EU Risk Management Plan for AGAMREE® (vamorolone)

RMP version to be assessed as part of this application:

RMP Version number:	1.1
Data lock point for this RMP:	30-Jun-2022
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Other RMP versions under evaluation:	None
QPPV name:	Peter Psarologos
QPPV signature:	

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LIST OF ABBREVIATIONS

AE	Adverse Event
ADR	Adverse Drug Reaction
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BL	Baseline
C_{max}	Maximum concentration
CCSI	Company Core Safety Information
CI	Confidence Interval
CYP	Cytochrome P450
CU	Compassionate Use
DDI	Drug-Drug Interaction
DMD	Duchenne Muscular Dystrophy
DSUR	Development Safety Update Report
EC	European Commission
ECG	Electrocardiogram
EAP	Expanded/Early Access Programme
EEA	European Economic Area
EMA	European Medicines Agency
EOT	End of Treatment
EPAR	European Public Assessment Report
EU	European Union
GC	Glucocorticoids
GGT	Gamma-glutamyl Transferase
GLP	Good Laboratory Practice
HI	Hepatic Impairment
IC	Inhibitory Concentration
INN	International Non-proprietary Name
kg	Kilogram
LD	Lethal Dose
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
mg	Milligram
ml	Millilitre
NOAEL	No Observed Adverse Effect Level
NP	Named Patient
OFU	Open Follow Up
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study

PBRER	Periodic Benefit Risk Evaluation Report
P-gp	P-glycoprotein
PK	Pharmacokinetic
PL	Patient Information Leaflet
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV/PhV	Pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious Adverse Event
SD	Standard deviation
SmPC	Summary of Product Characteristics
SNT	Santhera
SOC	System Organ Class
ULN	Upper Limit Normal

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Vamorolone
Pharmacotherapeutic group(s) (ATC Code)	Not yet assigned
Marketing Authorisation Applicant	Santhera Pharmaceuticals (Deutschland) GmbH Marie-Curie-Strasse 8, 79539 Lörrach, Germany
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	AGAMREE®
Marketing authorisation procedure	Centralised procedure Full application: Article 8(3) of Directive 2001/83/EC
Brief description of the product	Chemical class Vamorolone (17α,21-dihydroxy-16α-methyl-pregna-1,4,9(11)-triene-3,20-dione) is a novel dissociative steroidal anti-inflammatory drug. Vamorolone is formulated for oral administration as a flavoured oral suspension of.
	Summary of mode of action Vamorolone is a novel dissociative steroidal anti-inflammatory drug differing from corticosteroids in terms of chemical structure, mechanism of action, and physiologic effects. Vamorolone uniquely contains a delta 9,11 double bond and lacks the 11β-hydroxy or carbonyl moiety found in all members of the corticosteroid class. Consequently, vamorolone has a unique pharmacological activity profile and acts as dissociative agonist of the glucocorticoid receptor (GR), and as antagonist of the mineralocorticoid receptor (MR). Vamorolone maintains GR mediated gene trans repression activity (including a reduction in the expression of nuclear factor kappa light chain-enhancer of activated B cells (NFκB) mediated inflammatory gene activation needed for its anti-inflammatory efficacy, while reducing the glucocorticoid response element (GRE) mediated transactivation responses associated with some corticosteroid side effects. Furthermore, vamorolone effectively protects cell plasma membranes from physical damage; a mechanism particularly relevant to dystrophin deficient cells in DMD where plasma membranes are inherently unstable.

	The chemical structure of vamorolone with the delta 9,11 double bound means that the compound is not subject to systemic 11β-hydroxysteroid-dehydrogenase (11βHSD) metabolism, and local tissue targeted metabolism and amplification by the 11βHSD1 enzyme, which mediates deleterious off target actions (muscle wasting, bone loss, insulin resistance, hypertension, and weight gain) associated with classical glucocorticoid therapy (Fenton et al. 2019, Morgan et al. 2014).
	Important information about its composition Vamorolone is a white to off-white fine powder and has a molecular weight of 356.46 Da. The chemical stability of crystalline vamorolone is excellent and remains within specifications under normal and accelerated conditions. Vamorolone is very poorly soluble in water, freely soluble in methanol and dioxane and sparingly soluble in ethanol and acetone. The oral suspension contains vamorolone and the following inactive ingredients: citric acid (monohydrate), hydrochloric acid (for pH adjustment), disodium phosphate (anhydrous), glycerine, orange flavour, purified water, sodium benzoate, sucralose, xanthan gum.
Hyperlink to the Product Information	AGAMREE Product Information
Indication(s) in the EEA	AGAMREE is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older.
Dosage in the EEA	The recommended dose is 6 mg/kg once daily in patients weighing less than 40 kg. In patients weighing 40 kg and above, the recommended dose of vamorolone is 240 mg (equivalent to 6 ml) once daily. Daily dose may be down-titrated to 4 mg/kg/day or 2 mg/kg/day based on individual tolerability. Patients should be maintained at the highest tolerated dose within the dose range.
Pharmaceutical form(s) and strengths	Oral suspension, 40mg/ml
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Duchenne Muscular Dystrophy (DMD)

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

DMD is a rare disorder caused by mutations in the dystrophin gene, located in humans on the X chromosome (Koenig et al. 1987). The dystrophin gene codes for the protein (dystrophin) that provides structural stability to the dystroglycan complex on muscle cell membranes (Hoffman et al. 1987).

Incidence / prevalence:

DMD is the most common childhood muscular dystrophy, with a birth incidence worldwide of 1 in 3,600 to 9,300 males (Mah et al. 2014).

Due to the wide differences between each study (e.g. study design and setting, study population, data sources, case ascertainment, etc.) DMD prevalence and birth prevalence estimates are variable throughout the literature, ranging 0.9 to 16.8 per 100,000 males from 1.5 to 28.2 per 100,000 live male births, respectively (Crisafulli et al. 2020).

