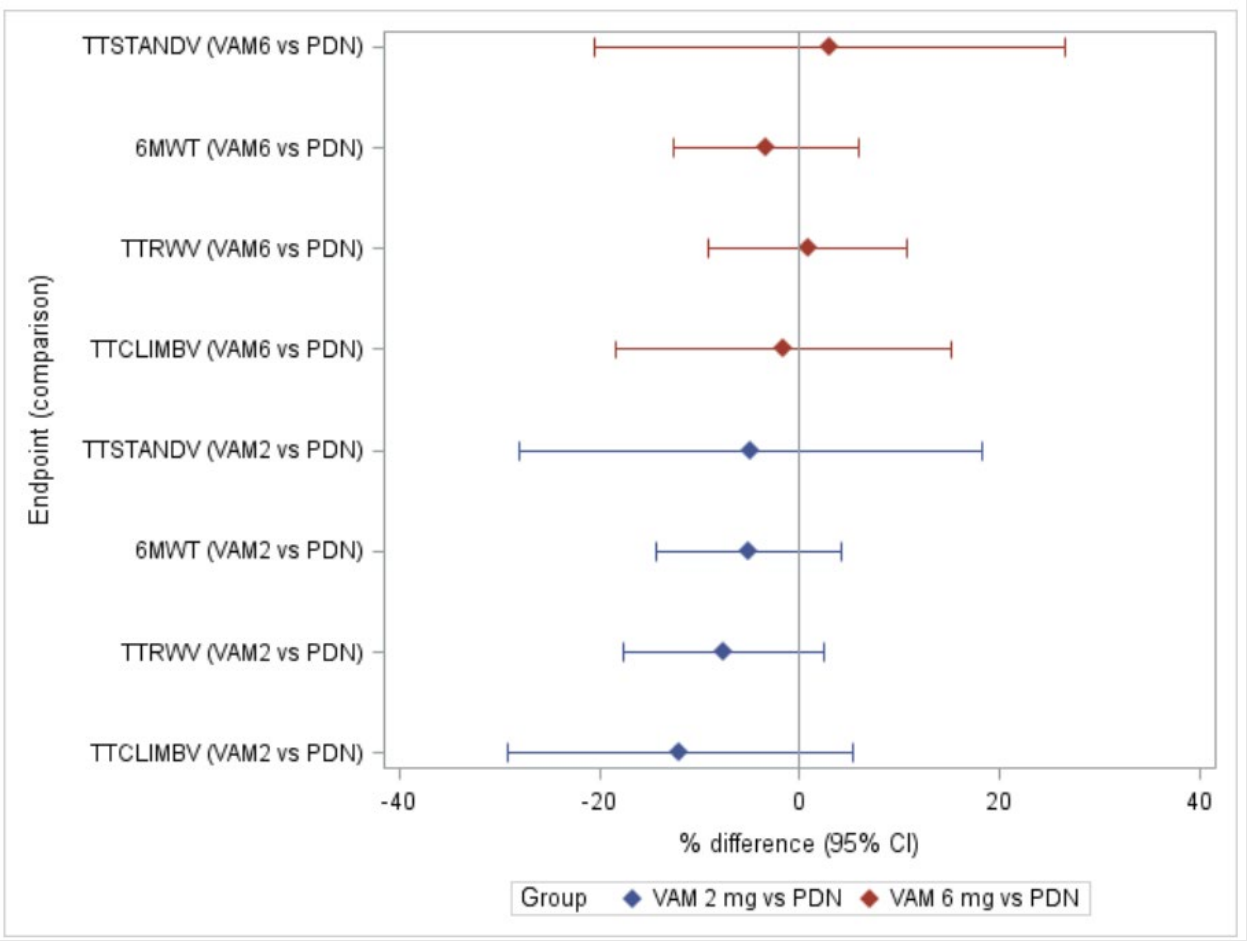
The fourth secondary efficacy endpoint of the pre-specified secondary endpoints was met: in the primary analysis (EMA analysis) of change from baseline in TTRW velocity at week 24, a statistically significant LSM difference of 0.237 meters/sec was demonstrated for vamorolone 6 mg/kg/day when compared against placebo (p = 0.0020) representing clinically relevance. TTRW velocity was increased under vamorolone 6 mg/kg group (LSM change from baseline 0.2372 meters/sec) and was almost unchanged in the placebo group at Week 24 with a very minimal increase of 0.0171 meters /sec (LSM change from baseline). With respect to the comparison of vamorolone 2 mg/kg against placebo, TTRW velocity increased only slightly from 1.563 meters/sec at baseline to 1.724 meters/sec at Week 24 for vamorolone and remained almost stable for placebo (LSM change from baseline 0.1387 and 0.0171, respectively). The LSM difference of 0.1216 meters/sec was not statistically significant (p = 0.1228). As the fifths secondary endpoint in the pre-specified hierarchical order was not met, thus, the hierarchical testing ended.

<u>Analyses Vamorolone vs Prednisone</u>

Sixth and sevenths pre-specified secondary endpoints: 6MWT Distance - Vamorolone 6 mg/kg and 2 mg/kg versus Prednisone

As the fifths secondary endpoint failed to show statistical significance, no formal statistical testing of 6MWT distance for vamorolone 6 mg/kg and 2 mg/kg vs prednisone was possible. While improvements from baseline at Week 24 in the mean 6MWT distance were almost comparable for both vamorolone treatment groups (6 mg/kg and 2 mg/kg), subjects under prednisone treatment improved numerically better (EMA analysis) with LSM (SE) changes from baseline for prednisone and vamorolone 6 mg/kg and 2 mg/kg of 44.12 (9.6444), 24.98 (10.0352) and 24.57 (10.0582), respectively. However, the LSM difference for change from baseline for vamorolone 6 mg/kg and for vamorolone 2 mg/kg each against prednisone was -19.55 (p = 0.14) and -19.14 (p = 0.17).

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



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

TTSTANDV=time to stand velocity; 6MWT=6-minute walk test; TTRWV=Time to run/walk 10 Meters Test velocity; TTCLIMBV=Time to climb 4 steps test velocity; VAM2=vamorolone 2 mg/kg; VAM6=vamorolone 6mg/kg PDN=Prednisone.

To account for baseline imbalances and to allow to examine efficacy endpoints globally in spite of different units, the applicant provided percentual changes from baseline at Week 24 for the relevant outcome parameters. The improvements seen with vamorolone 6 mg/kg in TTSTAND, TTRW, and TTCLIMB velocity were almost comparable to those seen with prednisone at Week 24, while for the 6MWT and the NSAA score prednisone provided better results. The improvements seen with vamorolone 2 mg/kg were overall slightly smaller than those seen with prednisone, when evaluated globally.

Additional secondary efficacy endpoints

TTCLIMB Velocity was increased in each of the vamorolone groups and slightly decreased in the placebo group from baseline at Week 24. The LSM difference was 0.07 tasks/sec for vamorolone 6 mg/kg from placebo (p= 0.0005 and p = 0.0008, respectively) and 0.06 tasks/sec for vamorolone 2 mg/kg from placebo in the EMA and the FDA analyses (p= 0.005 and p = 0.0056, respectively). The improvements in TTCLIMB velocity with vamorolone 2 and 6 mg/kg were both greater than the minimally clinical important difference. ***NSAA Score*** increased from baseline in the vamorolone groups and slightly

decreased in the placebo group at Week 24. The LSM difference was 3.6 points for vamorolone 6 mg/kg from placebo (p <0.0001 each) and 3.2 points for vamorolone 2 mg/kg from placebo in the EMA and FDA analyses (p=0.0003 and p=0.0002, respectively. The increases in each of the vamorolone groups at Week 24 (approximately +3 points) can be considered clinically meaningful. ***Hand-held myometry:*** Change from baseline to week 24 in hand-held myometry in vamorolone 6 mg/kg group for knee extensors was 0.0624 kg in the vamorolone group and 1.0147 kg in the prednisone group (p=0.0507) and for elbow flexors LSM change from baseline to week 24 was 0.4241 kg in the vamorolone group and 1.0218 kg in the prednisone group (p=0.0291). In the vamorolone 2 mg/kg group, change in hand-held myometry from baseline to week 24 for knee extensors was -0.03 kg in the vamorolone group (p=0.0388 when compared to prednisone) and for elbow flexors it was 0.5555 kg in the vamorolone group (p=0.1105 when compared to prednisone). Increase in muscle strength for elbow flexors was slightly higher in vamorolone 2 mg/kg than in the 6 mg/kg group. Comparison was not alpha controlled.

Week 48 Results

Vamorolone Treatment for 48 Weeks (continued Vamorolone Treatment)

Table 11: Change from baseline at week 24 and week 48 in motor function for vamorolone 2 mg/kg vs 6 mg/kg (mITT2 population)

TTSTAND velocity (rises/sec)	LSM (SE)	LSM Difference (SE) 95% CI	p value
Week 24 Change from Baseline			
Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	0.0521 (0.0130) vs. 0.0265 (0.0127)	0.0256 (0.0174) -0.0094, 0.0605	0.1478
Week 48 Change from Baseline			
Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	0.0446 (0.0138) vs. -0.0053 (0.0135)	0.0500 (0.0186) 0.0126, 0.0874	0.0099
6MWT distance (meters)			
Week 24 Change from Baseline			
Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	38.5721 (10.3041) vs. 29.2990 (10.5036)	9.2731 (14.0844) -19.1046, 37.6507	0.5137
Week 48 Change from Baseline			
Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	49.6823 (12.5359) vs. 14.9190 (12.3367)	34.7634 (17.0194) 0.4506, 69.0761	0.0472
TTRW velocity (meters/sec)			
Week 24 Change from Baseline			
Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	0.3080 (0.0516) vs. 0.1740 (0.0524)	0.1340 (0.0705) -0.0076, 0.2755	0.0631
Week 48 Change from Baseline			
Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	0.2519 (0.0747) vs. 0.1544 (0.0746)	0.0976 (0.1032) -0.1099, 0.3051	0.3492
NSAA Score	**LSM (SE)**	**LSM Difference (SE) 95% CI**	**p-value**
Week 24 Change from Baseline			
Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	3.0943 (0.6610) vs. 2.7050 (0.6697)	0.3893 (0.9033) -1.4266, 2.2052	0.6684
Week 48 Change from Baseline			
Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	3.0834 (0.8287) vs. 2.5933 (0.8259)	0.4901 (1.1404) -1.8041, 2.7843	0.6694

The LSM estimates are derived from a REML-based MMRM model with enrollment stratification age group (4-5 years; 6<7 years), treatment (vamorolone 2mg/kg/day and vamorolone 6mg/kg/day), week, baseline response, and the treatment-by-week interaction. Such week was included in the model as a categorical variable (weeks 6, 12,24,34, 40 and 48) along with the treatment-by-week interaction. An unstructured covariance structure is used, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom.
CI=confidence interval; LSM=least square mean; REML=restricted maximum likelihood; SED=standard error.

Analyses for the relevant motor function endpoints presented above are based on the mITT – 2 population, defined as "All randomised subjects who received at least one dose of study medication during period 2 and had at least one post-baseline efficacy assessment during Period 2". Based on the LSM changes from baseline to Week 24 and Week 48, the clinically meaningful improvements in TTSTAND velocity, TTRW velocity and NSAA score seen with vamorolone 6 mg/kg at 24 weeks can be considered to be maintained for up to 48 weeks of treatment. An additional improvement in 6MWT distance was seen from Week 24 to Week 48 with vamorolone 6 mg/kg. With regard to vamorolone 2 mg/kg, there

was observed a clinically significant decline in TTSTAND and 6MWT based on the LSM changes between week 24 and 48, where TTSTAND velocity after improvement at week 24 decreased at week 48 (LSM change from baseline was 0.0265 at week 24 and -0.0053 at week 48, the LSM difference of 0.05 between the two dosage groups at week 48 was clinically important); 6MWT distance after improvement at week 24 declined at week 48 (LSM change from baseline was 29.2990 at week 24 and 14.9190 at week 48, the LSM difference of 34.7934 between the two dosage groups at week 48 was clinically significant). Also, a decline in TTRW was observed although LSM changes at week 24 and at week 48 are not considered clinically significant (LSM change from baseline was 0.1740 at week 24 and 0.1544 at week 48, but no difference between two dosage groups at week 48 was observed). A decline in NSAA score at week 48 was also observed, however, the result was still clinically meaningful in vamorolone 2 mg/kg group at week 24 and week 48 (2.7050 at week 24 and 2.5933 at week 48), and no difference between two dosage groups were found at week 48.

Due to the uncontrolled design from Week 24 to Week 48, these data are generally of limited value regarding efficacy. Nevertheless, the respective data could be considered indicative, that the effect of vamorolone is maintained after Week 24, for vamorolone 6 mg/kg as there was no decline across the relevant outcome parameters. However, the observed decline for the vamorolone 2 mg/kg dose in TTSTAND velocity and 6MWT at week 48 cannot be dismissed. Given the lack of a pre-defined non-inferiority margin, analyses do not allow to compellingly compare the two treatment arms in terms of statistical significance, i.e. lack of statistically significant difference does not allow for a conclusion of equivalent efficacy.

Also, even if the study design was not appropriate to assess non-inferiority with prednisone, from descriptive data an important difference in most of the efficacy endpoints between prednisone and vamorolone 2 mg/kg was observed.

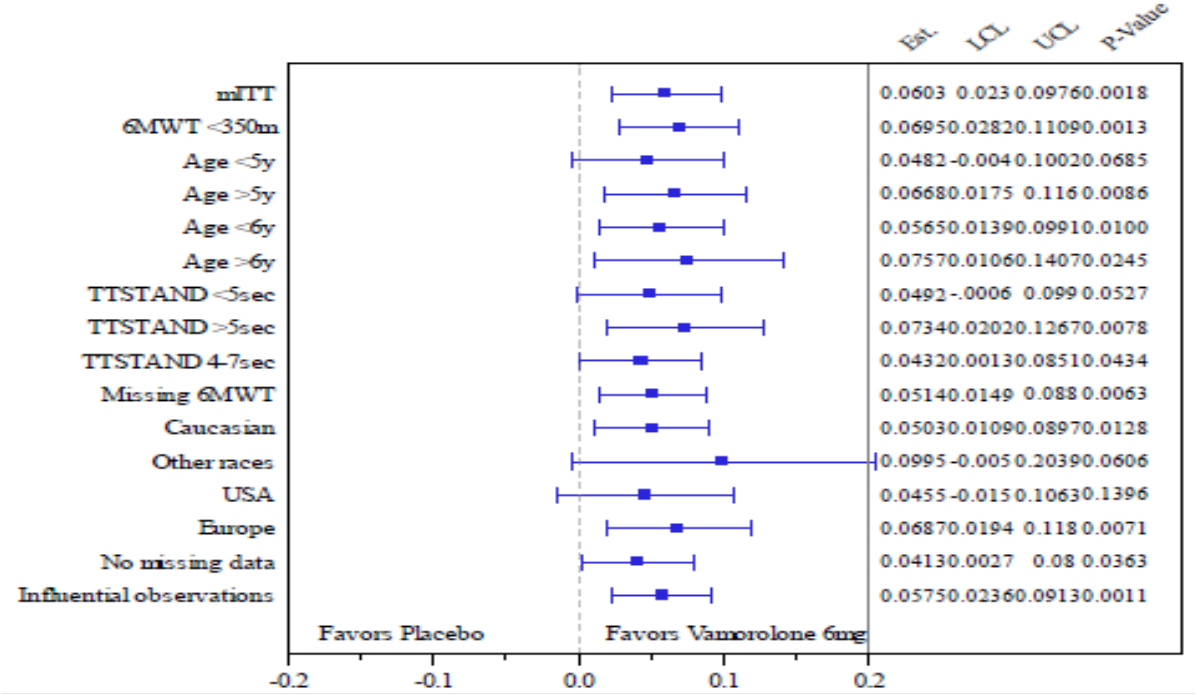
Switch from Prednisone to Vamorolone

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

- **Ancillary analyses**

Subgroup analyses for TTSTAND velocity

Figure 3: Forest plot of TTSTAND velocity in subgroups (FDA analysis, mITT-1 population)



6MWT=six-minute walk test; mITT=modified intent-to-treat; TTSTAND=time to stand; USA=United States of America.

Subgroup analyses of TTSTAND velocity were comparable across the different subgroups favouring vamorolone 6 mg/kg against placebo although they were only based on small number of patients.

Subgroup analyses based on 6MWT distance <350 meters and ≥350 meters at baseline.

Since only 3 subjects in the vamorolone 6 mg/kg group had a baseline 6MWT distance ≥350 meters, subgroup analyses in this group were not applicable.

Table 12: TTSTAND velocity MMRM, subgroup analysis - Patients with 6MWT distance <350 m at baseline (FDA analysis, mITT-1)

6MWT distance <350 m at baseline

Visit	Comparison	n	LSM (SE)	Between-Group LSM Difference (SE)	Between-Group LSM Difference 95% CI	Between-Group p-Value
Week 24 Change from Baseline	Vamorolone 6.0 mg/kg/day vs. Placebo	23 vs. 13	0.0511 (0.0127) vs. -0.0184 (0.0173)	0.0695 (0.0207)	0.0282, 0.1109	0.0013
	Vamorolone 6.0 mg/kg/day vs. Prednisone 0.75 mg/kg/day	23 vs. 13	0.0511 (0.0127) vs. 0.0655 (0.0166)	-0.0144 (0.0203)	-0.0550, 0.0262	0.4815
	Vamorolone 2.0 mg/kg/day vs. Placebo	17 vs. 13	0.0182 (0.0144) vs. -0.0184 (0.0173)	0.0367 (0.0219)	-0.0072, 0.0806	0.0997
	Vamorolone 2.0 mg/kg/day vs. Prednisone 0.75 mg/kg/day	17 vs. 13	0.0182 (0.0144) vs. 0.0655 (0.0166)	-0.0472 (0.0215)	-0.0903, -0.0042	0.0319
	Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	23 vs. 17	0.0511 (0.0127) vs. 0.0182 (0.0144)	0.0329 (0.0189)	-0.0048, 0.0706	0.0865

TTSTAND velocity=1/TTSTAND and is expressed as rises/second. MMRM=Mixed model for repeated measures; n=number of subjects with a valid response; LSM=least squares mean; SE=Standard error; CI=Confidence Interval.
The LSM estimates are derived from a restricted maximum likelihood (REML)-based MMRM model with enrollment stratification age group (4-5 year; 6<7 year), treatment (vamorolone 0.2mg/kg/day, vamorolone 0.6mg/kg/day, and placebo), week, baseline response, and the treatment-by-week interaction. Study week in the model as categorical variable (weeks 6,12, and 24) along with the treatment-by-week interaction. An unstructured covariance structure is used and the Kenward-Roger approximation is used to estimate denominator degrees of freedom.

Overall, results for the motor function endpoints, i.e., TTSTAND velocity, 6MWT distance, TTRW velocity, TTCLIMB velocity and NSAA score were comparable to those in the primary analyses when vamorolone 6 mg/kg was compared against placebo for change from baseline to Week 24. Although results for the vamorolone 2 mg/kg group in comparison to placebo only showed nominally significance, they point in the same direction, representing an effect in comparison to placebo. When interpreting these results, it needs to be considered, that the study was not powered for these analyses that are based on small sample sizes.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study, study VBP15-004, supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13: Summary of efficacy for trial VBP15-004

Title: A Phase IIB, 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)		
Study identifier	VBP15-004, EUDRACT CT: 2017-002704-27, NCT03439670	
Design	Phase 2b, multicenter, randomised, double blind, parallel group, placebo and active controlled study to evaluate the efficacy, safety, pharmacodynamics (PD), and population pharmacokinetics (PPK) of vamorolone (VAM) versus placebo (PBO) and prednisone (PRED), and to evaluate persistence of effect over a treatment period of 48 weeks in ambulant boys aged 4 to < 7 years with DMD. The study comprised two parts: Part 1 was a 24-week randomised, double-blind, parallel group, placebo and active controlled period. In Part 2 all subjects were treated with VAM (both PBO- and PRED-treated subjects crossed over to VAM).	
	Duration of main phase (Part 1):	24 weeks
	Duration of run-in phase:	Not applicable
	Duration of transition phase:	4 weeks (for subjects switching from PBO or PRED to VAM)
	Duration of extension phase (Part 2):	20-24 weeks
	Duration of dose tapering:	2-4 weeks (for subjects discontinuing VAM)
Hypothesis	Superiority	
Treatment groups	PBO	Placebo, 24 weeks, n=28

(Part 1) mITT population	PRED		Prednisone 0.75 mg/kg, 24 weeks, n=31
	VAM 2		Vamorolone 2 mg/kg, 24 weeks, n=30
	VAM 6		Vamorolone 6 mg/kg, 24 weeks, n=28
Treatment groups (Part 2) mITT population 2	VAM 2		Vamorolone 2 mg/kg, 24 weeks, n=28
	VAM 6		Vamorolone 6 mg/kg, 24 weeks, n=28
	PBO/VAM2		Vamorolone 2 mg/kg, 20 weeks, n=14
	PBO/VAM6		Vamorolone 6 mg/kg, 20 weeks, n=14
	PRED/VAM2		Vamorolone 2 mg/kg, 20 weeks, n=15
	PRED/VAM6		Vamorolone 6 mg/kg, 20 weeks, n=15
Endpoints and definitions (incl. the most relevant secondary and exploratory endpoints)	Primary endpoint	TTSTAND velocity	Change from baseline to week 24 in time to stand velocity (rises/sec)
	Secondary endpoint	6MWT distance	Change from baseline to week 24 in six-minute walk test distance (metres)
	Secondary Endpoint	TTRW velocity	Change from baseline to week 24 in time to run/walk 10 metres (metres/sec)
	Secondary endpoint	NSAA score	Change from baseline to week 24 in North Star Ambulatory Assessment total score
Database lock	17 Nov 2021		

<u>Results and Analysis</u>

Analysis description	**Primary (EMA) Analysis, primary endpoint**			
Analysis population and time point description	Modified intent to treat for Period 1 (mITT-1)(all randomised subjects who had at least one dose of study medication and had at least one post-baseline efficacy assessment during Period 1)			
TTSTAND velocity (rises/sec) Descriptive statistics and estimate variability for change from baseline to week 24	Treatment groups	VAM 6	PBO	
	Number of subjects	27	28	
	Mean (SD)	0.054 (0.0666)	-0.007 (0.0628)	
Effect estimate per comparison		Comparison groups	VAM 6 (N=28)	PBO (N=28)
		LSM (SE)	0.0464 (0.0135)	-0.0121 (0.0134)
		LSM difference (SE)	0.0586 (0.0187)	
		95% CI	0.0218, 0.0953	
		P-value	0.0018	
Analysis description	**Primary Analyses, secondary endpoints (in hierarchical order) and additional secondary endpoints**			
Analysis population and time point description	Modified intent to treat for Period 1 (mITT-1)			
TTSTAND velocity (rises/sec) Descriptive statistics and estimate variability for change from baseline to week 24	Treatment groups	VAM 2	PBO	
	Number of subjects	29	28	
	Mean (SD)	0.041 (0.0869)	-0.007 (0.0628)	
Effect estimate per comparison	<u>First secondary endpoint:</u>	Comparison groups	VAM 2 (N= 30)	PBO (N= 28)

	TTSTAND velocity (rises/sec) at Week 24; VAM 2 vs PBO	LSM (SE)	0.0309 (0.0130)	-0.0121 (0.0134)
		LSM difference (SE)	0.0430 (0.0184)	
		95% CI	0.0069, 0.0791	
		P-value	0.0196	
6MWT distance (m) Descriptive statistics and estimate variability for change from baseline to week 24	Treatment group	VAM 6	PBO	
	Number of subjects	20	19	
	Mean (SD)	28.8 (49.66)	-23.9 (59.62)	
Effect estimate per comparison	Second secondary endpoint: 6MWT distance (m) at Week 24; VAM 6 vs PBO	Comparison groups	VAM 6 (N= 28)	PBO (N= 28)
		LSM (SE)	24.5689 (10.0582)	-11.3670 (10.6082)
		LSM difference (SE)	35.9359 (14.2577)	
		95% CI	7.9867, 63.8851	
		P-value	0.0117	
6MWT distance (m) Descriptive statistics and estimate variability for change from baseline to week 24	Treatment group	VAM 2	PBO	
	Number of subjects	20	19	
	Mean (SD)	31.0 (51.12)	-23.9 (59.62)	
Effect estimate per comparison	Third secondary endpoint: 6MWT distance (m) at Week 24; VAM 2 vs PBO	Comparison groups	VAM 2 (N= 30)	PBO (N= 28)
		LSM (SE)	24.9788 (10.0352)	-11.3670 (10.6082)
		LSM difference (SE)	36.3458 (14.3319)	
		95% CI	8.2538, 64.4379	
		P-value	0.0112	
TTRW velocity (m/sec) Descriptive statistics and estimate variability for change from baseline to week 24	Treatment group	VAM 6	PBO	
	Number of subjects	25	24	
	Mean (SD)	0.277 (0.2788)	0.017 (0.3321)	
Effect estimate per comparison	Fourth secondary endpoint: TTRW velocity (m/sec) at Week 24: VAM 6 vs PBO	Comparison groups	VAM 6 (N= 28)	PBO (N=28)
		LSM (SE)	0.2542 (0.0550)	0.0171 (0.0565)
		LSM difference (SE)	0.2372 (0.0768)	
		95% CI	0.0867, 0.3876	
		P-value	0.0020	
TTRW velocity (m/sec) Descriptive statistics and estimate variability for change from baseline to week 24	Treatment group	VAM 2	PBO	
	Number of subjects	24	24	
	Mean (SD)	0.160 (0.2267)	0.017 (0.3321)	
Effect estimate per comparison	Fifth secondary endpoint	Comparison groups	VAM 2 (N= 30)	PBO (N= 28)
		LSM (SE)	0.1387 (0.0562)	0.0171 (0.0565)

	TTRW velocity (m/sec) at Week 24: VAM 2 vs PBO	LSM difference (SE)	0.1216 (0.0788)	
		95% CI	-0.0328, 0.2761	
		P-value	0.1228	
6MWT distance (m) Descriptive statistics and estimate variability for change from baseline to week 24	Treatment group	VAM 6	PRED	
	Number of subjects	20	22	
	Mean (SD)	28.8 (49.66)	39.7 (30.62)	
Effect estimate per comparison	Sixth secondary endpoint: 6MWT distance (m) at Week 24: VAM 6 vs PRED	Comparison groups	VAM 6 (N= 28)	PRED (N= 31)
		LSM (SE)	24.5689 (10.0582)	44.1212 (9.6444)
		LSM difference (SE)	-19.5523 (13.3737)	
		95% CI	-45.7672, 6.6626	
		P-value (nominal)	0.1438	
6MWT distance (m) Descriptive statistics and estimate variability for change from baseline to week 24	Treatment group	VAM 2	PRED	
	Number of subjects	20	22	
	Mean (SD)	31.0 (51.12)	39.7 (30.62)	
Effect estimate per comparison	Seventh secondary endpoint: 6MWT distance (m) at Week 24: VAM 2 vs PRED	Comparison groups	VAM 2 (N= 30)	PRED (N= 31)
		Least squares mean (LSM) (standard error [SE])	24.9788 (10.0352)	44.1212 (9.6444)
		LSM difference (SE)	-19.1424 (13.8002)	
		95% CI	-46.1926, 7.9079	
		P-value (nominal)	0.1654	
NSAA total score: Descriptive statistics and estimate variability for change from baseline to week 24	Treatment group	VAM 6	PBO	
	Number of subjects	26	25	
	Mean (SD)	3.2 (3.18)	-0.2 (2.57)	
Effect estimate per comparison	NSAA total score at Week 24: VAM 6 vs PBO	Comparison groups	VAM 6 (N= 28)	PBO (N= 28)
		LSM (SE)	2.8660 (0.6134)	-0.7345 (0.6287)
		LSM difference (SE)	3.6005 (0.8508)	
		95% CI	1.9330, 5.2680	
		P-value (nominal)	<0.0001	
NSAA total score: Descriptive statistics and estimate variability for change from baseline to week 24	Treatment group	VAM 2	PBO	
	Number of subjects	24	25	
	Mean (SD)	3.0 (3.11)	-0.2 (2.57)	
Effect estimate per comparison	NSAA total score at Week 24: VAM 2 vs PBO	Comparison groups	VAM 2 (N= 30)	PBO (N= 28)
		LSM (SE)	2.4907 (0.6378)	-0.7345 (0.6287)
		LSM difference (SE)	3.2252 (0.8782)	

		95% CI	1.5040, 4.9464	
		P-value (nominal)	0.0002	
TTSTAND velocity (rises/sec): Descriptive statistics and estimate variability for change from baseline to week 24	Treatment group	VAM 6	PRED	
	Number of subjects	27	30	
	Mean (SD)	0.054 (0.0666)	0.068 (0.0658)	
Effect estimate per comparison	TTSTAND velocity (rises/sec) at Week 24; VAM 6 vs PRED	Comparison groups	VAM 6 (N= 28)	PRED (N= 31)
		LSM (SE)	0.0464 (0.0135)	0.0661 (0.0129)
		LSM difference (SE)	-0.0197 (0.0185)	
		95% CI	-0.0559, 0.0165	
		P-value (nominal)	0.2865	
TTSTAND velocity (rises/sec): Descriptive statistics and estimate variability for change from baseline to week 24	Treatment group	VAM 2	PRED	
	Number of subjects	29	30	
	Mean (SD)	0.041 (0.0869)	0.068 (0.0658)	
Effect estimate per comparison	TTSTAND velocity (rises/sec) at Week 24; VAM 2 vs PRED	Comparison groups	VAM 2 (N= 30)	PRED (N= 31)
		LSM (SE)	0.0309 (0.0130)	0.0661 (0.0129)
		LSM difference (SE)	-0.0353 (0.0182)	
		95% CI	-0.0709, 0.0003	
		P-value (nominal)	0.0522	
Analysis description	**Relevant subgroup analyses (post-hoc)**			
Analysis population and time point description	Modified intent to treat for Period 1 (mITT-1)			
Effect estimate per comparison	Subgroup analysis: 6MWT distance (m) at Week 24: VAM 6 vs PRED for patients with baseline 6MWT <350 m	Comparison groups	VAM 6	PRED
		LSM (SE)	35.0101 (10.9607)	29.0478 (15.0114)
		LSM difference (SE)	5.9622 (17.4769)	
		95% CI	-28.2977, 40.2222	
		P-value (nominal)	0.7330	
Notes	Descriptive statistics are based on observed cases (without multiple imputation). Primary, secondary and subgroup analyses used a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) using multiple imputation based the assumption of missing not at random (MNAR). In this analysis, data that were missing due to COVID-19 were imputed based on assumption of missing at random (MAR) and all remaining missing data based on assumption of MNAR (using copy-reference imputation). Due to large baseline imbalance in 6MWT at baseline, especially between the vamorolone and prednisone groups, subgroup analyses are presented for 6MWT using a published threshold of baseline 6MWT distance of 350 m. All analyses, except the subgroup analysis that was conducted because of observed baseline imbalances were prospectively planned.			
Analysis description	**Exploratory analysis at Week 48**			

Analysis population and time point description	Modified intent to treat for Period 2 (mITT-2): all randomised subjects who had at least one dose of study medication and had at least one post-baseline efficacy assessment during Period 2			
TTSTAND velocity (rises/sec): Descriptive statistics and estimate variability for change from baseline to week 48	Treatment group	VAM 2	VAM 6	
	Number of subjects	28	27	
	Mean (SD)	-0.002 (0.0666)	0.048 (0.0715)	
Effect estimate per comparison	TTSTAND velocity (rises/sec) at Week 48: VAM 2 vs VAM 6	Comparison groups	VAM 6	VAM2
		LSM (SE)	0.0446 (0.0138)	-0.0053 (0.0135)
		LSM difference (SE)	0.0500 (0.0186)	
		95% CI	0.0126, 0.0874	
		P-value (nominal)	0.0099	
6MWT distance (m): Descriptive statistics and estimate variability for change from baseline to week 48	Treatment group	VAM 2	VAM 6	
	Number of subjects	21	19	
	Mean (SD)	4.7 (66.74)	56.7 (55.17)	
Effect estimate per comparison	6MWT distance (m) at Week 48: VAM 2 vs VAM 6	Comparison groups	VAM 6	VAM2
		LSM (SE)	49.6823 (12.5359)	14.9190 (12.3367)
		LSM difference (SE)	34.7634 (17.0194)	
		95% CI	0.4506, 69.0761	
		P-value (nominal)	0.0472	
TTRW velocity (m/sec) Descriptive statistics and estimate variability for change from baseline to week 48	Treatment group	VAM 2	VAM 6	
	Number of subjects	24	24	
	Mean (SD)	0.111 (0.3597)	0.249 (0.3598)	
Effect estimate per comparison	TTRW velocity (m/sec) at Week 48: VAM 2 vs VAM 6	Comparison groups	VAM 6	VAM2
		LSM (SE)	0.2519 (0.0747)	0.1544 (0.0746)
		LSM difference (SE)	0.0976 (0.1032)	
		95% CI	-0.1099, 0.3051	
		P-value (nominal)	0.3492	
NSAA total score Descriptive statistics and estimate variability for change from baseline to week 48	Treatment group	VAM 2	VAM 6	
	Number of subjects	23	24	
	Mean (SD)	2.3 (4.31)	3.3 (3.70)	
Effect estimate per comparison	NSAA total score at Week 48: VAM 2 vs VAM 6	Comparison groups	VAM 6	VAM2
		LSM (SE)	3.0834 (0.8287)	2.5933 (0.8259)
		LSM difference (SE)	0.4901 (1.1404)	
		95% CI	-1.8041, 2.7843	
		P-value (nominal)	0.6694	
Notes	Descriptive statistics are based on observed cases. Efficacy analyses at Week 48 were conducted using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with observed cases. The			

	patients included in mITT-2 who were randomised to receive VAM 2 or VAM 6 throughout the study (from baseline to Week 48) were included in the MMRM.

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

Comparison of efficacy results from study VBP15-004 with a matched population from Study FOR-DMD

To provide a comparison of efficacy and safety of vamorolone administered orally at daily doses of 2 and 6 mg/kg with corticosteroids over a 48-week treatment period, outcomes of vamorolone treated subjects in VBP15-004 were compared with the outcomes of prednisone- and deflazacort-treated boys from the FOR-DMD study. The FOR-DMD study was a multiple site, randomised, prospective, multicenter, double-blind, study to compare three corticosteroid regimens (0.75 mg/kg/day prednisone; 0.75 mg/kg/day prednisone 10 days on/10 days off; 0.9 mg/kg/day deflazacort) over a treatment period of 36 to 60 months in 196 boys aged ≥ 4 years and < 8 years with confirmed DMD. Included subjects who were corticosteroid naïve at study entry were able to rise independently from the floor and provided reproducible forced vital capacity (FVC) measurements. A composite primary outcome measure was used to assess the efficacy containing the time from supine to stand, percentage FVC and subject/parent global satisfaction with treatment. The study was conducted at 40 academic medical centers in the USA (14 sites), Canada (3 sites), UK (7 sites), Germany (4 sites) and Italy (4 sites).

While the studies were still ongoing, a comparison of study designs and conduct between the VBP15-004 and FOR-DMD was performed, in order to prospectively assess the feasibility of the FOR-DMD as an external control group for study VBP15-004.

The comparison of efficacy endpoints between vamorolone and prednisone (or deflazacort) groups at Week 48 focused on a global assessment of efficacy without formal statistical hypothesis testing, aiming to show whether the efficacy profile of the two vamorolone doses is comparable to prednisone (or deflazacort). There was no pre-defined order of the endpoints and the results were planned to be presented by summarising the treatment differences and 95% CIs for the endpoints. The following efficacy endpoints were planned to be analysed: TTSTAND velocity, 6MWT distance, TTRW velocity and NSAA score.

Subject Matching for Efficacy

All randomised subjects who had at least one dose of study medication during Treatment Period 2 of VBP15-004 (i.e., SAF-2) were considered for matching for efficacy.

A 2-stage matching approach was used to identify subjects from the FOR-DMD study to include in these analyses. In the first stage, subjects from the FOR-DMD study were matched based on the key inclusion criteria for this study, including confirmed DMD, between 4 and < 7 years of age at baseline, able to walk independently, and able to complete TTSTAND without assistance.

In the second stage, propensity scores were calculated using a logistic regression model and the following factors that are known to predict DMD disease progression/severity: baseline age; Baseline TTSTAND velocity (subjects with baseline TTSTAND > 10 secs were excluded); baseline NSAA score; baseline weight as z-score; Baseline height as z-score.

Efficacy Analyses

The pre-specified efficacy endpoints TTSTAND velocity, TTRW velocity, 6MWT distance, and NSAA score were compared for each vamorolone dose versus the matched external controls from the FOR-DMD study and analysed using the MMRM model, observed data (i.e., without imputation as there was no control group at 48 weeks), and mITT-2. The MMRM included the response values (as changes from baseline) from Weeks 24 and 48 as dependent values. The model included fixed effects for baseline age (as

stratified in randomisation), treatment group (vamorolone 2 mg/kg, vamorolone 6 mg/kg, prednisone 0.75 mg/kg), week (Week 24 or 48) and treatment-by-week interaction. The baseline value was included as a covariate. Within this model, pairwise comparisons (using LSM contrasts) were made to compare the treatment difference between vamorolone 6 mg/kg or 2 mg/kg with the FOR-DMD prednisone and deflazacort groups. An unstructured covariance structure was applied for MMRM. If this analysis failed to converge, Akaike's information criterion were used to select the best covariance structure from compound symmetry and autoregressive-1 (AR[1]). The denominator degrees of freedom were computed using the Kenward-Roger method. The observations were weighted by the weights generated using propensity scores.

Results

Investigation of the validity of the external comparisons

The subjects randomised to prednisone who met the common inclusion criteria were compared across studies in VBP15-004 Period 1 and the first 6 months of FOR-DMD to test the validity of the external control and provide additional context for interpretation of the FOR-DMD data. For efficacy, all 31 subjects randomised to prednisone in Study VBP15-004 were matched to 37 subjects treated with prednisone in FOR-DMD.

External Comparison Evaluation

Table 14: Analysis sets for external comparisons of Study VBP15-004 and matched subjects in the FOR-DMD Study

	VBP15-004 (treatment mg/kg)		FOR-DMD (treatment mg/kg)	
	Vamorolone 2.0	**Vamorolone 6.0**	**Prednisone 0.75**	**Deflazacort 0.90**
Randomized	30	30	65	65
Not matched for Safety comparison	**2**	**2**	**15**	**9**
Not treated	0	2	2	1
Not treated in VBP15-004 Period 2	2	0	Not applicable	
Age <4 or >7 years	0	0	7	7
Missing pretreatment TTSTAND without assistance or 6MWT	0	0	6	0
DMD not confirmed	0	0	0	1
Matched safety population for comparison	**28**	**28**	**50**	**56**
Matched for efficacy analyses on propensity score	26	27	39	47
Completed Month 6	Required for inclusion in analysis		48 (96.0%)	54 (96.4%)
Completed Month 12	28 (100.0%)	26 (92.9%)	48 (96.0%)	52 (92.9%)
Completed Month 30	Not applicable		43 (86.0%)	48 (85.7%)
Reason for discontinuation [a]				
Adverse event	0	1 (3.6%)	1 (2.0%)	2 (3.6%)
Withdrawal of consent/enrolled in another study/non-compliance/ lost to follow-up/other	0	1 (3.6%)	6 (12.0%)	5 (8.9%)
Withdrawal necessary	0	0	0	1 (1.8%)

6MWT=6-minute walk test; DMD=Duchenne muscular dystrophy; TTSTAND=time to stand test
[a] For VBP15-0404 up to month 12; Study FOR-DMD up to month 30.

Demographic and Other Baseline Characteristics

Although mean and median height were similar across the groups, the percentiles and z-scores for height indicate that subjects in the 2 mg/kg group in VBP15-004 were taller (mean percentile 32% and Z score -0.70 SDs) than those in the other treatment groups (mean percentile between 23 and 27% and z-score between -0.86 and -1.04). Weight and BMI including the percentiles and Z scores were generally similar across the groups. The matched prednisone groups were similar across the two studies. Imbalances were noted between the vamorolone groups and the matched prednisone and deflazacort groups, with subjects in the vamorolone groups having worse values at baseline; in particular, 6MWT distance was longer for the prednisone group in FOR-DMD compared with the deflazacort in FOR-DMD and vamorolone groups in VBP15-004. A similar finding was observed in the VBP15-004 case study report.

Efficacy Results

Validity of the external comparison for efficacy

The LSM changes in 6MWT distance were numerically higher for prednisone in FOR-DMD than in VBP15-004 at Months 3 (LSM change 40 vs. 26 meters) and Month 6 (55 vs. 39 meters). However, there were no clinically meaningful differences between the studies for any of the efficacy endpoints. A subgroup analysis was performed on the subjects with baseline 6MWT distance <350 meters and confirmed the results of the total population.

Table 15: MMRM analysis for change from baseline to month 6 and 12 in TTSTAND velocity: vamorolone compared with prednisone and deflazacort from the FOR-DMD Study (mITT-1 and mITT-2 populations)

TTSTAND Velocity (rises/sec)	n	LSM (SE)	LSM Difference (SE) 95% CI	p-value
Month 6 Change from Baseline				
Vamorolone 6 mg/kg vs prednisone	27 vs 37	0.0464 (0.0099) vs. 0.0441 (0.0137)[a]	0.0023 (0.0162) -0.0297, 0.0344	0.8855
Vamorolone 2 mg/kg vs prednisone	26 vs 37	0.0176 (0.0099) vs. 0.0441 (0.0137)	-0.0265 (0.0164) -0.0589, 0.0059	0.1078
Vamorolone 6 mg/kg vs deflazacort	27 vs 45	0.0464 (0.0099) vs. 0.0508 (0.0110)	-0.0044 (0.0143) -0.0326, 0.0238	0.7583
Vamorolone 2 mg/kg vs deflazacort	26 vs 45	0.0176 (0.0099) vs. 0.0508 (0.0110)	-0.0332 (0.0144) -0.0617, -0.0048	0.0224
Month 12 Change from Baseline				
Vamorolone 6 mg/kg vs prednisone	26 vs 36	0.0403 (0.0107) vs. 0.0419 (0.0148)	-0.0016 (0.0176) -0.0365, 0.0333	0.9287
Vamorolone 2 mg/kg vs prednisone	26 vs 36	-0.0029 (0.0106) vs. 0.0419 (0.0148)	-0.0448 (0.0177) -0.0798, -0.0098	0.0126
Vamorolone 6 mg/kg vs deflazacort	26 vs 42	0.0403 (0.0107) vs. 0.0418 (0.0121)	-0.0015 (0.0156) -0.0324, 0.0293	0.9225
Vamorolone 2 mg/kg vs deflazacort	26 vs 42	-0.0029 (0.0106) vs. 0.0418 (0.0121)	-0.0447 (0.0157) -0.0757, -0.0137	0.0050

[a] The LSM change from baseline at Month 6 for the internal prednisone control was 0.07 rises/sec.
The observations are weighted by the weights generated using propensity scores.
The LSM estimates are derived from a REML-based MMRM model with enrolment stratification age group (4-5 years; 6-<7 years), treatment (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day and deflazacort), week, baseline response, and the treatment-by-week interaction. Study week was included in the model as a categorical variable (Weeks 24 and 48 for VBP15-004 and Months 6 and 12 for FOR-DMD) along with the treatment-by-week interaction. An unstructured covariance structure was used, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom.
CI = confidence interval; LSM = least squares mean; MMRM = mixed model repeated measures; REML = restricted maximum likelihood; SD = standard deviation; SE = standard error; TTSTAND = Time to Stand Test

TTSTAND velocity had increased in the vamorolone 6 mg/kg, prednisone, and deflazacort groups at Months 6 and 12. The increases were similar for the vamorolone 6 mg/kg group (LSM change 0.05 and 0.04 at Months 6 and 12), deflazacort group (LSM changes 0.05 and 0.04 at Months 6 and 12,

respectively), and the prednisone group (LSM changes were 0.04 and 0.04 at Months 6 and 12, respectively); the vamorolone 2 mg/kg group showed minimal change (LSM changes 0.02 and -0.00).

The 6MWT distance was increased in all groups at Months 6 and 12. The largest increases were observed for the prednisone group at Months 6 and 12 (estimate 53 and 54 meters, respectively). At Month 6, the changes were larger for deflazacort than vamorolone 2 mg/kg (mean changes 39 and 31 meters, respectively), and smaller for vamorolone 6 mg/kg (mean change 26 meters) but at Month 12, the changes for vamorolone 6 mg/kg (45 meters) were larger than for deflazacort (39 meters) or vamorolone 2 mg/kg (11 meters). It is noted that the prednisone group in FOR-DMD also performed >10 meters better than the prednisone group in VBP15-004. The LSM increases in 6MWT distance were smaller with vamorolone 2 mg/kg compared with the prednisone and deflazacort groups. The difference in 6MWT distance between vamorolone 2 mg/kg and prednisone at Month 12 was 43.5 meters all other differences were <29 meters (i.e., below but close to the minimal clinically important difference).

2.6.5.4. Supportive study

The **FOR- DMD study** (Guglieri et al., 2022) was a phase 3 double blind study of 36-60 months duration comparing three corticoid regimens (daily deflazacort, daily prednisone and intermittent prednisone) with aim to find the optimal steroid regimen. It was used as external control for the long-term comparison versus vamorolone. A composite primary outcome measure was used to assess the efficacy containing the time from supine to stand, percentage FVC and subject/parent global satisfaction with treatment. With respect to this study, the submitted information only covers the study protocol, dated 24 June 2013, the report on external comparison of results of vamorolone study VBP15-004 with results of the FOR-DMD study (dated 23 September 2022), Appendix 4.2 of statistical analysis plan for study VBP15-004: VBP15-004 vs FOR-DMD: comparison of study designs and conduct and a publication of the study (Guglieri et al, 2022). According to the author, "among patients with DMD treatment with daily prednisone or daily deflazacort, compared with intermittent prednisone alternating 10 days on and 10 days off, resulted in significant improvement over 3 years in a composite outcome comprising measures of motor function, pulmonary function, and satisfaction with treatment; there was no significant difference between the 2 daily corticosteroid regimens.

Study VBP15-006

Study VBP15-006 is an ongoing phase 2, open-label, multiple dose study to assess the safety, tolerability, PK, PD, exploratory efficacy, behaviour and neuropsychology, and physical functioning of vamorolone over a treatment period of 12 weeks in boys aged 2 to <4 years and 7 to <18 years with DMD. Vamorolone (ROS2 formulation) is administered at daily doses of 2 mg/kg or 6 mg/kg in steroid-naïve boys aged 2 to <4 years, and in glucocorticoid-pretreated and previously untreated boys aged 7 to <18 years with DMD. The primary objective of the study is to evaluate the safety and tolerability of vamorolone. The study is included in the Paediatric Investigation Plan for vamorolone. The to-be-marketed formulation ROS2 is used in this study.

A total of 20 subjects are to be enrolled in the 2 to <4 year-old age group (10 each at the 2 and 6 mg/kg dose level), 24 subjects are to be enrolled in the 7 to >18 year-old age group (6 each in the 2 and 6 mg/kg dose groups, steroid-pretreated, 6 each in the 2 and 6 mg/kg dose groups, steroid-naive), plus 10 additional subjects aged 12 to <18 years and steroid-pretreated are to be enrolled in the 7 to <18 years age group at a 6 mg/kg dose level (Protocol Amendment 2). With regard to the 2 to <4-year-old group, the initial 10 eligible subjects were planned to be assigned to the 2 mg/kg treatment group, while the subsequent 10 eligible subjects were planned to be assigned to the 6 mg/kg treatment group. At the end of the 3-month Treatment Period (Week 12), subjects are given the option to receive

vamorolone in an Extended Access Programme (EAP) (currently ongoing Canadian EAP - VBP15-EAP-CAN), or to transition to standard of care treatment for DMD (may include glucocorticoids).

In subjects 2 to <4 years of age, efficacy is to be assessed based on muscle function using the Bayley-III Gross Motor scale (GMSS). Physical functioning was assessed using the PODCI.

Patient disposition: As of data cut-off date of 21 July 2023, ten subjects aged 2 to < 4 years have been treated with 2 mg/kg vamorolone and all have completed the 12-week study. Nine of these 10 subjects are continuing to receive vamorolone in the EAP and the other subject switched to standard of care glucocorticoid treatment. Median age at baseline was 3.3 years (range 2.8 to 4.0 years). Six subjects aged 2 to < 4 years have been treated with 6 mg/kg vamorolone and have completed the study and are continuing to receive vamorolone in the EAP. Median age at baseline was 3.6 years (range 3.3 to 4.0 years).

The applicant presented preliminary study results during this procedure in order to provide information on the identified knowledge gaps for extrapolation from the reference population 4 to <7 years to patients 2 to <4 years of age.

Preliminary efficacy results on the GMSS in patients 2 to <4 years of age: at baseline, median GMSS were lower than 7 indicating a delay in motor development compared to normal children of the same age. Subjects assigned to vamorolone 2 mg/kg had lower median value at baseline than those assigned to 6 mg/kg indicating a more pronounced motor delay. After 12 weeks, there was no relevant change from baseline in vamorolone 2 mg/kg suggesting no progression of developmental delay, while the mean score increased in the 6 mg/kg dose group with mean (SD) change from baseline to week 12 of 2.67 (1.211), suggesting an improvement in gross motor abilities.

For available clinical safety results, please see Clinical safety.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Vamorolone was initially proposed to be indicated for the treatment of DMD in patients 2 years of age and older. During the procedure, the applicant confirmed to restrict the indication to paediatric patients 4 years and older.

The applicant submitted 1 pivotal study, study VBP15-004, a Phase 2a study of 2 weeks duration (VBP15-002), a Phase 2 study of 24 weeks duration in subjects who completed study VBP15-002 (VBP15-003) and a Phase 2 study of additional 24 months duration in subjects who completed study VBP15-003 (VBP15-long-term), all studies were performed with the ROS1 formulation of vamorolone. Further, efficacy results from Study VBP15-004 at 48 weeks were compared with results of two matched DMD standard of care treatment groups from the FOR-DMD Phase 3 study. During the procedure, preliminary efficacy results were provided for the Phase 2 study VBP15-006.

Three open-label Phase 2 studies that contributed to the dose selection for the following study, study VBP15-004, have been conducted:

• Study VBP15-002 was a phase 2a, multicentre, open-label, first-in-patient, proof of concept, multiple-ascending dose study examining vamorolone doses of 0.25, 0.75, 2 and 6 mg/kg/day for 2 weeks, followed by a 2-week post-treatment follow-up period. 48 ambulatory corticosteroid naïve 4 to < 7 years old boys with DMD were included, diagnosed with DMD by confirmed dystrophin deficiency or identifiable mutation within the DMD gene, who were able to complete the TTSTAND without assistance at the study screening and baseline Visits. All completed the 4 weeks of the study. The evaluation of safety and

tolerability of multiple ascending oral doses of vamorolone was the primary objective, assessment of efficacy was defined as exploratory objective.

• Study VBP15-003, was a Phase 2, multi-center, open-label, multiple dose study to evaluate the long-term safety, tolerability, clinical efficacy, and PD of vamorolone at dose levels of 0.25 mg/kg/day, 0.75 mg/kg/day, 2 mg/kg/day and 6 mg/kg/day over a treatment period of 24 weeks in boys aged 4-7 years with DMD. Subjects who had previously completed study VBP15-002 were eligible for enrollment. Subjects continued to receive vamorolone for 24 weeks at the same dose levels they already had received in study VBP15-002, that have been considered to be safe and well-tolerated in study VBP15-002. In principle, study 003 included a selected (enriched) patient population, as all included subjects already had been treated with vamorolone for 2 weeks.

Primary study objective was the evaluation of long-term safety and tolerability of vamorolone, administered orally at daily doses up to 6 mg/kg over a 24-week Treatment Period, the assessment of efficacy was defined as a secondary objective. Results on clinical efficacy endpoints were compared for each vamorolone treatment arm/dose against an age-matched untreated historical control group from the CINRG-DNHS.

Unless otherwise noted, baseline was defined as the last measurement taken prior to first exposure to study drug (Baseline Visit for VBP15-002). Primary clinical efficacy endpoint was the comparison of each dose level of vamorolone for change from study VBP15-002 baseline to VBP15-003 Week 24 in TTSTAND velocity to the age-matched natural historical control group from the CINRG-DNHS.

• Study VBP15-LTE was a Phase 2, multicentre, open-label study of additional 24 months in subjects who completed the 6-months VBP15-003 study (i.e, total treatment for 30 months or 2.5 years) to evaluate the long-term safety, tolerability, clinical efficacy, and PD of vamorolone at dose levels of 0.25 mg/kg/day, 0.75 mg/kg/day, 2 mg/kg/day, 4 mg/kg/day, and 6 mg/kg/day. Dose adjustment was allowed between dose levels of 2, 4, and 6 mg/kg. Subjects who completed the Phase II extension study VBP15-003 Week 24 assessments were eligible for enrolment. The age range covered in this study was from 4 years at baseline to up to 9.6 years at the end of the study.

Efficacy was planned to be based on comparison to natural historical controls (CINRG-DNHS), however this was not feasible given the small number of corticosteroid-naïve subjects (n = 6) with 30-month data to match the VBP15-LTE 24-month outcome parameters.

Subjects initially received vamorolone at the same dose level they received in study VBP15-003 (0.25 mg/kg/day, 0.75 mg/kg/day, 2 mg/kg/day, or 6.0 mg/kg/day); subjects were allowed to escalate vamorolone dose to the next higher dose level after receiving their current dose for at least one month, to the maximum of 6 mg/kg/day; subjects were allowed to de-escalate vamorolone dose due to intolerability. Subjects whose dose was decreased from 6 mg/kg/day to 2 kg/kg/day could have their dose subsequently increased to 4 mg/kg/day if they had been taking the 2 mg/kg/day dose for at least one month and, in the opinion of the Investigator, balancing efficacy with safety concerns, they could have benefited from an intermediate higher dose. Subjects who transitioned off vamorolone treatment at the end of participation in the treatment period (24 months) received vamorolone for an additional 1-4 weeks according to a dose-tapering protocol following the end of the Treatment Period and prior to discharge from the study.

Primary objectives were to evaluate the long-term safety and tolerability of vamorolone at daily doses up to 6 mg/kg over a 24-month Treatment Period, in boys who completed study VBP15-003; and to compare the efficacy, as measured by the TTSTAND, of vamorolone at daily doses up to 6 mg/kg over a 24-month Treatment Period vs. untreated DMD historical controls in young boys with DMD.

The pivotal study, Study VBP15-004 was a randomised, double-blind, parallel-group, 48-week study, to evaluate the efficacy, safety, PD, and population PK of vamorolone in ambulatory, corticosteroid naïve,

4 to <7 years of age-old boys with DMD. The study consisted of a treatment period 1 (day 1 to week 24) followed by a 4-week transition period (week 25 to week 28) for subjects who received either placebo or prednisone in period 1 (subjects who received vamorolone in period 1 were continued on the same dose of vamorolone during this period), period 2 (week 28 +1 day to week 48) where all subjects received vamorolone 2 or 6 mg/kg for 20 weeks and a 4-week dose tapering period (week 49 to week 52) where subjects who elected not to continue vamorolone treatment had the vamorolone dose progressively reduced and discontinued. During Scientific advice/Protocol assistance the CHMP clarified that the pivotal study has not been conducted in full compliance with the recommendations, mainly pertaining to the lack of concurrent comparative data at Week 48, which would have been preferred over external controls.

In Period 1, subjects were randomised to 1 of 6 groups in a 2:2:1:1:1:1 ratio: vamorolone 2 mg/kg, vamorolone 6 mg/kg, 2 groups of placebo and 2 groups of prednisone 0.75 mg/kg/day, with randomisation stratified by age at study entry (<6 years and ≥6 years).

To maintain the double-blind in this treatment period, all subjects received either a matching placebo for vamorolone (i.e. a placebo oral suspension), a matching placebo for prednisone (i.e. a placebo tablet) or both (i.e. placebo oral suspension and placebo tablet). 0.75 mg/kg prednisone was used as an internal comparator representing the starting dose of standard-of-care treatment for DMD. Prednisone is formally not approved in the EU for this condition. However, several studies including short-term placebo-controlled studies (Griggs et al. Neurology 2016) as well as prospective long-term observational studies (CINRG-DHNS) have shown that glucocorticoid including prednisone have positive effects on the disease course.

Key inclusion criteria encompassed glucocorticoid naïve Duchenne patients diagnosed based on gene analysis and/or a muscle biopsy sample, tested for the presence of dystrophin protein. Included patients were defined to be ≥4 years and <7 years of age at time of enrollment, able to walk independently and able to complete the TTSTAND without assistance in <10 seconds.

Primary efficacy endpoint was the change from baseline in TTSTAND velocity for the vamorolone 6 mg/kg group compared vs placebo at week 24.

Change from baseline to week 24 was tested for the following secondary efficacy endpoints in a pre-specified hierarchical order:

- TTSTAND velocity for the vamorolone 2.0 mg/kg/day vs placebo group
- 6MWT distance for vamorolone 6.0 mg/kg vs placebo
- 6MWT distance for vamorolone 2.0 mg/kg vs placebo
- TTRW velocity for vamorolone 6.0 mg/kg vs placebo
- TTRW velocity for vamorolone 2.0 mg/kg vs placebo
- 6MWT distance for vamorolone 6.0 mg/kg vs prednisone
- 6MWT distance for vamorolone 2.0 mg/kg vs prednisone

Additional secondary efficacy endpoints for week 24 included the following comparing each of the vamorolone doses versus placebo and each vamorolone dose versus prednisone: change from baseline in TTCLIMB velocity, change from baseline in NSAA score, change from baseline in knee extension muscle strength and change from baseline in elbow extension muscle strength.

All the secondary efficacy endpoints were also analysed for the vamorolone groups at week 48, but not in a pre-defined hierarchical order.

Overall, the choice of endpoints is acceptable and in line with the EMA guideline for the treatment of Duchenne muscular dystrophy (EMA/CHMP/236981/2011, Corr.1) as well as EMA advice recommendations. However, it is noted, that the outcome of the secondary variables in the hierarchy, all of them principally timed function assessments for lower limb function, are expected to be correlated with results of the primary endpoint as they are covering the same dimensions of motor function. Strength in knees is most associated with ambulation function. Muscle strength might not be a sensitive measure for the included age group because it is not linearly correlated with function. Rapid decline starts after age of 7 and for this age group even small gains in muscle strength are associated with improvement in function (McDonald, 2013). Early start of corticosteroids has shown that increase in muscle strength is associated with prolongation of ambulation, therefore the impact on muscle strength is considered highly relevant for long-term outcomes.

Based on previous studies, the following MCIDs were chosen and are accepted: TTSTAND velocity 0.023 rise/sec, TTRW 0.212 m/sec and TTCLIMB 0.035 tasks/sec (Duong et al, 2021), 6MWTD of around 30 meters (McDonald et al, 2013) and NSAA total score 2.32 points (Haberkamp et al, 2019) while any estimates of MCIDs for muscle strength assessed with handheld myometry in patients with DMD are lacking. Due to the COVID-19 pandemic it was allowed for scheduled assessments to be performed remotely, except for screening assessments, which must be performed at the study site. Sample size calculation appears to be acceptable. It is estimated that 30 patients per group are needed to ensure 91% power to detect a clinically significant difference between 6.0 mg/kg/day and placebo on TTSTAND velocity at Week 24.

Randomisation is acceptable. Blinding is acceptable. Success of blinding was assessed at Week 24. Interim analyses were not planned and conducted.

Overall, the statistical approach for pivotal study is adequately described and is acceptable. The primary analysis population for efficacy at week 24 was the mITT-1 Population (all randomised subjects who received at least one dose of study medication during period 1 and had at least one post-baseline efficacy assessment during Period 1). However, analyses based on the ITT population with relevant missing data imputation are generally considered of primary relevance; evaluations in the ITT population have at least been defined as sensitivity analysis for the primary endpoint but were also provided for all other endpoints upon request.

The primary analysis of the primary efficacy endpoint for EMA consisted of a missing data imputation while for FDA only the observed measurements were used (without multiple imputation).

The proposed primary estimand is defined as the mean difference (vamorolone 6.0 mg/kg compared to placebo) according to the randomised groups, regardless of the treatment that was actually received in change from baseline to Week 24 in TTSTAND velocity in the target population, regardless of treatment discontinuation, regardless of treatment with co-medication, had there be no impact of the COVID-19 pandemic (hypothetical strategy), and assuming the worst outcome of the velocity (zero) in case of death (composite strategy). Overall, this approach is endorsed.

Intercurrent events are defined as premature discontinuation of study treatment, death and COVID-19 pandemic related events (missed or delayed assessments, assessments conducted with alternative methods).

For premature discontinuation of study treatment, the missing data were imputed under the assumption of MNAR. The missing data that have been recorded to be missing due to the COVID-19 pandemic were considered under the assumption of MAR. Only data for primary endpoint were imputed. Other missing data were not imputed. Missing data due to Covid-19 imputed under the MAR assumption can introduce bias in the analysis. The applicant clarified that the classification of missing data due to COVID-19 for the analysis of the primary endpoint was performed with consistent methods across the study.

Furthermore, the applicant clarified that measurement drop-outs that were not due to COVID-19 were imputed using Copy-Reference imputation and the measurement drop-outs that were due to COVID-19 were imputed using the assumption of MAR.

For data that are missing due to death, a composite strategy should have been used. In this scenario, the TTSTAND velocity value would be imputed as zero for the next visit that would have been scheduled following the death. Similar composite strategy would have been applied for the TTSTAND velocity values that are missing because the test could not be conducted due to disease progression. This approach is endorsed.

Multiplicity across primary and secondary endpoints was handled using hierarchical testing. This preserved the study-wise type I error rate and is acceptable. The primary efficacy outcome, TTSTAND (velocity) was to be compared between the 6.0 mg/kg/day vamorolone group and the placebo group using a REML-based MMRM. The chosen model appears to be acceptable. Proposed sensitivity analyses also are acceptable.

Internal comparisons for the two vamorolone treatment groups were performed for change from baseline at Week 48 in the set of subjects who were randomised to receive vamorolone in both Period 1 and Period 2. Because there was no placebo group up to Week 48, no multiple imputation analyses were conducted, and all analyses were based on observed cases only. The comparison focused on a global assessment of efficacy without formal statistical hypothesis testing.

Subgroup analyses were performed for the primary endpoint TTSTAND velocity (pre-specified) and the 6MWT distance based on: age, baseline TTSTAND velocity, baseline 6MWT distance, race and country. To take baseline imbalances with respect to disease severity into account and to define more homogeneous treatment groups, the applicant performed additional subgroup analyses (*post hoc*) in subjects with baseline 6MWT distances of <350 meters. The chosen threshold was justified based on a publication by McDonald 2013 that concluded that patients with a baseline 6MWT distance <350 meters have a greater functional decline than those ≥ 350 meters. However, due to the very small number of patients reflecting the latter subgroup, i.e., only 3 subjects in the vamorolone 6 mg/kg group, analyses in patients with a baseline 6MWTD ≥ 350 meters were not applicable.

Several sensitivity and supportive analyses were pre-defined in the SAP to show robustness of the primary analysis. Amongst others, two sensitivity analyses were conducted to assess the potential impact of the COVID-19 pandemic on TTSTAND velocity, including missing or delayed testing and the use of a video instead of in-person testing.

The FOR-DMD study was a phase 3, multiple site, multicentre, randomised prospective double-blind study in ambulatory DMD patients to compare the efficacy and safety of the most three commonly used corticosteroid regimens (0.75 mg/kg/day prednisone; 0.75 mg/kg/day prednisone 10 days on/10 days off; 0.9 mg/kg/day deflazacort) over a treatment period of 36 to 60 months in 196 boys aged ≥ 4 years and < 8 years with confirmed DMD and with the ability to rise independently from the floor and reproducible FVC measurements. A composite outcome measure comprising time from supine to stand, percentage FVC and subject/parent global satisfaction with treatment was chosen as primary endpoint.

Comparison of efficacy results from study VBP15-004 with a matched population from Study FOR-DMD

To provide a comparison of efficacy and safety of vamorolone administered orally at daily doses of 2 and 6 mg/kg with corticosteroids over a 48-week treatment period, outcomes of those subjects having received vamorolone throughout 48 weeks in study VBP15-004 were subsequently compared against outcomes of prednisone- and deflazacort-treated boys from the FOR-DMD study.

A 2-stage matching approach was used to identify subjects from the FOR-DMD study to include in these analyses. In the first stage, subjects from the FOR-DMD study were matched based on the key inclusion

criteria for this study, including confirmed DMD, between 4 and < 7 years of age at Baseline, able to walk independently, and able to complete TTSTAND without assistance. In the second stage, propensity scores were calculated using a logistic regression model and the following factors assessed at baseline: age, TTSTAND velocity (subjects with baseline TTSTAND > 10 secs were excluded), NSAA score, weight as z-score and height as z-score. The dependent variable of the logistic regression model was the outcome that would be observed if the subject received the treatment (1 = treatment, 0 = control). The factors listed above were used as independent variables. The pre-specified efficacy (TTSTAND velocity, 6MWT distance, TTRW velocity and NSAA score) and safety endpoints were compared for each vamorolone dose arm from study VBP15-004 with prednisone and deflazacort from the FOR-DMD study. Exploratory comparisons for the two prednisone groups served as validation for comparison across the two studies.

Study VBP15-006 (cut-off date of 21 July 2023) is an ongoing phase 2, open-label, multiple dose study to assess the safety, tolerability, PK, PD and exploratory efficacy of vamorolone over a treatment period of 12 weeks in boys aged 2 to <4 years and 7 to <18 years with DMD. Vamorolone is administered at daily doses of 2 mg/kg or 6 mg/kg in steroid-naïve boys aged 2 to <4 years, and in glucocorticoid-pretreated and previously untreated boys aged 7 to <18 years with DMD. In subjects 2 to <4 years of age efficacy was to be assessed based on muscle function using the Bayley-III Gross Motor scale. Physical functioning was assessed using the PODCI. With regard to the 2 to <4 year-old group, the initial 10 eligible subjects were planned to be assigned to the 2 mg/kg treatment group, while the subsequent 10 eligible subjects were planned to be assigned to the 6 mg/kg treatment group.

Efficacy data and additional analyses

Study VBP15-002: 48 subjects were enrolled and all 48 completed the 4-week study. Mean changes from baseline to the end of the treatment for the functional outcome assessments, e.g., TTSTAND velocity, were generally minimal and not dose-related. However, given the short treatment period of only 2 weeks duration and a rather less affected patient population this is not unexpected.

Study VBP15-003:

48 subjects were enrolled, 46 subjects completed the study. One subject in the 0.25 mg/kg/day dose level group was withdrawn by the parent/guardian to participate in another DMD clinical trial, and one subject in the 6 mg/kg/day dose level group was withdrawn by the parent/guardian for protocol burden.

The comparator group for efficacy consisted of 31 subjects from the CINRG-DNHS study who met all entry criteria of VBP15-003 and remained untreated through a 24-week period. With respect to safety, the comparator group consisted of 14 subjects who met the entry criteria of VBP15-003 and received daily prednisone therapy in the CINRG prednisone trial.

Efficacy results for TTSTAND-, TTRW- and TTCLIMB velocity in the CINRG control group were overall comparable to that seen for the lower vamorolone dosages, i.e., 0.25 and 0.75 mg/kg/day although the lowest vamorolone dose of 0.25 mg/kg appears to be worse than the natural history data. Mean improvements from baseline to Week 24 in TTSTAND velocity, TTRW velocity, and TTCLIMB velocity and 6MWT distance were greater for the vamorolone 2 and 6 mg/kg treatment arms when compared against the lower vamorolone doses and against the external untreated CINRG-DNHS control group, except for TTRW velocity (vamorolone 0.75 and 2 mg/kg provided similar changes). Results for quantitative muscle testing and PODCI showed height variability with no dose-dependent effect. Based on the MCIDs, the improvements for the vamorolone 2 and 6 mg/kg group in TTSTAND, TTRW and TTCLIMB velocity and 6MWT distance were considered clinically meaningful. Greater improvements for the vamorolone 6 mg/kg arm in comparison to the vamorolone 2 mg/kg dose were only seen for results on TTRW velocity and 6MWT distance.

Although the study provided several limitations with respect to the study design, results on efficacy indicate that the higher dosages provided better results than the lower dosages, i.e., 0.25 and 0.75 mg/kg. As the 6 mg/kg dose in comparison to the 2 mg/kg dose provided not clearly better results for all endpoints the most suitable/optimal dose with respect to efficacy could not sufficiently be defined at that time and therefore it is reasonable that both, the 2 mg/kg and the highest dose tested (6 mg/kg) have been carried forward to the phase II b study.

Study VBP15-LTE:

46 subjects were enrolled in the study (11 subjects [0.25 mg/kg/day], 12 subjects [0.75 mg/kg/day], 12 subjects [2 mg/kg/day], and 11 subjects [6 mg/kg/day]) and all 46 subjects were analysed for efficacy (FAS) and PD and safety (safety population); 41 subjects completed the study.

On the basis of the results received in the 24 months study VBP15-LTE, the evaluation of efficacy can be extended to a total treatment duration of up to 30 months.

Overall, the improvements in TTSTAND, TTRW and TTCLIMB velocity, and 6MWT distance seen with vamorolone 2 and 6 mg/kg at Week 24 in Study VBP15-003 were maintained up to Month 18 in Study VBP15-LTE followed by a gradual decline towards baseline after month 18. Eleven of 41 subjects were down titrated from 6 mg/kg/day to 2 or 4 mg/kg/day. Efficacy data for these 11 patients are rather limited. Although no consistency in results on motor function was seen, data are therefore difficult to interpret.

Pivotal Study VBP15-004:

A total of 121 subjects were randomised with 30 subjects in each of the vamorolone treatment arms and the combined placebo groups and 31 in the combined prednisone groups. 3 subjects (2 in the vamorolone 6 mg/kg arm and one randomised to placebo) were not treated and thus excluded from the safety and the mITT analysis populations (the mITT population excluded an additional subject in the placebo group who did not have any post-baseline efficacy assessments). In addition to these 4 subjects, 3 further subjects did not complete the study through week 24 with 2 subjects in the vamorolone 2 mg/kg treatment arm and one under prednisone treatment.

Completion rates were high in this double-blind study with 114 (94.2%) and 112 (92.6%) of the randomised subjects completed period 1 (through week 24) and period 2 (through week 48), respectively. The proportion of subjects who completed the study through week 24 was almost comparable across the treatment arms (each of 93.3 %) with only a slightly higher proportion of subjects who completed under prednisone treatment (combined: 96.8%). The proportion of subjects who completed the study under vamorolone 2 mg, vamorolone 6 mg, placebo and prednisone treatment was 93.3%, 86.7%, 93.3% and 96.8%, respectively. One subject in the prednisone group was prematurely discontinued before week 24 because of an adverse event. After week 24 two additional subjects who initially were randomised to vamorolone 6 mg/kg and who received vamorolone throughout the study did not complete the final study: 1 subject was prematurely withdrawn because of an AE and 1 subject withdrew consent.

Overall, the number of important and non-important deviations was similar across the treatment groups. The most frequent deviation due to Covid-19 was modification of study visit but only few (1-3 per treatment group) were outside permitted window. Placebo group had slightly higher number of important deviations but number of patients having deviations is similar across the groups. Number of patients randomised but not meeting eligibility criteria were low (0-3) and similar across treatment groups.

The included ambulatory patient population was a restricted patient population in the age range of 4 to 7 years with mean age around 5 years.

According to the study protocol patients had to have a confirmed diagnosis of DMD, either by genetic testing or based on muscle biopsy. While almost all patients were diagnosed based on genetic confirmation by DNA and had no additional muscle biopsy, there were three subjects solely diagnosed based on muscle biopsy. Genetic mutations were similar across the study arms.

The study population consisted of male subjects with a mean (SD) number of 37.8 (17.63) months (range 3 to 77 months) between the first symptoms of DMD and study entry. However, in reference to the time since first DMD symptoms and taking into account baseline results of relevant function tests chosen for efficacy in this study, subjects in the vamorolone treatment groups seemed to have more advanced disease at baseline compared to the other groups, i.e., placebo and prednisone, respectively.

Treatment compliance was assessed by maintenance of drug dispensing and return records at the study site to the Week 2 Visit and Week 30 Visit. Overall, 90% of participants reached compliance above 80% in both study periods. Compliance was similar across study arms.

To take these baseline imbalances, reflecting disease severity into account and to define more homogeneous treatment groups, the applicant performed additional post-hoc subgroup analyses for the efficacy endpoints in subjects with baseline 6MWT distances of <350 meters. The chosen threshold was justified based on a publication by McDonald et al, 2013 that concluded that patients with a baseline 6MWT distance <350 meters have a faster functional decline than those ≥ 350 meters.

Due to the very small number of patients reflecting the latter subgroup, i.e.,17 (54.8%) in the prednisone group compared with 9 (33.3%) or 3 (11.5%) in the vamorolone 2 mg/kg and 6 mg/kg group, respectively analyses in patients with a baseline 6MWTD ≥ 350 meters were not performed.

The study met its primary objective. In the primary analysis of change from baseline in TTSTAND velocity at week 24, a statistically significant difference was demonstrated when vamorolone 6 mg/kg/day was compared against placebo (p = 0.0018). TTSTAND velocity increased in the vamorolone 6 mg/kg group from 0.186 to 0.242 rises/sec and slightly decreased in the placebo group from 0.200 to 0.193 rises/sec at Week 24. The LSM difference for vamorolone 6 mg/kg from placebo was 0.0586 rises/sec in the EMA analysis and 0.0603 rises/sec in the primary FDA analysis. The improvement in TTSTAND velocity under vamorolone 6 mg/kg/day is considered clinically relevant as it is greater than the MCID for TTSTAND of 0.023 rises/sec.

A number of sensitivity and supportive analyses, including a Per Protocol Analysis, confirmed the results of the primary analysis, e.g., they demonstrated that the COVID-19 pandemic, missing data, and influential observations did not affect the results received. The primary EMA analysis repeated in the ITT analysis set was also in accordance with the primary EMA analysis (mITT population). Using the ITT population at least for sensitivity analysis is appreciated as this is the preferred analysis population. In a supportive analysis of the primary efficacy estimate, a higher respondent rate was observed in TTSTAND velocity at week 24 (mITT-1 population) in vamorolone 6 mg group, compared to placebo (71.4% vs 35.7 %)**.** However, the pre-defined responder analysis was based on any versus non-improvement and magnitude of improvement was not considered.

As expected, results for the change from baseline to Week 24 for TTSTAND in seconds were in accordance with results of the primary analysis. TTSTAND in seconds decreased in the vamorolone 6 mg/kg group and slightly increased in the placebo group at Week 24 with LSM (SE) changes from baseline of -1.0523 (0.3604) and 0.6187 (0.3664), respectively. The LSM difference for vamorolone 6 mg/kg from placebo was -1.67 seconds in favour of vamorolone (p=0.0009).

In addition, the four secondary efficacy endpoints ranked highest in the hierarchical testing order showed statistically significant differences between vamorolone at doses of 2 and 6 mq/kg compared to placebo:

In the primary analysis (EMA analysis) of change from baseline in TTSTAND velocity at week 24, a statistically significant difference was demonstrated when vamorolone 2 mg/kg was compared against placebo (p = 0.0196). TTSTAND velocity increased in the vamorolone 2 mg/kg group from 0.184 to 0.225 rises/sec and slightly decreased in the placebo arm from 0.200 to 0.193 rises/sec at week 24. The LSM difference for vamorolone 2 mg/kg from placebo was 0.0430 rises/sec (EMA analysis) and comparable to the primary FDA analysis. The improvement in TTSTAND velocity mg/kg/day is considered clinically relevant also for 2 mg/kg as it is greater than the MCID for TTSTAND of 0.023 rises/sec. The provided sensitivity and supportive analyses confirmed the results of the primary analysis.