In a recent systematic review, the pooled global epidemiology of DMD was evaluated. The pooled global prevalence and birth prevalence of DMD were 7.1 (95% CI: 5.0–10.1) and 19.8 (95% CI: 16.6–23.6) per 100,000 males, respectively. The birth prevalence is much higher than the prevalence because children with DMD may not survive beyond paediatric age likely in developing countries with low adherence to standards of care. When considering as denominator the general population, the pooled global prevalence of DMD decreases, as expected, to 2.8 (95% CI: 1.6–4.6) cases per 100,000 as only males can be affected by the disease (Crisafulli et al. 2020).

Demographics of the population in the proposed indication for the disease and risk factors for the disease:

Due to the localization of the dystrophin gene on the X chromosome, DMD predominantly affects male children, while females are likely to be asymptomatic "healthy carriers" (Crisafulli et al. 2020).

The epidemiology of DMD is expected to be generally similar globally, because there is no specific population with a known higher risk (Crisafulli et al. 2020).

Main treatment options:

Currently, there is no cure for DMD and the progression and complications of DMD show little variation across patients.

The only medications that have consistently demonstrated efficacy in clinical trials are glucocorticoid receptor (GR) agonists, such as prednisone and deflazacort (Malik et al. 2012). Both drugs are currently recommended for treatment of patients with DMD according to American Academy of Neurology practice guidelines (Topaloglu et al. 2016). Deflazacort (EMFLAZA®) was approved for use in DMD by the Food and Drug Administration (FDA) in 2017; it is registered in the United Kingdom (Calcort®) and Spain

(Zamene®), but is not indicated in DMD in these countries. Prednisone is available and widely used in the United States (US) and in the European Union, but is not specifically indicated for DMD.

Daily high dose corticosteroids (agonists of the glucocorticoid receptor) are considered standard of care for DMD, with acute gains in strength and extension of ambulatory function (loss of ambulation 2 to 4 years later compared to untreated patients) (Bushby et al. 2010a; Bushby et al. 2010b). Efficacy is assumed to be obtained via anti-inflammatory activity (Hoffman et al. 2012). However, extensive adverse effects, including cushingoid features, stunting of growth, bone fragility, and adrenal suppression, cause declines in quality of life, limit the use of corticosteroids at young ages, and lead to broad variations in clinical practice as families and physicians balance efficacy and safety (Griggs et al. 2013; Bello et al. 2015).

Vamorolone is a novel dissociative anti-inflammatory steroid that contains a delta 9,11 double bond in its chemical structure and is differentiated from glucocorticoid/corticosteroid compounds which, in their active form, contain a hydroxyl group in the 11-β position. Consequently, vamorolone has a unique pharmacological activity profile and acts as a selective agonist of the GR and an antagonist of the mineralocorticoid receptor (MR). Vamorolone maintains GR-mediated transrepression activity (including a reduction in the expression of NF-κB-mediated inflammatory activity) needed for its anti-inflammatory efficacy, while reducing the glucocorticoid response element-mediated transactivation responses associated with some corticosteroid side effects [Liu et al, 2020, Heier et al, 2019]. Furthermore, vamorolone effectively protects cell plasma membranes from physical damage, a mechanism particularly relevant for dystrophin-deficient cells in DMD where plasma membranes are inherently unstable. The chemical structure of vamorolone with the delta 9,11 double bond means that the compound is not subject to systemic 11-β hydroxysteroid dehydrogenase (11-βHSD) metabolism and local tissue targeted metabolism and amplification by the 11-βHSD 1 enzyme, which mediates deleterious off target actions associated with classical glucocorticoid therapy (muscle wasting, bone loss, insulin resistance, hypertension, and weight gain) [Fenton et al, 2019; Morgan et al, 2014; Fenton et al, 2021; Webster et al, 2021]. Based on this differentiated profile, vamorolone has the potential to combine potent anti-inflammatory properties with the potential for a better safety profile.

Mortality and morbidity (natural history):

DMD causes long-term disability and is life threatening. Duchenne muscular dystrophy patients show a chronic inflammatory disease of muscle, with bouts of muscle degeneration and regeneration leading to muscle wasting, disability, and early death (Rosenberg et al. 2015). The disease usually leads to death in adolescence or early adulthood.

Important co-morbidities found in the target population:

DMD is characterized by a progressive degeneration of skeletal muscles, with symptoms that manifest early, usually at around 3 years of age, causing loss of ambulation within the 13th year of life, followed by cardiac complications (e.g. dilated cardiomyopathy and arrhythmia) and respiratory disorders, including chronic respiratory failure. In the first phase of the disease, the child experiences difficulty in running, climbing stairs, jumping, getting up from the ground, falls frequently and develops a wadding gait with a positive "Gowers' sign". The subsequent impairment of the cardiac and respiratory systems is the main cause of death for these patients (Crisafulli et al. 2020).

DMD represents the most aggressive secondary osteoporotic condition of childhood due to the underlying myopathy plus the prolonged, high-dose glucocorticoid exposure, rivalling any other chronic bone fragility condition in childhood (Emery 1991; Ward et al. 2016). The potent osteotoxicity of glucocorticoids combined with the progressive myopathy, both of which are risk factors for reduced bone strength, provide an underlying mechanism by which up to 44% of boys with DMD will have at least one

extremity fracture (Larson et al. 2000; McDonald et al. 2002; King et al. 2007; Joseph et al. 2019). Virtually all boys will develop at least one vertebral fracture during their paediatric years if they remain on treatment (Singh et al. 2018; Bothwell et al. 2003). Vertebral fractures can occur as early as 6 months following initiation of glucocorticoids in DMD, on average after about 2 years (Ma et al. 2017). If left untreated, vertebral fractures can cause back pain and spine deformity while leg fractures can lead to premature loss of ambulation and, in some reported cases, death due to fat embolism, postulated to arise from mechanical disruption and circulation of bone marrow adipocytes due to weakening of the normally protective adjacent bone tissue (Medeiros et al. 2013; McAdam et al. 2012; Bugnitz et al. 2016; Feder et al. 2017). Loss of ambulation is an additional cause of osteoporosis. Due to the patients' immobility, constipation also frequently is associated with the disease.

A proportion of DMD patients also experience behavioural and cognitive impairment with intellectual disability, attention hyperactivity disorder and autism spectrum disorders (Crisafulli et al. 2020).

Part II: Module SII - Non-clinical part of the safety specification

Key Safety findings (from non- clinical studies)	Relevance to human usage:
Toxicity	
Single and repeat-dose toxicity In the 7-day dose-range toxicity study in monkeys the vamorolone-related effects on clinical pathology and particularly the approximate 10% loss in body weight following 7-days of oral gavage administration at 600 mg/kg/day, the MTD was determined to be <600 mg/kg/day.	The result of the monkey study is regarded not clinically relevant.
A 4-week repeated dose GLP-compliant toxicology study in mice with a 2-week recovery period showed no vamorolone-related effects on clinical observations, food consumption, ophthalmological examination, or urinalysis during the study. At the terminal collection, mild increases in neutrophils were present in all treatment groups, and mild decreases in lymphocytes were present in males and females administered ≥30 mg/kg/day, relative to controls. Observed hepatic changes included increased AST, ALT, and/or ALP in males and females at 100 mg/kg/day compared to controls.	It is well established clinically that an administration of glucocorticoids, such as prednisolone and dexamethasone can result in an increase of leucocyte count which are predominantly neutrophils. The effects of these glucocorticoids on liver enzymes such as increased AST, ALT, and/or ALP are consistent with the pharmacological effects related to the GR agonist activity, and is also part of vamorolone's MOA. The level of clinical relevance of the hepatic effects and effects on blood parameters including on leukocyte counts observed with vamorolone in mice will need to be monitored in clinical studies and routine clinical practice.
The 26-week repeated-dose GLP-compliant study with a 4-week recovery period in mice did not produce any adverse effects. Pharmacologically mediated effects on the adrenal glands were noted at ≤ 30 mg/kg/day in mice with correlative decreases in organ weight. Recovery or partial recovery was demonstrated in the 4-week recovery period. The exposure margins related to adrenal effects are 2.8 times the MRHD based on AUC.	Observed changes on adrenal glands were considered pharmacologically mediated and consistent with suppression of the hypothalamic-pituitary-adrenal (HPA) axis. The level of clinical relevance of the HPA axis suppression will need to be monitored in clinical studies and routine clinical practice.

Evidence of minimal to mild vamorolone-related hepatic effects were observed in males at ≥5 mg/kg/day, indicated by mild to moderate increases in ALP, AST, ALT, and/or total bilirubin. These findings correlated with microscopic hepatocellular vacuolation, inflammation, and/or necrosis in males at ≥15 mg/kg/day. The hypertrophy, hepatocyte vacuolation and effects on liver enzymes were generally reversible, however, there was still evidence of necrosis following cessation of dosing.	The effects on liver enzymes such as increased AST, ALT, ALP and/or total bilirubin as well as effects on lymphatic tissues and subsequent increase in neutrophils and decrease in lymphocytes in mice are consistent with the agonistic pharmacological effect on GR receptors located in the liver and lymphatic tissues. Effects described are well-known for glucocorticoids and is also part of vamorolone's MOA.
A decrease on spleen and thymus weights, which correlated with lymphoid atrophy associated with increases in neutrophils and decreases in lymphocytes in mice. These findings were considered test article related but not adverse.	The level of clinical relevance of the effects of vamorolone on the HPA axis, liver and lymphatic tissues will need to be monitored in clinical studies and routine clinical practice.
An increased incidence of decreased anagen hair follicles occurred in mice at 45 mg/kg/day. Decreased anagen hair follicles was documented for individual animals when there were no anagen hair follicles in the section of skin. Incidence in controls and mice at 5 and 15 mg/kg/day were similar. This change was not considered adverse.	The effects on skin/hair follicle are consistent with an agonistic effect of the GR agonist activity, and or well known for glucocorticoids; GR agonist activity is also part of vamorolone's MOA. The level of clinical relevance of the skin effects observed with vamorolone in pre-clinically will need to be monitored in routine clinical practice.
A 4-week GLP-compliant study of vamorolone for 28 consecutive days with a 2-week recovery period was conducted in Beagle dogs. On Day 29, dogs administered vamorolone at 50 mg/kg/day had higher platelet count, lower mean platelet volume, minimally shorter activated partial thromboplastin time compared to controls, and increased ALP and GGT. In addition, dogs receiving 10 or 50 mg/kg/day had higher liver and lower adrenal gland and thymus weights with correlating histological changes observed in the adrenal glands, liver, and thymus. The clinical pathology effects and organ weight changes were resolved following recovery, and the histologic changes were generally reversible during the recovery. The NOAEL was considered to be 10 mg/kg/day by the study director. This is in contrast to the conclusion drawn by the study	The functional and quantitative effects on platelets volume and platelet count as well as a shortening of activated partial thromboplastin has been described as effects of high-dose GC therapy in the clinic. They are consistent with GR agonist activity and are known for glucocorticoids, GR agonist activity is also part of vamorolone's MOA. The effects on liver enzymes such as increased ALP and GGT in dogs are consistent with the agonistic pharmacological effect on GR receptors located in the liver and lymphatic tissues. The level of clinical relevance of the effects on platelets and platelet count, HPA axis, liver, and lymphatic tissues effects seen in dogs will need to be monitored in clinical studies and routine clinical practice.