In the primary analyses (EMA analysis) of change from baseline in the 6MWT distance at week 24, statistically significant differences were demonstrated for the vamorolone 6 mg/kg and the 2 mg/kg treatment arms when compared against placebo (p=0.0117 and p = 0.0112, respectively). While in the vamorolone treatment groups the 6MWT distance increased it showed some decline under placebo. The LSM (SE) change from baseline for placebo, vamorolone 6 mg/kg and 2 mg/kg was -11.37 (10.6082), 24.57 (10.0582) and 24.98 (10.0352), respectively. The LSM difference for vamorolone 6 mg/kg and 2 mg/kg was 35.9 meters and 36.2 meters, respectively, which is compellingly clinically relevant. Provided sensitivity analyses supported the primary analyses, demonstrating that missing data and the analysis method had no impact on the results received.

The fourth of the pre-specified secondary efficacy endpoints was met: the change from baseline to week 24 for TTRW velocity showed a statistically significant LSM difference of 0.237 meters/sec for vamorolone 6 mg/kg/day when compared against placebo (p=0.0020) representing clinically relevance. TTRW velocity was increased under vamorolone 6 mg/kg group (LSM change from baseline 0.2372 meters/sec) and was almost unchanged in the placebo group at Week 24 with a very minimal increase of 0.0171 meters /sec (LSM change from baseline).

With respect to the comparison of vamorolone 2 mg/kg against placebo, TTRW velocity increased only slightly from 1.563 meters/sec at baseline to 1.724 meters/sec at Week 24 under vamorolone and remained almost stable for placebo (LSM change from baseline 0.1387 and 0.0171, respectively). The LSM difference of 0.1216 meters/sec was not statistically significant (p=0.1228). In the sensitivity analyses to assess the impact of the analysis method (pooled motor function tests), the LSM differences from baseline in TTRW velocity at Week 24 for vamorolone 6 mg/kg and for vamorolone 2 mg/kg from placebo were nominally statistically significant, even though the difference for vamorolone 2 mg/kg against placebo was not significant in the primary analysis. Interpretation of the comparisons on the pooled motor function tests remains difficult, and the result may be driven by one component only.

As the fifths secondary endpoint in the pre-specified hierarchical order failed to show statistical significance, no formal statistical testing of 6MWT distance for vamorolone 6 mg/kg and 2 mg/kg vs prednisone was possible. While improvements from baseline at Week 24 in the mean 6MWT distance were similar for both vamorolone treatment groups (6 mg/kg and 2 mg/kg), subjects under prednisone treatment improved numerically more (EMA analysis) with LSM (SE) changes from baseline for prednisone and vamorolone 6 mg/kg and 2 mg/kg of 44.12 (9.6444), 24.98 (10.0352) and 24.57 (10.0582), respectively.

The LSM change from baseline in TTSTAND velocity at Week 24 in the vamorolone 6 mg/kg and in the prednisone group was 0.0464 rises/sec and 0.0661 rises/sec, respectively with a LSM difference of -0.0197 that is not considered clinically relevant. The LSM change from baseline to Week 24 in TTSTAND velocity was numerically lower in the vamorolone 2 mg/kg group when compared to prednisone (0.03 rises/sec vs 0.07 rises/sec, respectively).

Comparisons between vamorolone and prednisone: to account for baseline imbalances and to allow to examine efficacy endpoints globally in spite of different units, the applicant provided percent changes from baseline at Week 24 for relevant outcome parameters. The improvements seen with vamorolone 6

mg/kg in TTSTAND, TTRW, and TTCLIMB velocity were very similar to those seen with prednisone at Week 24, while for the 6MWT and the NSAA score prednisone provided better results. The improvements seen with vamorolone 2 mg/kg were overall slightly smaller than those for prednisone, when evaluated globally. Change from baseline to week 24 in hand-held myometry (knee extensors) was 0.0624 kg in vamorolone group and 1.0147 kg in prednisone group. Comparison with prednisone were not alfa controlled.

Differences (not alfa controlled) between vamorolone and prednisone was in hand-held myometry (elbow flexors), where LSM change from baseline to week 24 was 0.4241 kg in vamorolone group and 1.0218 kg in prednisone group, however, better result in elbow flexors was observed in vamorolone 2 mg/kg than 6 mg/kg (LSM change from baseline 0.5555 kg vs 0.4241 kg). At baseline better strength in elbow flexors were observed in vamorolone 6 mg/kg group, however, this difference at baseline could not solely explain increase in muscle strength in prednisone group. An increase in muscle strength in elbow flexors were not dose-dependent, where higher increase was seen in 2 mg/kg group compared to 6 mg/kg vamorolone group. It is not clear why increase in muscle strength was more pronounced in prednisone group, and whether increase in muscle strength would be observed in later disease stages.

Additional secondary efficacy endpoints

TTCLIMB Velocity was increased in each of the vamorolone groups and slightly decreased in the placebo group from baseline at Week 24. The LSM difference was 0.07 tasks/sec for vamorolone 6 mg/kg from placebo (p= 0.0005 and p = 0.0008, respectively) and 0.06 tasks/sec for vamorolone 2 mg/kg from placebo in the EMA and the FDA analyses (p= 0.005 and p = 0.0056, respectively). The improvements in TTCLIMB velocity with vamorolone 2 and 6 mg/kg were both greater than the MCID.

NSAA Score increased from baseline in the vamorolone groups and slightly decreased in the placebo group at Week 24. The LSM difference was 3.6 points for vamorolone 6 mg/kg from placebo (p <0.0001 each) and 3.2 points for vamorolone 2 mg/kg from placebo in the EMA and FDA analyses (p=0.0003 and p=0.0002, respectively. The increases in each of the vamorolone groups at Week 24 (approximately +3 points) can be considered clinically meaningful.

Hand-held myometry (elbow flexors and knee extensors)

MMRM analysis for change from baseline to week 24 in knee extension indicated improvement in vamorolone 6 mg/kg vs placebo (LSM difference was 0.1634 kg) and also in vamorolone 2 mg/kg group (LSM difference was 0.0710 kg). Also, for elbow flexors both vamorolone doses resulted in a slight improvement, when compared with placebo (LSM difference 0.4132 kg in vamorolone 6 mg/kg and 0.5885 kg in vamorolone 2 mg/kg group). Muscle strength measurements were not alfa controlled.

The reason why muscle strength significantly improved in prednisone group, and in vamorolone groups knee extension muscle strength and elbow flexor muscle strength only slightly increased which could be translated as stability of results in patients 4 to <7 years of age, is not clear. Measurements that reflect muscle strength are highly important, and total evidence of clinical efficacy and effect on motor function should be supported by an effect on muscle strength. The difference between prednisone and vamorolone in muscle strength cannot be solely explained by difference in baseline assessment between vamorolone and prednisone, where in vamorolone arms overall were weaker results. Intra- and inter- rater variability could be high in hand-held myometry tests; however, this could have influenced all study groups similarly.

Regarding treatment satisfaction, which was exploratory efficacy endpoint, no differences between vamorolone 2 and 6 mg/kg groups compared with either the placebo or prednisone groups in the scores for the effectiveness, convenience, and global satisfaction domains of the TSQM were observed.

Subgroup analyses of TTSTAND velocity yielded comparable results across the different subgroups favouring vamorolone 6 mg/kg against placebo although they were only based on small number of patients.

Results of the subgroup analyses based on 6MWD <350 meters: Overall, results for the motor function endpoints were comparable to those in the primary analyses when vamorolone 6 mg/kg was compared against placebo for change from baseline to Week 24. Although results for the vamorolone 2 mg/kg group in comparison to placebo only showed nominally significance, they point in the same direction, representing an effect in comparison to placebo. When interpreting these results, it needs to be considered, that the study was not powered for these analyses that are based on small sample sizes.

Vamorolone Treatment for 48 Weeks (continued Vamorolone Treatment)

Based on the LSM changes from baseline to Week 24 and Week 48, the clinically meaningful improvements in TTSTAND velocity, TTRW velocity and NSAA score seen with vamorolone 6 mg/kg at 24 weeks can be considered to be maintained for up to 48 weeks of treatment. An additional improvement in 6MWT distance was seen from Week 24 to Week 48 with vamorolone 6 mg/kg.

Due to the uncontrolled design from Week 24 to Week 48, these data are difficult to interpret. Nevertheless, the respective data indicate that the effect of the vamorolone 6 mg/kg dosage is maintained up to Week 48 as there was no decline across the relevant outcome parameters and the results were generally better than for the 2 mg/kg dosage. Based on the current scientific knowledge the appropriate treatment duration for corticosteroids in DMD is still unknown. However, it is recommended to continue treatment after the loss of ambulation, based on the observation that long-term treatment with GC steroids results in the delay in time to loss of disease related milestones across the disease spectrum from delay in time to loss of ambulation, time to loss of upper limb function and time to crossing respiratory function thresholds.

The efficacy of 2 mg/kg dose appears not to be maintained up to Week 48. There was observed a clinically significant decline in TTSTAND and 6MWT at week 48 compared to results at week 24 and 6 mg/kg dose. To justify maintenance of efficacy for the 2 mg/kg dose, the applicant compared the efficacy results of 2 mg/kg from study VBP15-005 at week 48 with the results from the placebo treated group at week 52 of the POLARIS-DMD Trial (Finkel R. et al., 2021). The POLARIS-DMD study was a randomised, double-blind, placebo-controlled, global phase 3 study of Edasalonexent in paediatric patients with DMD over a treatment period of 52 weeks in 131 boys aged ≥4 years and ≤8 years with confirmed DMD. Included subjects who were corticosteroid naïve at study entry were able to perform the TTSTAND without assistance in ≤ 10 seconds. The study included the assessment of change from baseline in the NSAA as primary endpoint and timed motor function tests (TTRW, TTCLIMB, TTSTAND). Although the difference of means after 48/52 weeks between the vamorolone 2 mg/kg treatment arm and placebo-treated patients from POLARIS-DMD in TTSTAND velocity, TTCLIMB velocity and NSAA score were in favour of vamorolone 2 mg/kg and larger than the published MCIDs for the different endpoints, the comparisons of the vamorolone dose group against the placebo group from the POLARIS DMD study is of limited value. Due to the lack of concurrent controls, randomised and pre-specified comparisons confirmatory evidence of superior efficacy for vamorolone 2mg/kg against this external placebo group after 48/52 weeks of treatment cannot be assumed. Even if baseline characteristics are similar, a non-randomised between-study comparison is not accepted as confirmatory evidence since bias cannot be excluded.

In addition, the applicant provided a comparison of the results received in a subgroup of patients from the open-label long-term Study VBP15-LTE in comparison to patients from the For-DMD study. Subjects who received in Study VBP-LTE vamorolone in the dose range of 2-6 mg/kg throughout the study were compared against matched data from the FOR-DMD study over 2.5 years. Although it is admitted that the provided results for the different endpoints were comparable between the pooled vamorolone

dosages and prednisone or deflazacort, this analysis does not provide further information for the separate vamorolone 2 mg/kg dose regarding maintenance of efficacy.

Switch from Prednisone to Vamorolone

Overall, the treatment effects achieved under prednisone were maintained until week 48 after subjects had been switched to vamorolone 6 mg/kg (at Week 24).

When subjects switched from prednisone to vamorolone 6 mg/kg, the mean TTSTAND velocity, TTRW velocity and NSAA score only slightly decreased and TTCLIMB velocity minimally increased. There was a small decline in the 6MWT distance after the switch from prednisone to vamorolone, while subjects who continuously were treated with vamorolone 6m/kg continued to improve until Week 48, a finding that is difficult to interpret.

When subjects switched from prednisone to vamorolone 2 mg/kg, the mean TTSTAND and TTCLIMB velocity decreased more than the 6MWTD and TTRW velocity. No mean changes were seen for the NSAA score.

Comparison of efficacy results from study VBP15-004 with a matched population from Study FOR-DMD

The comparisons of the vamorolone dose groups to both, prednisone and deflazacort from FOR-DMD are of limited value.

In order to assess comparable efficacy, the lower limit of the CI would have to be taken into account and compared to a reasonable non-inferiority margin. However, due to the lack of placebo-controlled studies of prednisone and deflazacort in the relevant population, a reasonable non-inferiority margin cannot be given. Furthermore, due to the lack of a pre-specified multiplicity procedure only unadjusted CIs are given.

Investigation of the validity of the external comparisons

The subjects randomised to prednisone who met the common inclusion criteria were compared across studies in VBP15-004 Period 1 and the first 6 months of FOR-DMD to test the validity of the external control and provide additional context for interpretation of the FOR-DMD data. For efficacy, all 31 subjects randomised to prednisone in Study VBP15-004 were matched to 37 subjects treated with prednisone in FOR-DMD.

The LSM changes in 6MWT distance were numerically higher for prednisone in FOR-DMD than in VBP15-004 at Months 3 (LSM change 40 vs. 26 meters) and Month 6 (55 vs 39 meters). However, there were no clinically meaningful differences between the studies for any of the efficacy endpoints. A subgroup analysis was performed on the subjects with baseline 6MWT distance <350 meters and confirmed the results of the total population.

TTSTAND velocity had increased in the vamorolone 6 mg/kg, prednisone, and deflazacort groups at Months 6 and 12. The increases were similar for the vamorolone 6 mg/kg group (LSM change 0.05 and 0.04 at Months 6 and 12), deflazacort group (LSM changes 0.05 and 0.04 at Months 6 and 12, respectively), and the prednisone group (LSM changes were 0.04 and 0.04 at Months 6 and 12, respectively); the vamorolone 2 mg/kg group showed minimal change (LSM changes 0.02 and -0.00).

The 6MWT distance was increased in all groups at Months 6 and 12. The largest increases were observed for the prednisone group at Months 6 and 12 (estimate 53 and 54 meters, respectively). At Month 6, the changes were larger for deflazacort than vamorolone 2 mg/kg (mean changes 39 and 31 meters, respectively), and smaller for vamorolone 6 mg/kg (mean change 26 meters) but at Month 12, the changes for vamorolone 6 mg/kg (45 meters) were larger than for deflazacort (39 meters) or vamorolone 2 mg/kg (11 meters). It is noted that the prednisone group in FOR-DMD also performed >10 meters better than the prednisone group in VBP15-004. The LSM increases in 6MWT distance were smaller with

vamorolone 2 mg/kg compared with the prednisone and deflazacort groups. The difference in 6MWT distance between vamorolone 2 mg/kg and prednisone at Month 12 was 43.5 meters all other differences were <29 meters (i.e., below but close to the MCID).

Even in case unadjusted CIs are considered, the results indicate that vamorolone at the 2 mg/kg dosage has inferior efficacy compared to both comparators, i.e., prednisone and deflazacort. Although the results for the 6 mg/kg dosage appear more similar esp. to those of deflazacort, equivalent efficacy cannot be concluded for methodological reasons. Hence, no conclusion of comparable efficacy can be given for neither dose. On the contrary, the comparisons of the vamorolone 2 mg/kg dose seem to indicate a relevant inferiority with nominally significant differences and lower confidence limits, indicating a potentially highly relevant difference to the disadvantage of vamorolone. It should be noted that these confidence limits are unadjusted limits. Using CIs adjusted for multiplicity would have resulted in even considerably lower confidence limits. In order to contextualise the comparisons between vamorolone and both comparators**,** the applicant provided an overview of the current scientific knowledge regarding information on placebo-controlled studies for the treatment with corticosteroids in the different stages of the disease. While studies in the ambulatory population have several shortcomings based on the underlying study designs, no randomised controlled studies are available in the later, non-ambulatory patients. Relevant information cannot be provided, e.g., on estimated treatment effects and their CIs.

In summary, although confirmatory evidence of long-term efficacy comparable to that of either prednisone or deflazacort cannot be concluded from the analyses provided, this does not question the maintenance of efficacy for vamorolone, for the vamorolone 6 mg/kg dose that can be concluded from the Week 48 results of Study VB15-004.

Despite progressive muscular impairment, DMD boys are not significantly declining in motor function tests from 4- <7 year age (McDonald et al, 2013). Subjects below the age of 4 years, as well as ambulatory patients in the decline phase, non-ambulatory patients and patients with symptomatic cardiomyopathy were excluded from the study. However, the originally proposed target population included all patients with DMD. During the procedure, the applicant presented an extrapolation report with discussion on disease similarity across age ranges, and pharmacology and comparable response to treatment. In general, extrapolation based on disease similarity with regard to the underlying pathomechanism is supported. This is also the case for the claimed pharmacological similarity with corticosteroids currently used for the treatment of DMD patients, where vamorolone has agonist activity towards the glucocorticoid receptor, thereby maintaining anti-inflammatory activity, and antagonist activity towards the mineralocorticoid receptor.

Vamorolone PK properties have been established in healthy adult volunteers and in the reference population aged 4 to <7 years, while the target population originally applied for also included patients 2 to <4-years and 7 – <18 years. During the procedure, an updated PopPK model has been submitted with data from the ongoing study VBP15-006; PK data from subjects in the target age ranges have been added to the previously established PopPK model. Furthermore, study VBP15-006 was the first study to administer ROS2 (final formulation) to patients with DMD.

In general, the proposed extrapolation to the target population could have been supported from the PK point of view, as the pathophysiology of the disease is the same in children aged 2 to 4 years and 4 to 7 years and inflammatory processes have been shown to be present in DMD early-on, suggesting that for similar PK exposure, efficacy (anti-inflammatory effects) of vamorolone is likely to be similar between these two groups.

The previously established vamorolone PK model was further refined to describe exposure in paediatric patients with DMD following treatment with the ROS2 formulation. The original PopPK model was used to predict vamorolone exposure at different ages and weights based on simulations. A predefined exposure range of the 6 mg/kg dose (5^{th} to 95^{th} AUC percentile of the age range 4-7 years) was assumed

to correspond to the effective dose range, and similar exposure was to be achieved for all age groups. The model was used to evaluate various cut-off points for a fixed dose regime. According to the simulations, dosing of 6 mg/kg up to a body weight of 50 kg followed by a fixed dose of 300 mg for patients of 50 kg and above would lead to the highest percentage (≥86%) of patients within the age range from 2-18 years to fall consistently within the predefined exposure range.

A refined popPK model was developed to better simulate a potential effective dose for patients 2 to 4 years old that could as well be used to mitigate tolerability issues. According to simulations, AUC levels of ROS2 formulation are increased about 20% across all doses compared to ROS1. 4 mg/kg of ROS2 is expected to achieve 82% of the exposure of 6 mg/kg ROS1 and 246% of 2 mg/kg ROS1. Predicted drug exposure of 4 mg/kg ROS2 for all age groups is within the originally predefined exposure target range of the 5th to 95th exposure percentile of 6 mg/kg of the ROS1 formulation in the age range 4-7 years. Although the original target range appears somewhat arbitrarily defined it still provides some valuable insight into the potential efficacy of other doses, as the ROS1 6 mg/kg dose is the primary source of efficacy information.

Since even the 2 mg/kg dose with the lower exposure levels of the ROS1 formulation, which are well outside the predefined target exposure range provided evidence of some clinical benefit (despite not showing sufficient maintenance of efficacy in 4 to 7 years old patients), there is a strong rationale that the 4 mg/kg ROS2 dose should be well within the effective dose range based on exposure data.

Moreover, a majority of subjects in the EAP/ Compassionate Use programme (CUPs) with available dosing information are likewise being dosed at 4 mg/kg and this dose appears acceptable from a clinical safety perspective.

With regard to similarity in efficacy across the previously postulated age range, the applicant refers to a prospectively designed cohort study (CINRG-DNHS) (McDonald et al., 2018a) that included 440 DMD patients between 2 and 28 years of age who were followed up for 10 years. The study showed prolongation of ambulation and reduced risk in upper limb disease progression in patients using glucocorticoids for a period of more than one year. However, mean age at the baseline visit was 10.7 years (SD 5.7) and therefore the study does not provide sufficient evidence to postulate an effect for starting treatment in patients in the pre-symptomatic phase or in children <4 years of age.

Up to now, there are only limited data assessing the effect of steroids in the youngest DMD patients. In this context, the applicant refers to a study published by Connolly et al. (2019) that included 25 infants with DMD in the age of 0.4 to 2.4 years who were treated with 5 mg/kg prednisone twice weekly. In comparison to an external untreated control group, treated subjects showed a significant effect in change in the Bayley III Scales of Infant Development (Bayley-III). Notwithstanding, interpretation of these data is hampered by the open-label design, the small number of patients included and the use of an external control.

With regard to the most appropriate time to initiate treatment in DMD boys, the applicant refers to the recent publication by Hiebeler et al., 2023, to confirm the existence of earlier diagnosis in DMD over the last decade. According to Hiebeler et al., 2023, the mean age of onset of symptoms is 2.9 years with some differences across different countries, e.g., first symptoms were observed in Austria and Germany around 3 years, compared with 2.6 years in Italy, 2.7 years in the UK and in the USA, and 2.85 years in Australia. To justify an early treatment initiation, the applicant again refers to recent treatment guidelines (Birnkrant et al 2018), which recommend discussing the use of steroids already at the stage of diagnosis. In the applicant´s view these "considerations reflect the most current view of the scientific community on starting treatment as soon as patients are diagnosed in order to maximise the benefits in preserving physical function". However, Birnkrant et al, 2018 also recommends starting corticosteroid therapy before "substantial physical decline" (Birnkrant et al 2018), that may be interpreted as a recommended start at the age of 4-6 years. Moreover, Duan et al. (2021) states "the age of initiating steroids varies

between patients but should not be before the patient reaches 2 years of age and is generally around 4-5 years of age"[1].

In summary, although there is a shift in treatment recommendations to start treatment of Duchenne patients earlier in order to maximise treatment benefit, exact age specifications do not exist. This is supported by the review of Landfeldt et al. (2022), who states that "there is currently no up-to-date scientific summary of the impact of early treatment in DMD"[2].

The pathogenesis of DMD clearly starts very early, i.e., prenatally, and causes cumulative muscle destruction (Connolly et al 2019). Muscle degeneration is already recognised in early symptomatic patients, although strength and functioning continue to progress in early disease due to natural development and growth. Based on the pathogenesis of DMD with the same underlying pathomechanism at all stages of the disease and existing inflammation also already at the pre-symptomatic stages of the disease (Chen Y-W et al, 2005), early treatment initiation with vamorolone is considered reasonable[3]. In this context it should also be considered that deflazacort (Emflaza) is approved by the FDA in Duchenne patients from 2 years of age.

In summary, extrapolation of efficacy for vamorolone is generally considered possible.

During the procedure, the applicant also provided preliminary efficacy results for study VBP15-006. As of the data cut-off date, ten subjects aged 2 to < 4 years have been treated with 2 mg/kg vamorolone and all have completed the study. Nine of these 10 subjects are continuing to receive vamorolone in the EAP and the other subject switched to standard of care glucocorticoid treatment.

At baseline, median GMSS were lower than 7 indicating a delay in motor development compared to normal children of the same age. Subjects assigned to vamorolone 2 mg/kg had lower median value at baseline than those assigned to 6 mg/kg indicating a more pronounced motor delay. After 12 weeks, there was no relevant change from baseline in vamorolone 2 mg/kg suggesting no progression of developmental delay, while the mean score increased in the 6 mg/kg dose group with mean (SD) change from baseline to week 12 of 2.67 (1.211), suggesting an improvement in gross motor abilities.

The applicant further discussed these results in comparison to the results of the study published by Connolly et al. (2019), that included 25 infants with DMD at the age of 0.4 to 2.4 years who were treated with 5 mg/kg prednisone twice weekly. In comparison to an external untreated control group, prednisone treated subjects showed a significant effect in change in the Bayley III Scales of Infant Development (Bayley-III). Treated boys gained an average of 0.5 points on the Bayley-III gross motor scale score while the historical control cohort on average declined by 1.3 points.

The provided preliminary efficacy results of study VBP15-006 are indicative of a dose-depending effect of vamorolone also in the youngest DMD patients. Also, the comparison to historical data supports the claimed efficacy of vamorolone in the youngest patients. However, the data have to be interpreted carefully, given the open-label study design, the small number of patients included and the use of an external control.

While the overall evidence supports vamorolone as being effective in the treatment of DMD patients between 2 and < 4 years of age, an issue remained regarding the adequacy of the proposed dose of 4 mg/kg/day based on the refined popPK model. However, the originally claimed indication also including patients from 2 to <4 years of age has finally not been further pursued by the applicant.

[1] Duan, D., Goemans, N., Takeda, S. et al. Duchenne muscular dystrophy. Nat Rev Dis Primers 7, 13 (2021).
[2] Landfeldt E, Ferizović N, Buesch K. Timing of Clinical Interventions in Patients With Duchenne Muscular Dystrophy: A Systematic Review and Grading of Evidence. J Neuromuscul Dis. 2022;9(3):353-364.
[3] Chen YW, Nagaraju K, Bakay M, McIntyre O, Rawat R, Shi R, Hoffman EP. Early onset of inflammation and later involvement of TGFbeta in Duchenne muscular dystrophy. Neurology. 2005 Sep 27;65(6):826-34.

With regard to extrapolation in patient population >7 years of age, there is an inevitable clinical regression in patients with DMD and worsening of muscle strength also occurs in patients who are clinically improving according to functional evaluation. As the pathogenic mechanism in DMD patients with different stages of the disease is the same, patients with DMD in the late ambulatory and early non-ambulatory phase are expected to benefit from vamorolone treatment. Studies have shown that steroid use after loss of ambulation in DMD was associated with delayed progression of important pulmonary, cardiac and upper extremity functional deficits (McDonald et al, 2023, Functional and clinical outcomes associated with Steroid treatment among non-ambulatory patients with Duchenne muscular dystrophy, journal of neuromuscular disease); furthermore, steroids prolonged hand-to-mouth function and ability to turn in bed at night unaided. However, uncertainty remains about the glucocorticoid effect in late stage of disease e.g., during the late non-ambulatory phase. There are limited data in this population and, in general, the steroid effect decreases with the progression of the disease. Some studies have shown that the rate of decline in function or strength in non-ambulatory patients is not affected by steroid use (Connolly et al., 2016) but this could partially be explained by lack of sensitivity of the proposed measures in the late stage of the disease. Despite these uncertainties, considering the disease similarity as well as the pharmacological mechanism of vamorolone, some benefit on pulmonary, cardiac and motor functions can be anticipated also in patients in the late non-ambulatory stage; however, the effect size remains unknown.

2.6.7. Conclusions on the clinical efficacy

No classical dose-finding study was performed but for both, vamorolone 6 mg/kg/day and 2 mg/kg/day in the primary analysis (EMA analysis) of change from baseline in TTSTAND velocity at week 24, statistically significant and clinically relevant differences were demonstrated when vamorolone was compared against placebo in ambulatory, corticosteroid naïve ≥ 4 to <7 years old DMD patients in study VBP15-004. Effects of the primary analyses were corroborated by a number of sensitivity and supportive analyses of the primary endpoint as well as secondary endpoints evaluating motor function in Duchenne. The effect on TTSTAND velocity was generally consistent in pre-specified subgroups. Additional *post hoc* subgroup analyses for the efficacy endpoints in subjects with comparable 6MWT distances at baseline of <350 meters also provided comparable results to those in the primary analyses.

Based on global assessments, the improvements in motor function with vamorolone 6 mg/kg were overall similar to those seen with prednisone at Week 24, except for the 6MWT and the NSAA score for which prednisone provided better results. The improvements seen with vamorolone 2 mg/kg were overall slightly smaller than those seen with prednisone.

Except for TTSTAND velocity, no clinically meaningful differences were seen in functional outcomes for vamorolone 2 mg/kg compared with vamorolone 6 mg/kg after 6 months of treatment. Due to the uncontrolled design from Week 24 to Week 48, these data are difficult to interpret. Nevertheless, the respective data indicate that the effect of the vamorolone 6 mg/kg dosage is maintained up to Week 48 as there was no decrease across the relevant outcome parameters but an additional increase in the 6MWT distance from Week 24 to Week 48 and the results were generally better than for the 2 mg/kg dosage. Results across the efficacy outcome measures for the vamorolone 2 mg/kg dose were rather inconsistent with observed clinically significant declines in relevant functional outcome parameters at Week 48, i.e., TTSTAND velocity and 6MWT but only minimal decrease in the NSAA score. Maintenance of efficacy for the vamorolone 2 mg/kg dose has not compellingly been shown, also based on the analyses provided during the procedure since pre-defined comparisons against placebo are lacking.

The applicant initially claimed that the recommended 6 mg/kg dose of vamorolone may be down titrated in a stepwise manner to 2 mg/kg as a minimum dose, based on individual tolerability. Generally, there should be an established effect on relevant outcome parameters even for the lower dose given the fact

that vamorolone is intended for long-term use in a chronic disease. There is a high patient-to-patient variability in disease onset and progression observed over shorter periods of time with variations in remaining muscle mass that drives the progression and clinical presentation. Although, the effect of the 2 mg/kg dose appears not to be sufficiently maintained up to Week 48, there should be an option to down-titrate the recommended dose 6 mg/kg to a lower dose in case of tolerability issues. This is in line with clinical practice where physicians may change the dosage for corticosteroids individually based on relevant case by case aspects.

Meanwhile, the applicant changed the proposed dose for down-titration to 4 mg/kg or to 2 mg/kg in case of tolerability issues by stating that patients should be maintained at the highest tolerated dose within the dose range. On the basis of the simulations from the new PopPK model, predicting a generally higher exposure for the ROS2 formulations compared to the ROS1 formulation across all dosages, the intermediate 4 mg/kg dose (ROS2 formulation) is expected to sufficiently maintain efficacy. Down-titration to the 4 mg/kg dose due to tolerability issues is therefore agreed with from an efficacy perspective and this has been further supported by the updated popPK model showing that AUC distributions predicted for the vamorolone 4 mg/kg dose (ROS2) overlap with the vamorolone 6 mg/kg dose (ROS1 fed) for the majority of patients in the claimed age range 4 years and older. Nevertheless, there might be situations when 4 mg/kg as a reduced dose can still not sufficiently mitigate tolerability issues, e.g., weight gain. Although, only partial efficacy can be attributed to the 2 mg/kg dose, which is similar to other GC treatment regimens that are, for example, administered intermittently or at lower than standard doses for the treatment of DMD in the absence of other treatment options, a small number of patients is effectively treated with this dose in the EAP.

The pre-planned matched comparison of the vamorolone 6 mg/kg group to the continuous prednisone and deflazacort groups from study FOR-DMD (comparing different GCs and dosing regimens) at 1 year suggest similar efficacy esp. to deflazacort, but equivalent efficacy cannot be concluded for methodological reasons. However, the pre-specified comparison of vamorolone at the 2 mg/kg dosage to these comparators showed inferior efficacy compared to both, i.e. prednisone and deflazacort.

No loss of efficacy was seen when subjects were switched from prednisone to vamorolone 6 mg/kg at Week 24, whereas small but also inconsistent declines were seen after the switch from prednisone to vamorolone 2 mg/kg.

With regard to the revised indication including patients from 4 years and above, extrapolation to DMD patients above 7 years of age can be supported.

The CHMP recommends that the applicant explore the possibility of further evaluating long-term efficacy, e.g. time to and age at loss of ambulation. Although, this data is not impacting B/R considerations, it could be valuable for patients, their families and their treating physicians.

2.6.8. Clinical safety

The body of the integrated vamorolone safety database includes four clinical phase 2a/b studies, one randomised controlled study (with an uncontrolled extension; VBP15-004), and three uncontrolled open-label studies (VBP15-002, VBP15-003, and VBP15-LTE). Subjects who completed the clinical trials were offered access to continue treatment with vamorolone 2-6 mg/kg in an EAPs and CUPs. VBP15-006, a Phase 2 open-label, multiple dose study to assess safety, tolerability, PK, PD, and exploratory efficacy of vamorolone in boys 2 to <4 years of age and 7 to <18 years with DMD, was in the recruitment phase at the data cut-off for the MAA. For this study, preliminary safety data have become available during the procedure. Supportive safety information derives from external comparison with three glucocorticoid

regimens prospectively assessed in a 3660 month, randomised, interventional, double-blind study (FOR-DMD study). To enable comparison to vamorolone, patients were matched.

Safety data were presented by pooling the four clinical studies: the primary focus on safety evaluation is set on **Pool 1**, which includes the Period 1 (24-weeks) controlled data from study VBP15-004 for vamorolone 2 mg/kg, 6 mg/kg, placebo and prednisone. **Pool 2** provides data the uncontrolled vamorolone-treated safety population (period 2 of study VBP15-004 and sequential open-label studies VBP15-002, VBP15-003, and VBP15-LTE). **Pool 3** comprises data of all vamorolone-treated subjects in any multiple dose DMD study to account for longer-term safety data.

2.6.8.1. Patient exposure

164 male patients with DMD aged 4 to <7 years at study entry were treated with vamorolone 0.25-6 mg/kg in clinical studies. The total age range across studies was 4 to 9.6 years.

Randomised controlled data are available from the 24-week Period 1 of Study VBP15-004: 29 subjects received placebo, 31 subjects received 0.75 mg/kg prednisone, 30 received vamorolone 2 mg/kg, and 28 received vamorolone 6 mg/kg. 92.9% to 96.8% of subjects completed Period 1. Median duration of exposure of 5.5 months for each treatment group. Over 90% of subjects in each group received study treatment for ≥ 6 months.

In studies VBP15-002/-003/ -LTE, 48 patients were randomised in the core study (-002) and were also treated in study -003. The safety population for study –LTE includes 46 subjects. Regarding the overall vamorolone exposure, it has been noted that there was a drug-free period in the range of 13 to 44 days between open-label studies -002 and -003, and -003 and –LTE.

In Pool 3, 153 of 163 subjects (93.3%) with vamorolone doses 2 - 6 mg/kg completed the studies. The reason for premature withdrawal in 8 out of 10 subjects was parent/ guardian decision. One patient each in the vamorolone 6 mg/kg group withdrew due to an AE (acute hepatitis) and consent withdrawn. The dominant dose was 2 mg/kg for 66 subjects (40.5%) and 6 mg/kg for 85 subjects (52.1%); 11 subjects (6.7%) were down titrated from 6 mg/kg, in 10 of them, this was because of a treatment-emergent adverse event (TEAE) of weight increased.

The median duration of exposure was 11.0 months for subjects who received vamorolone 2-6 mg/kg across all DMD studies, with 61.3% of subjects receiving vamorolone 2-6 mg/kg for ≥12 months and 12.3% for ≥30 months. Median duration of exposure was 10.9 months and 11.0 months in the 2 mg/kg and 6 mg/kg dominant dose group, respectively, and 30.5 months for the down-titrated dose group (of note, the down-titrated group included subjects only from the VBP15-LTE study, the other treatment groups mainly included subjects from VBP15-004). Based on the dominant dose definition, safety data ≥12 months (≥30 months) for 2 mg/kg and 6 mg/kg vamorolone are available for 35 and 54 patients (7 and 25 patients), respectively, in the total pool. Safety data of ≥12 months by age are available for 18 patients aged <5 years and 17 patients ≥5 years for 2 mg/kg vamorolone and for 25 patients aged <5 years and 29 patients ≥5 years for 6 mg/kg vamorolone.

As of 15 March 2023, 171 subjects from clinical vamorolone studies (age range 2 to 17 years) have received treatment with vamorolone 2-6 mg/kg in EAPs/CUPs of up to 11 months for subjects entering from study VBP15-006, to up to 4.6 years for subjects entering from study VBP15-004, to up to 6.7 years for subjects entering from studies VBP15-002/003/LTE.

The updated recommended dose for vamorolone in DMD patients 4 years and older is 6 mg/kg once daily in patients weighing less than 40 kg. In patients weighing 40 kg and above, the recommended dose is 240 mg once daily. Daily dose may be down titrated to 4 mg/kg/day or 2mg/kg/day, based on individual tolerability. 4 patients had an intermediate dose of 4 mg/kg at the end of study VBP15-LTE. A majority

of subjects in the EAP/CUPs with available dosing information is also being dosed at 4 mg/kg up to the data cut-off.

Up to the DCO for study VBP15-006 (21 July 2023) focussing on the cohort of children 2 to <4 years of age, median duration of exposure was 12.3 weeks in the 2 mg/kg dose group and 11.9 weeks in the 6 mg/kg dose group. 10 patients in this age cohort received 2 mg/kg and 6 patients were treated with the 6 mg/kg dose. So far, a total of 15 subjects continue treatment in the EAP. Age as per 21 July 2023 ranges from 3.9 to 5.4 years and the longest duration of exposure in the EAP for the 2 to <4 years paediatric subjects in the EAP is 9 months.

2.6.8.2. Adverse events

The overall incidence of TEAEs in Pool 1 was lowest in the placebo group, followed by vamorolone 2 mg/kg, prednisone, and vamorolone 6 mg/kg (79.3%, 83.3%, 83.9%, and 89.3%). Half of the overall TEAEs in the combined vamorolone 2-6 mg/kg group were drug-related (33.3% and 67.9% for vamorolone 2 mg/kg and 6 mg/kg, respectively). No subject on vamorolone experienced severe TEAEs or TEAEs leading to permanent study treatment discontinuation. One serious adverse event (SAE) was recorded in the vamorolone 2 mg/kg group (viral gastroenteritis). TEAEs of special interest were similarly recorded in the vamorolone 6 mg/kg and prednisone group (78.6% and 77.4%).

TEAEs reported by >2% of subjects in any vamorolone group and at a higher incidence compared to placebo are summarised in Table 16. Within this table, the TEAEs reported for ≥10% of subjects in the vamorolone 2-6 mg/kg group in Pool 1 are shaded in grey.