pathologist and stated in the pathology report that considered the NOAEL to be 50 mg/kg/day. The 39-week repeated-dose GLP-compliant study with a 4-week recovery period in dogs showed decreased activity (considered adverse), struggling during dosing, soft feces, alopecia/hypotrichosis and atrophy of the skin, impaired limb function, interdigital cysts, and unkempt appearance (considered adverse). Test article-related findings occurred in the liver (hepatocellular vacuolation, panlobular hypertrophy, inflammation/necrosis, bile duct hypertrophy and hyperplasia, and cytoplasmic vacuolation of the bile duct epithelium), adrenal gland (atrophy of the zona fasciculata and zona reticularis and hypertrophy/hyperplasia of the zona glomerulosa), gall bladder (haemorrhage in the gall bladder of one 50 mg/kg/day female), ovaries (absent corpora lutea at 2, 10, 50 mg/kg/day), and testes (minimal to mild spermatocyte/spermatid degeneration). There was also an increase in ALP, AST, ALT, and GGT enzymes (considered adverse at 50 mg/kg/day). At 10 mg/kg/day adverse microscopic findings were limited to adrenal atrophy. The liver effects at 10 mg/kg/day were not considered adverse and demonstrated reversibility. Due to the magnitude of hypertrophy and vacuolation, there were (likely secondary) foci of hepatocellular necrosis and inflammation which were considered adverse at 50 mg/kg/day. Additionally, non-adverse bile duct hyperplasia and hypertrophy were noted at 50 mg/kg/day. The margins for liver findings in dogs were less than 1-fold for AUC and C_{max}.	Behavioural changes observed in adult dogs may be indicative for neurobiological effects in human. For glucocorticosteroids it is known that they can induce mood changes in humans. For vamorolone, the level of clinical relevance of the behavioural changes will need to be monitored in clinical studies and routine clinical practice. Skin effects such as atrophy is a well-established pharmacological effect of glucocorticosteriods. For vamorolone the level of clinical relevance of skin effects will need to be monitored in routine clinical practice. The effects on hepatic tissues such as vacuolation, hypertrophy, inflammation/necrosis and increases in ALP, AST, ALT, and GGT enzymes are consistent with pharmacological agonistic effect on the GR, which is also part of vamorolone's MOA. Bile duct hyperplasia and hypertrophy are consistent with the agonistic pharmacological effect on GR receptors located in the biliary tissues. Observed changes on adrenal glands were considered pharmacologically mediated and consistent with suppression of the HPA axis. Based on the microscopic findings in the ovaries a NOAEL was not established in females, however, this finding is not relevant to the DMD population. The effects on testes in adult dogs were partially reversible. Furthermore, the pivotal 10-week juvenile mouse study no vamorolone-related effects on reproductive system has been noted. For vamorolone, the level of clinical relevance of the HPA axis, hepatic, biliary and lymphatic effects will need to be monitored in clinical studies and routine clinical practice.
Reproductive and developmental toxicity A detailed and comprehensive reproductive assessment was incorporated into the pivotal 10-week juvenile mouse study. Animals were treated	No relevance to human usage since mice has undergone all developmental milestones while being treated with drug.

on Postnatal day (PND) 21 which coincides with weaning and is considered equivalent to children as young as 2 years of age based on comparative ontogeny. In this study there were no vamorolone-related effects on reproductive indices, including sexual maturation, first day of estrous, estrous cyclicity, reproductive and fertility indices, uterine examinations, or sperm evaluations. Safety margins corresponding to 1.2-times the MRHD based on AUC.	
The 26-week repeated-dose GLP-compliant study with a 4-week recovery period in mice were no effects on sperm analysis (motility, concentration, or morphology) or on reproductive tissues.	No relevance to human usage
In the 39-week dog study, minimal to mild spermatocyte/spermatid degeneration in testes was observed at a dose of 50 mg/kg/day leading to minimal to mild oligospermia and germ cell debris in epididymides. Furthermore, decreases in prostate gland weights in males at 50 mg/kg/day with reduced secretory product was observed. These findings were partially reversed by the end of the 4-week recovery period indicating no safety margins to the MRHD based on AUC. Safety margins corresponding to less than 1-times the MRHD based on AUC. This dog study also showed absent corpora lutea in the ovaries in all groups in a dose-responsive manner. NOAEL was not identified for females in the study. However, these findings are not applicable for the male only DMD patient population.	The effects on testes in adult dogs were partially reversible. Furthermore, in the pivotal 10-week juvenile mouse study no vamorolone-related effects on reproductive system have been noted. Subsequent studies such as developmental and reproductive toxicity studies might clarify the relevance of effects to human usage.
Genotoxicity A standard battery of in vitro and in vivo genetic toxicology studies has shown that vamorolone does not have any mutagenic or clastogenic potential. Vamorolone was not mutagenic in the bacterial reverse mutation assay. Vamorolone was negative for inducing chromosomal aberrations in cultured mouse lymphocytes and was tested negative in the in vivo micronucleus assay in CD-1 mice. In addition, in silico assessment of mutagenic potential of potential epoxide contaminants was also negative.	Based on these results, it is expected that vamorolone has no genotoxic activity and it does not pose a risk of producing genetic damage in humans.

Carcinogenicity No studies performed	Carcinogenicity studies will be conducted post-marketing as agreed with CHMP.
Immunotoxicity To assess the T-cell dependent antibody response mice received vamorolone orally at doses of 10, 30, or 100 mg/kg/day over 4-weeks. The data indicate immunosuppressive activity of vamorolone.	These effects are consistent with a pharmacological agonistic effect on the GR, which is also part of vamorolone's MOA. The level of clinical relevance of immunosuppressive properties of vamorolone will need to be monitored in clinical studies and routine clinical practice.
General safety pharmacology	
Cardiovascular (including potential for QT interval prolongation) The non-GLP in vitro human Ether-à-go-go-related gene (hERG) study did not show inhibitory effects of vamorolone. Based on comparison of the unbound human maximum peak plasma concentration data for vamorolone and the in vitro hERG data, there is a safety margin of approximately 45-fold between the maximum achieved total human plasma concentration of vamorolone under clinical use conditions and effects on the hERG potassium current. In the single oral dose cardiovascular and respiratory safety pharmacology study in beagle dogs vamorolone at doses of 2, 10 and 50mg/kg did not showed effects on clinical observations, blood pressure, ECG parameters, and respiratory parameters, the NOAEL was determined to be 50 mg/kg.	These observations do not suggest any relevance to human usage
Mechanisms for drug interactions Vamorolone was screened against a panel of recombinantly expressed Cytochrome P450 (CYP) enzymes. Induction of CYP3A4 was observed but is not considered clinically relevant at therapeutic drug levels.	Clinical relevance of the observed effects for drugs being CYP3A4 substrates co-administered with vamorolone will need to be further assessed in clinical practice with vamorolone.