Table 16: TEAEs Reported by > 2% of subjects in any vamorolone group and at a higher incidence than placebo – controlled safety population (Pool 1) and incidence of these TEAEs in POOL 3 (compiled by the Assessor)

	Pool 1					Pool 3		
System Organ Class Preferred Term	**Placebo (N = 29) n (% ; EAIR) ; f (Rate)**	**Prednisone 0.75 mg/kg (N = 31) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 mg/kg (N = 30) n (% ; EAIR) ; f (Rate)**	**Vamorolone 6 mg/kg (N = 28) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 – 6 mg/kg (N = 58) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 mg/kg (N = 97) n (% ; EAIR) ; f (Rate)**	**Vamorolone 6 mg/kg (N = 99) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 – 6 mg/kg (N = 163) n (% ; EAIR) ; f (Rate)**
Ear and labyrinth disorders	0 ; 0	2 (6.5 ; 0.14) ; 2 (0.14)	0 ; 0	1 (3.6 ; 0.08) ; 2 (0.16)	1 (1.7 ; 0.04) ; 2 (0.08)	6 (6.2 ; 0.09) ; 6 (0.08)	7 (7.1 ; 0.08) ; 9 (0.09)	11 (6.7 ; 0.07) ; 15 (0.09)
Ear pain	0 ; 0	2 (6.5 ; 0.14) ; 2 (0.14)	0 ; 0	1 (3.6 ; 0.08) ; 2 (0.16)	1 (1.7 ; 0.04) ; 2 (0.08)	6 (6.2 ; 0.09) ; 6 (0.08)	7 (7.1 ; 0.08) ; 9 (0.09)	11 (6.7 ; 0.07) ; 15 (0.09)
Endocrine disorders	0 ; 0	7 (22.6 ; 0.53) ; 7 (0.50)	2 (6.7 ; 0.15) ; 2 (0.15)	8 (28.6 ; 0.70) ; 8 (0.63)	10 (17.2 ; 0.40) ; 10 (0.38)	5 (5.2 ; 0.07) ; 5 (0.07)	14 (14.1 ; 0.16) ; 14 (0.15)	19 (11.7 ; 0.12) ; 19 (0.11)
Cushingoid	0 ; 0	7 (22.6 ; 0.53) ; 7 (0.50)	2 (6.7 ; 0.15) ; 2 (0.15)	8 (28.6 ; 0.70) ; 8 (0.63)	10 (17.2 ; 0.40) ; 10 (0.38)	5 (5.2 ; 0.07) ; 5 (0.07)	14 (14.1 ; 0.16) ; 14 (0.15)	19 (11.7 ; 0.12) ; 19 (0.11)
Gastrointestinal disorders	7 (24.1 ; 0.64) ; 9 (0.69)	8 (25.8 ; 0.69) ; 12 (0.86)	10 (33.3 ; 0.92) ; 16 (1.19)	9 (32.1 ; 0.85) ; 13 (1.02)	19 (32.8 ; 0.88) ; 29 (1.11)	29 (29.9 ; 0.57) ; 61 (0.84)	41 (41.4 ; 0.68) ; 91 (0.95)	64 (39.3 ; 0.61) ; 154 (0.91)
Abdominal pain	2 (6.9 ; 0.16) ; 2 (0.15)	3 (9.7 ; 0.23) ; 3 (0.21)	3 (10.0 ; 0.23) ; 3 (0.22)	2 (7.1 ; 0.16) ; 2 (0.16)	5 (8.6 ; 0.20) ; 5 (0.19)	7 (7.2 ; 0.10) ; 10 (0.14)	10 (10.1 ; 0.11) ; 10 (0.10)	16 (9.8 ; 0.10) ; 20 (0.12)
Abdominal pain upper	1 (3.4 ; 0.08) ; 1 (0.08)	3 (9.7 ; 0.23) ; 3 (0.21)	0 ; 0	2 (7.1 ; 0.17) ; 3 (0.23)	2 (3.4 ; 0.08) ; 3 (0.11)	4 (4.1 ; 0.06) ; 7 (0.10)	12 (12.1 ; 0.14) ; 19 (0.20)	16 (9.8 ; 0.10) ; 26 (0.15)
Constipation	2 (6.9 ; 0.16) ; 2 (0.15)	1 (3.2 ; 0.07) ; 1 (0.07)	3 (10.0 ; 0.24) ; 3 (0.22)	1 (3.6 ; 0.08) ; 1 (0.08)	4 (6.9 ; 0.16) ; 4 (0.15)	7 (7.2 ; 0.10) ; 11 (0.15)	12 (12.1 ; 0.14) ; 17 (0.18)	19 (11.7 ; 0.13) ; 28 (0.16)
Diarrhoea	1 (3.4 ; 0.08) ; 1 (0.08)	2 (6.5 ; 0.15) ; 3 (0.21)	1 (3.3 ; 0.08) ; 1 (0.07)	2 (7.1 ; 0.16) ; 2 (0.16)	3 (5.2 ; 0.12) ; 3 (0.11)	7 (7.2 ; 0.10) ; 8 (0.11)	11 (11.1 ; 0.13) ; 13 (0.14)	18 (11.0 ; 0.12) ; 22 (0.13)
Nausea	0 ; 0	0 ; 0	1 (3.3 ; 0.08) ; 1 (0.07)	0 ; 0	1 (1.7 ; 0.04) ; 1 (0.04)	2 (2.1 ; 0.03) ; 2 (0.03)	2 (2.0 ; 0.02) ; 8 (0.08)	4 (2.5 ; 0.02) ; 10 (0.06)
Toothache	0 ; 0	0 ; 0	1 (3.3 ; 0.07) ; 1 (0.07)	1 (3.6 ; 0.08) ; 1 (0.08)	2 (3.4 ; 0.08) ; 2 (0.08)	2 (2.1 ; 0.03) ; 2 (0.03)	2 (2.0 ; 0.02) ; 2 (0.02)	4 (2.5 ; 0.02) ; 4 (0.02)
Vomiting	2 (6.9 ; 0.16) ; 3 (0.23)	2 (6.5 ; 0.15) ; 2 (0.14)	5 (16.7 ; 0.40) ; 7 (0.52)	4 (14.3 ; 0.34) ; 4 (0.31)	9 (15.5 ; 0.38) ; 11 (0.42)	13 (13.4 ; 0.21) ; 21 (0.29)	15 (15.2 ; 0.18) ; 22 (0.23)	27 (16.6 ; 0.19) ; 44 (0.26)
General disorders and administration site conditions	6 (20.7 ; 0.53) ; 8 (0.61)	2 (6.5 ; 0.15) ; 3 (0.21)	6 (20.0 ; 0.50) ; 7 (0.52)	1 (3.6 ; 0.08) ; 1 (0.08)	7 (12.1 ; 0.29) ; 8 (0.30)	23 (23.7 ; 0.43) ; 48 (0.66)	21 (21.2 ; 0.26) ; 34 (0.35)	41 (25.2 ; 0.33) ; 82 (0.48)
Influenza like illness	0 ; 0	0 ; 0	0 ; 0	1 (3.6 ; 0.08) ; 1 (0.08)	1 (1.7 ; 0.04) ; 1 (0.04)	0 ; 0	4 (4.0 ; 0.04) ; 4 (0.04)	4 (2.5 ; 0.02) ; 4 (0.02)
Pyrexia	6 (20.7 ; 0.53) ; 8 (0.61)	2 (6.5 ; 0.15) ; 3 (0.21)	6 (20.0 ; 0.50) ; 7 (0.52)	0 ; 0	6 (10.3 ; 0.24) ; 7 (0.27)	20 (20.6 ; 0.37) ; 43 (0.60)	14 (14.1 ; 0.16) ; 23 (0.24)	33 (20.2 ; 0.25) ; 66 (0.39)
Immune system disorders	0 ; 0	0 ; 0	1 (3.3 ; 0.08) ; 1 (0.07)	0 ; 0	1 (1.7 ; 0.04) ; 1 (0.04)	3 (3.1 ; 0.04) ; 3 (0.04)	2 (2.0 ; 0.02) ; 2 (0.02)	5 (3.1 ; 0.03) ; 5 (0.03)
Seasonal allergy	0 ; 0	0 ; 0	1 (3.3 ; 0.08) ; 1 (0.07)	0 ; 0	1 (1.7 ; 0.04) ; 1 (0.04)	3 (3.1 ; 0.04) ; 3 (0.04)	2 (2.0 ; 0.02) ; 2 (0.02)	5 (3.1 ; 0.03) ; 5 (0.03)

	Pool 1					Pool 3		
System Organ Class Preferred Term	**Placebo (N = 29) n (% ; EAIR) ; f (Rate)**	**Prednisone 0.75 mg/kg (N = 31) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 mg/kg (N = 30) n (% ; EAIR) ; f (Rate)**	**Vamorolone 6 mg/kg (N = 28) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 – 6 mg/kg (N = 58) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 mg/kg (N = 97) n (% ; EAIR) ; f (Rate)**	**Vamorolone 6 mg/kg (N = 99) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 – 6 mg/kg (N = 163) n (% ; EAIR) ; f (Rate)**
Infections and infestations	10 (34.5 ; 0.96) ; 20 (1.52)	9 (29.0 ; 0.79) ; 18 (1.29)	11 (36.7 ; 1.07) ; 17 (1.26)	8 (28.6 ; 0.77) ; 15 (1.17)	19 (32.8 ; 0.92) ; 32 (1.22)	46 (47.4 ; 1.10) ; 111 (1.54)	43 (43.4 ; 0.71) ; 111 (1.15)	74 (45.4 ; 0.81) ; 223 (1.31)
Conjunctivitis	1 (3.4 ; 0.08) ; 1 (0.08)	0 ; 0	0 ; 0	1 (3.6 ; 0.08) ; 1 (0.08)	1 (1.7 ; 0.04) ; 1 (0.04)	3 (3.1 ; 0.04) ; 3 (0.04)	4 (4.0 ; 0.04) ; 5 (0.05)	6 (3.7 ; 0.04) ; 8 (0.05)
Ear infection	1 (3.4 ; 0.08) ; 2 (0.15)	1 (3.2 ; 0.07) ; 1 (0.07)	1 (3.3 ; 0.08) ; 1 (0.07)	1 (3.6 ; 0.08) ; 1 (0.08)	2 (3.4 ; 0.08) ; 2 (0.08)	5 (5.2 ; 0.07) ; 5 (0.07)	6 (6.1 ; 0.06) ; 7 (0.07)	10 (6.1 ; 0.06) ; 12 (0.07)
Enterobiasis	0 ; 0	0 ; 0	1 (3.3 ; 0.07) ; 1 (0.07)	1 (3.6 ; 0.08) ; 1 (0.08)	2 (3.4 ; 0.08) ; 2 (0.08)	2 (2.1 ; 0.03) ; 2 (0.03)	3 (3.0 ; 0.03) ; 4 (0.04)	4 (2.5 ; 0.02) ; 6 (0.04)
Gastroenteritis viral	0 ; 0	0 ; 0	2 (6.7 ; 0.16) ; 2 (0.15)	0 ; 0	2 (3.4 ; 0.08) ; 2 (0.08)	5 (5.2 ; 0.07) ; 5 (0.07)	2 (2.0 ; 0.02) ; 2 (0.02)	8 (4.9 ; 0.05) ; 8 (0.05)
Influenza	1 (3.4 ; 0.08) ; 1 (0.08)	1 (3.2 ; 0.07) ; 1 (0.07)	1 (3.3 ; 0.08) ; 1 (0.07)	0 ; 0	1 (1.7 ; 0.04) ; 1 (0.04)	5 (5.2 ; 0.07) ; 5 (0.07)	9 (9.1 ; 0.10) ; 10 (0.10)	13 (8.0 ; 0.08) ; 15 (0.09)
Nasopharyngitis	3 (10.3 ; 0.24) ; 6 (0.46)	3 (9.7 ; 0.23) ; 9 (0.64)	1 (3.3 ; 0.07) ; 1 (0.07)	2 (7.1 ; 0.17) ; 6 (0.47)	3 (5.2 ; 0.12) ; 7 (0.27)	16 (16.5 ; 0.28) ; 39 (0.54)	18 (18.2 ; 0.22) ; 37 (0.38)	30 (18.4 ; 0.22) ; 76 (0.45)
Pharyngitis streptococcal	1 (3.4 ; 0.08) ; 1 (0.08)	0 ; 0	1 (3.3 ; 0.08) ; 2 (0.15)	0 ; 0	1 (1.7 ; 0.04) ; 2 (0.08)	5 (5.2 ; 0.07) ; 12 (0.17)	3 (3.0 ; 0.03) ; 3 (0.03)	7 (4.3 ; 0.04) ; 15 (0.09)
Rhinitis	1 (3.4 ; 0.08) ; 2 (0.15)	0 ; 0	1 (3.3 ; 0.08) ; 2 (0.15)	2 (7.1 ; 0.16) ; 2 (0.16)	3 (5.2 ; 0.12) ; 4 (0.15)	3 (3.1 ; 0.04) ; 4 (0.06)	5 (5.1 ; 0.05) ; 6 (0.06)	8 (4.9 ; 0.05) ; 10 (0.06)
Upper respiratory tract infection	4 (13.8 ; 0.33) ; 7 (0.53)	4 (12.9 ; 0.31) ; 6 (0.43)	6 (20.0 ; 0.52) ; 7 (0.52)	2 (7.1 ; 0.16) ; 3 (0.23)	8 (13.8 ; 0.34) ; 10 (0.38)	19 (19.6 ; 0.30) ; 24 (0.33)	12 (12.1 ; 0.13) ; 24 (0.25)	28 (17.2 ; 0.19) ; 48 (0.28)
Viral infection	0 ; 0	0 ; 0	0 ; 0	1 (3.6 ; 0.08) ; 1 (0.08)	1 (1.7 ; 0.04) ; 1 (0.04)	2 (2.1 ; 0.03) ; 3 (0.04)	3 (3.0 ; 0.03) ; 3 (0.03)	4 (2.5 ; 0.02) ; 6 (0.04)
Viral upper respiratory tract infection	0 ; 0	1 (3.2 ; 0.07) ; 1 (0.07)	0 ; 0	0 ; 0	0 ; 0	3 (3.1 ; 0.04) ; 4 (0.06)	4 (4.0 ; 0.05) ; 6 (0.06)	7 (4.3 ; 0.04) ; 10 (0.06)
Injury, poisoning and procedural complications	2 (6.9 ; 0.16) ; 4 (0.30)	4 (12.9 ; 0.31) ; 8 (0.57)	6 (20.0 ; 0.50) ; 6 (0.45)	6 (21.4 ; 0.54) ; 7 (0.55)	12 (20.7 ; 0.52) ; 13 (0.50)	15 (15.5 ; 0.24) ; 23 (0.32)	17 (17.2 ; 0.21) ; 30 (0.31)	31 (19.0 ; 0.22) ; 53 (0.31)
Arthropod bite	1 (3.4 ; 0.08) ; 3 (0.23)	0 ; 0	1 (3.3 ; 0.08) ; 1 (0.07)	2 (7.1 ; 0.16) ; 2 (0.16)	3 (5.2 ; 0.12) ; 3 (0.11)	3 (3.1 ; 0.04) ; 3 (0.04)	3 (3.0 ; 0.03) ; 3 (0.03)	6 (3.7 ; 0.04) ; 6 (0.04)
Contusion	0 ; 0	1 (3.2 ; 0.07) ; 1 (0.07)	3 (10.0 ; 0.24) ; 3 (0.22)	0 ; 0	3 (5.2 ; 0.12) ; 3 (0.11)	4 (4.1 ; 0.06) ; 4 (0.06)	1 (1.0 ; 0.01) ; 1 (0.01)	5 (3.1 ; 0.03) ; 5 (0.03)
Fall	1 (3.4 ; 0.08) ; 1 (0.08)	4 (12.9 ; 0.31) ; 7 (0.50)	0 ; 0	3 (10.7 ; 0.26) ; 4 (0.31)	3 (5.2 ; 0.12) ; 4 (0.15)	6 (6.2 ; 0.09) ; 8 (0.11)	11 (11.1 ; 0.13) ; 19 (0.20)	16 (9.8 ; 0.10) ; 27 (0.16)
Limb injury	0 ; 0	0 ; 0	0 ; 0	1 (3.6 ; 0.08) ; 1 (0.08)	1 (1.7 ; 0.04) ; 1 (0.04)	3 (3.1 ; 0.04) ; 4 (0.06)	1 (1.0 ; 0.01) ; 1 (0.01)	4 (2.5 ; 0.02) ; 5 (0.03)
Muscle strain	0 ; 0	0 ; 0	1 (3.3 ; 0.07) ; 1 (0.07)	0 ; 0	1 (1.7 ; 0.04) ; 1 (0.04)	2 (2.1 ; 0.03) ; 2 (0.03)	2 (2.0 ; 0.02) ; 2 (0.02)	4 (2.5 ; 0.02) ; 4 (0.02)
Skin laceration	0 ; 0	0 ; 0	1 (3.3 ; 0.07) ; 1 (0.07)	0 ; 0	1 (1.7 ; 0.04) ; 1 (0.04)	2 (2.1 ; 0.03) ; 2 (0.03)	3 (3.0 ; 0.03) ; 4 (0.04)	5 (3.1 ; 0.03) ; 6 (0.04)

	Pool 1					Pool 3		
System Organ Class Preferred Term	**Placebo (N = 29) n (% ; EAIR) ; f (Rate)**	**Prednisone 0.75 mg/kg (N = 31) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 mg/kg (N = 30) n (% ; EAIR) ; f (Rate)**	**Vamorolone 6 mg/kg (N = 28) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 – 6 mg/kg (N = 58) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 mg/kg (N = 97) n (% ; EAIR) ; f (Rate)**	**Vamorolone 6 mg/kg (N = 99) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 – 6 mg/kg (N = 163) n (% ; EAIR) ; f (Rate)**
Investigations	1 (3.4 ; 0.08) ; 1 (0.08)	2 (6.5 ; 0.15) ; 2 (0.14)	0 ; 0	3 (10.7 ; 0.24) ; 3 (0.23)	3 (5.2 ; 0.12) ; 3 (0.11)	6 (6.2 ; 0.08) ; 6 (0.08)	18 (18.2 ; 0.21) ; 20 (0.21)	24 (14.7 ; 0.16) ; 26 (0.15)
Weight increased	1 (3.4 ; 0.08) ; 1 (0.08)	2 (6.5 ; 0.15) ; 2 (0.14)	0 ; 0	3 (10.7 ; 0.24) ; 3 (0.23)	3 (5.2 ; 0.12) ; 3 (0.11)	4 (4.1 ; 0.06) ; 4 (0.06)	13 (13.1 ; 0.15) ; 15 (0.16)	17 (10.4 ; 0.11) ; 19 (0.11)
Metabolism and nutrition disorders	0 ; 0	1 (3.2 ; 0.07) ; 1 (0.07)	2 (6.7 ; 0.15) ; 2 (0.15)	3 (10.7 ; 0.25) ; 3 (0.23)	5 (8.6 ; 0.20) ; 5 (0.19)	2 (2.1 ; 0.03) ; 2 (0.03)	9 (9.1 ; 0.10) ; 11 (0.11)	11 (6.7 ; 0.07) ; 13 (0.08)
Vitamin D deficiency	0 ; 0	1 (3.2 ; 0.07) ; 1 (0.07)	2 (6.7 ; 0.15) ; 2 (0.15)	3 (10.7 ; 0.25) ; 3 (0.23)	5 (8.6 ; 0.20) ; 5 (0.19)	2 (2.1 ; 0.03) ; 2 (0.03)	9 (9.1 ; 0.10) ; 11 (0.11)	11 (6.7 ; 0.07) ; 13 (0.08)
Musculoskeletal and connective tissue disorders	3 (10.3 ; 0.25) ; 3 (0.23)	4 (12.9 ; 0.31) ; 6 (0.43)	0 ; 0	2 (7.1 ; 0.16) ; 2 (0.16)	2 (3.4 ; 0.08) ; 2 (0.08)	19 (19.6 ; 0.30) ; 28 (0.39)	27 (27.3 ; 0.36) ; 38 (0.40)	42 (25.8 ; 0.31) ; 66 (0.39)
Arthralgia	0 ; 0	1 (3.2 ; 0.07) ; 1 (0.07)	0 ; 0	1 (3.6 ; 0.08) ; 1 (0.08)	1 (1.7 ; 0.04) ; 1 (0.04)	2 (2.1 ; 0.03) ; 2 (0.03)	2 (2.0 ; 0.02) ; 2 (0.02)	4 (2.5 ; 0.02) ; 4 (0.02)
Back pain	1 (3.4 ; 0.08) ; 1 (0.08)	1 (3.2 ; 0.07) ; 1 (0.07)	0 ; 0	0 ; 0	0 ; 0	4 (4.1 ; 0.06) ; 4 (0.06)	3 (3.0 ; 0.03) ; 4 (0.04)	7 (4.3 ; 0.04) ; 8 (0.05)
Myalgia	1 (3.4 ; 0.08) ; 1 (0.08)	0 ; 0	0 ; 0	1 (3.6 ; 0.08) ; 1 (0.08)	1 (1.7 ; 0.04) ; 1 (0.04)	2 (2.1 ; 0.03) ; 2 (0.03)	5 (5.1 ; 0.05) ; 7 (0.07)	7 (4.3 ; 0.04) ; 9 (0.05)
Pain in extremity	1 (3.4 ; 0.08) ; 1 (0.08)	3 (9.7 ; 0.23) ; 4 (0.29)	0 ; 0	0 ; 0	0 ; 0	11 (11.3 ; 0.16) ; 17 (0.24)	12 (12.1 ; 0.14) ; 16 (0.17)	22 (13.5 ; 0.15) ; 33 (0.19)
Nervous system disorders	1 (3.4 ; 0.08) ; 1 (0.08)	1 (3.2 ; 0.07) ; 1 (0.07)	2 (6.7 ; 0.15) ; 2 (0.15)	2 (7.1 ; 0.17) ; 2 (0.16)	4 (6.9 ; 0.16) ; 4 (0.15)	11 (11.3 ; 0.17) ; 16 (0.22)	12 (12.1 ; 0.13) ; 22 (0.23)	21 (12.9 ; 0.14) ; 38 (0.22)
Headache	1 (3.4 ; 0.08) ; 1 (0.08)	1 (3.2 ; 0.07) ; 1 (0.07)	2 (6.7 ; 0.15) ; 2 (0.15)	2 (7.1 ; 0.17) ; 2 (0.16)	4 (6.9 ; 0.16) ; 4 (0.15)	11 (11.3 ; 0.17) ; 16 (0.22)	12 (12.1 ; 0.13) ; 22 (0.23)	21 (12.9 ; 0.14) ; 38 (0.22)
Psychiatric disorders	0 ; 0	3 (9.7 ; 0.24) ; 3 (0.21)	1 (3.3 ; 0.08) ; 1 (0.07)	3 (10.7 ; 0.25) ; 4 (0.31)	4 (6.9 ; 0.16) ; 5 (0.19)	6 (6.2 ; 0.09) ; 6 (0.08)	11 (11.1 ; 0.13) ; 14 (0.15)	17 (10.4 ; 0.11) ; 20 (0.12)
Agitation	0 ; 0	0 ; 0	0 ; 0	1 (3.6 ; 0.08) ; 1 (0.08)	1 (1.7 ; 0.04) ; 1 (0.04)	2 (2.1 ; 0.03) ; 2 (0.03)	3 (3.0 ; 0.03) ; 3 (0.03)	5 (3.1 ; 0.03) ; 5 (0.03)
Behaviour disorder	0 ; 0	1 (3.2 ; 0.07) ; 1 (0.07)	1 (3.3 ; 0.08) ; 1 (0.07)	0 ; 0	1 (1.7 ; 0.04) ; 1 (0.04)	3 (3.1 ; 0.04) ; 3 (0.04)	1 (1.0 ; 0.01) ; 1 (0.01)	4 (2.5 ; 0.02) ; 4 (0.02)
Emotional disorder	0 ; 0	1 (3.2 ; 0.07) ; 1 (0.07)	0 ; 0	0 ; 0	0 ; 0	1 (1.0 ; 0.01) ; 1 (0.01)	2 (2.0 ; 0.02) ; 3 (0.03)	3 (1.8 ; 0.02) ; 4 (0.02)
Irritability	0 ; 0	1 (3.2 ; 0.07) ; 1 (0.07)	0 ; 0	3 (10.7 ; 0.25) ; 3 (0.23)	3 (5.2 ; 0.12) ; 3 (0.11)	0 ; 0	7 (7.1 ; 0.08) ; 7 (0.07)	7 (4.3 ; 0.04) ; 7 (0.04)
Renal and urinary disorders	0 ; 0	0 ; 0	1 (3.3 ; 0.07) ; 1 (0.07)	1 (3.6 ; 0.08) ; 1 (0.08)	2 (3.4 ; 0.08) ; 2 (0.08)	2 (2.1 ; 0.03) ; 2 (0.03)	2 (2.0 ; 0.02) ; 2 (0.02)	4 (2.5 ; 0.02) ; 4 (0.02)
Chromaturia	0 ; 0	0 ; 0	1 (3.3 ; 0.07) ; 1 (0.07)	1 (3.6 ; 0.08) ; 1 (0.08)	2 (3.4 ; 0.08) ; 2 (0.08)	2 (2.1 ; 0.03) ; 2 (0.03)	2 (2.0 ; 0.02) ; 2 (0.02)	4 (2.5 ; 0.02) ; 4 (0.02)
Respiratory, thoracic and mediastinal disorders	2 (6.9 ; 0.16) ; 3 (0.23)	3 (9.7 ; 0.23) ; 5 (0.36)	3 (10.0 ; 0.24) ; 6 (0.45)	3 (10.7 ; 0.25) ; 3 (0.23)	6 (10.3 ; 0.24) ; 9 (0.34)	16 (16.5 ; 0.26) ; 23 (0.32)	25 (25.3 ; 0.32) ; 38 (0.40)	39 (23.9 ; 0.29) ; 61 (0.36)

	Pool 1					Pool 3		
System Organ Class Preferred Term	**Placebo (N = 29) n (% ; EAIR) ; f (Rate)**	**Prednisone 0.75 mg/kg (N = 31) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 mg/kg (N = 30) n (% ; EAIR) ; f (Rate)**	**Vamorolone 6 mg/kg (N = 28) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 – 6 mg/kg (N = 58) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 mg/kg (N = 97) n (% ; EAIR) ; f (Rate)**	**Vamorolone 6 mg/kg (N = 99) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 – 6 mg/kg (N = 163) n (% ; EAIR) ; f (Rate)**
Cough	1 (3.4 ; 0.08) ; 1 (0.08)	3 (9.7 ; 0.23) ; 3 (0.21)	3 (10.0 ; 0.24) ; 6 (0.45)	2 (7.1 ; 0.16) ; 2 (0.16)	5 (8.6 ; 0.20) ; 8 (0.30)	13 (13.4 ; 0.21) ; 19 (0.26)	17 (17.2 ; 0.21) ; 24 (0.25)	30 (18.4 ; 0.22) ; 43 (0.25)
Nasal congestion	0 ; 0	2 (6.5 ; 0.15) ; 2 (0.14)	0 ; 0	1 (3.6 ; 0.08) ; 1 (0.08)	1 (1.7 ; 0.04) ; 1 (0.04)	0 ; 0	7 (7.1 ; 0.08) ; 8 (0.08)	7 (4.3 ; 0.04) ; 8 (0.05)
Oropharyngeal pain	1 (3.4 ; 0.08) ; 2 (0.15)	0 ; 0	0 ; 0	0 ; 0	0 ; 0	4 (4.1 ; 0.06) ; 4 (0.06)	4 (4.0 ; 0.04) ; 6 (0.06)	7 (4.3 ; 0.04) ; 10 (0.06)
Skin and subcutaneous tissue disorders	1 (3.4 ; 0.08) ; 1 (0.08)	1 (3.2 ; 0.07) ; 1 (0.07)	1 (3.3 ; 0.07) ; 1 (0.07)	1 (3.6 ; 0.08) ; 1 (0.08)	2 (3.4 ; 0.08) ; 2 (0.08)	1 (1.0 ; 0.01) ; 1 (0.01)	5 (5.1 ; 0.05) ; 5 (0.05)	6 (3.7 ; 0.04) ; 6 (0.04)
Hypertrichosis	1 (3.4 ; 0.08) ; 1 (0.08)	1 (3.2 ; 0.07) ; 1 (0.07)	1 (3.3 ; 0.07) ; 1 (0.07)	1 (3.6 ; 0.08) ; 1 (0.08)	2 (3.4 ; 0.08) ; 2 (0.08)	1 (1.0 ; 0.01) ; 1 (0.01)	5 (5.1 ; 0.05) ; 5 (0.05)	6 (3.7 ; 0.04) ; 6 (0.04)

Rate is calculated as Events per patient per year of exposure. EAIR is calculated as number of patients reporting the event at least once divided by total time spent at risk for the event to occur. The total time spent at risk is calculated as time to first occurrence of event or total treatment time for patients not experiencing the event in question. EAIR is annualised. Preferred Term is kept only if it is more common in Vamorolone than in Placebo group. EAIR = exposure adjusted incidence rate; f = event count; n = patient count; TEAE = Treatment-emergent adverse event. Source: EU Outputs

Severity of events: the vast majority of TEAEs was mild in severity. There was a higher frequency of moderate TEAEs in the prednisone group compared with the other treatment groups (1.29, 0.69, 0.82, 0.47 moderate events per subject-year in the prednisone, placebo, vamorolone 2 and 6 mg/kg group, respectively). One subject in the prednisone group had a severe TEAE (aggression).

Drug-related TEAEs (possibly, probably, or definitely related) were reported for a higher number of subjects in the vamorolone 6 mg/kg and prednisone group (67.9% and 45.2%) and a lower and similar number of subjects on placebo and vamorolone 2 mg/kg (27.6% and 33.3%). The event rate for drug related TEAEs was, however, higher for prednisone compared with the other treatment groups. The most frequently reported drug-related preferred term (PT) that was also highest for patients treated with vamorolone was Cushingoid.

Justification of ADRs to be included in section 4.8 of the SmPC was provided by the applicant and comprised TEAEs by PT reported by more than 2 subjects in either vamorolone dose group and reported by at least 1 more subject in either of the vamorolone groups compared to placebo from the randomised Period 1 of Study VBP15-004. Causality assessment was based on a dose-response, the extent to which the AE was consistent with the pharmacology of drug, and whether the AE is known to be caused by related drugs.

For *gastroenteritis, viral and upper respiratory infection*, *fall, contusion*, *cough, constipation, rhinitis, arthropod bite, and Vitamin D deficiency,* a causal relationship with vamorolone could not be identified based on the criteria mentioned above. Vitamin D deficiency has been reviewed by the applicant as potential adverse drug reaction (ADR) to be included upon request of CHMP; however, there seems to be no direct correlation between glucocorticoid dose and vitamin D concentrations in DMD patients, while DMD itself is strongly associated with high rates of vitamin D deficiency despite supplementation.

The following TEAEs were identified as potential ADRs: *cushingoid (*dose-response, pharmacology, known effect for GCs*), abdominal pain/abdominal pain upper (*higher incidence vs. placebo; known effect for GCs*), diarrhoea (*dose-response, known effect of GCs*), vomiting (*dose-response in Pool 3; known effect for GCs*), weight increased (*dose-response, supported by measures of weight and BMI; known effect of GCs*), headache, and irritability (*dose-response, known effect of GCs*).* The inclusion of these TEAEs as ADRs is supported by review of adverse events of special interest (AESIs) (i.e., grouping events based on the known effects of GCs), which confirmed a causal relationship. The review of laboratory and other safety parameters revealed additional ADRs, i.e. *blood triglycerides increased* (dose-dependent increase in the vamorolone groups early after treatment initiation with mean increase from baseline of 20% and 25% in the vamorolone 2 and 6 mg/kg groups and no change in the placebo group), and *cortisol decreased* (dose-dependent mean and median decrease from baseline in morning cortisol at Week 12 and Week 24 in the vamorolone and prednisone groups). The frequency categories of ADRs are in line with reported frequencies in Pool 1 for the 6 mg/kg dose that serves as the basis for inclusion and frequency categorisation.

Long-term adverse effects of vamorolone can be retrieved from Pool 3 safety data. The incidences were higher in Pool 3 than in Pool 1 for severe TEAEs, non-mild TEAEs, clinically relevant TEAEs, TEAEs of special interest and serious TEAEs. TEAEs leading to dose reduction were only described for Pool 3 since dose reduction was not allowed during the controlled period of study VBP15-004.

Severity of TEAEs in Pool 3: Two severe TEAEs were recorded in the 2 mg/kg group (i.e., seizure and behaviour disorder), and 8 severe events occurred in the 6 mg/kg group (influenza-like illness, appendicitis perforated, dehydration, agitation, myoglobinuria [2 events], testicular torsion, asthma, and hypoxia).

TEAEs considered related to study drug by the investigator with ≥ 5 events (PTs) in the vamorolone 2-6 mg/kg group were cushingoid (19 events), weight increased (19 events), abdominal pain (8 events),

and abdominal pain upper (8 events), irritability (7 events), hypertrichosis (6 events), and increased appetite (5 events). Apart from Abdominal pain, the rates of these events were generally higher in the vamorolone 6 mg/kg group compared with the 2 mg/kg group.

For some systemic organ class (SOCs) and respective PTs, the incidences slightly increased during longer treatment duration, e.g. for gastrointestinal (GI) disorders, general disorders and administration site conditions, infections and infestations, investigations, musculoskeletal and connective tissue disorders, and respiratory, thoracic and mediastinal disorders, which can at least in parts be explained by the underlying disease (see Table 16 for TEAEs in Pool 1 that were also reported in Pool 3). With the limited data available for longer (uncontrolled) treatment duration in Pool 3, no additional safety concerns arise at present up to 30 months of exposure to vamorolone.

Moreover, the incidences of TEAEs after switching from prednisone or placebo to vamorolone 2 mg/kg and 6 mg/kg have been evaluated. Vitamin D deficiency increased after switch from prednisone to vamorolone 6 mg/kg (0% and 13.3%), which supports inclusion as an ADR in section 4.8 of the SmPC. Fatigue had a higher incidence after switch from prednisone (0%) to vamorolone 2 mg/kg and 6 mg/kg (13.3% each).

Clinically relevant TEAEs

Clinically relevant TEAEs (defined as either at least moderate in severity or leading to withdrawal from study or being a serious event) were reported most frequently in the prednisone group (42%), followed by placebo (31%), vamorolone 2 mg/kg (26.7%), and vamorolone 6 mg/kg (14.3%). The only clinically relevant TEAEs reported by > 1 subject were Vitamin D deficiency in the vamorolone 2-6 mg/kg group (1 subject each at 2 and 6 mg/kg) and aggression (2 subjects, 1 of which was severe) in the prednisone group. In Pool 3, clinically relevant TEAEs were reported in 34% and 40.4% of subjects in the vamorolone 2 mg/kg and 6 mg/kg group, respectively. Apart from weight increased, which was reported for 3.1% of subjects in the vamorolone 2 mg/kg group (Exposure adjusted incidence rate (EAIR) 0.04, rate 0.04) and 8.1% in the vamorolone 6 mg/kg group (EAIR 0.09, rate 0.08), no other clinically relevant TEAEs appeared to occur at a notably higher frequency in the 6 mg/kg compared with the 2 mg/kg group.

Summary of TEAEs in study VBP15-006 in children 2 to <4 years of age (DCO 21 July 2023) as compared to patients 4 to <7 years of age in study VBP15-004 (in the first 12 weeks of treatment):

- There was no serious AE, TEAE leading to permanent discontinuation, or TEAE leading to dose interruption in children 2 to <4 years of age for 2 and 6 mg/kg.
- At the 2 mg/kg dose level, TEAEs were generally similar for the subjects 2 to <4 years and the 4 to <7 year (reference) group from study VBP15-004, although there was a higher frequency of infections in the younger children.
- A higher frequency of TEAEs with the 6 mg/kg dose was observed in the 2 to <4 years children in study VBP15-006 as compared to 4 to <7 years-old (100% vs. 71.4%). The rate of events per year was more than double as high in the youngest age group treated with 6 mg/kg as compared to 4 to <7 years – old (16.44 vs. 8.231).
- In the 6 mg/kg dose group, paediatric patients 2 to <4 years differed from those 4 to <7 years in GI disorders TEAEs (100% vs. 21.4%), adrenal suppression (50% vs. 0%), and psychiatric disorders (33.3% vs. 10.7%; event rate 2.86 vs. 0.621).

Adverse events of special interest

AESI were defined by known side effects of glucocorticoids using a broad search strategy of Medical Dictionary for Regulatory Activities (MedDRA) customised medical queries (CMQ). AESI and their respective frequencies in Pool 1 and Pool 3 are depicted in Table 17. Overall incidence of AESI was higher during the first 90 days of treatment in either group in Pool 1 of study VBP15-004 as compared

to AESI occurring after 90 days (and up to 6 months). Based on Pool 3 data, a majority of AESI had an onset in the first 6 months of treatment.