Part II: Module SIII - Clinical trial exposure

The clinical development program for vamorolone in the treatment of DMD was conducted globally and included 11 studies: 10 clinical completed studies and one ongoing study:

- 6 clinical pharmacology studies in healthy and hepatic impaired subjects (studies VBP15-001, VBP15-MB, VBP15-PK- FORM, VBP15-PK-FORM-002, VBP15-DDI and VBP15-HI),
- 4 completed studies in boys with DMD (studies VBP15-002, VBP15-003, VBP15-LTE and VBP15-004).
- 1 ongoing clinical trial in boys with DMD (Study VBP15-006)

The clinical pharmacology studies evaluated the safety and pharmacokinetics (PK) of vamorolone, including the potential for a drug-drug interaction (DDI), in healthy adult male and female subjects.

The completed clinical studies in DMD were conducted in ambulant boys between 4 to < 7 years of age who were corticosteroid naïve and included the following:

- Study VBP15-002, a Phase 2a, open-label, multiple-ascending dose study of vamorolone doses of 0.25, 0.75, 2, and 6 mg/kg once daily for 2 weeks.
- Study VBP15-003, a Phase 2, open-label study in which vamorolone doses of 0.25, 0.75, 2, and 6 mg/kg were administered once daily for 6 months to subjects who completed Study VBP15-002.
- Study VBP15-LTE, a Phase 2, open-label study in which vamorolone doses of up to 6 mg/kg were administered once daily for an additional 24 months to subjects who completed the 6-month VBP15-003 study (i.e., total treatment for 30 months or 2.5 years)
- Study VBP15-004, a pivotal Phase 2b, randomized, double-blind, placebo- and active-controlled (prednisone), parallel group study of vamorolone doses of 2 and 6 mg/kg

The ongoing clinical study in DMD is conducted in boys ages 2 to <4 years and 7 to <18 years:

- Study VBP15-006, a Phase 2, open-label study to assess the safety, tolerability, PK, PD and exploratory efficacy of vamorolone.

In addition, the Expanded Access Program (VBP15-EAP) is ongoing and provides continued access to vamorolone at a dose of 2.0 mg/kg, 4.0 mg/kg, or 6.0 mg/kg. Country specific-compassionate use (CU) and named patient (NPs) mechanisms are being utilized to supply vamorolone to these individuals.

As of the DLP of the RMP (30-Jun-2022), a total of 145 healthy volunteers, 8 adult subjects with HI, and 164 subjects with DMD have been exposed to vamorolone in ReveraGen-sponsored clinical trials.

In total, approximately 473 subjects have been exposed to vamorolone.

DMD indication

The following tables present exposure to vamorolone in male patients with DMD by dose and duration, age and sex (all male patients) and racial group across the DMD completed clinical trials. Exposure from EAP, CUP and ongoing clinical trials are not included.

In total 164 subjects have received vamorolone across the DMD clinical studies (studies VBP15-004, VBP15-002, VBP15-003 and VBP15-LTE). Patients from VPB15-006 are not included.

The dose and duration of exposure to vamorolone across the DMD clinical studies are shown in Tables SIII.1 (exposure sorted by received dose) and SIII.2 (dose and duration of treatment).

Table SIII.1 Summary of exposure by received dose (DMD studies)

Dose of exposure	Patients*	Person-Years
0.25mg	12	9.0
0.75mg	23	10.5
2mg	97	72.2
4mg	3	1.3
6mg	99	96.0
Total	**164**	**189.1**

*Some patients have been exposed to different doses, this is why the total number of patients is different from the sum of all of the patients per dosage.

Table SIII.2 Dose and Duration of exposure

Exposure	Vamorolone 0.25mg (N=12)	Vamorolone 0.75mg (N=23)	Vamorolone 2mg (N=97)	Vamorolone 4mg (N=3)	Vamorolone 6mg (N=99)	Person Time (years) Vamorolone 0.25-6mg (N=164)
1 day to <3m, n(%)	0	9	4	1	1	0.3
3m to <6m, n(%)	1	2	41	1	33	23.3
6m to <12m, n(%)	8	12	39	1	36	48.9
12m to <30m, n(%)	3	0	11	0	22	19.3
>30m, n(%)	0	0	2	0	7	97.2
Total person time (years)	**9.0**	**10.5**	**72.2**	**1.3**	**96.0**	**189.1**

Table SIII.3 summarizes demographic characteristics (age and sex) for subjects across DMD studies (VBP15-002, VBP15-003, VBP15-LTE and VBP15-004). Patients from VPB15-006 are not included.

Table SIII.3: Summary of Demographic and Baseline Characteristics by age group and gender (DMD)

Exposure	Patients		Person Years	
	M	F	M	F
Children < 5 years	65	0	81.7	0
Children ≥ 5 years	99	0	107.4	0
Total	**164**	**0**	**189.1**	**0**

Table SIII.4 summarizes exposure by ethnic or racial group for subjects across DMD studies (VBP15-002, VBP15-003, VBP15-LTE and VBP15-004).

Table SIII.4: Summary of exposure by ethnic or racial origin (DMD)

Race	Patients	Person Time (years) Vamorolone 0.25-6mg
American Indian Or Alaska Native	1	0.3
Asian	13	11.0
Black or African American	3	4.5
Multiple	4	1.9
Unknown	2	2.9
White	141	168.4
Total	**164**	**189.1**