Table 17: AESI: side effects of glucocorticoid drugs –safety population pool 1 and pool 3 (summarised by the Assessor)

	Pool 1					Pool 3		
AESI	**Placebo (N = 29) n (% ; EAIR) ; f (Rate)**	**Prednisone 0.75 mg/kg (N = 31) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 mg/kg (N = 30) n (% ; EAIR) ; f (Rate)**	**Vamorolone 6 mg/kg (N = 28) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 – 6 mg/kg (N = 58) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 mg/kg (N = 97) n (% ; EAIR) ; f (Rate)**	**Vamorolone 6 mg/kg (N = 99) n (% ; EAIR) ; f (Rate)**	**Vamorolone 2 – 6 mg/kg (N = 163) n (% ; EAIR) ; f (Rate)**
Total number of AESI TEAEs	20 (69.0 ; 2.87) ; 45 (3.43)	24 (77.4 ; 3.93) ; 69 (4.93)	20 (66.7 ; 2.70) ; 49 (3.64)	22 (78.6 ; 3.41) ; 52 (4.07)	42 (72.4 ; 3.03) ; 101 (3.85)	69 (71.1 ; 2.48) ; 254 (3.51)	80 (80.8 ; 2.66) ; 335 (3.48)	126 (77.3 ; 2.67) ; 592 (3.49)
Behavior problems	4 (13.8 ; 0.34) ; 5 (0.38	10 (32.3 ; 0.99) ; 16 (1.14)	5 (16.7 ; 0.43) ; 6 (0.45)	6 (21.4 ; 0.53) ; 9 (0.70)	11 (19.0 ; 0.48) ; 15 (0.57)	20 (20.6 ; 0.34) ; 21 (0.29)	24 (24.2 ; 0.31) ; 32 (0.33)	42 (25.8 ; 0.33) ; 53 (0.31)
Bone fractures						2 (2.1 ; 0.03) ; 2 (0.03)	7 (7.1 ; 0.08) ; 8 (0.08)	8 (4.9 ; 0.05) ; 10 (0.06)
Cushingoid features	0 ; 0	7 (22.6 ; 0.53) ; 7 (0.50)	2 (6.7 ; 0.15) ; 2 (0.15)	8 (28.6 ; 0.70) ; 8 (0.63)	10 (17.2 ; 0.40) ; 10 (0.38)	5 (5.2 ; 0.07) ; 5 (0.07)	14 (14.1 ; 0.16) ; 14 (0.15)	19 (11.7 ; 0.12) ; 19 (0.11)
Diabetic conditions	1 (3.4 ; 0.08) ; 1 (0.08))	3 (9.7 ; 0.22) ; 3 (0.21)	0 ; 0	1 (3.6 ; 0.08) ; 1 (0.08)	1 (1.7 ; 0.04) ; 1 (0.04)	1 (1.0 ; 0.01) ; 1 (0.01)	10 (10.1 ; 0.12) ; 11 (0.11)	11 (6.7 ; 0.07) ; 12 (0.07)
Gastrointestinal symptoms	8 (27.6 ; 0.75) ; 10 (0.76)	8 (25.8 ; 0.69) ; 13 (0.93)	9 (30.0 ; 0.82) ; 16 (1.19)	8 (28.6 ; 0.74) ; 12 (0.94)	17 (29.3 ; 0.78) ; 28 (1.07)	29 (29.9 ; 0.57) ; 70 (0.97)	40 (40.4 ; 0.66) ; 103 (1.07)	61 (37.4 ; 0.58) ; 175 (1.03)
Hypertension	0; 0	1 (3.2 ; 0.07) ; 1 (0.07)	1 (3.3 ; 0.07) ; 1 (0.07)	0; 0	1 (1.7 ; 0.04) ; 1 (0.04)	2 (2.1 ; 0.03) ; 2 (0.03)	1 (1.0 ; 0.01) ; 1 (0.01)	3 (1.8 ; 0.02) ; 3 (0.02)
Immune suppression	13 (44.8 ; 1.38) ; 25 (1.90)	12 (38.7 ; 1.14) ; 22 (1.57)	13 (43.3 ; 1.30) ; 20 (1.49)	9 (32.1 ; 0.90) ; 16 (1.25)	22 (37.9 ; 1.10) ; 36 (1.37)	55 (56.7 ; 1.48) ; 142 (1.96)	52 (52.5 ; 0.94) ; 137 (1.42)	90 (55.2 ; 1.15) ; 280 (1.65)
Other adrenal disorders						1 (1.0 ; 0.01) ; 1 (0.01)	3 (3.0 ; 0.03) ; 3 (0.03)	4 (2.5 ; 0.02) ; 4 (0.02)
Skin/ hair changes	2 (6.9 ; 0.16) ; 2 (0.15)	4 (12.9 ; 0.30) ; 4 (0.29)	3 (10.0 ; 0.24) ; 3 (0.22)	1 (3.6 ; 0.08) ; 1 (0.08)	4 (6.9 ; 0.16) ; 4 (0.15)	5 (5.2 ; 0.07) ; 5 (0.07)	6 (6.1 ; 0.07) ; 6 (0.06)	11 (6.7 ; 0.07) ; 11 (0.06)
Weight gain	2 (6.9 ; 0.16) ; 2 (0.15)	3 (9.7 ; 0.23) ; 3 (0.21)	1 (3.3 ; 0.08) ; 1 (0.07)	5 (17.9 ; 0.42) ; 5 (0.39)	6 (10.3 ; 0.24) ; 6 (0.23)	5 (5.2 ; 0.07) ; 5 (0.07)	18 (18.2 ; 0.21) ; 20 (0.21)	23 (14.1 ; 0.16) ; 25 (0.15)

Source: EU Outputs Table 14.2.3.15a.1 and Table 14.2.3.15c.1

Adrenal suppression

In Pool 1, vamorolone and prednisone showed a greater and dose-dependent decrease in morning cortisol compared with placebo. Mean (SD) baseline morning cortisol [µg/dL] was 7.21 (2.228), 7.69 .383), 8.63 (2.999), and 8.52 (2.412) for placebo, prednisone, vamorolone 2 mg/kg, and vamorolone 6 mg/kg. The mean change from baseline to Month 6 in the respective treatment groups was: 0.69 (2.769), -5.17 (2.89), -3.58 (3.044), and -7.06 (3.028). In Pool 3, a similar dose-dependent suppression of morning cortisol was seen after 6 and 12 months of exposure.
The proportion of subjects who presented with a low morning cortisol value (<100 nmol/L) suggestive of adrenal suppression at Week 24 (Pool 1) was higher for vamorolone 6 mg/kg (92.6%) than prednisone (74.1%) followed by 26.1% for vamorolone 2 mg/kg and 4% on placebo.

During study VBP15-006, the same trend was observed for patients 2 to <4 years of age; however, within 12 weeks of treatment, half of the children treated with the 2 mg/kg dose and all of those treated with the 6 mg/kg dose had a morning cortisol value <100 nmol/L.

ACTH stimulation testing simulating stress situations was conducted in study VBP15-004. As a result, cortisol decreased in the order: vamorolone 6 mg/kg> prednisone> vamorolone 2 mg/kg> placebo. The vast majority of subjects on vamorolone (6 mg/day group> 2 mg/kg group) had a peak cortisol level below the response threshold level (i.e., <18 µg/dL [<500 nmol/L] after 30 min and 60 min, respectively) following ACTH stimulation, which suggests adrenal suppression.

ACTH concentrations (time of collection not controlled) showed a dose-dependent reduction from VBP15-002 baseline values by approximately 30% at VBP15-LTE Month 18 and 24 (months 24 and 30, respectively, of the total 30-month treatment period) in the 2.0 mg/kg dominant dose group and by approximately 60% in the 6.0 mg/kg dominant dose group.

Data on vamorolone *withdrawal and dose tapering* have not been systematically collected in the DMD programme. Adrenal suppression was found to be reversible 2 weeks after a 2-week daily exposure in study VBP15-002. In the 2 weeks after treatment, no AEs were reported indicative of adrenal insufficiency. The effects on long-term treatment cannot be deduced from the available clinical study data. Based on the level of adrenal suppression with vamorolone, there is no need for dose tapering when switching from recommended doses of daily glucocorticoids in DMD; it is recommended to commence vamorolone at 6 mg/kg daily to minimise the adrenal insufficiency risk while switching treatments.

Cushingoid features with vamorolone in Pool 1 were generally mild in severity, were more frequently reported in the 6 mg/kg group than with prednisone (28.6% and 22.6%) and were more frequently reported after 90 days of treatment in Pool 1. The incidence for vamorolone 2 mg/kg was lower (6.7%). Only one TEAE in the vamorolone 6 mg/kg group was moderate in severity. No subject interrupted or discontinued vamorolone at either dose due to cushingoid features. One subject reported Cushingoid features after switching from prednisone to vamorolone 6 mg/kg. No subject reported Cushingoid features in the 002/003/LTE study where this TEAE was not elicited at each visit. Reporting of cushingoid features did not increase with longer treatment duration in Pool 3.

Only a single TEAE (serious) of adrenal insufficiency has been reported so far in a patient in the EAP. Adrenal insufficiency is a consequence of long—term glucocorticoid treatment and it can lead to a potentially life-threatening adrenal crisis in times of stress. To avoid adrenal crisis, hydrocortisone (or prednisone) stress dosing was permitted during an illness, injury, or surgical procedure in clinical studies. No data are available on an adequate vamorolone stress dose on top of the regular treatment dosage.

Weight gain

The AESI weight gain (including PTs increased appetite and weight increased) was found dose-related with vamorolone and higher in the 6 mg/kg group as compared to prednisone in Pool 1. The incidences for placebo, prednisone, vamorolone 2 mg/kg and 6 mg/kg were 6.9%, 9.7%, 3.3%, and 17.9%, respectively. Moreover, weight gain was more frequently reported after 90 days of treatment with the 6 mg/kg dose in Pool 1.

In Pool 3, weight gain was reported for 5.2% and 18.2% of subjects on vamorolone 2 mg/kg and 6 mg/kg, respectively. For 6.7% of subjects in the total vamorolone 2-6 mg/kg group, weight gain was clinically relevant and led to down-titration from 6 mg/kg to lower doses. AESI of weight gain following switch from prednisone or placebo to vamorolone in study VBP15-004 were not found increased suggesting that most of the weight gain occurred in Period 1.

Weight increased has not been reported as TEAE in children 2 to <4 years in the ongoing study VBP15-006.

Weight and Body-Mass Index – Pool 1

At Pool 1 baseline, median weight, weight percentiles and z-scores were lower in the vamorolone groups than in the placebo and prednisone group. Median change in weight at Month 6 was 0.70 kg, 2.1 kg, 1.4 kg, and 2.3 kg, for subjects in the placebo, prednisone, vamorolone 2 mg/kg, and vamorolone 6 mg/kg group, respectively. Median change in weight percentile (z-score) was -1.52 (-0.13 SD) for placebo, 5.50 (0.32 SD) for prednisone, and 4.30 (0.22 SD) and 10.73 (0.43 SD) for vamorolone 2 and 6 mg/kg, respectively. Clinically relevant increases in weight z-score (i.e. ≥1.0 SD) at Month 6 were more frequently seen in vamorolone 6 mg/kg (25.9%) than on prednisone (3.3%) while none was seen in vamorolone 2 mg/kg or placebo.

Comparison of changes in *BMI* between active groups are more appropriate since it accounts for prednisone's height stunting effect since weight changes are corrected for height changes. At baseline, median BMI was similar across groups (16.09 to 16.80 kg/m^2), while baseline median BMI percentiles and z-scores were higher in the prednisone group compared with the other groups (range 68.16 to 81.43 and 0.47 to 0.89 SD, respectively). Median BMI change at Month 6 was -0.24 kg/m^2 for placebo, 1.13 kg/m^2 for prednisone, and 0.60 and 0.56 kg/m^2 for vamorolone 2 and 6 mg/kg, respectively. Consistently, median changes for BMI percentiles and z-scores did not show a pattern of larger changes with vamorolone 6 mg/kg compared to prednisone. However, when mean instead of median changes are compared, these were higher for vamorolone 6 mg/kg than for prednisone.

A clinically relevant change in BMI z-score defined as a change of ≥1.0 SD was observed in 1 subject on prednisone and 3 subjects in each of the vamorolone groups, all of them completing the study. The 3 cases in vamorolone 6 mg/kg led to overweight (defined as >1.0 SD) or obesity (defined as >2.0 SD). All reported at least one TEAE of either cushingoid features or weight gain or increased appetite reflecting the clinical relevance of the changes. According to the applicant, these cases might be confounded by COVID restrictions with remote visits in early 2020.

Weight and Body-Mass Index – Pool 3

Change in median body weight, percentiles and z-scores increased from baseline to Month 6 and up to Month 30 in the order vamorolone 2 mg/kg< vamorolone 6 mg/kg< vamorolone 6 mg/kg down-titrated. Median changes in BMI, percentiles, and z-scores from baseline at Month 6 for the 2 mg/kg dominant dose group were smaller than for the 6 mg/kg group and the 6 mg/kg down-titrated group. At Month 30, median changes BMI, percentiles and z-scores were 1.10 kg/m^2, 2.28 and -0.08 SD, respectively for the 2 mg/kg group; 1.30 kg/m^2, 2.02, and 0.09 SD, respectively, for the 6 mg/kg group; and 7.70 kg/m^2, 9.60 and 1.00 SD, respectively, for the 6 mg/kg down-titrated group.

At Month 30, clinically relevant BMI z-score changes (≥1.0 SD) were reported in 28.6% and 16% of patients in the vamorolone 2 mg/kg and 6 mg/kg group, respectively.

Switching from prednisone/ placebo to vamorolone 2 mg/kg and 6 mg/kg in VBP15-004 resulted in increase in weight z-score in the 6 mg/kg group after the switch but not for BMI z-score.

Weight changes in the EAP

Based on the provided weight percentiles and z-score results from baseline to last follow-up measurement prior to DCO in the EAP for all doses combined, weight percentiles clearly increased from median 65.4 to 88.0 (with a substantial median increase in z-score from 0.4 to 1.2).

An exploratory analysis has been conducted in patients with sufficient information on weight before and after down-titration. In patients with down-titration from vamorolone 6 mg/kg to 4 mg/kg, with weight gain being the most frequently reported reason, the annual rate of change in weight percentiles (and 95% CI) decreased from 19.0 (7.5, 30.5) with vamorolone 6 mg/kg to 4.6 (-0.8, 9.9) after down-titration to 4 mg/kg. A similar annual rate of change in weight percentiles has been observed before and after patients up-titrated from vamorolone 2 mg/kg to 4 mg/kg, i.e. 12.35 (95% CI 0.42, 24.29) to 10.60 (95% CI 3.81, 17.38).

Assessment of body composition by Dual-energy X-ray absorptiometry (DXA) measurements in Period 1 in study VBP15-004 was subject to robustness issues as indicated by the applicant. However, at Week 24, increases (measured as %-change from baseline) in *total body fat mass* were similar in the placebo and vamorolone 2 mg/kg groups (10.9% and 11.5%, respectively), and higher in the prednisone and vamorolone 6 mg/kg groups (17.6% and 27.6%, respectively). The mean percentage change in *lean body mass* at Week 24 was +6.0% in the placebo group, +10.5% and +12.7% in the vamorolone 2 and 6 mg/kg groups, respectively, and +13.5% in the prednisone group. During Period 2 of study VBP15-004 (up to Week 48), further dose-related increases in mean total body fat mass and lean body mass were noted.

Behaviour problems

In Pool 1, behaviour problems were reported for 13.8%, 32.3%, 16.7%, and 21.4% of subjects in the placebo, prednisone, and in the vamorolone 2 and 6 mg/kg groups. The most relevant finding for vamorolone 6 mg/kg was irritability as TEAE (10.7%) that did not occur with vamorolone 2 mg/kg and placebo and for 3.2% of subjects on prednisone. Clinically relevant behaviour problems were highest for prednisone (22.6%), similar for placebo and vamorolone 2 mg/kg (3.4% and 3.3%), and not reported for vamorolone 6 mg/kg. The majority of behaviour problem TEAEs were reported in the first 6 months of treatment, with only few events reported beyond 6 months. Findings on clinically relevant worsening in psychosocial adjustment based on the PARS-III (Personal Adjustment and Role Skills) scores in the controlled period of Study VBP15-004 support the findings of a reduction in the incidence and severity of behaviour problems with vamorolone 6 mg/kg compared to prednisone. The incidence of clinically relevant worsening in any subscale with vamorolone 2 mg/kg was similar to placebo.

In Pool 3, behaviour problems were reported for 25.8% of subjects in the vamorolone 2-6 mg/kg group, similarly distributed across the treatment groups. Irritability was the TEAE with the largest difference between vamorolone 6 mg/kg and 2 mg/kg (7.1% vs. 0%).

Switching from prednisone to vamorolone in VBP015-004 was not related to an increase in behavioural problems; however, as expected, an increased incidence was noted after the switch from placebo to vamorolone 6 mg/kg.

In the 2 to <4 years cohort in the ongoing study VBP15-006, the 6 mg/kg dose led to behavioural problems in 2 of 6 treated patients (33.3%).

Gastrointestinal problems

Gastrointestinal symptoms have been reported in Pool 1 with similar incidence across groups (25.8% - 30%). Nevertheless, 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%). Slightly increased incidences were reported with longer treatment duration with vamorolone 6 mg/kg but not 2 mg/kg based on Pool 3 data. No altered GI tolerability was noted after switching from placebo/ prednisone to vamorolone in study VBP15-004 after 6 months. In children 2 to <4 years in the ongoing study VBP15-006, the 6 mg/kg dose led to GI disorders in all of the patients treated with this dose (and in only 1 patient on the 2 mg/kg dose).

GI disorder TEAEs, i.e. abdominal pain upper, vomiting, and diarrhoea have been included in the ADR table in section 4.8 of the SmPC.

Bone fractures / bone health

No AESI of bone fractures were reported for vamorolone in Pool 1.

Across all DMD studies (Pool 3), 10 fractures were reported in 8 subjects (4.9%); the frequency of these events was lower with vamorolone 2 mg/kg (2.1%) than with 6 mg/kg (7.1%). Upper limb fracture and spinal compression fracture were reported for three and two subjects on vamorolone 6 mg/kg, all of them being clinically relevant. No such events were reported for vamorolone 2 mg/kg. Other fractures reported were foot fracture (2 patients), humerus fracture, spinal fracture, and thoracic vertebral fracture (one patient each). No bone fracture AESI were reported after switching from either prednisone or placebo to vamorolone in VBP15-004.

Vertebral Fractures by Spine X-ray Surveys and Centralised Reading

Vertebral fractures by systematic lateral spine X-ray survey have been evaluated at baseline and at 24 weeks (but not at Week 48) in 117 patients in VBP15-004 and in 39 subjects at 30 months in VBP15-LTE, respectively. Baseline vertebral fractures were present for one patient each in the vamorolone 2 mg/kg and 6 mg/kg group. Two subjects (1.7%) had a total of five vertebral fractures identified by the Genant semi-quantitative method: 1/29 (3.4%) in the placebo group and 1/31 (3.2%) in the prednisone group. All fractures were grade 1 (mild) and occurred in the upper- and mid-thoracic regions. No treatment-emergent fractures have been noted at Week 24 in VBP15-004 in the vamorolone groups. Four (10.3%) patients had a total of seven vertebral fractures after 30 months of treatment in the VBP15-LTE study (fractures were grade 1 (mild) and occurred in the mid-thoracic region and thoracolumbar junction) while no baseline readings were available, which hampers interpretability of the results. Comparison of matched patient data (for 36 months of treatment) from the VBP15-LTE (i.e. 12.8% after adjustment for duration of treatment) and the FOR-DMD study data revealed significantly higher rates of vertebral fractures in the external comparison for daily deflazacort (30.4%) and prednisone (26.9%), while intermittent prednisone in FOR-DMD was the most benign regimen with regard to vertebral fracture prevalence (0%). Of note intermittent prednisone had a lower effect on muscle strength compared to daily deflazacort and prednisone. Again, the lack of baseline lateral spine X-rays for either study, i.e. VBP15-LTE and FOR-DMD, limits interpretation of the comparison since it remains unknown whether vertebral fractures were already present at baseline.

Bone Age Results from Hand-Wrist X-rays of the phalanges (VBP15-LTE Fracture and Bone Age Report at 30 months)

In clinical practice, bone age is considered to be delayed when it is delayed more than a year relative to chronological age. Bone age has been determined in study VBP15-LTE after 30 months of vamorolone exposure in 39 patients and it was found to be delayed in these patients (mean difference between bone

age and chronological age was -1.1 ± 1. 2 years; mean CI -1.5 to -0.7). In the absence of bone age determinations at baseline, these data are difficult to interpret.

The proportion of patients who had bone ages that were more than 2 SD above or below the mean were also calculated. More than 2 SD below the mean was reported in 19/39 boys (48.7%) consistent with maturational delay outside of the normal range. 25/39 boys (64%) in VBP15-LTE had a bone age that was more than a year delayed relative to chronological age.

*Bone biomarker*s

Conventional GCs rapidly induce a decrease in bone formation (decrease in osteocalcin and P1NP blood concentration) and provoke an increase in bone resorption (elevation in serum CTX concentration). In Pool 1, mean values for osteocalcin, s-CTX1, and P1NP were similar across treatment groups at baseline. At Week 24, osteocalcin and P1PN decreased from baseline in a similar magnitude in the placebo and vamorolone 6 mg/kg group and more pronounced in the prednisone group and slightly increased from baseline to Week 24 in the vamorolone 2 mg/kg group. CTX was found increased from baseline in patients on vamorolone 2 mg/kg and 6 mg/kg versus placebo, while it was decreased in patients on prednisone, which is not in line with data on prednisone in healthy adults (Kauh et al., 2012). Similar results were also found in shift analysis with more subjects in the prednisone group having shifts from normal to low in CTX as compared to the other treatment groups. The applicant explained that the increase in CTX levels with vamorolone treatment compared with prednisone does not indicate bone loss per se, but rather a higher bone turnover resulting from improved linear growth, which is supported by literature data in healthy children (Rauchenzauner et al., 2007). This is different to the interpretation in adults for whom an increase in CTX reflects resorption of bone. After the switch from prednisone to vamorolone, osteocalcin and P1PN increased and remained stable, while CTX also increased after switching to vamorolone.

In Pool 3, biomarkers are more difficult to interpret but appear to change dose-dependently. Osteoblast activity tends to be higher with vamorolone 2 mg/kg as compared to vamorolone 6 mg/kg, while osteoclast activity is affected vice versa. The interpretation is hampered by the lack of a comparator and the low number of patients with evaluable data at later timepoints.

Following the switch from prednisone to vamorolone, all bone biomarkers recovered to baseline values. Bone biomarkers did not decrease in subjects with continuous vamorolone treatment.

Bone Mineral Content (BMC) and Bone Mineral Density (BMD)

Available data for %-change in BMD and BMC during Period 1 in study VBP15-004 do not indicate significant differences across treatment groups. The median percent change from baseline to Week 24 for lumbar spine BMC was similar in the vamorolone 2 and 6 mg/kg and placebo group (5.9%, 6.0% and 6.5%, respectively), and lower in the prednisone group (2.7%). When normalised for lumbar vertebrae area, median percent change at Week 24 in lumbar spine BMD was slightly decreased in the prednisone group (-0.32%), mildly increased in the vamorolone groups (+0.68% and +0.83% for the vamorolone 2 and 6 mg/kg groups, respectively), and highest in the placebo group (+3.6%).

At least half of the patients in each treatment group in study VBP15-004 had serial measures of BMC and BMD for either two or three time points over 48 weeks. These data support that vamorolone did not worsen Lumbar spine bone mineral content (LS-BMC) and Lumbar spine bone mineral density (LS-BMD) in the vamorolone treated patients contrasting the negative effect elicited by prednisone. The clinical relevance of the differences seen between vamorolone and placebo in both LS-BMC and LS-BMC is not clear, but the median percent change (increase) appeared lower with vamorolone as compared to placebo.

Based on *post hoc* analysis of LS-BMD z-scores in study VBP15-004, lumbar spinal BMD z-score adjusted for height was negative at baseline and remained stable in all treatment groups over 48 weeks.

Growth

In general, study patients in the vamorolone programme were shorter than the reference population as shown by the negative height z-score at baseline. In Study VBP15-004, there was a baseline imbalance in median height z-scores with lower values in the vamorolone 6 mg/kg group compared with the other treatment groups (-0.54 SD for placebo, -0.56 SD for prednisone, and -0.74 and -1.04 SD for vamorolone 2 and 6 mg/kg, respectively). Median height percentiles for these groups were 29.42, 28.85, 22.99, and 14.85 for placebo, prednisone, vamorolone 2 and 6 mg/kg, respectively.

After 24 weeks of treatment, median height percentile and z-scores decreased in the prednisone group, whereas the other treatment groups showed a median increase. Median change in height percentile (z-scores) in the placebo, prednisone, and vamorolone 2 mg/kg and 6 mg/kg group was 0.49, -1.79, 1.73, and 1.64 (0.13 SD, -0.10 SD, 0.07 SD, and 0.11 SD).

Change from baseline in median height z-score increased from -0.03 SD to +0.11 SD in patients, who switched from prednisone to vamorolone 2 mg/kg and from -0.13 SD to +0.05 SD in patients, who switched from prednisone to vamorolone 6 mg/kg in Period 2.

A *post hoc analysis* was conducted using cut offs of +/- 0.2 SD to evaluate changes exceeding random annual changes observed in ambulant glucocorticoid-naïve children with DMD (0.03 SD) and in line with annual changes observed in ambulant glucocorticoid-treated children (-0.25 SD with daily deflazacort and -0.16 SD for daily prednisolone) (Stimpson et al., 2022). In Pool 1, height z-score data reveal a majority of patients in the prednisone group with decreases (<0.2 SD or -0.2 -<0 SD) at Month 6 and a majority of patients in both vamorolone groups with increases (0.0 - <0.2 SD and ≥0.2 SD) in height z-scores. Similar proportions of subjects in the placebo and vamorolone 6 mg/kg group had increases of ≥0.2 SD in height z-score (32.1% and 34.6%) compared with 16.7% and 18.5% in the prednisone and vamorolone 2 mg/kg groups, respectively.

Across all studies in DMD (Pool 3), the change of median height z-score after 3, 6, 12, and 30 months of treatment positively increased for both vamorolone groups but remained lower in the 6 mg/kg group. *Post hoc* categorical analysis of Pool 3 height z-score data reveals a stable percentage of patients with ≥0.2 SD in height z-scores in the vamorolone 6 mg/kg group up to Month 30, while increasing in the 2 mg/kg group.

According to the external comparison on growth in study VBP15-004 with the FOR-DMD results at Month 12, height z-scores slightly increased with vamorolone 2 mg/kg and 6 mg/kg (median (SD) height z-score change from baseline 0.13 (0.277) and 0.29 (0.355)) while inhibition of growth resulted from treatment with deflazacort and prednisone (median (SD) height z-score change from baseline -0.47 (0.442) and -0.32 (0.310)). A comparison after 30 months of treatment in VBP15-LTE and FOR-DMD further supports the absence of negative effect on height velocity with height z-scores remaining stable in boys treated with vamorolone (median change from baseline was +0.13 SD), whereas boys on deflazacort and prednisone in the FOR-DMD study lost -1.14 SD and -0.66 SD, respectively.

Patients aged 2 to <4 years from study VBP15-006, who have been transitioned to the EAP, were found to have a median height percentile at baseline of 26.3 (interquartile range 12.7; 36.1), and 5 of the 9 subjects for whom measurements are available so far, had a decrease in height percentile over the EAP (between -1.4 and -52.2) and 4 subjects had an increase in height percentile (between 1.2 and 17.3). Median height percentile for the last postbaseline measurement before the DCO was 12.9 (interquartile range 5.5; 40.2).

Diabetic conditions

Evaluation of biomarkers of insulin resistance after 6 months of treatment in VBP15-004 revealed a dose-dependent increase in fasting insulin that was of similar magnitude in the prednisone and vamorolone 6 mg/kg group (median change from baseline 4.47 and 5.20, respectively), while the increase for vamorolone 2 mg/kg was similar to placebo (median change 1.44 and 0.60). There were no relevant changes in fasting glucose in any group (median change from baseline -1.00 to 2.00). Hemoglobin A1c (HbA1c) slightly increased in the prednisone group (median change 0.10) but not in the placebo and vamorolone 2 mg/kg and 6 mg/kg group (-0.10, -0.10, and 0.00). Nearly half of all patients on vamorolone 6 mg/kg had shifts from normal to high insulin versus 26.9% on prednisone, 18.2% on vamorolone 2 mg/kg, and 0% on placebo. Moreover, switching from prednisone to vamorolone 6 mg/kg but not to vamorolone 2 mg/kg led to an increase in fasting insulin from normal to high. Glucose and HbA1c remained nearly unaffected after switching. The pattern observed in Pool 1 could also be found in Pool 3: fasting insulin increased and mean changes were higher for vamorolone 6 mg/kg compared to 2 mg/kg after 12 months of treatment. No relevant changes were noted for fasting glucose and HbA1c over time.

There was no evidence for an increased incidence of diabetic condition AESIs in Pool 1 for vamorolone. TEAEs in the prednisone group were glycosylated haemoglobin increased, hypertriglyceridaemia, and thirst. Dehydration was reported in a patient on vamorolone. Thirst and dehydration were not associated with hyperglycaemia. There was no pattern to suggest an increased incidence after switching from either prednisone or placebo to vamorolone. In Pool 3, 10% vs. 1% of such conditions were reported in the vamorolone 6 mg/kg vs. 2 mg/kg group (mainly blood triglycerides increased, dehydration, hyperlipidaemia, polydipsia). Diabetes mellitus type 1 was reported as SAE in a 5-year-old patient in the CUP, who was treated with vamorolone for approx. one year prior to the event. Given that type 1 diabetes is an autoimmune disease, it is unlikely that vamorolone caused the diabetic condition in this patient.

Skin and hair changes

In Pool 1, skin and hair change AESI were reported at a low frequency (in ≤10% of subjects in each of the groups). Hypertrichosis was the most frequently reported skin and hair change AE with similar incidence across groups (3.2% - 3.6%). No AE were reported in more than a single subject in each group (PTs in the vamorolone groups were hypertrichosis, erythema, and skin hyperpigmentation). There were no AESI of skin and hair changes following the switch from prednisone or placebo to vamorolone. Across all DMD studies, skin and hair change AEs were reported for 6.7% of subjects in the vamorolone 2-6 mg/kg group, similarly in both treatment groups. Hypertrichosis was the only AESI more frequently reported in the vamorolone 6 mg/kg than in the 2 mg/kg group (5.1% vs. 1%). No clinically relevant skin and hair change AEs were reported in the vamorolone 2-6 mg/kg group.

Infections (Immune Suppression CMQ)

Infection and immune-mediated TEAEs under the Immune Suppression CMQ were frequently reported in the DMD clinical programme. The incidence in Pool 1 was 44.8%, 37.7%, 43.3%, and 32.1% in the placebo, prednisone, vamorolone 2 mg/kg and 6 mg/kg group. Reporting of AESI correspond largely with infections in the Infections and infestations SOC since no immune-mediated TEAEs were reported. Clinically relevant infection AESI occurred with a higher incidence in the placebo and prednisone group (10.3% and 12.9%) as compared to vamorolone 2 mg/kg (6.7%) and 6 mg/kg (0%). Clinically relevant AESI with vamorolone 2 mg/kg (one patient each) were: ear infection, gastroenteritis viral, influenza, and respiratory syncytial virus infection. A single infection in Pool 1 was serious (gastroenteritis viral, vamorolone 2 mg/kg).

In Pool 3, AESI of infections were reported for 55.2% of subjects in the vamorolone 2-6 mg/kg and similar in both dose groups. The most frequently reported infection AESI were nasopharyngitis, upper

respiratory tract infection, influenza, and ear infection. Clinically relevant AESIs reported by > 1 subject in the vamorolone 2-6 mg/kg group were pharyngitis streptococcal, ear infection, influenza, pneumonia, upper respiratory tract infection, otitis media, conjunctivitis, gastroenteritis viral, respiratory syncytial virus infection, sinusitis and tooth infection.

Infections did not increase after switching from prednisone or placebo to vamorolone and were obviously not related to dose (neither in Pool 1 nor in Pool 3) and lacking a specific pattern.

Immunosuppression is an important potential risk for vamorolone in the RMP and long-term data are scarce and uncontrolled. Section 4.4 of the SmPC includes a warning on vaccination regarding the response to live or live attenuated vaccines. Live or live attenuated vaccines are not recommended in patients with immunosuppressive doses of corticoids and should strictly be avoided. In the clinical vamorolone studies, patients were required to have had evidence of chicken pox immunity confirmed either by the presence of IgG varicella antibodies or two doses of varicella vaccine. A warning has therefore been included in section 4.4 of the SmPC regarding vaccination against varicella zoster virus and a contraindication for live or live-attenuated vaccines in line with conventional GCs in the 6 weeks prior to starting treatment.

Hypertension

An effect of vamorolone on blood pressure could not be deduced from single-or repeated-dose studies in dogs during the preclinical programme. However, it is a dose-related effect with glucocorticoids.

Mean diastolic blood pressure (DBP) at baseline in Pool 1 was similar across treatment groups (ranging from 59.64 to 63.10 mmHg). The percentiles and height-adjusted z-scores for DBP in the placebo, prednisone, and vamorolone 2 mg/kg and 6 mg/kg group were: 77.03 and 0.98 SD; 69.35 and 0.70 SD; 77.20 and 0.94 SD; and 68.36 and 0.65 SD, indicating high baseline DBP values in children with DMD. Over 6 months of treatment, mean DBP/ percentile/ z-score change from baseline was higher in the vamorolone 6 mg/kg group as compared to the other treatment groups. No group showed an increase or decrease in mean DBP exceeding 5 mmHg.

Mean systolic blood pressure (SBP), percentiles and z-scores for SBP at baseline was 102.03 mmHg, 73.90 and 0.90 SD for placebo, 102.45 mmHg, 74.81 and 0.91 SD for prednisone, 99.90 mmHg, 68.57 and 0.70 SD for the vamorolone 2 mg/kg, and 97.86 mmHg, 69.04 and 0.62 SD for the vamorolone 6 mg/kg group. Over 6 months of treatment, mean SBP/ percentile/ z-score change from baseline was higher in both vamorolone groups as compared to the other treatment groups. The change from baseline in the vamorolone 2 and 6 mg/kg groups was an increase of not more than 5 mmHg at different time points up to 6 months of treatment. Three patients on vamorolone 6 mg/kg had a shift from baseline Stage 1 or lower hypertension to Stage 2 hypertension for DBP and a single subject on placebo. Shifts were, however, similar in active groups for SBP. There was no pattern to suggest an effect due to switching to vamorolone from prednisone or placebo. In Pool 3, baseline mean DBP, percentile, and z-score was 61.88 mmHg, 74.35, and 0.85 SD in the 2 mg/kg group; and 60.61 mmHg, 70.92, and 0.73 SD, respectively in the 6 mg/kg group. Baseline mean SBP, percentile, and z-score was 100.27 mmHg, 70.55, and 0.74 SD, respectively, in the 2 mg/kg group; and 99.52 mmHg, 69.79, and 0.69 SD, respectively, in the 6 mg/kg group. Data up to 30 months of treatment indicate small increases in mean change from baseline over time in DBP and SBP. When adjusted for height and age (percentiles and z-scores) to correct for the expected increase in blood pressure in growing children, values over time for both DBP and SBP slightly increased from baseline over 12 to 30 months in the vamorolone 2 mg/kg group but remained roughly stable for the vamorolone 6 mg/kg group. Shifts from baseline Stage 1 or lower hypertension to Stage 2 hypertension for DBP and SBP were dose dependent.

2.6.8.3. Serious adverse event/deaths/other significant events

No deaths were reported across all DMD studies.

Serious adverse events

The incidence of SAEs in the DMD clinical studies was low and none was considered drug-related by the investigator. In total, 8 SAEs have been reported in clinical trials in patients receiving vamorolone and none in the prednisone and placebo group in the controlled period of study VBP15-004 (Table 18).

Table 18: SAEs in vamorolone DMD studies

Study	Subject	Treatment	Preferred Term	Location of Narratives
VBP15-004 Part 1	283901	2 mg/kg	Viral gastroenteritis	VBP15-004 CSR Section 14.3.4
VBP15-004 Part 2	282702	6 mg/kg	Appendicitis perforated	
VBP15-004 Part 2	283402	6 mg/kg	Asthma	
VBP15-003	231901	0.75 mg/kg	Pneumonia	ISS Appendix 3
VBP15-003	233104	6 mg/kg	Dehydration	
VBP15-003	233105	6 mg/kg	Testicular torsion; Hypoxia	
VBP15-LTE	230801	0.75 mg/kg	Pneumonia	
VBP15-LTE	232307	6 mg/kg	Myoglobinuria (2 events)	

One subject had an SAE in the controlled period of study VBP15-004 (SAE: *viral gastroenteritis;* moderate in severity): a 6-year-old in the vamorolone 2 mg/kg group, who was hospitalised 2 months after initiation of vamorolone with suspected dehydration secondary to diarrhoea and vomiting. Study drug was interrupted for 2 days due to vomiting and hydrocortisone stress dosing was administered. The subject was released from hospital after 3 days, study drug was resumed, and the subject continued in the study.

5 of 8 SAEs were reported in the 6 mg/kg vamorolone group and included *Appendicitis perforated, Asthma, Dehydration, Testicular torsion/ hypoxia*, and *myoglobinuria* (2 events). For the SAE of asthma, an underlying medical history in this patient was reported and the patient also had viral bronchiolitis. The SAE of dehydration was reported in the context of influenza infection. The two SAEs of myoglobinuria occurred after excessive activity and resolved with ongoing study treatment and corrective measures (IV hydration). Two SAEs of pneumonia in subjects treated with vamorolone 0.75 mg/kg were reported in the context of a virus infection and resolved with corrective treatment despite continuous study treatment. Overall, an infectious aetiology in 5 of 8 SAEs is to be assumed.

No SAEs were reported after switching from either prednisone or placebo to vamorolone.

As per the data cut-off 15 March 2023 in the ongoing study VBP15-006, one subject in the 4 to <7 years steroid naïve group on vamorolone 2 mg/kg, experienced a serious AE of gastroenteritis viral (rated as unrelated to vamorolone). One subject in the 7 to <12 years steroid-treated group on vamorolone 6 mg/kg, experienced a serious AE of rhabdomyolysis (possibly related to vamorolone; treatment was interrupted for 4 days and restarted without reoccurrence).

Up to 15 March 2023, 18 SAEs have been reported among 171 patients who entered the CUP/ EAP, i.e.

- *talipes correction, vomiting/ viral infection, viral wheeze, tibial fracture, epileptic seizures (2 SAEs in one patient), rectal bleeding, and diabetes mellitus* in CUP.
- *appendicitis perforated, food poisoning, metapneumovirus infection, viral infection, respiratory distress, adrenal insufficiency/ COVID-19, atrial flutter, femur fracture, and gastroenteritis viral* in VBP15-EAP.

SAEs either occurred in the 6 mg/kg group or 4 mg/kg group. The SAEs of vomiting/ dehydration, viral wheeze, tibia fracture, diabetes mellitus, metapneumovirus infection, rhabdomyolysis/ viral syndrome, and adrenal insufficiency/ COVID infection are not unexpected given the pre-specified AESIs for vamorolone. One patient in the EAP (subject 31-313103) had 3 SAEs reported at different time points (food poisoning, metapneumovirus infection, rhabdomyolysis/ viral syndrome). The SAE of atrial flutter was probably caused by post-COVID arrhythmia. The overall clinical and biochemical presentation around reporting of two epileptic seizures in a single patient on vamorolone 4 mg/kg is likely in line with untreated DM type 1 at that time. After initiation of insulin treatment, no additional seizures occurred despite ongoing vamorolone treatment (without interruption).

2.6.8.4. Laboratory findings

Haematology

In Study VBP15-004, a dose-dependent increase in *lymphocyte counts* was observed in both vamorolone groups (mean increase ~23% and ~50% from baseline with vamorolone 2 and 6 mg/kg, respectively) as early as Week 2 that was roughly stable thereafter. Increases in lymphocyte counts with prednisone were of similar magnitude and with a similar time course as with vamorolone 6 mg/kg. No relevant changes were observed in the placebo group. Lymphocyte counts were similar before and after switching from prednisone to vamorolone 6 mg/kg.