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Had major renal or hepatic impairment, diabetes mellitus, or immunosuppression or a history of any of these conditions	Different PK and/or potential higher risk expected in these patients, which could pose safety risks and also make study interpretation difficult	Hepatic impairment: No	Clinical Trial data are available on the use of vamorolone in patients with moderate hepatic impairment. Modifications of the vamorolone posology in patients with moderate hepatic impairment are included in the AGAMREE SmPC. In addition, in the AGAMREE SmPC it is stated that the use of the product in patients with severe hepatic impairment is contraindicated. The use of vamorolone in patients with hepatic impairment will be further assessed through routine pharmacovigilance procedures.
		Renal insufficiency: No	Renal excretion is of relative minor importance in the excretion of vamorolone, however use of vamorolone in patients with renal impairment will be further assessed through routine pharmacovigilance procedures.
		Diabetes mellitus: No	Use of vamorolone in patients with diabetes mellitus is not considered for inclusion in missing information as it is well known by HCP, and from their experience with glucocorticoid treatment, that the use of drugs with agonistic effect on GR prompt close monitoring of their blood sugar and other diabetic blood parameters. HCP are familiar with adopting antidiabetic medication according to fluctuations in diabetic mellitus blood parameters.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
		Patients with infections due to immunosuppression: No	Vamorolone showed no effect on neutrophil counts or immature granulocytes in clinical trials. Eosinophil counts were similar in the vamorolone and placebo groups. The type of infections reported were consistent with the pattern in a population of immunocompetent children. There was no increased of opportunistic infections. Therefore, clinically important infections due to immunosuppression is considered as potential important risk for vamorolone and will be monitored in this context, by using routine pharmacovigilance procedures.
Had a chronic systemic fungal or viral infection or a history of these infections	Due to structural and pharmacological similarities with glucocorticoids, increased risk of infections due to immunosuppression with vamorolone was a potential risk prior to conducting pivotal study 004	No	Pivotal study VBP15-004 did not reveal an increased risk of infections with vamorolone compared with placebo. However infections due to immunosuppression remains a potential important risk which will be monitored.
Had an acute illness within 4 weeks prior to the first dose of study medication	Standard exclusion criterion in pivotal studies to avoid interference with clinical outcomes and interpretation	No	Standard exclusion criterion in pivotal studies to avoid interference with clinical outcomes and interpretation Not relevant for missing safety information

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Had used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), mexrenone (mexrenoate potassium) within 4 weeks prior to the first dose of study medication.	Vamorolone has mineralocorticoid receptor antagonist activity based on pre-clinical data. No clinical evidence of mineralocorticoid antagonism at the tested doses to date.	No	Routine PV procedures considered sufficient to monitor and manage the risk. If from this monitoring, the relevance of the interaction with this type of drug would show potentially more important than anticipated, the use of these drugs in combination with vamorolone treatment will be added to the area of interactions as missing information in future versions of the RMP.
Had a history of primary hyperaldosteronism	Patients with primary hyperaldosteronism usually present with hypertension and increased cardiovascular risk, inclusion in CT is not appropriate for the patient safety and study interpretation.	No	Vamorolone has mineralocorticoid receptor antagonist activity. MR inhibitors such as eplerenone are used as a treatment option for primary aldosteronism. Vamorolone is not expected to introduce a particular risk for patients who may suffer from both DMD and PA. If from this monitoring, the relevance of the interaction with this type of drug would show potentially more important than anticipated, the use of these drugs in combination with vamorolone treatment will be added to the area of interactions as missing information in future versions of the RMP.
Had evidence of symptomatic cardiomyopathy. Note: an asymptomatic cardiac abnormality was not exclusionary	Standard exclusion criterion in pivotal studies to avoid interference with clinical outcomes and interpretation	No	Unlike glucocorticoids, Vamorolone has mineralocorticoid receptor antagonist activity. No additional cardiovascular risk due to vamorolone is expected and no safety signal was detected in the clinical program. Routine PV procedures are therefore deemed adequate for this population as part of the general DMD population treated with vamorolone, without classifying this group as a particular group in which

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			information is specifically missing.
Was currently being treated or had received previous treatment with oral glucocorticoids or other immunosuppressive agents.	Focus on corticoid-naïve population allowing comparison to placebo and estimation of the size of the vamorolone effect	No	The comparability of vamorolone efficacy to prednisone and pharmacodynamic effects on cortisol was established in the clinical program, associated with a more favourable safety profile in some aspects for vamorolone. In the absence of a new safety issue compared to glucocorticoids, this supports that patients receiving glucocorticoid can safely switch to vamorolone. This population will be monitored as part of the general DMD population using routine methods.
Had an allergy or hypersensitivity to either study medication or any of its constituents	Standard exclusion criterion in pivotal studies	No	Not relevant for missing safety information, SmPC includes contraindication that AGAMREE is contraindicated in patients with known hypersensitivity to vamorolone or to any of the inactive ingredients.
Had used idebenone within 4 weeks prior to the first dose of study medication	Idebenone is a drug which was investigated in other clinical trials at the time VBP15-004 was recruiting. Exclusion to avoid incorrect attribution of any persistent idebenone effects to treatment received in VBP15-004	No	Idebenone not approved in DMD. Not relevant for missing safety information
Had severe behavioural or cognitive problems that precluded participation in the study in the Investigator's opinion	Standard exclusion criterion in pivotal studies related to the ability of the patient to participate in the trial	No	Subjects with behavioural or cognitive problems of the type expected for DMD were included in the study. No increased risk for deterioration of pre-existing behavioural problems was seen with vamorolone. Not relevant for missing safety information.
Had a previous or ongoing medical condition, medical	Standard exclusion criterion in pivotal studies related to the	No	Not relevant for missing safety information

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
history, physical findings, or laboratory abnormalities that could affect safety, make it unlikely that treatment and follow-up would be correctly completed or impair the assessment of study results in the opinion of the Investigator	ability of the patient to participate in the trial and/or possibility to interpret the results		
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	Avoid confounding factors to compare the effects of vamorolone to placebo and prednisone and establish effect size	No	Not relevant for missing safety information. Exondys was not approved in the EU. Translarna has a very distinct mechanism of action, is used on top of any glucocorticoid treatment and has not been shown to interfere with steroidal anti-inflammatory treatment in DMD patients. DMD patients receiving Translarna and vamorolone will be adequately monitored as part of PV routine activities.
Had received a live attenuated vaccine within 14 days prior to the first dose of study medication	Glucocorticoids are deemed interfere with the effect of live attenuated vaccine, either by allowing the infection to develop or by impairing the immunization process. At the time of VBP15-004 initiation, a potential risk with vamorolone was envisaged	No	Conservatively, a precaution has been made in section 4.4 of the SmPC to not administer live-attenuated or live vaccines within 6 weeks prior to starting vamorolone. Listed as a non-important potential risk; to be monitored using routine PV methods. It is considered that the inclusion of a precaution is considered sufficient to manage the risk in routine practice and together with its inclusion in the list of non-important potential risks it is not needed to include further this as a specific area of missing information in the RMP.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Was currently taking any other investigational drug or had taken any other investigational drug within 3 months prior to the first dose of study medication	Standard exclusion criterion in pivotal studies	No	Not relevant for missing safety information
Had previously been enrolled in the study	Standard exclusion criterion in pivotal studies	No	Not relevant for missing safety information

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain kinds of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, and adverse events caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not included in clinical trial development plan

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme. Not relevant in DMD.
Breastfeeding women	Not included in the clinical development programme. Not relevant in DMD.
Children below 4 years of age with DMD	Not included in the clinical development programme. VBP15-006 is currently ongoing and including children below 4 years of age.
Elderly patients	Not included in the clinical development programme. Not relevant in DMD.
Patients with hepatic impairment	DMD patients with hepatic impairment not included in the clinical development programme.