Changes in *monocyte counts* followed a pattern similar to lymphocyte counts. The pattern of *leukocyte counts* was similar to that for lymphocytes, although, mean changes from baseline were slightly smaller: at Week 2, these were ~11% and 23% for vamorolone 2 mg/kg and 6 mg/kg, respectively, compared with prednisone (~50%) in line with the absence of an increase in neutrophil counts in the vamorolone groups.

No relevant changes in mean *neutrophil counts* were observed in either vamorolone group, with counts similar to placebo at each post-baseline visit. A significant increase in mean neutrophil counts (i.e., up to 100% from baseline) was observed in the prednisone group. Neutrophil counts returned to baseline after switching from prednisone to vamorolone. Consistent results were observed for *immature granulocytes*, with no relevant changes in vamorolone groups compared to placebo at Week 24, but up to a 100% increase in the prednisone group. However, after the first 2 weeks of treatment, an increase from baseline in immature granulocytes was also observed in the vamorolone 6 mg/kg group. This early increase was smaller compared to prednisone, i.e., 50% vs. 64% mean increase from baseline to Week 2. There was no difference between vamorolone 2 mg/kg and placebo. The initial increase seen with vamorolone 6 mg/kg progressively disappeared with continuous treatment. At Week 18 and 24, there was no difference between vamorolone 2 mg/kg or 6 mg/kg and placebo, while the increase with prednisone persisted.

In line with the mean changes in WBC, shifts from normal to high values were seen in higher proportions of subjects in the prednisone and vamorolone groups (dose-dependent) compared with placebo for leukocytes, lymphocytes, monocytes and immature granulocytes. Shifts in lymphocyte counts were higher in the vamorolone 6 mg/kg group compared to prednisone. A lower proportion of subjects on vamorolone 6 mg/kg vs. prednisone had shifts from normal to high for leukocytes, monocytes and immature granulocytes.

Eosinophil counts were similar in the vamorolone and placebo groups. A decrease in eosinophil counts was observed with prednisone.

In Pool 3, changes from baseline remained roughly stable with dose-dependent differences in lymphocytes, leukocytes, monocytes, and neutrophils.

For red blood cells, haemoglobin and haematocrit, mean changes from baseline increased with dose in the vamorolone groups, with similar increases in the 6 mg/kg vamorolone and prednisone group in Pool 1 after 6 weeks of treatment up to the first 24 weeks of treatment. Mean values for erythrocytes, haemoglobin, and haematocrit were at the respective upper reference ranges. No relevant changes in mean values were observed for placebo. Haematocrit stabilised between Week 24 and 48 in the vamorolone 2 and 6 mg/kg groups, while haemoglobin continued to increase in Period 2 of Study VBP15-004. In those subjects switching from prednisone to vamorolone, red blood cell counts, haemoglobin, and haematocrit values decreased to a level similar to subjects with continuous vamorolone 2 and 6 mg/kg treatment. No progressive increases were noted with longer treatment duration in Pool 3.

Chemistry

Lipid profile

In Pool 1, there was a dose-dependent small increase in high density lipoprotein (HDL) cholesterol in the vamorolone 2 mg/kg and 6 mg/kg group and with prednisone early after starting treatment (approx. 7%, 10%, and 13% mean increase from baseline). There was no change in the placebo group. Shifts in HDL-cholesterol from normal to low occurred most frequently with placebo (31%), followed by vamorolone (~14%) and prednisone (6.5%).

Triglycerides dose-dependently increased in the vamorolone 2 mg/kg and 6 mg/kg group and with prednisone early after starting treatment. The mean increase from baseline was approx. 20%, 25%, and 50%, respectively. No relevant change was noted in the placebo group. A similar proportion of subjects had shifts in triglycerides from normal to high for vamorolone and prednisone.

Total cholesterol increased in the vamorolone groups in line with HDL and triglyceride changes and more pronounced in the prednisone group. More subjects in the vamorolone groups (3.4% and 17.9%) had shifts from normal to high cholesterol compared with the other treatment groups. Shifts from normal to high low density lipoprotein (LDL) solely occurred in the vamorolone groups (3.4% and 10.7%, respectively).

After the prednisone tapering period at the start of Period 2 in Study VBP15-004, total and HDL cholesterol returned to baseline values, but rose again when vamorolone was introduced during Period 2. LDL cholesterol remained unchanged. Triglycerides returned to baseline levels after the prednisone tapering period and slightly increased after starting on vamorolone.

In Pool 3, there was a small dose-dependent increase in HDL cholesterol in the vamorolone groups. For LDL, total cholesterol and triglycerides, no specific pattern could be identified.

Liver function

Nonclinical experience with vamorolone has shown liver toxicity in mice and dogs consistent with the class of glucocorticoids for which the liver is a target organ.

In the Phase 1 MAD study VBP15-001, three liver-related TEAEs (two of which were possibly related to study drug) were reported, occurring in 1 subject on placebo, and 1 subject in the 20 mg/kg vamorolone group presenting each with *hepatic enzyme increased/ ALT increased*. The latter event prompted discontinuation from the study. One subject on vamorolone 8 mg/kg was reported with blood bilirubin increased. In Pool 1, there were two subjects with TEAEs of hepatobiliary disorders, i.e. hepatitis acute with vamorolone 6 mg/kg and hyperbilirubinaemia with vamorolone 2 mg/kg. Hepatitis acute led to discontinuation of vamorolone. In Pool 3, one additional patient presented with hepatomegaly in the vamorolone 2 mg/kg group, and one patient was reported with a TEAE of ALT increased (vamorolone 6 mg/kg).

Mean liver parameters and shifts over time

As expected for patients with DMD, ALT and AST were abnormally high (>3 x upper limit of normal (ULN)) at baseline for all subjects. Mean changes in ALT and AST were highly variable in line with muscle disease and did not per se represent changes in liver function. AP declined in the prednisone group, but no changes were recorded up to Week 24 for vamorolone groups and placebo. In Pool 1, ALP progressively decreased in the vamorolone 6 mg/kg group from Month 12 on and fluctuated in the 2 mg/kg group. There were some changes in mean GGT and glutamate dehydrogenase (GLDH) values in Pool 1 but lacking clinically relevance: mean GGT was within normal ranges at baseline and slightly increased in the prednisone and vamorolone 6 mg/kg group in Pool 1, but not with placebo and vamorolone 2 mg/kg. A similar slight increase in both vamorolone groups was found during longer treatment in Pool 3. Mean GLDH was normal at baseline and slightly increased up to Week 24 in all treatment groups in Pool 1. No further changes were noted in Pool 3. No relevant change occurred for bilirubin. Shifts from normal at baseline to high post-baseline in Pool 1 were absent for GGT and similar across treatment groups for GLDH and there was no increase in Pool 3. During this procedure, upon inspection request, a review of liver function data and interpretation of GLDH changes in study VBP15-004 has been provided, which did not change previous conclusions regarding liver function in patients treated with vamorolone.

Significant liver parameters

In Pool 1, there were no post-baseline abnormalities for GGT. High values of GLDH were already present at baseline in individual subjects. GLDH > ULN post-baseline was similar for placebo and vamorolone 2 mg/kg (34.5% and 33.3%), and higher for vamorolone 6 mg/kg and prednisone (42.9% and 54.8%). A single patient had a post-baseline increase of GLDH >3x ULN (6 mg/kg vamorolone; patient with acute hepatitis), which was accompanied by GGT > ULN. Bilirubin > ULN post-baseline was found highest in patients on placebo (27.6%) and lower in the active treatment groups (3.6% - 16.7%). Bilirubin >2 x ULN or > 3 x ULN was reported in a similar low number of patients in all treatment groups.

In Pool 3, the proportion of subjects with GLDH > ULN was 48.5% for vamorolone 2-6 mg/kg and 4 patients had abnormal GLDH > 2 x ULN. One of them is suspect to have had liver damage ("*acute hepatitis*" leading to drug interruption) since a sudden rise of ALT and AST at Week 18 was associated with an increase of GGT, GLDH and no increase in bilirubin or ALP. A second episode of liver enzyme increases was noted several weeks after restart of vamorolone leading to permanent discontinuation. Acute hepatitis was not serious, moderate in intensity and rated probably related to vamorolone. Significant changes of >ULN for total bilirubin were reported in both vamorolone groups (22.7% and 18.8%). 6.1% and 3.5% of patients had total bilirubin >2x ULN.

Overall, 8 subjects met Hy's law criteria (ALT or AST > 3x ULN and total BILI > 2× ULN) in Pool 1. Common for subjects with DMD, AST and ALT were always >3x ULN, so the bilirubin level determined whether the subject met the definition of Hy's law. Except for Subject 284503 ("*acute hepatitis*"), all other cases had high bilirubin level already at baseline and were not associated with a concomitant increase in GLDH, GGT, ALP or ALT/AST. The event "acute hepatitis" (vamorolone 6 mg/kg) presented with post-baseline increase of GLDH >3x ULN, which was accompanied by GGT > ULN and positive but delayed de-challenge and re-challenge, and thus indicative of liver damage. It remains uncertain whether vamorolone was directly or indirectly involved in the deterioration of the patient's liver function. From the timely course and in the absence of alternative causes so far, drug-induced liver injury seems likely in this patient. Four additional cases were reported in Pool 3; all except for a single event also occurred in study VBP15-004. These patients also had high baseline bilirubin values and absence of other liver enzyme abnormalities despite ALT/ AST increases.

Hepatotoxicity is referred to as important potential risk for vamorolone in the RMP based on the well-known potential of glucocorticoids to exert hepatotoxic effects due to their stimulation of the

glucocorticoid receptors in the liver. Based on the lack of a clear clinical signal for significant liver parameters in Pool 1, a warning on hepatic effects has not been proposed in the product information for vamorolone.

Renal function was assessed in the vamorolone clinical programme but seems to be unaffected by vamorolone during short- and longer-term treatment and therefore, no risk minimisation measures are in place.

Other chemistry parameters

No relevant changes were observed in albumin, total protein, electrolytes, ALP and amylase in the vamorolone groups. Vitamin D (25-OH-Vitamin D) was low at baseline in all groups in Pool 1 in line with observations in the DMD population. Small increases from baseline in vitamin D levels were observed in the placebo group and lower mean increases in the vamorolone 2 and 6 mg/kg groups. A small decrease from baseline was observed in the prednisone group. There was no pattern of shifts for Vitamin D in Pool 1 and Pool 3 for vamorolone. Laboratory Vitamin D data contrast the reporting of TEAEs of Vitamin D deficiency in Pool 1, which increased after switch from prednisone to vamorolone 6 mg/kg in study VBP15-004 (0% and 13.3%). However, it could be clarified that reporting of vitamin D deficiency TEAEs in study VBP15-004 was probably influenced by the late inclusion of (adult) reference ranges from the central lab into the system. Moreover, the interpretation of TEAEs is further hampered by the lack of validated reference ranges for paediatric patients in the study, and thus, TEAE reporting was related to the adult 25-OH Vitamin D reference ranges.

Vital signs, physical findings, and other observations related to safety

In Pool 1, mean heart rate and respiratory rate were similar at baseline and did not significantly change up to Month 6 in neither treatment group. Moreover, no specific pattern was noted in Pool 3 for vamorolone treatment groups up to Month 30.

Vamorolone did not inhibit hERG potassium currents up to the highest concentration of 20 µM *in vitro* (study Bio-VBP-002-hERG). Moreover, vamorolone did not impact on the cardiovascular system in mice and dogs in the preclinical programme (reference is made to the nonclinical section).

Cardio-dynamic evaluation for vamorolone was performed as part of VBP015-001 in healthy male adults. In the SAD/ MAD portions of the trial, single/ multiple doses of vamorolone of up to 20 mg/kg or placebo were administered (for 14 days in the MAD portion). Based on the pooled SAD and MAD analysis, an effect on ΔΔQTcF exceeding 10 ms could be excluded within the full observed range of plasma concentrations of vamorolone. Vamorolone at the tested doses produced a small heart rate increase but had no effect on cardiac repolarisation (QTcF) or other ECG parameters.

Descriptive statistics of the QTcF interval in Pool 1 demonstrated small mean decreases up to Month 6 in the placebo and prednisone group (~ -5 msec) and small mean increases in both vamorolone groups (~ +4 msec in the 2-6 mg/kg vamorolone group). In Pool 3, small mean increases from baseline in QTcF were dose-related. Mean changes from baseline in ECG parameters in Pool 1 were small and not clinically meaningful. The majority of subjects (96.2% on vamorolone 2 mg/kg and 100% for other treatment groups) had a maximum QTcF value below the range of potential clinical concern (≤450 msec), and 84.6% to 100% of patients across treatment groups had a maximum on-treatment increase from baseline for QTcF of <30 msec. Suspicious ECG results of 11 subjects from Pool 3, including those with perceived QTcF >60 msec and >500 msec were reviewed by an external cardiologist. None of these subjects was confirmed to have had an abnormal ECG in clinical studies with vamorolone.

In Pool 3, a maximum QTcF increase from baseline of >30 - <60 msec was twice as high in the vamorolone 6 mg/kg group as compared to 2 mg/kg, while the incidence of maximum QTcF increase from baseline of >60 msec was low and similar between groups (3.9% in the combined group). A single

subject on vamorolone 6 mg/kg also had an absolute QTcF of >500 msec. No related TEAEs were reported in these patients and drug was not discontinued based on these outliers.

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

Intrinsic factors

Age: Baseline age <5 years and ≥5 years: higher incidences/ rates of severe TEAEs (7.8% vs. 3%), AESIs (82.8% vs. 73.7%), and SAEs (6.3% vs. 2%) were reported in the younger versus the older age group. The proportion of subjects with behaviour problems and GI symptoms was >10 pp higher in the younger than the older subgroup. Additionally, the event rate for infection TEAEs grouped under the Immune Suppression CMQ was higher in the younger than the older subgroup (>0.1 difference between event rates). Instead, bone fractures, cushingoid, and weight gain occurred more frequently in the older subgroup.

Race: The majority of DMD patients were Caucasian (~86%). The numbers of Asians, Hispanics, Blacks, and patients of other races were too low to draw meaningful conclusions.

Weight: Safety according to baseline weight z-scores either below or above median revealed the incidence of drug-related TEAEs (> 10 pp difference across the subgroups) as well as the event rate to be higher in the heavier subgroup whereas total number of TEAEs was more frequent in the lower weight subgroup. As to be expected, subgroups by weight z-scores differed in that AESIs in line with metabolic conditions, i.e., cushingoid features, diabetic conditions, and weight gain, were more frequently reported in patients with weight z-scores above the median.

Height: Safety according to baseline height z-scores either below or above median revealed that the incidence of drug-related TEAEs, non-mild TEAEs, clinically relevant TEAEs, and TEAEs leading to dose reduction were more frequent in the taller subgroup. Incidences of AEs, AESI, and AEs leading to temporary dose interruption were more frequent in the shorter subgroup.

BMI: Safety according to baseline BMI z-scores either below or above median revealed the incidence of non-mild TEAEs and clinically relevant TEAEs were more frequent in the lower BMI subgroup (< 10 and ≥ 5 pp difference across the subgroups for each type of event). The incidences of diabetic conditions and weight gain were higher in the higher BMI subgroup (>10 pp higher for weight gain).

Renal impairment: There is no clinical experience in patients with renal impairment. Vamorolone is not excreted unchanged via the kidney and increases in exposure due to renal impairment are considered unlikely.

Hepatic impairment: The effect of moderate hepatic impairment on vamorolone was studied in humans (Study VBP15-HI). Vamorolone C_{max} and $AUC_{0\text{-}inf}$ values were approx. 1.7 and 2.6-fold higher in subjects with moderate hepatic impairment (Child-Pugh B) compared to age-, weight-, and sex-matched healthy adults. A *post hoc* analysis of the VBP-HI study data was performed and based on these data, exposure parameters of subjects with mild HI might be even less affected and should represent an increase in vamorolone concentration of between 10 and 15% compared to those of individuals with normal liver function. Therefore, the applicant recommends to only reduce the dose of vamorolone by one-third in patients with moderate hepatic impairment (Child-Pugh B), i.e., the 6 mg/kg dose should be reduced to 2 mg/kg for patients up to 40 kg and to 80 mg for patients >40 kg. Moreover, and based on the

exposure increase to vamorolone in patients with moderate HI, a contraindication for patients with Child Pugh C has been implemented in the SmPC.

Extrinsic factors

Geographical region (USA [including Canada and Australia] and Europe [including Israel])

The incidence of non-mild AEs, clinically relevant TEAEs, and TEAEs leading to dose reduction (> 10 pp difference across the subgroups) and severe TEAEs, SAEs and TEAEs leading to temporary dose interruption (~< 10 and ≥ 5 pp difference across the subgroups) were more frequent in the USA region. Behaviour problems, Infections grouped as Immune suppression CMQ and Weight gain were reported > 10 pp more frequently in the USA region, whereas Cushingoid features were more < 10 and ≥ 5 pp more frequent in the Europe region.

2.6.8.7. Immunological events

N/A

2.6.8.8. Safety related to drug-drug interactions and other interactions

Since oxidation via CYP3A4 was observed *in vitro*, an *in vivo* DDI study was conducted to assess the effect of a strong CYP3A4 inhibitor (itraconazole) on the PK of vamorolone (VBP15-DDI). The study showed a weak effect of itraconazole on vamorolone PK (1.45-fold increase of vamorolone AUC and no significant effect on C_{max}) and confirmed that metabolism via CYP3A4 is a minor pathway for vamorolone. No dose adjustment is recommended when vamorolone is co-administered with CYP3A4 modulators.

Vamorolone induces CYP3A4 *in vitro* and DDI with sensitive CYP3A4 substrates cannot be excluded. Co-administration of vamorolone with such compounds may lead to decrease the plasma concentrations of the substrates and appropriate dose adjustments may be necessary for these drugs.

Vitamin D is frequently administered in patients with DMD to prevent demineralisation of bone. Whether or not vamorolone causes a decrease in the synthesis of active vitamin D and impairing its biological action at the tissue level similar to glucocorticoids remains unknown.

2.6.8.9. Discontinuation due to adverse events

The incidence of discontinuations from study drug due to AEs was low across all studies. Two of 164 subjects treated with vamorolone (Pool 3) had a TEAE that led to study drug discontinuation:

- Subject 232102 (vamorolone 2 mg/kg) reported a TEAE of *Muscular weakness* (with repeated falls), which was moderate in severity and rated unrelated to vamorolone, while leading to study drug discontinuation upon request of the parent/guardian: AE onset was on VBP15-LTE Study Day 545 (Day 741 from the start of VBP15-002), approximately 6 weeks after down titrating vamorolone from 6 to 2 mg/kg due to weight gain. Muscular weakness is most likely to be explained by progression of the underlying disease in this patient and probably ineffectiveness of the lower vamorolone dose.
- Subject 284503 (vamorolone 6 mg/kg) was discontinued from Period 2 of Study VBP15-004 due to a moderate TEAE of *Hepatitis acute,* which was the second episode of liver enzyme increases over half a year with vamorolone treatment and after drug interruption for the first episode.

In addition, 2 subjects discontinued a clinical pharmacology study due to a TEAE, 1 receiving placebo and 1 receiving vamorolone 20 mg/kg: Subject 2027 (vamorolone 20 mg/kg) was discontinued from

Study VBP15-001 due to a TEAE of ALT increased, with onset on Day 7 and dosing discontinued on Day 10. The increase in ALT peaked at Day 12-14 and then returned to within normal limits. The TEAE was considered related to vamorolone.

2.6.8.10. Post marketing experience

N/A

2.6.9. Discussion on clinical safety

From the safety database, all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The main body of evidence with regard to clinical safety for vamorolone in the treatment of DMD for the to-be approved dose 6 mg/kg includes 163 patients aged 4 to <7 years at study entry (the maximum age was 9.6 years at the end of VBP15-LTE) and dosed in four clinical studies that have been pooled for safety analysis. The most relevant safety data derives from Pool 1 providing comparison between vamorolone fixed doses 2 mg/kg and 6 mg/kg, placebo and prednisone 0.75 mg/kg for 24 weeks of treatment based on the phase 2b study VBP15-004, Period 1. For Period 2, patients were switched from either placebo or prednisone to vamorolone 2 mg/kg or 6 mg/kg or remained on the initial dose of vamorolone and continued treatment for an additional 20 weeks. Switch data enable detection of changes in adverse events after the switch.

Long-term safety of vamorolone currently relies on data from patients continuously treated in study VBP15-004 up to 48 weeks, and open-label treatment in study VBP15-LTE (combined VBP15-002, 003, and LTE) forming Pool 3, which allows for evaluation of clinical safety for approx. 30 months of vamorolone exposure. Between open-label studies -002 and -003, and -003 and –LTE there was a mean drug-free period of 18.27 days for 48 subjects. Moreover, long-term data for 171 patients, who have completed one of the vamorolone clinical studies (also including patients from study VBP15-006), are currently collected in EAPs (USA, Canada, and Israel) and CUPs. Therefore, the overall age range of patients in these programmes up to 15 March 2023 spans from 2 to 17 years. As per the updated data cut-off 21 July 2023, the applicant clarified that 83 of 99 subjects are being treated in one of three EAPs. A majority of 16 patients, who withdrew from the EAP did so because of subject or parent/ guardian decision, while only a single patient withdrew because of a TEAE (weight gain).

Updated safety data have been provided from the ongoing 12-week open-label study VBP15-006 for the age group 2 to <4 years (data cut-off 21 July 2023) in support of the originally claimed indication, i.e. patients 2 years and older. No new data became available for age groups 7 to <12 years (steroid-naïve and steroid-treated) and 12 to <18 years (steroid-naïve and steroid-treated). The safety profile appears not different for the older age groups 7 to <12 years and 12 to <18 years compared to the reference population (4 to <7 years), with the limitation that pubertal development has not been evaluated for vamorolone so far.

The safety of vamorolone in the youngest patients (i.e. 2 to <4 years) is based on few available data (10 patients on vamorolone 2 mg/kg, and 6 patients on 6 mg/kg) suggesting that the 6 mg/kg dose is more likely to cause AEs of interest in these patients, i.e., behavioural events and adrenal suppression. Thus, titration from a lower dose (2 mg/kg) to an intermediate dose (4 mg/kg) was initially proposed until patients turn 4 years of age when treatment with 6 mg/kg is recommended. Longer-term safety data for 15 patients 2 to <4 years have been made available for those having been transferred from VBP1-006 to an EAP. These subjects have a median of 9 months duration of treatment with vamorolone with a maximum of 15 months, mainly for the 4 mg/kg intermediate dose. Although, reporting of TEAEs

was high in the 6 mg/kg dose group during the first 12 weeks of treatment, all these patients entered the EAP and remained on the 6 mg/kg dose. No unexpected or serious AEs have been reported with most of the TEAEs being infections. No psychiatric or endocrine events have been reported in the EAP at neither dose, while any effects on height and weight are difficult to interpret for the 2 to <4 years group based on the limited data. Nevertheless, in the view of the CHMP objection to the proposed posology, the applicant agreed to restrict the indication to DMD patients aged 4 years and above.

In VBP15-LTE, vamorolone doses could be up- or down-titrated after the first month of treatment. Consequently, almost all patients with initial doses of 0.25/ 0.75/ 2 mg/kg had up-titration. 10 out of 11 subjects who escalated to 6 mg/kg had to reduce it again to a lower dose due to an increase in weight. 4 patients had an intermediate dose of 4 mg/kg at study end. Moreover, a majority of subjects in the EAP/ CUPs (of all ages) are currently dosed with 4 mg/kg. Efficacy and safety for the 4 mg/kg vamorolone dose has not been systematically evaluated. However, available data from patients currently treated in the EAP indicate that safety for this dose for some of the safety issues is probably closer to the 6 mg/kg, e.g. for effects on the HPA axis (based on updated PKPD modelling of morning cortisol), and for weight increased. TEAEs of weight increased remain the most common reason for dose reductions from 6 to 4 mg/kg in the EAP. Meanwhile, the recommendation is to lower the dose to 4 mg/kg in case of tolerability issues or further down to 2 mg/kg, when tolerability issues are not sufficiently mitigated. Based on the experience in the EAPs, down titration from either 6 mg/kg or 4 mg/kg to 2 mg/kg was reported for 8 patients mainly due to weight gain. Given that the maintenance of effect for the 2 mg/kg dose (based on the ROS1 formulation) has been questioned, the posology section further advises to maintain patients at the highest tolerated dose within the dose range. Drug interruptions have more frequently been reported with the 4 mg/kg dose as compared to 6 mg/kg in the EAPs; however, this was explained by a higher rate of infection in this dose group, which required hydrocortisone stress dosing and thus, temporary interruption of vamorolone has been considered by the treating physicians. External data from study FOR-DMD comparing three different glucocorticoid regimens (i.e., daily prednisone 0.75 mg/kg, intermittent 10 days on-off prednisone, and deflazacort 0.9 mg/kg) are deemed generally acceptable by CHMP to overcome limitations with regard to the short –term prednisone control in study VBP15-004. However, this external comparison still underlies different methods or sensitivity in safety data collection and has to be cautiously interpreted.

Overall, 58 patients with DMD had exposure to vamorolone 2 mg/kg and 6 mg/kg in the controlled Part 1 of study VBP15-004, while 4 patients discontinued prior to Week 24 due to parent or physician decision. 28 and 27 patients had at least 6 months of exposure to vamorolone 2 mg/kg and 6 mg/kg. The safety population for the uncontrolled study VBP15-LTE includes 46 subjects.

The median duration of exposure was 11 months for subjects, who received vamorolone 2-6 mg/kg across all DMD studies with a cumulative exposure of ≥12 months for 100 patients (61.3%) and ≥30 months for 20 patients (12.3%). Based on the dominant dose definition, safety data of ≥12 months for 2 mg/kg and 6 mg/kg vamorolone are available for 35 and 54 patients, respectively. The exposure in patients <5 years and ≥5 years to both vamorolone doses was balanced. Patients 2 to <4 years from VBP15-006, who continue in an EAP, have at present a median duration of treatment with vamorolone of 9 months, and it is highest for the 4 mg/kg group.

In Pool 1, a majority of subjects (>83%) across active treatment groups reported at least one TEAE (versus 79.3% in the placebo group). No subject on vamorolone experienced a severe TEAE or TEAE leading to permanent study treatment discontinuation. Half of the overall TEAEs in the combined vamorolone 2-6 mg/kg group were rated related to treatment. Clinically relevant TEAEs (i.e. those being at least moderately severe or leading to study withdrawal or being SAEs) with vamorolone 2-6 mg/kg compared favourably to both, placebo and prednisone (20.7%, 31%, and 42%). AESI based on the known side effects of glucocorticoid drugs were reported in up to 78.6%. Onset of AESI in Pool 1 was reported to be within the first 6 months of treatment based on Kaplan-Meier curves. Specifically, the

overall incidence of AESI was higher during the first 90 days of treatment in either group in Pool 1 of study VBP15-004 as compared to AESI occurring after 90 days (and up to 6 months), with some differences between AESI groups. Cushingoid features with vamorolone were more frequently reported after 90 days and weight gain was more frequently reported for the 6 mg/kg dose (but not for 2 mg/kg) after 90 days of treatment as compared to the first 90 days (10.7% vs. 7.1%).

No additional concern derives from longer treatment duration with vamorolone in Pool 3 based on limited and uncontrolled data with regard to the overall incidence of TEAEs and drug-related TEAEs. The incidences slightly increased during longer treatment duration for some SOCs/ PTs, which can at least in parts be explained by the underlying disease. Likewise, no additional safety concern derived from ongoing treatment with vamorolone in patients 2 to 4 years from the preliminary safety data in the EAPs.

No death occurred in the clinical DMD studies and from the EAPs up to the data cut-off. Eight SAEs were reported in patients on vamorolone and none in the prednisone and placebo group. None was rated related to vamorolone, but all led to hospitalisation. One SAE was recorded in the vamorolone 2 mg/kg group (viral gastroenteritis) in Pool 1, while 7 SAEs were reported in the uncontrolled studies. 5 of 8 SAEs were reported in the 6 mg/kg vamorolone group and included *Appendicitis perforated, Asthma, Dehydration, Testicular torsion/ hypoxia, and myoglobinuria* (2 events). An infectious aetiology in 5 of 8 SAEs has to be assumed. In a majority of SAEs, hydrocortisone stress dosing was reported, and corrective treatment was applied. Vamorolone either remained unchanged or was interrupted for a short period. None of the SAEs led to discontinuation of study drug. 18 SAEs have been reported so far among 171 patients in CUPs/ EAPs as per the March 2023 DCO and roughly complied with the defined AESIs. One SAE of atrial flutter was probably caused by post-COVID arrhythmia. Two SAEs of epileptic seizures likely occurred after untreated diabetes mellitus type 1 and are thus not causally related to vamorolone. Moreover, two SAEs have meanwhile been reported from the ongoing study VBP15-006, one in a subject aged 2 to <4 years (viral gastroenteritis) and one in a subject 7 to <12 years from the corticosteroid-treated group receiving 6 mg/kg vamorolone (rhabdomyolysis; possibly related).

Four subjects discontinued treatment due to TEAEs, one on prednisone and three on vamorolone: one subject in VBP15-LTE with *muscular weakness* on 2 mg/kg vamorolone after down-titration from 6 mg/kg (rated unrelated by the investigator but could be indicative of a lack of efficacy); one subject in Period 2 of VBP15-004 on 6 mg/kg vamorolone due to a moderate TEAE of *hepatitis acute* (probably related); one subject in VBP15-001 on 20 mg/kg vamorolone due to *ALT increased* (related).

When focussing on the recommended dose of 6 mg/kg, the most commonly reported TEAEs reported in ≥10% of patients were Cushingoid (28.6%), vomiting (14.3%), fall (10.7%), weight increased (10.7%), Vitamin D deficiency (10.7%), and irritability (10.7%). Of these, Cushingoid, Vitamin D deficiency, and headache dose-dependently increased.

No noteworthy concerns arise from the incidences of TEAEs after switching from prednisone or placebo to vamorolone 2 mg/kg and 6 mg/kg, except for an increase in Vitamin D deficiency and fatigue after switching from prednisone to vamorolone.

ADRs with vamorolone were based on adverse events for the recommended 6 mg/kg dose from Pool 1 taking into account dose-response and pharmacological plausibility. Evaluation of laboratory data additionally identified blood triglycerides increased and cortisol decreased as potential ADRs, but these have not been included in the ADR table in section 4.8 of the SmPC. Upon request, it could be clarified that the increase in blood triglycerides was not rated as clinically significant. Moreover, a decrease in morning cortisol is a pharmacodynamic effect rather than an adverse drug reaction, which is described in other parts of the SmPC (section 5.1 and 4.4). The presentation of ADRs and frequency categorisation in section 4.8 has been revised upon request and adequately reflects Pool 1 data.

The relevant safety concerns for vamorolone pertain to the following AESI:

Vamorolone causes a dose-dependent adrenal suppression in line with low morning cortisol levels in Pool 1 that was even more pronounced as with prednisone. Mean change from baseline at Week 24 was highest in the vamorolone 6 mg/kg group, followed by prednisone and vamorolone 2 mg/kg. In support of this finding is the number of patients with a morning cortisol <100 nmol/L (indicative of adrenal insufficiency) that was almost 100% for vamorolone 6 mg/kg and 74% in the prednisone group. ACTH stimulation testing further confirmed inability to generate an adequate cortisol level in response to severe stress in the order vamorolone 6 mg/kg> prednisone> vamorolone 2 mg/kg> placebo. Adrenal suppression remained roughly stable at later time points based on Pool 3 data. Switching from prednisone to vamorolone did not result in an increase in adrenal suppression, which supports direct switch from prednisone 0.75 mg/kg to vamorolone 6 mg/kg in clinical practise. In the 2 to <4 year-old patients in study VBP15-006, a TEAE of adrenal suppression was reported in half of those treated with 6 mg/kg, while all patients treated with 6 mg/kg had a morning cortisol below 100 nmol/L at Week 12. In line with adrenal suppression, Cushingoid features with vamorolone in Pool 1 were more frequently reported in the 6 mg/kg group compared to prednisone (28.6% vs. 22.6%) and less in the 2 mg/kg group (6.7%). Events were predominantly mild, did not lead to treatment discontinuation, and did not increase with longer treatment duration in Pool 3. TEAEs of adrenal insufficiency have not been reported with vamorolone in the clinical DMD programme, except for a single SAE in the EAP in a patient, who did not receive hydrocortisone supplementation in the context of a stress situation. Hydrocortisone (or prednisone) stress dosing was permitted in clinical studies during an illness, injury, or surgical procedure to avoid an adrenal crisis. In line with the study protocol of VBP15-004 reflecting clinical practice recommendations for management of the risk for adrenal insufficiency after long-term systemic glucocorticoid treatment (Bowden at al. 2019), information has been included in section 4.4 of the SmPC. This includes the need for dose tapering and the risk of aprupt withdrawal of vamorolone, as well as symptoms of adrenal crisis adequately reflected in the SmPC. Dose tapering and withdrawal of vamorolone have not been evaluated systematically in the clinical programme. It is expected that adrenal suppression persists depending on the dose and duration of treatment. Adequate information has been included in SmPC section 4.2. 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.

Treatment with vamorolone is associated with a dose-dependent increase in weight and BMI percentiles/ z-scores, which was not readily expected given the differential profile of vamorolone on glucocorticoid-like effects. Weight gain as AESI (combined increased appetite and weight increased) was reported more frequently in the vamorolone 6 mg/kg group as compared to prednisone or vamorolone 2 mg/kg. During VBP15-LTE, 11 of 41 subjects (i.e. 6.7% of the overall study population) were down-titrated from 6.0 mg/kg due to a clinically relevant TEAE of weight increased in 10 subjects ("6 mg/kg down-titrated group" in Pool 3). BMI percentiles and z-scores reported in order to account for the stunting effect of prednisone on height indicated greater mean increases from baseline to Month 6 for both vamorolone 2 mg/kg and 6 mg/kg compared to prednisone. Clinically relevant changes in BMI z-scores at Month 6 of ≥1.0 were observed more frequently with vamorolone 2 mg/kg and 6 mg/kg compared to prednisone (11.1%, 11.5%, and 3.3%). In a majority of these subjects, cushingoid features were present. Switch from prednisone led to a decrease in median BMI z-score from baseline with vamorolone 2 mg/kg and further increase with vamorolone 6 mg/kg. As expected with longer treatment of up to 30 months, median BMI percentile and z-score changes fluctuated up to Month 30.

Evaluation from the EAPs as per the DCO 21 July 2023 revealed that weight percentiles clearly increased from a baseline median 65.4 (start of EAP) to last follow-up measurement median 88.0. The median z-score increased from 0.4 to 1.2.

An analysis of the effect of down- and up-titration of vamorolone on weight changes was conducted by categorising patients to the High Dose Analysis set (6 mg/kg, reduced to 4 mg/kg) and to the Low Dose

Analysis set (2 mg/kg, increased to 4 mg/kg). From the available plots for the HDS it appears that in a number of these patients dose reduction from 6 to 4 mg/kg led to a plateau in weight percentile (no additional increase in weight percentile after dose reduction). This is additionally supported by the calculation of the annual rate of change in weight percentiles that is found to be lower after the switch from 6 to 4 mg/kg in the HDS. From the available plots for the LDS it appears that the dose increase from 2 to 4 mg/kg does not prevent from further increase in weight percentiles. This is supported by the fact that the annual rate of change in weight percentiles remains similar after the switch from 2 to 4 mg/kg in the LDS. While this analysis is informative regarding weight changes in a very small sample size with only 17 and 16 subjects included, it cannot reliably reassure that the proposed dose reduction from 6 mg/kg to 4 mg/kg is sufficient to mitigate further weight increases with vamorolone given that the 4 mg/kg dose (ROS2 formulation) is assumed to provide ~79% of the exposure of the 6 mg/kg dose with the ROS1 formulation in the 4 to <7-years-old.

Results of body composition with DXA at Week 24 showed an increase in total body fat that was highest in the vamorolone 6 mg/kg group. Of interest is a concomitant increase in lean body mass, which was in a similar range across active treatment groups (10.5% - 13.5%). Based on the DXA body composition measures alone, it cannot be differentiated whether the increase in lean body mass derives from an increase in muscle mass or indicates a certain degree of fluid retention.

Patients receiving vamorolone should be informed and monitored for the possibility of important weight gain and provided with age-appropriate dietary advice; adequate information has been included in section 4.4 of the SmPC.

The increase in weight and BMI needs to be set into context of an obvious lack of vamorolone to inhibit growth, which is a well-known adverse outcome of classical GCs like prednisone. While after 24 weeks of treatment patients on prednisone lost -0.1 SD in height z-score, vamorolone led to positive median changes from baseline (0.07 SD for 2 mg/kg and 0.11 SD for 6 mg/kg), which was similar to placebo (0.13 SD). Switching from prednisone after 24 weeks to vamorolone led to an increase in median height z-score up to Week 48. In Pool 3, the changes of median height z-scores remained positive after 3, 6, 12, and 30 months of treatment with vamorolone 2 mg/kg, with slightly lower z-scores in the 6 mg/kg group. Furthermore, external comparison of median height z-scores in VBP15-004 to the FOR-DMD groups at Month 12 underlines the growth stunting effect of deflazacort and prednisone as compared to vamorolone. Comparison over 2.5 years (VBP15-LTE vs. FOR-DMD), revealed stable median height z-scores with vamorolone (+0.13 SD), and growth stunting with deflazacort and prednisone-treatment (-1.14 SD and -0.66 SD).

Height changes for children 2 to <4 years from study VBP15-006 over 12 weeks were inconclusive.

Children 2 to <4 years, who entered one of the EAPs, and for whom two measurements from EAP baseline to the first dose increase to 4 mg/kg are available as per the DCO (i.e. for 9 patients), height percentiles (height z-scores have not been reported) revealed increases but also decreases. While the decreases generally reflect natural variability, a single patient had an unexpected high decrease in height percentile (-52.2), which does not concur with the height percentile changes that have been presented for all age groups in the EAPs, i.e. the median height percentile that could be retrieved for the majority of subjects in the EAPs as per the DCO (n=99) was 22.7 at first measurement in the EAP and 30.5 at last measurement before data cut-off, suggesting that there is no negative effect of vamorolone on growth. The outlier in a single patient might be attributed to the known limitations regarding height measurements in young paediatric patients, and especially those with DMD (non-standardised height measurements, scoliosis, etc.).

Bone health has been extensively evaluated in the clinical programme: no TEAEs/ AESI of bone fracture were reported for vamorolone over six months of treatment in Pool 1. In Pool 3, bone fracture AESI were reported more frequently in the vamorolone 6 mg/kg than in the 2 mg/kg group (7 patients vs.

2 patients). Clinically relevant bone fractures (including upper limb fracture, foot fracture, spinal compression fracture and humerus fracture) were reported in 1% and 6.1% of subjects in the vamorolone 2 mg/kg and 6 mg/kg group. Four patients had spinal/ spinal compression fractures and thoracic vertebral fractures. Vertebral fractures are common in DMD and often remain asymptomatic and thus undetected. Spine X-ray survey was performed at baseline and at 24 weeks (VBP15-004) and 30 months (VBP15-LTE), respectively. While no vertebral fractures were noted in patients on vamorolone at Week 24 in VBP15-004, 10.3% of patients on vamorolone after 30 months of treatment in VBP15-LTE had vertebral fractures. Since no baseline readings were available, it remains unknown whether vertebral fractures in these patients were already present at baseline.

Comparison of spinal fractures reported by central review in Study VBP15-LTE (n=39) with a matched corticosteroid-treated historical control cohort from FOR-DMD (n=70) revealed a lower frequency of vertebral fractures for vamorolone compared with daily prednisone and deflazacort based on a 30 months adjusted treatment duration. Again, the lack of baseline lateral spine X-rays for either study, i.e. for VBP15-LTE and FOR-DMD, severely limits interpretation of the comparison.

Comparison of bone age by hand X-rays in VBP15-LTE and chronological age after 30 months (2.5 years) of treatment with vamorolone revealed a delay of -1.1 ± 1.2 years, which does not favourably compare to literature data with a delay of -1.6 ± 2.2 years after 5.2 years of GC treatment in patients with DMD. Moreover, the bone age delay noted with vamorolone in study LTE after 30 months of treatment seems to be also more pronounced than noted for GC naïve patients with DMD (Annexstad et al. 2019).

Biomarkers of bone remodelling have been analysed but interpretation is difficult. In Pool 1, osteoblast-related bone biomarkers were found significantly depressed by prednisone while the decrease from baseline in the placebo and vamorolone 6 mg/kg group was less pronounced, and even slightly increased with vamorolone 2 mg/kg at Week 24. Interpretation of bone resorption parameter CTX is even more challenging since it was found decreased with prednisone and increased for placebo and vamorolone in Pool 1. Bone metabolism in children is complex, and greatly differs from that of adults as it reflects both skeletal growth and modelling; thus, increase in CTX is not necessarily associated with bone resorption in paediatric patients but rather indicates bone turnover resulting from improved linear growth (Rauchenzauner et al., 2007). This has been supported by shift analysis at Week 24 resulting in few shifts from normal to low in the vamorolone groups for P1NP, osteocalcin and CTX compared to prednisone (shifts from normal to low were significant for prednisone after 24 weeks).

After switching from prednisone to vamorolone, osteoblast markers improved on vamorolone, while osteoclast biomarker likewise increased probably indicative of bone turnover. Over up to 30 months of treatment with vamorolone, osteoblast activity tended to be higher with vamorolone 2 mg/kg as compared to vamorolone 6 mg/kg, while osteoclast activity was affected vice versa.

The median percent change from baseline to Week 24 for lumbar spine BMC was similar in the vamorolone 2 and 6 mg/kg and placebo group (5.9%, 6.0% and 6.5%, respectively), and lower in the prednisone group (2.7%). When normalised for lumbar vertebrae area, median percent change at Week 24 in lumbar spine BMD was slightly decreased in the prednisone group (-0.32%), mildly increased in the vamorolone groups (+0.68% and +0.83% for the vamorolone 2 and 6 mg/kg groups, respectively), and highest in the placebo group (+3.6%).

During Period 2 (up to Week 48), for BMC and BMD, there was a median % increase during (uncontrolled) Period 2 with vamorolone 2 mg/kg and 6 mg/kg. While prespecified BMD z-score analysis was not conducted as planned, the applicant provided post-hoc BMD z-scores adjusted for height z-scores for baseline, Week 24, and Week 48. As a result, LS-BMD z-scores remained stable in all treatment groups over the 48 weeks of study lacking clinically significant changes, which are generally defined by a ≥0.5 decline in spine BMD z-score on serial BMD measurements over a 12-month period (Ward et al. 2018). Moreover, longitudinal DXA measures of lumbar spine DXA and total body DXA (i.e.

screening+W 24+W 48, screening+W 24, screening+W 48, or W 24+W 48) are available for ~50 – 67.5% of patients from study VBP15-004, while a number of subjects missed one or more post-baseline DXA measurements due to COVID-19 pandemic restrictions and other reasons. Regarding the robustness of DXA measures, it should be noted that the scanners were not cross-calibrated but instrument quality controls demonstrated acceptable quality according to the provided data. In summary, patients, who received vamorolone in Period 1 of study VBP15-004 and continued on vamorolone in Period 2 retained LS-BMC and LS-BMD or even slightly improved at Week 48. In contrast, there is a clear negative effect for these parameters elicited by prednisone in the first 24 weeks of treatment in study VBP15-004, that is caught up in Period 2 after switching to vamorolone. Based on these data, vamorolone is less likely to contribute to an increased risk for factures in paediatric DMD patients as compared to prednisone, while it remains unclear whether long-term treatment would elicit differential effects compared to an untreated (placebo) population. DXA measurement in order to predict the risk for fractures in patients with DMD is not readily supported in the scientific community since fractures can likewise occur in patients with BMD z-scores higher than those used to define osteoporosis and given that DMD patients present with distinct features (e.g. stature and increased weight). However, LS- BMC/BMD measurements are still assumed to contribute to the overall trajectory of bone health. This is also in line with the recommendations provided by Birkrant et al. 2018 (i.e. spine x-ray to be prioritised over BMD). Taken together the totality of the bone health results, vamorolone seems to have differential effects on bone health as compared to prednisone; however, the prediction of future fractures in DMD patients treated with vamorolone is not possible based on the provided data. In the RMP, bone fracture has been specified within safety on long-term use as missing information.

Treatment with vamorolone 6 mg/kg was associated with an increased risk of presenting with AESIs of behaviour problems compared to placebo but lower as compared to prednisone, supported by results from the PARS III scale measuring psychosocial adjustment. There was a clear difference in clinically significant events that were highest for prednisone (22.6%) and not reported for vamorolone 6 mg/kg. While in the prednisone group psychomotor activity and aggression predominated, more subjects reported irritability in the vamorolone 6 mg/kg group as compared to prednisone (10.7% vs. 3.2%). Moreover, after up titration to 6 mg/kg from lower doses in VBP15-LTE, 4 subjects reported TEAEs from the psychiatric disorders SOC. The vast majority of events were mild, and none led to treatment interruption, down-titration, or discontinuation. Behaviour problems slightly differed between age subgroups <5 and ≥5 years (in Pool 1, behaviour problems with vamorolone were found increased over placebo and prednisone in the younger subgroup). This finding is corroborated by newly emerging data from 2 to <4 years-old in study VBP15-006, who reported behavioural disorder TEAEs with the 6 mg/kg dose but not with the 2 mg/kg dose during the first 12 weeks of treatment. Similarly, no such events have been reported after increasing the dose after 12 weeks in the EAP. Switching from prednisone to vamorolone in VBP15-004 was not related to an increase in behavioural problems. No increased risk for long-term treatment could be deduced from Pool 3. Given that behavioural problems were not severe or serious, were not considered clinically relevant or required active management or led to discontinuation, it is agreed that a warning statement might not be of clear value. Moreover, additional information in section 4.8 regarding behavioural ADRs (description of selected AEs section and update of an increased frequency of behavioural events in younger patients has been included.

The incidence of gastrointestinal symptoms was similar across treatment groups up to Week 24 in Pool 1, with vomiting being more frequently reported in patients from both vamorolone groups as compared to placebo and prednisone. All patients in the 2 to <4 years cohort treated with 6 mg/kg in study VBP15-006 reported GI disorders TEAEs during the first 12 weeks of treatment. None of the events was clinically significant. No increased risk was noted upon switching from placebo/ prednisone to vamorolone.

Vamorolone did not induce diabetic conditions in paediatric patients with DMD in study VBP15-004. Fasting glucose and HbA1c remained nearly unchanged in all groups. However, vamorolone led to a

dose-dependent increase in fasting insulin, which was found higher in the vamorolone 6 mg/kg group as compared to prednisone. Likewise, nearly half of all patients on vamorolone 6 mg/kg had shifts from normal to high insulin with fewer patients in the prednisone, vamorolone 2 mg/kg, and placebo group (26.9%, 18.2%, and 0%). Moreover, switching from prednisone to vamorolone 6 mg/kg (but not to vamorolone 2 mg/kg) in the EAP led to an increase in fasting insulin from normal to high. Glucose and HbA1c remained nearly unaffected after switching. In Pool 3, fasting insulin further increased dose-related up to Month 12. The data are indicative of adaptive ß-cell processes to maintain normoglycaemia that are more pronounced with the high dose (6 mg/kg) vamorolone than with the prednisone dose used in the clinical trial. In line with study VBP15-004, there were no relevant changes for fasting glucose or HbA1c for subjects across the age groups in study VBP15-006 receiving vamorolone 2 mg/kg and 6 mg/kg; however, no data on fasting insulin have been presented due to a shipment error. Any long-term implications on glucose homeostasis remain unknown and will be more relevant for patients with pre-existing risk factors. There was no evidence for an increased incidence of diabetic condition AESI in Pool 1 for vamorolone, while AESI in Pool 3 occurred more frequently in the 6 mg/kg group as compared to 2 mg/kg (10% vs. 1%). One subject in the EAP reported a SAE of new onset "diabetes mellitus type 1" rated not related to vamorolone, which is agreed to given that it is of autoimmune origin. The product information includes adequate warning with regard to diabetic conditions.

There were few AESIs of skin and hair changes in Pool 1 (i.e. hypertrichosis, erythema, skin hyperpigmentation) in patients on vamorolone. Over the long term, the frequency of these events remained low and similar in both vamorolone groups.

There were no reports of cataracts or glaucoma in any subject treated for up to 30 months.

No evidence for an increased risk for infections with vamorolone was observed, and specific viral and opportunistic infections typically observed with immune suppression were not reported. During the first 6 months of controlled treatment, the incidence of infection AESI was slightly lower for the vamorolone groups than for placebo but similar to prednisone. Although, infections and infestations being the most frequently reported SOC throughout the DMD studies, the pattern of infections was in line with seasonal infections and those seen in immunocompetent paediatric patients. One event of gastroenteritis viral (vamorolone 2 mg/kg) was rated serious but did not lead to discontinuation. No additional concern derives from Pool 3 with regard to the infection AESI. Vaccination should be considered to safeguard immuno-compromised patients from serious infections. A warning in section 4.4. recommending vaccination against varicella zoster virus for patients without history of chicken pox or vaccination and a contraindication for the use of live or live-attenuated vaccines in the 6 weeks prior to starting treatment and during the treatment in section 4.3 has been included. 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 has been included in section 4.4 of the SmPC. The absence of a relevant safety issue of vamorolone with regard to infections is probably related to its differential effects on blood cells. A dose-dependent increase in lymphocyte counts (~23% and 50% from baseline for vamorolone 2 mg/kg and 6 mg/kg, respectively) was observed in the first weeks of treatment similar to prednisone, while monocyte and leukocyte counts behaved similarly for vamorolone 2 mg/kg and 6 mg/kg but remained lower as compared to prednisone. While treatment with prednisone was associated with up to 100% increase in neutrophil counts, these (and immature granulocytes) remained nearly unchanged in vamorolone- and placebo-treated subjects. In Pool 3, all white blood cell lines slightly increased in a dose-dependent manner from baseline up to Month 30.

An effect of vamorolone on blood pressure could not be deduced from a cardiovascular and respiratory safety pharmacology study in telemetered Beagle dogs during the preclinical programme, and likewise, no effects were noted in single and repeated dose studies in dogs. Baseline DBP and SBP in Pool 1 show a tendency for increased **blood pressure** in in all treatment groups. Mean DBP change from baseline up to Month 6 was higher with vamorolone 6 mg/kg as compared to the other treatment groups, with the

highest mean change from baseline at Week 18 (5 mm/Hg). For SBP, higher mean change increases were reported for both vamorolone groups compared to placebo and prednisone of 5 mmHg (at Week 24). Data on blood pressure collected in the clinical trials was not sufficiently standardised to robustly assess an effect of the drug on blood pressure. In addition, assessments of blood pressure in clinical trials with young children are known to be highly challenging. Studies VBP15-002/003/LTE and VBP15-004 only collected single blood pressure measurements, which could explain high variability, which in turn hampers an accurate assessment of small changes in blood pressure over time. More subjects presented with shifts from Stage 1 or lower to Stage 2 hypertension in SBP than in DBP but most of the shifts occurred at a single visit without confirmation at the next consecutive visit. In Pool 3, values over time for both diastolic and systolic blood pressure slightly increased from baseline over 12 to 30 months in the vamorolone 2 mg/kg group but remained roughly stable for the 6 mg/kg group after adjusting for height and age (percentiles and z-scores) to correct for the expected increase in blood pressure in growing children. Shifts from baseline Stage 1 or lower to Stage 2 hypertension for DBP and SBP were dose-dependent in Pool 3. No additional concern arose from study VBP15-006 with regard to blood pressure changes. No additional TEAEs have been reported as per the DCO 21 July 2023 in subjects participating in an EAP. Given the above-mentioned observations, a warning statement as well as monitoring of blood pressure in the SmPC has been discussed. In summary, the blood pressure increases with vamorolone are not in line with animal findings, and a plausible mechanism that could explain increase is absent. Moreover, clinical data are of limited quality to establish an effect of vamorolone on blood pressure and show high variability of measurements. Last not least, the observed weight increases with vamorolone may have contributed to the changes in blood pressure. At present, the overall data do not support a warning while long-term outcome needs to be addressed post-marketing. Hypertension is included as missing information regarding safety on long-term use in the RMP.

ALT and AST were not considered specific parameters to assess hepatic function due the underlying disease (muscle loss) because these were already found increased at baseline and fluctuated during the studies. No relevant changes in liver specific mean GGT, GLDH, ALP or bilirubin values occurred in any group in Pool 1, and there was no consistent pattern to support treatment related changes over time. Clinically significant changes of specific parameters GLDH and GGT were either similar across treatment groups (GLDH) or even absent (GGT). Upon clarification by the applicant, there were three cases of treatment-emergent Hy's law in Pool 1 not meeting criteria for Hy's law at screening/ at baseline, one patient on prednisone and two patients on vamorolone 6 mg/kg. While Gilbert's syndrome was suspected in one of the vamorolone 6 mg/kg patients (direct bilirubin was normal), a single patient had GLDH > 3x ULN and increases in other liver parameters in the context of *hepatitis acute*, and this case remains suspect of Hy's law (drug-induced liver injury) while no firm conclusion can be drawn based on limited information available. The patient was reported with splenomegaly at various time points. Two additional cases of treatment-emergent Hy's law criteria were reported in Pool 3, one on vamorolone 2 mg/kg and one on 6 mg/kg. While no concomitant increases of ALT, AST, GGT or GLDH or signs of liver damage were noted for these patients, direct bilirubin values are not available. Seven TEAEs in line with potential hepatic impairment have been reported across all studies. 3 out of 7 occurred in VBP15-001 (hepatic enzyme increased on placebo, ALT increased on vamorolone 20 mg/kg, and blood bilirubin increased on vamorolone 8 mg/kg). Hyperbilirubinaemia (2 mg/kg dose) and hepatitis acute (6 mg/kg) occurred in study VBP15-004. Two TEAEs were reported in Pool 3, hepatomegaly in the 2 mg/kg group and ALT increased in the 6 mg/kg group. Overall, three TEAEs related to liver function (acute hepatitis, increased hepatic enzyme, and increased alanine aminotransferase) led to the discontinuation of vamorolone treatment during the DMD programme. Hepatic toxicity is referred to as important potential risk in the RMP and the applicant agrees to further characterise and quantify hepatotoxicity (amongst other potential safety issues) as part of the long-term safety in an observational PASS. Further, section 4.4 of the SmPC states that vamorolone has not been studied in patients with severe pre-existing hepatic injury (Child-Pugh class C) and must not be used in these patients (see section 4.3).

Haematology parameters of red blood cells, haemoglobin and haematocrit showed dose-dependent mean increases mainly around the first 6 to 12 weeks of treatment that were similar for 6 mg/kg vamorolone and prednisone; no progressive increases were noted with longer treatment duration.

No changes in lipid profile were noted in the placebo group, while HDL cholesterol and triglycerides dose-dependently increased for vamorolone from baseline in Pool 1. Increases were lower compared to prednisone for triglycerides and similar for HDL. LDL was found to be decreased from baseline up to Month 6 in Pool 1 in all treatment groups and no pattern could be identified with longer treatment duration (Pool 3).

The following noteworthy observations have been made for chemistry parameters*:* alkaline phosphatase decreased with prednisone but not with vamorolone or placebo in Pool 1; however, in Pool 3, ALP progressively decreased from Month 12, especially in the vamorolone 6 mg/kg group, questioning preservation of a "bone-saving" effect with longer treatment duration.

Mean changes from baseline in 25-OH-Vitamin D were low and not related to dose, and did not support a progressive decrease over longer duration of treatment contrasting a dose-related reporting of Vitamin D deficiency TEAEs in the clinical studies. Upon review of TEAEs in line with vitamin D deficiency, several methodological issues were noted, i.e., more frequent reporting after implementation of reference ranges in Period 2 of study VBP15-004 (but not during Period 1), and use of the adult reference ranges for Vitamin D instead of lower paediatric reference ranges. Shift analyses for 25-OH vitamin D in Pool 1 and Pool 3 do not indicate an increased incidence of shifts from normal to low during treatment with vamorolone, thus, inclusion as an ADR in section 4.8 of the SmPC is not considered necessary.

Thyroid function has not been assessed in the vamorolone clinical programme. However, it seems reasonable and in line with glucocorticoid effects to conclude that – depending on the thyroid function of the patient – clearance might be reduced or increased. Respective warning has been included in section 4.4 of the SmPC. Few and random assessments of thyroid function in patients during VBP15-004 do not indicate reduction of TSH with vamorolone.

The DMD population is known to be susceptible to ECG changes (Thrush et al. 2009). Vamorolone was not found to affect ECG parameters in a chronic toxicity study in dogs in the preclinical programme. Some significant ECG changes have been noted for vamorolone in Pool 1 and Pool 3, which may in part be contributed to the underlying disease (abnormal Q waves, right bundle branch block). Suspicious ECG results of 11 subjects from Pool 3, including those with perceived QTcF >60 msec and >500 msec, have been transferred to an external cardiologist. Upon review, none of these subjects was confirmed to have had an abnormal ECG. The expert identified transcription errors of ECG values in the SCS, reporting of QTcB instead of QTcF, and ECG machine failures (false positives). Thus, vamorolone does not bear an effect on cardiac conduction in paediatric subjects with DMD. There were 3 subjects on vamorolone with increases from baseline in QTcF of >60 msec in Pool 1.

Special populations have been studied, including (amongst others) age groups (<5 and ≥5 years), and subjects with hepatic impairment. AESIs of behaviour problems, GI symptoms, as well as rates of infections were more frequently reported in the younger patients. In contrast, higher reporting for bone fractures, Cushingoid features and weight gain was noted in the older subgroup. In study VBP15-HI, a single dose of 2 mg/kg vamorolone caused an increase in exposure in patients with moderate HI compared to age, weight and sex matched healthy adults. Consequently, the dose administered in DMD patients with HI should not exceed 2 mg/kg. A contraindication for patients with Child-Pugh C (severe HI) has been included in section 4.3 given the observed increase in exposure in healthy volunteers with moderate HI and known liver effects of GCs.

The potential for clinically significant drug-drug interactions with vamorolone as victim or perpetrator drug seems not to be of clinical concern given that elimination occurs by various routes involving

numerous metabolic enzymes. This is supported by results of an in-vivo DDI study and an in-vitro study. Wording with regard to the (uneventful) outcome of these studies is depicted in section 4.5 of the SmPC.

2.6.10. Conclusions on the clinical safety

The safety database for vamorolone includes 163 patients in the age group 4 to <7 years treated with doses of 2 mg/kg and 6 mg/kg in the clinical programme, which is considered acceptable when considering that DMD is an orphan condition affecting 1 in 3600 – 9300 live male births. In order to extrapolate clinical safety from the reference population to the broader target population, the applicant provided preliminary data from the ongoing phase 2 open-label study VBP15-006 that contribute to clinical safety of vamorolone in steroid-naïve patients 2 to <4 years of age and patients 7 to <18 years with and without previous steroid treatment. The target population has been revised during the procedure from 2 years of age and older to 4 years of age and older, thus, it does not include paediatric patients 2 to <4 years of age.

The main limitations of the clinical programme are the restricted study population and the lack of active prednisone control beyond 6 months. While the overall length of follow-up in the clinical programme is rather short for concluding on the long-term safety of vamorolone as compared to prednisone, additional safety data from the EAPs are meanwhile available for 99 patients with a median exposure to vamorolone of 2.1 years in addition to the duration of exposure in the parent clinical studies (the longest duration was 4.4 years in the EAP as per the DCO).

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.

Based on the controlled safety data up to 6 months it appears that vamorolone - compared to prednisone at the administered dose – does not induce growth inhibition or bone loss, while effects on glucose metabolism, blood pressure and infections (as a consequence of immunosuppression) are uncertain. Despite the lack of an extended active prednisone control in study VBP15-004, the preliminary safety data from the EAPs suggest that the potential advantages of vamorolone over prednisone can probably be maintained with longer treatment while supportive external comparison with different GC treatment regimens from the FOR-DMD study needs to be interpreted with caution based on known limitations.

On the other hand, some AESI were found to occur with a frequency for the recommended vamorolone 6 mg/kg dose at least in the same magnitude or even slightly higher as compared to prednisone in the controlled study period, e.g., adrenal suppression and Cushingoid features. The long-term consequences of adrenal insufficiency following discontinuation of vamorolone cannot be determined with the available data. Moreover, the increase in weight and BMI was higher in the vamorolone 6 mg/kg group as compared to prednisone and led to down titration in 10 patients in the uncontrolled setting. Down titration to lower doses, i.e. 4 mg/kg (proposed as a consequence of the updated popPK model) or 2 mg/kg is considered to mitigate tolerability issues (e.g. weight gain) with vamorolone, while maintaining the patient on the highest tolerable dose should be aimed at.

The provided short-term safety data from patients studied in the ongoing study VBP15-006 and long-term safety through expanded access programmes allow extrapolation of clinical safety from the reference population (patients 4 to <7 years of age) to patients >7 years of age with and without steroid experience.

In summary, the identified safety issues for vamorolone across the applied age range appear manageable with the proposed risk minimisation measures, i.e. adequate labelling in the product information and

routine pharmacovigilance activities. Moreover, an observational PASS study has been proposed to further characterise and quantify the long-term safety profile of vamorolone.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 19: 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, hyperglycaemia, dyslipidaemia and hypertension)

2.7.2. Pharmacovigilance plan

Table 20: Ongoing 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, hyperglycaemia, dyslipidaemia and hypertension)" Missing information "use in patients above 12 years of age"	Final protocol	Q3 2024

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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) Ongoing	To evaluate safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy data	Missing information "use in patients above 12 years of age"	Last Patient Last Visit Final Clinical Study Report	30/06/2024 Q4 2024

2.7.3. Risk minimisation measures

Table 21: 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 sections 4.4, 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
Important potential risk 2: Hepatotoxicity	**Routine risk minimisation measures:** SmPC sections 4.2, 4.3 and 4.4 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
Important potential risk 3: Acute Adrenal insufficiency (adrenal crisis)	**Routine risk minimisation measures:** SmPC sections 4.2 and 4.4 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 to further characterise and quantify long-term safety profile of Agamree

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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:** • VBP15-006, Final study report due date: Q4 2024 • An observational PASS to further characterise and quantify long-term safety profile of Agamree
Missing information 2: Safety on long-term use (in particular regarding bone fractures, weight gain, growth, hyperglycaemia, dyslipidaemia 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

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 26. October 2023.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Agamree (vamorolone) is included in the additional monitoring list as it is a new active substance which on 1 January 2011 was not in a medicinal product authorised in the EU.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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).

The current application of vamorolone is for the treatment of DMD in patients aged 4 years and older, which reflects the majority of the DMD patient population.

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

3.1.2. Available therapies and unmet medical need

There are no approved treatments to cure or stop the ultimately fatal progression of DMD. Even with the introduction in the 1990s of assisted ventilation in the later stages of the disease, the mean age of survival (for those ventilated patients who do not develop early and severe cardiomyopathy) is still only 24 years. Supportive care (e.g., physiotherapy) and glucocorticoids remain the mainstays of DMD treatment and should continue after loss of ambulation (Birnkrant *et al*., 2018). Although, glucocorticoid treatment recommended by pertinent treatment guidelines is well-established, i.e. prednisone and deflazacort, these treatments are not licensed for the treatment of DMD in Europe. Moreover, uncertainty exists regarding the most adequate corticosteroid dosing regimen and duration of treatment for DMD.

Translarna (ataluren) has received conditional marketing authorisation in the EU but its use is limited to ambulatory DMD patients aged 2 years and older with nonsense mutations. Therefore, an unmet medical need remains for the broader DMD patient population.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a single phase 2b, multicentre, randomised, double-blind, parallel group, placebo (n= 30) - and active-controlled (prednisone, n = 31) study of 24 weeks duration

with double-blind extension till week 48 to assess the efficacy and safety of 2 dosages of vamorolone, i.e. 6 mg/kg/day (n= 30) and 2 mg/kg/day (n= 30) in ambulant boys with DMD.

The study included boys aged ≥4 years and <7 years with a centrally confirmed diagnosis of DMD based on gene analysis and/or a muscle biopsy sample, tested for the presence of dystrophin protein. Included subjects had to be able to walk independently without assistive device and be able to complete the

TTSTAND without assistance in <10 seconds. With regard to statistical aspects, the primary Analysis of the primary efficacy endpoint for EMA consisted of a missing data imputation while for FDA only the observed measurements were used (without multiple imputation).

A pre-planned matched comparison of both vamorolone doses over the 48-treatment period to the continuous prednisone and deflazacort groups from the external FOR-DMD study was also provided. The FOR-DMD study was a multiple site, randomised, prospective, multicenter, double-blind study to compare three corticosteroid regimens (0.75 mg/kg/day prednisone; 0.75 mg/kg/day prednisone 10 days on/10 days off; 0.9 mg/kg/day deflazacort) over a treatment period of 36 to 60 months in 196 boys aged ≥ 4 years and < 8 years with confirmed DMD.

3.2. Favourable effects

The primary endpoint was the change from baseline in TTSTAND velocity for the vamorolone 6 mg/kg treatment arm compared vs placebo at week 24. TTSTAND velocity increased for vamorolone from mean (SD) 0.186 (0.0588) to mean (SD) 0.242 (0.0785) rises/sec and slightly decreased in the placebo group from mean (SD) 0.200 (0.0642) to mean (SD) 0.193 (0.0918) rises/sec at Week 24. The LSM difference for vamorolone 6 mg/kg from placebo was 0.0586 rises/sec in the primary EMA analysis (p = 0.0018) and 0.0603 rises/sec in the primary FDA analysis (p= 0.0018).

Several sensitivity analyses and supportive analyses have been performed that were in line with the results of the primary analysis. Overall, sensitivity analyses demonstrate that the COVID-19 pandemic, missing data, and influential observations did not affect the results of the primary analysis at Week 24. The primary EMA analysis repeated in the ITT analysis set was also in accordance with the primary EMA analysis (mITT population).

With respect to the first pre-specified secondary endpoint, change in TTSTAND velocity for the vamorolone 2 mg/kg treatment arm compared to placebo at week 24, a statistically significant difference was demonstrated when vamorolone was compared against placebo (p = 0.0196). TTSTAND velocity increased in the vamorolone 2 mg/kg group from 0.184 to 0.225 rises/sec and slightly decreased in the placebo arm from 0.200 to 0.193 rises/sec at week 24. The LSM difference for vamorolone 2 mg/kg from placebo was 0.0430 rises/sec (EMA analysis) and comparable to the primary FDA analysis.

Regarding the second and third pre-specified secondary endpoint, change from baseline to week 24 in the 6MWT distance for vamorolone 6 mg/kg and 2 mg/kg vs placebo, statistically significant differences were demonstrated for the vamorolone treatment arms when compared against placebo (p=0.0117 and p = 0.0112, respectively). While in the vamorolone treatment groups the 6MWT distance increased it showed some decline under placebo. The LSM (SE) change from baseline for placebo, vamorolone 6 mg/kg and 2 mg/kg was -11.37 (10.6082), 24.57 (10.0582) and 24.98 (10.0352), respectively. The LSM difference for vamorolone 6 mg/kg and 2 mg/kg against placebo was 35.9 meters and 36.2 meters, respectively.

With respect to change from baseline to week 24 in the 6MWT distance for vamorolone 6 mg/kg and 2 mg/kg vs prednisone, improvements from baseline at Week 24 were similar for both vamorolone treatment groups (6 mg/kg and 2 mg/kg) while subjects under prednisone treatment improved numerically more (EMA analysis) with LSM (SE) changes from baseline for prednisone and vamorolone

6 mg/kg and 2 mg/kg of 44.12 (9.6444), 24.98 (10.0352) and 24.57 (10.0582), respectively. The LSM difference for change from baseline for vamorolone 6 mg/kg and 2 mg/kg each against prednisone was -19.55 (p = 0.14) and -19.14 (p = 0.17), respectively.

In the comparison of efficacy endpoints between the vamorolone groups and prednisone for changes from baseline at week 24 that focused on global assessments, to account for baseline imbalances and to allow to examine efficacy endpoints globally in spite of different units, the improvements seen with vamorolone 6 mg/kg in TTSTAND, TTRW, and TTCLIMB velocity were very similar to those seen with prednisone at Week 24, while for the 6MWT and the NSAA score prednisone provided numerically better results. Overall, the improvements seen with vamorolone 2 mg/kg were slightly smaller than those seen with prednisone.

The improvements in TTSTAND velocity, TTRW velocity and NSAA score seen with vamorolone 6 mg/kg at 24 weeks were maintained for up to 48 weeks of treatment. There was no decrease across the relevant outcome parameters but an additional increase in the 6MWT distance from Week 24 to Week 48. Results with the 6 mg/kg dosage were generally better than those for the vamorolone 2 mg/kg dosage.

When subjects switched from prednisone to vamorolone 6 mg/kg at week 24, the mean TTSTAND velocity, TTRW velocity and NSAA score only slightly decreased and TTCLIMB velocity minimally increased. There was a small decline in the 6MWT distance after the switch from prednisone to vamorolone, while subjects who were continuously treated with vamorolone 6 mg/kg continued to improve until Week 48. When subjects switched from prednisone to vamorolone 2 mg/kg, the mean TTSTAND and TTCLIMB velocity decreased more than the 6MWTD and TTRW velocity. No mean changes were seen for the NSAA score.

Subgroup analyses of TTSTAND velocity yielded comparable results across the different subgroups favouring vamorolone 6 mg/kg against placebo although they were only based on small number of patients.

Results on motor function endpoints in an additional post-hoc subgroup of patients with a 6MWT distance <350 meters were comparable to those in the primary analysis population when vamorolone 6 mg/kg was compared against placebo for change from baseline to Week 24. Although effects observed for the vamorolone 2 mg/kg group in comparison to placebo were smaller, they point in the same direction and were nominally significant.

3.3. Uncertainties and limitations about favourable effects

The updated but preliminary PK modelling results based on data from study VBP15-006 indicate that the exposure to vamorolone from the ROS2 formulation (final formulation) for the 6 mg/kg dose is significantly higher than from the ROS1 formulation that has been used in the pivotal study, often significantly exceeding the upper threshold of the target exposure range. In contrast, the 2 mg/kg dose in humans is consistently below the lower pre-defined threshold. The popPK model was further refined to better simulate a potential effective dose for patients 2 to 4 years old, who have originally been envisaged for being part of the indication. Moreover, this dose should also be used to mitigate tolerability issues. According to simulations, AUC levels of ROS2 formulation are increased about 20% across all doses compared to ROS1. 4 mg/kg of ROS2 is expected to achieve 82% of the exposure of 6 mg/kg ROS1 and 246% of 2 mg/kg ROS1. Predicted drug exposure of 4 mg/kg ROS2 for all age groups is within the originally predefined exposure target range of the 5th to 95th exposure percentile of 6 mg/kg of the ROS1 formulation in the age range 4-7 years. Although, the original target range appears somewhat arbitrarily defined it still provides some valuable insight into the potential efficacy of other doses, as the ROS1 6 mg/kg dose is the primary source of efficacy information.

Since even the 2 mg/kg dose with the lower exposure levels of the ROS1 formulation, which are well outside the predefined target exposure range provided evidence of some clinical benefit (despite not showing sufficient maintenance of efficacy in the reference population 4 to 7 years-old), there is a strong rational that the 4 mg/kg ROS2 dose should be well within the effective dose range based on exposure data. Moreover, a majority of subjects in the EAP/ CUPs with available dosing information are likewise being dosed at 4 mg/kg and this dose appears acceptable from a clinical safety perspective.

Regarding maintenance of efficacy, results across the efficacy outcome measures for the vamorolone 2 mg/kg dose were rather inconsistent with observed clinically significant declines in relevant functional outcome parameters at Week 48, i.e. TTSTAND velocity and 6MWT but only minimal decrease in the NSAA score. While evidence of short-term efficacy for the 2 mg/kg vamorolone dose based on the results of study VBP15-004 is not questionable, maintenance of efficacy could still not convincingly be demonstrated.

Therefore, an intermediate dose of 4 mg/kg also used in the EAPs was considered to be suitable as a reduced dose in case of tolerability issues. Based on the updated popPK model it could be shown that the AUC distributions predicted for the 4 mg/kg dose (ROS2) overlap with the 6 mg/kg dose (ROS1 fed) for the majority of patients in the age range 4 years and older, which supports that the exposure of the 4 mg/kg dose is within the target range. Based on clinical safety, this dose might, however, still not sufficiently mitigate all tolerability issues, mainly weight gain. Thus, the 2 mg/kg dose - despite uncertainties on the maintenance of effect – remains an alternative for down titration provided that patients should be maintained on the highest tolerable dose. This is in line with clinical practice with other GC regimens in the treatment of DMD.

The comparisons of the vamorolone dose groups to both, prednisone and deflazacort from a matched external control group from the study FOR-DMD are of limited value. However, even if only the unadjusted confidence intervals are considered, the results indicate that vamorolone at the 2 mg/kg dosage has inferior efficacy compared to both comparators, i.e. prednisone and deflazacort. Although the results for the 6 mg/kg dosage appear more similar esp. to those for deflazacort, equivalent efficacy cannot be concluded for methodological reasons. Hence, equivalent efficacy cannot be established based on this comparison with an external control group.

3.4. Unfavourable effects

Vamorolone shares the effective transcriptional repression at the GR (i.e. inhibition of NFκB-mediated inflammations) with established corticosteroids. Due to its structural difference, however, vamorolone shows limited transactivation of genes, whose expression is driven by the GRE. This may lower its potential for typical GC side effects. The structural peculiarity of vamorolone further entails that it acts as an MR antagonist, which contrasts the agonistic MR activity of other GCs. In addition, vamorolone is not a substrate for 11-β HSD enzymes, thereby potentially reducing the risk for typical GC side effects (muscle atrophy, bone loss, insulin resistance, hypertension and weight gain).

The target organs for vamorolone toxicities identified from non-clinical studies comprised the lymphatic system, liver/gall bladder, pancreas, adrenal glands and kidneys, reproductive organs of both sexes, thyroid, salivary glands, skin and skeletal muscle.

The safety of vamorolone 2- 6 mg/kg has been evaluated in 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. Preliminary safety data for patients aged 2 to <4 years (10 patients on vamorolone 2 mg/kg, and 6 of 10 patients planned on 6 mg/kg) and 7 to <18 years (9 patients on vamorolone 2 mg/kg, and 4 patients on 6 mg/kg, either being steroid-naïve or steroid-treated) derive from the ongoing PIP study VBP15-006

with a data cut-off of 15 March 2023. As of 15 March 2023, 171 patients continued vamorolone use through various EAP (including CUPs), with safety data available from patients aged 2-17 years.

No patient died in the DMD programme. Two patients discontinued vamorolone across the four clinical studies (due to muscular weakness and hepatitis acute). A total of 8 SAEs were reported for vamorolone across these studies (none for placebo or prednisone). In addition, 18 SAEs were reported in EUPs and CUPs up to March 2023. None of these SAEs was rated related to vamorolone.

Like glucocorticoids, vamorolone exhibited some characteristic properties, such as adrenal suppression, Cushingoid features, weight gain, and behavioural changes. These had similar or higher incidences in the vamorolone 6 mg/kg group when compared with prednisone in the controlled period in study VBP15-004.

Vamorolone induced adverse adrenal cortical atrophies in repeat-dose toxicity studies in mice and dogs, which did not completely reverse following vamorolone cessation. Similarly, vamorolone caused a dose-dependent adrenal suppression in human subjects. 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.

Cushingoid features 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 a defined ADR in section 4.8 of the SmPC.

Long-term vamorolone administration in repeat-toxicity studies was found to increase food consumption leading to weight gain in mice and dogs, which tended to recover after vamorolone administration was terminated. Treatment with vamorolone in DMD patients was associated with a dose-dependent increase in body weight and BMI mainly during the first 6 months of treatment, which was supported by an increase in total body fat mass that was 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 subjects versus 1 subject). Median changes in BMI dose-dependently increased with longer treatment of up to 30 months, while median z-score changes fluctuated. AESIs of weight gain in Pool 1 (24-week data) were more frequently reported with vamorolone 6 mg/kg as compared with 2 mg/kg (17.9% vs. 3.3%) and more frequently than with prednisone (9.7%) and placebo (6.9%), but did not further increase with longer treatment duration. Weight increased and increased appetite are defined ADRs for vamorolone in section 4.8 of the SmPC.