Type of special population	Exposure
	Hepatic impairment study VBP15-HI-001 was conducted in subjects with moderate HI who received a single dose of vamorolone 2mg/kg. The treatment was well tolerated. No treatment emergent AEs (TEAEs), deaths or serious AEs (SAEs) were reported during the study. No clinically significant findings were noted with respect to vital signs, clinical laboratory results, ECG parameters, or physical examinations.
Patients with renal impairment	Not included in the clinical development programme
Patients with cardiovascular impairment	Not included in the clinical development programme
Immunocompromised patients	Not included in the clinical development programme
Patients with other relevant co-morbidity	Not included in the clinical development programme
Population with relevant different ethnic origin	Different ethnicities included in the clinical development programme (White in majority, with representation of Black, Asian and Multiple ethnicities).
Subpopulations carrying relevant genetic polymorphisms	Genetic testing for DMD diagnosis was carried out for inclusion in clinical studies. All variants were accepted.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

SV.1.1 Method to calculate exposure

Not applicable

SV.1.2 Exposure

Not applicable

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Vamorolone has not demonstrated to have potential for misuse for illegal purposes like recreational drug, assault facilitation or doping.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 – Risks considered important for inclusion in the list of safety concerns and risks considered as non-important for inclusion in the list of safety concerns.

Vamorolone is a dissociative steroidal anti-inflammatory drug and glucocorticoid receptor (GR) selective agonist with differences from corticosteroids in terms of chemical structure, mechanism of action, and physiologic effects. Because it exerts part of its pharmacological effect through an agonistic action on the Glucocorticoid Receptor (GR), the typical risks associated with glucocorticoids (GC) should be considered as potential risks also for vamorolone. The clinical data obtained with vamorolone to date in controlled and uncontrolled studies have shown that AEs which are typical for GC like*, Hypercorticolism (Cushingoïd symptoms, Irritability, Vomiting, abdominal pain upper and diarrhoea)* can also occur with vamorolone but in most cases are only of mild to moderate severity and should not be considered important risks for the drug.

Cushingoid features was the most frequently reported adverse reaction with vamorolone. Subjects treated with the 6 mg/kg daily dose had a higher incidence of cushingoid features than subjects treated with 2 mg/kg daily.

For these reasons the following adverse events are considered as identified risks that are considered not important for inclusion in the list of safety concerns:

- Hypercortisolism
    - Cushingoid features
- Irritability
- Vomiting, abdominal pain upper and diarrhoea

It is not considered that vamorolone would pose any higher risk for overdose, off-label use or medication errors than what is on average the case for other drugs.

In vitro and in vivo genotoxicity studies were negative and the risk for exposure of a pregnancy to the product is low, considering the target population profile.

Because they are known to be possibly caused by glucocorticoids and because of current lack of clear clinical safety signals with vamorolone, the following adverse events will be considered as potential risks that are not important for inclusion in the list of safety concerns:

- Ophthalmic effects

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Identified Risks
Hypercortisolism • **Cushingoid features** Cushingoid features was the most frequently reported AE with vamorolone and was reported in a higher proportion of patients with vamorolone 2 mg/kg (6.7%) and 6 mg/kg (28.6%) than with placebo, and with a similar frequency to prednisone group (22.6%). All Cushingoid features were mild and moderate. No patient interrupted or discontinued vamorolone due to this AE. In one subject, dose adjustment was necessary out of the 164 patients treated in controlled and uncontrolled clinical studies.
Irritability In study VBP15-004, AEs related to Behavioural problems were reported in a similar percentage of subjects in the vamorolone 2 mg/kg (16.7%) and placebo (13.8%) groups and in a higher percentage of subjects in vamorolone 6 mg/kg (21.4%), and prednisone (32.3%) groups during the first 24 weeks of the study. All the events in the vamorolone groups were reported as mild to moderate and did not lead to study drug interruption of discontinuation. While the events in the vamorolone groups were mild to moderate and none led to treatment interruption or discontinuation, in the prednisone group 1 subject reported a severe event of Aggression, and 1 subject presented with a Personality change that abated with prednisone discontinuation. Considering the necessary reservations to be made concerning the still relatively small size of population studied, for vamorolone a safety signal, a weak signal, could only be concluded for irritability.
Vomiting, abdominal pain upper and diarrhoea In study VPB15-004 Gastrointestinal symptoms were reported for 27.6% in the placebo group, 25.8% in the prednisone group, and 30.0% and 28.6% in the vamorolone 2 and 6 mg/kg groups, respectively. Considering the necessary reservations to be made concerning the still relatively small size of population studied, for vamorolone a safety signal, a weak signal, could only be concluded for vomiting, abdominal pain upper and diarrhoea. Vomiting and Abdominal pain upper considered as clinically relevant were reported by > 1 subject in the vamorolone 2 6 mg/kg group.

Potential Risks
Ophthalmic Effects No subject presented with elevated intraocular pressure. Intraocular pressure increase is a known possible effect of corticosteroids in general. Intraocular Pressure did not increase in vamorolone-treated patients and actually decreased to Baseline values after switching from prednisone to vamorolone.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Not applicable

Known risks that do not impact the risk-benefit profile: these risks are considered well understood by DMD physicians experienced with glucocorticoid standard of care, they are similar in nature and similar or milder in severity.