In juvenile toxicity studies, vamorolone doses ≥15 mg/kg reduced tibia and body length pointing towards growth retardation known from other glucocorticoids. However, clinical vamorolone therapy 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.

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%).

Bone age was evaluated in study VBP15-LTE and found to be delayed after 30 months of vamorolone exposure (mean difference between bone age and chronological age was -1.1 ± 1.02 years). Mean changes in bone biomarkers osteocalcin, s-CTX1, and P1NP from Baseline to Month 6 were more similar in the placebo and vamorolone 2 and 6 mg/kg groups, whereas these bone markers decreased in the prednisone group. Heterogeneous results were found for bone biomarkers when analysed over a 2.5-year period.

Vamorolone did not induce neurobehavioural changes in adult and juvenile mice, but adversely decreased activity and impaired limb function at 50 mg/kg/day doses in the chronic toxicity study in dogs, which might be reflective of psychiatric symptoms known from clinical therapy of high glucocorticoid doses (Harris *et al.*, 2015). Behavioural 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. AESI of behavioural problems 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 defined as 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 clinical studies 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.

Pancreatic islet hypertrophy was noted in the chronic toxicity study in mice at vamorolone doses of 45 mg/kg/day, which was interpreted as adaptive change due to the stimulation of hepatic gluconeogenesis by vamorolone. 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. One subject in the EAP reported a SAE of new onset "diabetes mellitus type 1", which is of autoimmune origin and thus not considered related.

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. Immunosuppression is an important potential risk for vamorolone.

Hypertension is a known adverse effect of glucocorticoids, but blood pressure was not affected by vamorolone in single- and repeated dose studies in dogs. In patients, 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.

Vamorolone was found to reversibly elevate triglycerides and cholesterol in long-term toxicity studies in mice and dogs. Effects of vamorolone on clinical lipid parameters in Pool 1 include dose-dependent increases in HDL cholesterol and triglycerides from baseline, which were lower (for triglycerides) or similar (for HDL) as for prednisone. No relevant mean changes were seen in LDL cholesterol while shifts from normal to high LDL in Pool 1 solely occurred in the vamorolone groups (3.4% and 10.7%, respectively).

Liver function: In all toxicity studies in mice and dogs, ≥10 mg/kg/day vamorolone induced partially reversible liver changes (hypertrophy, vacuolation, inflammation/ necrosis) associated with elevated hepatic enzymes. In patients, ALT and AST were already increased at baseline in line with the underlying muscle damage, while sporadic GLDH and bilirubin values above ULN were additionally noted. Small increases in mean GGT and GLDH have been noted mainly during the first 6 months. Two TEAEs of hepatobiliary disorders were reported with vamorolone in the controlled part of VBP15-004 (hepatitis acute and hyperbilirubinaemia). Across all studies, two additional TEAEs were reported (hepatomegaly and ALT increased). 2 patients treated with vamorolone (and one patient on prednisone) met the criteria for treatment-emergent Hy's law in Pool 1 (with an additional 2 patients in Pool 3). One of these subjects was diagnosed with "acute hepatitis". The event of "Acute hepatitis" and a TEAE of ALT increased in a pharmacology study (VAM 20 mg/kg) led to treatment discontinuation. Hepatotoxicity is referred to as important potential risk in the RMP based on the well-known potential of glucocorticoids to exert hepatotoxic effects.

TEAEs of Vitamin D deficiency were reported for vamorolone in a dose-dependent manner (6.7% and 10.7% for vamorolone 2 mg/kg and 6 mg/kg) and in 3.2% of patients on prednisone (not on placebo) and increased after switch from prednisone to vamorolone 6 mg/kg (0% and 13.3%).

Skin and hair changes 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.

There were no reports of cataracts or glaucoma in any subject treated for up to 2.5 years.

3.5. Uncertainties and limitations about unfavourable effects

Overall, the safety profile of patients aged 4 to <7 years is based on a limited controlled dataset of 58 patients exposed to vamorolone 2 – 6 mg/kg in study VBP15-004, with comparison to placebo and active prednisone for 6 months only. Uncontrolled data are available from Period 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 are thus limited even though, additional data have become 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. 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%).

This is supported by findings from a *post hoc* analysis separating patients by age group <5 years and ≥5 years based on Pool 3 data for the reference population with quantitative differences in AESI, especially higher incidences of behaviour problems, GI symptoms, but also higher rates of infections in the younger compared to the older subgroup.

Identified AESI for vamorolone with an impact on long-term safety (i.e. bone health/ fractures, adrenal suppression, weight gain) are difficult to be judged for their implications in very young patients since these few young patients so far have a rather short median exposure to vamorolone of 9 months.

Although, the safety profile in patients 7 to <12 years and 12 to <18 years is based on a limited number of patients at present, data are continuously collected in EAPs for patients treated with vamorolone during VBP15-002, -003, VBP15-LTE, VBP15-004, and VBP15-006.

Importantly, a delay in puberty is a well-known side effect with prolonged glucocorticoid treatment. Vamorolone has not been clinically studied for affecting pubertal development and any effect is unknown at present. Although, vamorolone did not affect male sexual maturation and fertility in juvenile mice, incompletely reversible adverse sperm degenerations and reduced prostate exudate were observed after 50 mg/kg/day vamorolone in male in dogs of the chronic toxicity study, which seems mechanistically related to the known interference of exogenous glucocorticoids with the hypothalamus-pituitary-gonadal axis and the direct suppression of testicular steroidogenesis (reviewed by Whirledge and Cidlowski, 2010). The androgen biosynthesis can be further impacted by adrenal insufficiency. Additional information on pubertal development, i.e., on the hypothalamic-pituitary-gonadal axis, with vamorolone 6 mg/kg will be collected in an additional cohort of 10 patients aged 12 to <18 years in study VBP15-006. The extent of previous steroid treatment might, however, compromise the interpretation. The use in patients above 12 years of age is missing information in the RMP.

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, adrenal insufficiency, hyperglycaemia, dyslipidaemia and hypertension.

Uncertainty has been raised regarding 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. This has been dealt with inclusion of cautious wording in the product information. So far, only a single SAE of adrenal insufficiency has been reported in a patient in the EAP but 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. A warning regarding use of a steroid emergency card has been included in the SmPC. However, revision is needed according to PRAC Rapp comments (patient alert card; SmPC).

Uncertainty has been raised regarding appropriate management of weight increases: During VBP15-LTE, 10 of 11 patients on vamorolone 6 mg/kg were down-titrated to 2 or 4 mg/kg because of weight gain TEAEs. For these 10 subjects, baseline weight/ BMI percentiles and z-scores were higher as in the 2 mg/kg and 6 mg/kg dominant dose groups, which probably predestined them for significant weight gain. Dose reduction led to stabilisation of weight in these patients. As per the DCO 21 July 2023 in the EAP, an exploratory analysis of the effect of down- and up-titration of vamorolone on weight changes was conducted (6 mg/kg, reduced to 4 mg/kg and 2 mg/kg, increased to 4 mg/kg). Uptitration from 2 to 4 mg/kg appears not to prevent from further increase in weight percentiles but probably at a similar annual rate of change as with 2 mg/kg. Dose reduction from 6 to 4 mg/kg led to a plateau in weight percentiles (i.e., no additional increase in weight percentile after dose reduction). While this analysis is informative regarding weight changes in a small sample size, dose reduction from 6 mg/kg to 4 mg/kg might not be sufficient in clinical practise to mitigate weight increases with vamorolone in all patients necessitating further reduction to 2 mg/kg in a subset of patients. Information and provision with age-appropriate dietary advice has been included in the product information.

Growth retardation is a well-known effect of glucocorticoid treatment of children and was also observed in juvenile mice administered vamorolone. However, no effect on growth could be retrieved for vamorolone based on controlled data up to 6 months and an effect also seems to be absent based on uncontrolled data up to 30 months compared to external FOR-DMD study data with conventional GCs.

Uncertainties have been raised regarding long-term effects on bone health, for which 'bone fractures' has been included as missing information in the RMP. Vertebral fractures have not been evaluated at baseline in study VBP15-002, therefore hampering interpretation of such fractures in 10.3% of patients after 30 months of treatment in VBP15-LTE. Biomarker data can only be supportive. There seems to be no difference between biomarkers of osteoblast activity between placebo and vamorolone based on Month 6 data (with clear decreases in the prednisone group). Moreover, osteoclast activity by CTX1 was found decreased for prednisone but increased for vamorolone, which is supported by an increase in CTX1 after the switch from prednisone to vamorolone in VBP15-004. While it is acknowledged that the interpretation of bone formation and resorption markers differs for different populations, i.e., bone metabolism in children is more complex, and greatly differs from that of adults as it reflects both skeletal growth and modeling (Rauchenzauner et al., 2007; Bowden et al., 2016), a clear correlation of increases/ decreases in the controlled part of study VBP15-004 is lacking. DXA measurements have also been conducted and longitudinal DXA measures of lumbar spine DXA and total body DXA (i.e. screening+W 24+W 48, screening+W 24, screening+W 48, or W 24+W 48) are available for ~50 – 67.5% of patients from study VBP15-004: Based on these data, a drug-related adverse effect on bone mineralisation cannot be deduced for vamorolone but for prednisone; thus, vamorolone is less likely to contribute to an increased risk for factures in paediatric DMD patients as compared to prednisone, while it remains unclear whether long-term treatment would elicit differential effects compared to an untreated (placebo) population.

The observed bone age delay of -1.1 ± 1.2 years compared to chronological age in study VBP15-LTE after 2.5 years of vamorolone exposure in 39 patients seems to be in line with literature data of a mean bone age delay of -1.6 ± 2.2 years ($p < 0.01$) after 5.2 years of classic glucocorticoid therapy in DMD

patients (Annexstad *et al*. 2019). However, in the absence of bone age determinations at baseline, these data are difficult to interpret. It should also be mentioned that bone age and the timing of onset of puberty are related. These are however minor issues in the context of the severity of the underlying disease.

Uncertainty remains with regard to long-term effects of vamorolone on glucose metabolism and insulin resistance**.** Vamorolone caused an increase in pancreatic islet activity in animal studies corroborated by a dose-dependent increase in fasting insulin in line with prednisone in Pool 1 (remaining constantly increased during longer treatment duration). The observed increase in fasting insulin can be interpreted as compensatory ß-cell adaption process to maintain normoglycaemia indicating decreased insulin sensitivity. No relevant changes were noted for fasting glucose and HbA1c, neither for short-term nor long-term treatment up to 30 months. However, it is generally thought that glucocorticoids result mainly in an increase in postprandial blood glucose levels (Clore et al. 2009). These data have not been evaluated for vamorolone in the clinical studies. The diabetogenic potential of vamorolone (hyperglycaemia) will be further evaluated post-marketing by means of a PASS.

Uncertainty has been raised whether the differential effects of vamorolone on leukocyte subpopulations as compared to conventional glucocorticoids, mainly pertaining to the absence of neutrophil count increases, prevents from acquiring infections typical for immunosuppression (e.g., opportunistic infections) during longer treatment duration. Section 4.4 of the SmPC includes a warning regarding the possibility for an increased risk for infections with vamorolone. Information on the use and consequences of live or live-attenuated vaccines is included in section 4.4 of the SmPC, while the use of live or live-attenuated vaccines is contraindicated 6 weeks prior to treatment initiation and during treatment (section 4.3).

At present, a risk for drug-induced liver injury with vamorolone cannot readily be inferred from clinical trial data. While liver function parameters bilirubin, GLDH, and GGT in Pool 1 and Pool 3 were not clearly affected by vamorolone, a number of cases suspect of Hy's law have been reported in Pool 1 and Pool 3; however, with some of them formally fulfilling criteria already at baseline, thus, not being suspect of treatment-emergent Hy's law. A single patient presenting with acute hepatitis and a post-baseline increase of GLDH >3x ULN, which was accompanied by GGT > ULN, remains suspect of DILI due to the timely course the absence of alternative causes. Moreover, an increase in vamorolone exposure was found in a dedicated hepatic impairment study in healthy volunteers with moderate HI entailing dose reduction in the product information (sections 4.2, 4.4, and 5.2). Therefore, and since patients with severe hepatic impairment were excluded from clinical studies with vamorolone, a contraindication has been included in section 4.3, and a reduced dose is to be applied in patients with moderate hepatic impairment.

While effects on blood pressure were not observed in preclinical studies in dogs, the absence of an effect in humans cannot be ruled out from comparative data during the first 6 months of treatment despite the fact that vamorolone does not share the mechanisms associated with GC-associated hypertension. It remains uncertain as to which extent the underlying disease (for example as a consequence of cardiomyopathy) and increases in weight as a consequence of vamorolone treatment contribute to small increases seen in SBP and DBP. Moreover, blood pressure measurements in the clinical trials were not sufficiently standardised. In addition, assessments of blood pressure in clinical trials with young children are known to be highly challenging. Studies VBP15-002/003/LTE and VBP15-004 collected single blood pressure measurements only, which could explain a high variability, which in turn hampers an accurate assessment of small changes in blood pressure over time. Hypertension will be further addressed as part of safety on long-term use in the RMP.

Although, some scientific literature supports vitamin D metabolism to be affected by glucocorticoids, thereby decreasing the synthesis of active vitamin D and impairing its biological action at the tissue

level. (Mazziotti et al., 2018; Catalano et al., 2022), laboratory 25-Hydroxy-Vitamin D values lacked a clear decrease with vamorolone across studies and are thus not in support of the reports of some TEAEs in the clinical DMD studies. Shift analyses for 25-OH vitamin D in Pool 1 and Pool 3 do not indicate an increased incidence of shifts from normal to low during treatment with vamorolone.

It is known that metabolic clearance of glucocorticoids is decreased in hypothyroid patients and increased in hyperthyroid patients. In the light of absence of clinical data of an effect of thyroid function on vamorolone clearance a warning in SmPC section 4.4 has been included.

3.6. Effects Table

Table 22: Effects table for vamorolone, indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older (data cut-off: 30 June 2022 for clinical studies except for ongoing study VBP15-006 (data cut-off 21 July 2023)).

Effect	Short Description	Unit	Vamorolone	Placebo	Prednisone 0.75 mg /kg	Uncertainties/ Strength of evidence	References
Favourable Effects							
LSM change from baseline in TTSTAND velocity at week 24	Primary endpoint	LSM change from baseline LSM difference (SE) 95%CI	Vam 6: 0.046 (0.014) 0.059 (0.019) 0.0218;0.0953	-0.012 (0.0134)		Superiority of vamorolone 6 mg/kg against placebo p= 0.0018	(1)
LSM change from baseline in TSTAND velocity at week 24	First pre-specified secondary endpoint	LSM change from baseline LSM difference (SE) 95%CI	Vam 2: 0.031 (0.013) 0.0430 0.0069;0.0791	-0.012 (0.0134)		Superiority of vamorolone 2 mg/kg against placebo p= 0.0196	(1)
LSM change from baseline to week 24 in 6MWT distance	Second pre-specified secondary endpoint	LSM change from baseline LSM difference (SE) 95%CI	Vam 6: 24.57 (10.058) 35.936 (14.258) 7.9867:63.8851	-11.367 (10.6082)		Superiority of vamorolone 6 mg/kg against placebo p= 0.0117	(1)
LSM change from baseline to week 24 in 6MWT distance	Third pre-specified secondary endpoint	LSM change from baseline LSM difference (SE) 95%CI	Vam 2: 24.979(10.035) 36.346 (14.332) 8.2538;64.4379	-11.367 (10.6082)		Superiority of vamorolone 2 mg/kg agaianst placebo p= 0.0112	(1)
LSM change from baseline to week 24 in 6MWT distance	Sixth pre-specified secondary endpoint	LSM change from baseline LSM difference (SE) 95%CI	Vam 6: 24.57 (10.058) -19.552 (13.374) -45.767,6.663		44.121 (9.644)	Superiority of vamorolone 6 Hierarchical testing ended before. (p = 0.1438)	(1)
LSM change from baseline to week 24 in 6MWT distance	Seventh pre-specified secondary endpoint	LSM change from baseline LSM difference (SE) 95%CI	Vam 2: 24.979(10.035) -19.142 (13.800) -46.192;7.908		44.121 (9.644)	Superiority of vamorolone 6 See above (p=0.1654)	(1)

Effect	Short Description	Unit	Vamorolone	Placebo	Prednisone 0.75 mg /kg	Uncertainties/ Strength of evidence	References
LSM change from baseline to week 48 in TTSTAND velocity	Pre-specified	LSM change from baseline LSM difference (SE) 95%CI	Vam 6: 0.045 (0.014) Vam 2: -0.005 (0.014) 0.050(0.019) 0.0126;0.087			Effects only can be considered to be maintained for up to 48 weeks; uncontrolled design from Week 24 to Week 48; lack of a pre-defined non-inferiority margin; no formal statistical hypothesis testing planned (p=0.0099)	(4)
LSM change from baseline at month 12 in TTSTAND velocity	Pre-specified	LSM change from baseline LSM difference (SE) 95%CI	Vam 6: 0.040 (0.011) -0.002 (0.018) -0.037,0.033		0.042 (0.015)	Confidence limits were unadjusted limits Although the results appear similar, equivalent efficacy cannot be concluded for methodological reasons. Hence, no conclusion of comparable efficacy can be given (p=0.9287)	
LSM change from baseline at month 12 in TTSTAND velocity	Pre-specified	LSM change from baseline LSM difference (SE) 95%CI	Vam 2: -0.003 (0.011) -0.045 (0.018) -0.0798,-0.0098		0.042 (0.015)	Confidence limits were unadjusted limits; results indicate that Vam 2 has inferior efficacy compared to prednisone (p=0.0126)	
Unfavourable Effects							
Adrenal suppression	Mean (SD) change in morning cortisol from baseline	µg/dL	6 mg/kg: -7.06 (3.028) 2 mg/kg: -3.58 (3.044)	0.69 (2.769)	-5.17 (2.890)	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)
Cushingoid features	Number of patients with TEAEs	%	6 mg/kg: 28.6 2 mg/kg: 6.7	0	22.6	See adrenal suppression	(1)

Effect	Short Description	Unit	Vamorolone	Placebo	Prednisone 0.75 mg /kg	Uncertainties/ Strength of evidence	References
Weight gain	Number of patients with TEAEs	%	6 mg/kg: 17.9 2 mg/kg: 3.3	6.9	9.7	Weight gain was more pronounced with VAM 6 mg/kg as compared to prednisone; it is uncertain to which extent the absence of growth inhibition of VAM attributes to weight gain; 10 patients with down-titration from 6 mg/kg to 2 mg/kg due to weight increased in VBP15-LTE; lack of controlled long-term data	(1)
Growth (height restriction)	Median change in height z-score from baseline	SD	6 mg/kg: 0.11 2 mg/kg: 0.07 0.13	0.13	- 0.10 -0.66 (prednisone daily)	No controlled long-term data available	(1) (3)
Bone fractures Vertebral fractures	Number of patients with TEAEs	%	0 6 mg/kg: 7.1 2 mg/kg: 2.1 12.8 (adjusted for 36 months)	0 -	0 - 26.9 (prednisone daily)	Uncertainties regarding vertebral fractures: no baseline lateral spine X-rays readings were available. Uncertainty regarding bone age delay of more than 1 year vs. chronological age after 30 months of treatment. Uncertainty regarding inconsistent bone biomarker results. Uncertainty regarding a robustness issue with DXA measurement in VBP15-004. No scans beyond week 24. No controlled long-term data available	(1) (2) (3)
Behaviour problems	Number of patients with TEAEs	%	6 mg/kg: 21.4 2 mg/kg: 16.7 6 mg/kg: 33.3 2 mg/kg: 0	13.8	32.3	TEAE irritability was more frequently reported with VAM 6 mg/kg compared to prednisone (10.7% vs. 3.2%); no TEAEs reported in the placebo and 2 mg/kg group; The incidence is higher in younger children	(1) (5)
Gastro-intestinal symptoms	Number of patients with TEAEs	%	6 mg/kg: 28.6 2 mg/kg: 30	27.6	25.8		(1)

Effect	Short Description	Unit	Vamorolone	Placebo	Prednisone 0.75 mg /kg	Uncertainties/ Strength of evidence	References
Diabetic conditions (including changes in diabetes-related laboratory parameters)	Number of patients with TEAEs	%	6 mg/kg: 3.6 2 mg/kg: 0	3.4	9.7	No controlled long-term data available. Increases in fasting insulin without concomitant increase in fasting glucose and HbA1c indicative of compensatory ß-cell adaption processes (insulin resistance)	(1)
Immunosuppression (i.e., infections grouped under the immune suppression CMQ)	Number of patients with TEAEs	%	6 mg/kg: 32.1 2 mg/kg: 43.3	44.8	38.7	Infections did not increase after switching from prednisone or placebo to vamorolone and were obviously not related to dose	(1)
Hypertension	Number of patients with TEAEs	%	6 mg/kg: 0 2 mg/kg: 3.3	0	3.2	No effects on blood pressure in telemetered dogs; SBP and DBP already increased at baseline; increases in mean DBP and SBP during the first 6 months of treatment with VAM in Pool 1 (~5mmHg) and slight dose-dependency observed in Pool 3; however, measures were not standardised; known challenges in paediatric patients;	(1)
Skin/ hair changes	Number of patients with TEAEs	%	6 mg/kg: 3.6 2 mg/kg: 10	6.9	12.9		(1)
Liver function	Number of patients meeting treatment-emergent Hy's law criteria (ALT or AST > 3 x ULN and Total BILI > 2 × ULN)	Number of patients	2	0	1	ALT and AST not specific to assess hepatic function due the underlying disease (muscle loss); in a majority of subjects, bilirubin was already >2x ULN at baseline; a single patient remains suspect of DILI (diagnosed with acute hepatitis). 2 patients discontinued vamorolone as a consequence of hepatitis acute and ALT increased	(1)

Abbreviations:
Notes: (1) Placebo- and active controlled Period 1 of study VBP15-004 (Pool 1); (2) All vamorolone treated safety population (Pool 3); (3) comparison of VBP15-LTE data and external FOR-DMD: (4) Study VBP15-004: Analysis based on the mITT – 2 population, defined as "All randomised subjects who received at least one dose of study medication during Period 2 and had at least one post-baseline efficacy assessment during Period 2. (5) ongoing open-label study VBP15-006, cohort 2 to <4 year old patients with DMD (cut-off 21 July 2023)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy

In the pivotal study, Study VBP15-004, vamorolone at daily doses of 2 and 6 mg/kg demonstrated convincing efficacy in the treatment of early ambulatory stage DMD patients between 4 to <7 years of age at study entry when compared to placebo at 24-weeks.

Vamorolone produced clinically meaningful, statistically significant, and robust improvements in multiple measures of motor function, including TTSTAND and TTRW velocity, 6MWT distance and the NSAA score versus placebo. The improvements in motor function with vamorolone 6 mg/kg were overall similar to those seen with prednisone at Week 24 except for the 6MWT for which prednisone provided numerically better results. The improvements seen with vamorolone 2 mg/kg were overall slightly smaller than those seen with prednisone. Except for TTSTAND velocity, no clinically meaningful differences were seen in functional outcomes for vamorolone 2 mg/kg compared with vamorolone 6 mg/kg after 6 months of treatment.

Results at week 48 from study VBP15-004 (with observed cases only) suggest that the effect of vamorolone 6 mg/kg is maintained up to Week 48 as there was no decline across the relevant outcome parameters and the results were generally better than for the 2 mg/kg dosage. Significant decrease in several efficacy endpoints was observed with vamorolone 2 mg/kg between Week 24 and Week 48. Thus, maintenance of efficacy for the 2 mg/kg dose could not convincingly be demonstrated. Additional analyses could not solve the uncertainties.

The pre-planned matched comparison of the vamorolone 6 mg/kg group to the continuous prednisone and deflazacort groups from study FOR-DMD (comparing different GCs and dosing regimens) at 1 year suggest similar efficacy esp. to deflazacort, but equivalent efficacy cannot be concluded for methodological reasons. However, the pre-specified comparison of vamorolone at the 2 mg/kg dosage to these comparators suggests inferior efficacy compared to both, i.e. prednisone and deflazacort.

No loss of efficacy was seen when subjects were switched from prednisone to vamorolone 6 mg/kg, whereas small but also inconsistent declines were seen after the switch from prednisone to vamorolone 2 mg/kg.

Generally, there should be an option to reduce the recommended 6 mg/kg dose to a lower dose in case of tolerability issues. This is assumed to be in line with clinical practice as physicians may change the dosage for corticosteroids individually based on relevant case by case aspects. Since vamorolone is intended for long-term use in a chronic disease, there should be an established effect on relevant outcome parameters even for the lower dose. Since the 2 mg/kg dose could not convincingly maintain efficacy, an intermediate dose of 4 mg/kg already used in the EAPs has been proposed to mitigate tolerability issues. On the basis of the results from the new popPK model, that predicts a higher exposure for the ROS2 formulations compared to the ROS1 formulation across all dosages, the intermediate 4 mg/kg dose (ROS2 formulation) is expected to sufficiently maintain efficacy. Down-titration to the 4 mg/kg dose due to tolerability issues is therefore agreed with from efficacy perspective.

The 2 mg/kg dose is still considered adequate in case of moderate hepatic impairment as stated in the SmPC, section 4.2. In addition, even taking into account a certain loss of effect with this dose during maintenance treatment, this likewise occurs with standard steroid treatment regimens, either when lower doses are administered or when an intermittent course regimen is applied, and this is also depending on age and the baseline disability status. Thus, partial efficacy of the 2 mg/kg dose should be acceptable in the context of the severity of the underlying disease.

The proposed target population has now been restricted to DMD patients aged 4 years and over. While the main (active-controlled) study solely included patients aged 4 to < 7 years, preliminary data from the uncontrolled study VBP15-006 on 2- <4 year-old DMD patients have become available suggesting treatment benefit with regard to gross-motor function. However, due to methodological issues, the results should be interpreted with caution.

Based on the same pathomechanism with inflammation being present across all stages of the disease, extrapolation of efficacy for vamorolone is considered possible. Although, data on corticosteroid treatment in boys with DMD are generally limited and scientific knowledge regarding the appropriate treatment duration is still evolving, corticosteroids are recommended in the decline phase and early non-ambulatory phase of the disease. Studies have shown that steroid use after loss of ambulation in DMD was associated with delayed progression of important pulmonary, cardiac and upper extremity functional deficits (McDonald et al, 2023). In addition, it is recommended to continue treatment after loss of ambulation. 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. In addition, very limited data in patients >7 and up to 18 years suggest a similar safety profile in older compared to younger patients. Consequently, no upper age limit was included in the indication.

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 could have been a treatment option already below the age of 4 years.

Safety

Overall, no new safety issues have been identified with vamorolone treatment as compared to conventional glucocorticoids. The limitations of the safety database of vamorolone regarding the lack of controlled comparative data with prednisone beyond 6 months, have been aimed to be addressed by long-term external comparison to the safety data of the FOR-DMD study covering aspects on growth and bone fractures for three different glucocorticoid regimens. While this comparison is generally considered acceptable by the CHMP, there are nonetheless different underlying methods or sensitivities in the collection of safety data for external comparison of safety variables that must be considered when interpreting these data. Moreover, further long-term safety data for patients transitioning from a clinical study to an EAP have been provided during this procedure.

The safety profile of vamorolone partly differs from that of conventional GCs. Based on 6 months controlled data, there are quantitative differences in favour of vamorolone on the one hand. On the other hand, there are safety issues for vamorolone for which the incidences are at least in the same magnitude as with prednisone or even increased.

Quantitative differences in the safety profile in favour of vamorolone over prednisone treatment in the controlled setting with positive trends up to 30 months of uncontrolled treatment and further supported by new emerging safety data from ongoing treatment of patients with vamorolone in EAPs were found for:

- effects on growth (i.e., the absence of a growth stunting effect of vamorolone), and

- effects of vamorolone on bone health outcomes, which are important given that there is an unmet medical need for DMD anti-inflammatory treatments lacking deleterious bone effects. While the disease itself predestines for long-bone fractures as a consequence of muscle atrophy, vertebral fractures are considered a direct side effect of long-term corticosteroid use (Parera et al., 2016). Vertebral fractures with vamorolone occurred less frequently as compared to prednisone and deflazacort treatment regimens based on an external comparison. However, assessment of the risk for fractures will need a longer follow-

up (>3 years) (Guglieri et al., 2022), which weakens the significance of the 30 months data for vamorolone. Furthermore, lumbar spine BMD by DXA is recommended at diagnosis and annually in all patients to determine the overall bone health trajectory on serial measurements, which then informs on the frequency of spine radiography (Birnkrant et al., 2018). Serial measures of BMD by DXA have been generated in the pivotal study, but with some limitations (i.e., not all patients had such measures for all predefined time points, which was due to different reasons, including COVID restrictions). Nevertheless, available data do not point towards a decrease in LS-BMC and LS-BMD in vamorolone-treated subjects over 48 weeks of treatment, which could support that the risk for vertebral fractures is lower as for glucocorticoids. The risk for bone fractures will be further addressed post-marketing. Biomarkers of bone remodelling are valuable in assessing treatment compliance and in the response or failure to anti-resorptive treatment in GC-induced osteoporosis but are not sufficient to predict bone loss and increase/ reduction in fracture risk (Devogelaer et al., 2017). Moreover, a major prerequisite for using bone turnover markers in children and adolescents is sex- and age-specific reference curves enabling calculation of z-scores, but these have neither been established (Rand et al., 2022) nor have they been presented for vamorolone. Evaluation of bone biomarkers in vamorolone – treated DMD patients is thus supportive information but can neither assess bone fragility nor predict future fracture risk (Bruckner et al. 2015). In summary, the totality of bone health evaluations based on 48 weeks of observation indicate that bone turnover markers as well as lumbar vertebral bone mineralisation is not impaired with vamorolone as compared to prednisone. This is corroborated by the fact that the negative effects observed with prednisone during the first 6 months of treatment are reversed after switching to vamorolone. However, neither bone turnover markers nor DXA results do allow to conclude on the risk for future fractures.

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. 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.

Aspects of the safety profile for vamorolone that are at least not better than for prednisone or even disfavour vamorolone 6 mg/kg over prednisone in the controlled setting and similar trends during vamorolone treatment up to 30 months, and also supported by new emerging safety data from ongoing treatment of patients with vamorolone in EAPs:

- Adrenal suppression: the totality of data indicate adrenal suppression to be more pronounced for vamorolone 6 mg/kg as for prednisone, and this was likewise observed for Cushingoid features, while these were rarely reported as clinically relevant. The duration of recovery from adrenal insufficiency after treatment cessation remains unknown, which sets the 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.
- Weight gain and increase in BMI were found to be directionally consistent, which implies that the increase in body weight and fat mass rather than increase in height is the driver. 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.
- Increased fasting insulin levels (absence of increased fasting glucose and HbA1c values). The available long-term data at present do not indicate diabetogenic effects.

With regard to behaviour-related problems, a clear benefit of vamorolone over prednisone is difficult to be confirmed by the totality of data; while these were less frequently reported and not rated as clinically

relevant for vamorolone as compared to prednisone in the reference population (4 to <7 years of age), younger paediatric patients were found to be more susceptible to these events at the 6 mg/kg dose in an uncontrolled setting.

In the context of the overall safety data, the proposed dose reduction to 4 mg/kg or 2 mg/kg in case of tolerability issues while patients should be remained on the highest tolerable dose, is a conservative approach in order to minimise safety issues during treatment with vamorolone.

The safety profile has been determined in clinical studies in patients 4 to <7 years of age. For patients beyond 7 years of age, extrapolation of clinical safety from the reference population studied in VBP15-004 can be supported by the available clinical data from study VBP15-006, extension study VBP15-LTE, and patients being follow-up in EAPs.

3.7.2. Balance of benefits and risks

Short-term efficacy over 24 weeks for vamorolone 6 mg/kg and 2 mg/kg has adequately been demonstrated in ambulatory, corticosteroid naïve ≥ 4 to <7 years old DMD patients. The safety of vamorolone in DMD patients aged 4 to <7 years generally presents with findings qualitatively similar to conventional glucocorticoids, with quantitative differences, which are considered to be manageable with appropriate labelling in the product information and routine risk minimisation measures in the RMP. The short-term safety profile is considered established based on 6 months-controlled data in a rather limited number of patients, which of course precludes the detection of rare side effects.

The provided data indicate that the effect of the vamorolone 6 mg/kg dosage is maintained up to Week 48 and the results were generally better than for the 2 mg/kg dosage at Week 48. Data from an external comparison of vamorolone to prednisone and deflazacort at 1 year can only be interpreted to a limited extent for methodological reasons but are generally supportive of the maintenance of effect. Results across the efficacy outcome measures for the vamorolone 2 mg/kg dose were rather inconsistent with significant decrease in several efficacy endpoints between Week 24 and Week 48. Thus, maintenance of efficacy for the 2 mg/kg dose could not compellingly be shown. No loss of efficacy was seen when subjects were switched from prednisone to vamorolone 6 mg/kg, whereas small declines were seen after the switch from prednisone to vamorolone 2 mg/kg.

The use of an intermediate dose of 4 mg/kg is expected to sufficiently maintain efficacy as indicated by further refinement of the updated popPK simulations, and it is a relevant dose for down-titration in case of tolerability issues. Nevertheless, even if maintenance of efficacy for vamorolone could not be demonstrated for the 2 mg/kg dose, a small subset of patients might be in need for this dose due to safety issues not sufficiently be mitigated with the 4 mg/kg dose. Partial efficacy of the 2 mg/kg dose should therefore be accepted in the absence of treatment alternatives and given that up- and down-titration with standard GCs is common in clinical practice. This proceeding is also adequately reflected in the posology wording stating that patients should be maintained on the highest tolerable dose.

Currently available corticosteroids, esp. at high doses, are fraught with several serious side effects such as stunted growth, impaired bone mineralisation, accelerated weight gain, diabetogenic effects, RR increase, infections, HPA suppression and changes in mood and behaviour.

Even though, there is a lack of controlled long-term safety data to confirm the absence of some of these glucocorticoid-specific side effects with longer treatment duration, available data suggest that vamorolone, a modified corticosteroid lacking transactivation properties, does not or at least to a lesser extent than prednisone adversely affect growth and bone health, while the clinical effects on blood pressure (no effects reported in animals) and glucose homeostasis (corroborated by pancreatic islet hypertrophy in animal studies), behavioural effects, increases in weight and suppression of the HPA axis

do not allow to conclude on a benefit over classic GCs at present. At present, long-term safety observations are available for a median duration of exposure to vamorolone of 2.1 years for doses 2 – 6 mg/kg and up to a maximum of 4 years on top of the duration of exposure in the clinical studies.

The 6 mg/kg dose was shown to cause unwanted weight gain and HPA suppression and, when given as starting dose, behavioural issues in very young paediatric patients. While treatment with vamorolone should generally aimed at the highest tolerable dose, dose reductions might become necessary when tolerability/ safety issues occur, and this is reflected in the product information.

Adequate post-authorisation measures (i.e., by mean of a PASS study) have been provided to address remaining uncertainties.

Extrapolation of efficacy and safety data from the reference study population to DMD patients ≥7 years and over, including patients in the ambulatory declining and non-ambulatory phase of the disease, is supported by the same pharmacological mechanism of DMD, while the risks appear not different.

3.7.3. Additional considerations on the benefit-risk balance

Patients' perception of benefits and risks of a medicine may be different from the view of medical experts. That is why EMA engages with patients and their representatives at multiple stages of its activities and the added value of including their perspectives in the evaluation of medicines has been well demonstrated. To that effect, CHMP invited World Duchenne Organisation to share patients' perspectives on behalf of its patient/carer members with respect to Agamree (vamorolone) in the treatment of Duchenne Muscular Dystrophy. The following points are noted from the response from World Duchenne Organisation:

• **standard treatments and how acceptable they are**. Care considerations for DMD are published, last update 2018 Lancet (Birnkrant, 3 parts). Standard treatment includes use of steroids from 4-5 years on. ACE-inhibitors starting at 10 years (preventive) or earlier if needed. Betablockers and other cardiac medication when cardiac involvement (cardiomyopathy) becomes apparent. Use of prednisone is off-label and deflazacort is only FDA-approved. In some countries Deflazacort is received through a named-patient procedure. A comparison between prednisone and deflazacort is published (For-DMD study). Given the side-effects (lower bone density, growth retardation/short stature, weight gain, behavioural issues, cushingoid appearance, adrenal suppression) not all patients start or continue the steroid treatment. Side effects are often underreported.

• **Any aspects about the condition or its treatments that you feel are not well-understood or not sufficiently considered** Treatment and drug development very much focussed on motor function, but there is also cardiac, pulmonary, behavioural, and smooth muscle involvement (resulting in GI symptoms). Psychological issues are dominant in the daily lives of patients and their families.

• **quality of life:** several publications about QoL in DMD. Assistance in life/reimbursement plays a role in how well DMD patients can live their life; psychological issues are often not taken into account. For steroids, the above-mentioned side effects have a negative effect on QoL. Feeling and looking different because of the use of GCs in addition to the disease itself is troublesome for many patients.

• **therapeutic/unmet medical needs**. There is a high unmet need for a treatment with the same or better efficacy than GCs in slowing down the progression of the disease with less side effects.

• **what benefits they would hope for in new medicines** Slowing down or even stopping the progression of the disease with preferable as little side effects as possible.

• **what level of side effects they would consider acceptable** If improved efficacy compared to the current treatment, a vast majority of patients would accept similar side effects as when treated with prednisone or deflazacort.

• **if there are large differences between groups of patients/carers about these aspects or if these views are generally similar across the condition**. No large differences in patient perspectives. As mentioned above some families don't start their child on steroids or stop using it because of the (risk for) side effects.

3.8. Conclusions

The overall benefit/risk balance of Agamree is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Agamree is not similar to Translarna within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Agamree is favourable in the following indication(s): the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.

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.

- **Additional risk minimisation measures**

Patient Alert Card

This patient is on long term treatment with Agamree (vamorolone), a dissociative corticosteroid for the chronic treatment of Duchenne Muscular Dystrophy, and therefore is physically dependent on daily steroid therapy as a critical medicine.

If this patient is unwell (excess fatigue, unexpected weakness, vomiting, diarrhea, dizziness or confusion), acute adrenal insufficiency or crisis must be taken into consideration.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that vamorolone is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.