- Hypercortisolism (Cushingoid symptoms)
- Irritability
- Vomiting, abdominal pain upper and diarrhoea

Other reasons for considering the risks not important: risks for which no safety signal has been observed with AGAMREE, but deemed potential risk based on structural and pharmacological similarities with glucocorticoids

- Ophthalmic effects

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks:

No identified risks are currently considered as important for vamorolone.

Important Potential Risks:

- **Important Potential Risk 1: Infections due to immunosuppression**

This risk is considered potential because part of the pharmacological effect of vamorolone results from an agonistic activity on the GR receptor and it is a known risk for glucocorticoids.

Risk-benefit impact: Vamorolone showed no effect on neutrophil counts or immature granulocytes in clinical trials. Eosinophil counts were similar in the vamorolone and placebo groups. The type of infections

reported were consistent with the pattern in a population of immunocompetent children. There was no increased of opportunistic infections.

Therefore, clinically important infections due to immunosuppression is considered as potential important risk for vamorolone.

- **Important Potential Risk 2: Hepatotoxicity**

In pre-clinical animal toxicity studies increased liver weight associated with microscopic observations of hepatocellular hypertrophy, vacuolation, single cell necrosis and increased liver enzymes was observed in the liver of mice. Similar observations have also been made with other steroids and the liver is a known 'target organ' for steroids.

Glucocorticoid use can result in hepatic enlargement and steatosis or glycogenosis. Corticosteroids can trigger or worsen non-alcoholic fatty liver disease (NAFLD). Long term use can also exacerbate chronic viral hepatitis.

Risk-benefit impact: In 164 patients treated with vamorolone for up to 32 months in controlled and uncontrolled clinical studies, there was one case of acute hepatitis reported which was classified by the investigator as not serious, moderate in intensity and probably related to vamorolone. The Company's opinion upon review of this single case is that the episode of acute Hepatitis did not meet the criteria of DILI or Hy's law as there was evidence of ongoing inflammatory co morbidities.

Routine pharmacovigilance activities will further monitor the risk of hepatotoxicity with respect to number of reports, seriousness, outcome, and risk factors, including patient history.

- **Important Potential Risk 3: Acute adrenal insufficiency (Adrenal crisis)**

Dose-dependent adrenal suppression is a pharmacodynamic effect of vamorolone consistently observed in all clinical trials, in line with known effects of corticosteroids. This risk is considered potential because despite of the observed adrenal suppression, in the pivotal clinical trial programme no events of acute adrenal insufficiency (adrenal crisis) were reported in Study VB15-004. Similarly, no events of acute adrenal insufficiency (adrenal crisis) have been reported in Study VB15-006 (cut-off date of 21 July 2023). However, TEAEs of adrenal suppression have been reported at 6mg/kg doses in the 2-4 year old age group. Only single events of suspected adrenal crisis have been reported in the long-term programs.

Risk-benefit impact: Dose-dependent adrenal suppression is a recognised effect following steroid usage. Physicians treating DMD are familiar with this risk.

At Week 12, morning cortisol levels were reduced in a dose-dependent manner in all age groups. The vast majority of subjects treated with vamorolone 6 mg/kg and approximately 1/3 of subjects treated with vamorolone 2 mg/kg at all ages showed morning cortisol values <100 nmol/L suggestive of clinically relevant adrenal suppression. TEAEs suggestive of adrenal suppression have been reported in single patients in the open-label studies. Single events of suspected adrenal insufficiency have been reported in the long-term programs, i.e. Expanded Access Programs / Compassionate Use.

Adrenal suppression can occur at any vamorolone dose and symptomatic adrenal insufficiency can be triggered by infections, which are frequently reported in paediatric patients. Younger children are likely to be more susceptible to significant stress (e.g., due to an increased incidence of infections).

Acute adrenal insufficiency (adrenal crisis) may therefore be considered an important potential risk.

Missing Information

- **Missing information 1:** Use in patients above 12 years of age

Currently data in this age group are not sufficiently available from clinical trials. As of the cut-off date of this initial RMP, there is limited data on vamorolone use in patients above 12 years of age. The majority of patients who participated in the pivotal trial have been subsequently treated in the expanded access programme.

Risk-benefit impact: There is no particular risk anticipated. Additional data will be generated in the 12-18 year old cohort of study VBP15-006 to further characterize the safety profile as well as in the PASS.

- **Missing information 2:** Safety on long-term use (in particular regarding bone fractures, weight gain, growth, hyperglycemia, dyslipidemia and hypertension).

The safety of long-term use of vamorolone has not been established. Limited long-term data is available in particular regarding bone fractures, weight gain, growth, hyperglycemia, dyslipidemia and hypertension.

Risk-benefit impact: considering that there was no new safety signal observed with vamorolone compared to standard of care glucocorticoid therapy in the studied population for the duration of the clinical trials, no particular risk is anticipated for the long-term treatment. The demonstrated differences in the safety profile of vamorolone (effects on bone fracture, growth, behaviour) are expected to remain relevant in long-term use.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Potential risk: Infections due to immunosuppression	
MedDRA terms	MedDRA SMQ: Opportunistic infections Searches at MedDRA HLGT level for following HLGTs: • HLGT Immune disorders NEC • HLGT Immunodeficiency syndromes
Potential mechanisms	Interaction with GR receptor resulting in effects on several levels of the immune response.
Evidence source and strength of evidence	This is a known effect of glucocorticoids but clinically relevant infections due to immunosuppression trend has not been yet detected with vamorolone.
Characterisation of the risk	Based on current knowledge, if severe and/or opportunistic infections related to the potential risk of infections due to immunosuppression would be occurring with vamorolone the expected frequency would be low. The severity of the risk in such cases will depend on potential underlying existing immunodeficiencies in the patient (population at risk), the type of opportunistic infections that it may trigger. In addition, a risk could be theoretically observed for live attenuated vaccines to develop the actual infection in case of immunosuppression. Immunosuppressive effects are suspected to be reversible at treatment interruption or cessation.
Risk factors and risk groups	Immunocompromised patients Concomitant use with live attenuated vaccines Duration of treatment and dose
Preventability	Avoid use in association with live vaccines. Allow sufficient time window between temporary stop and restart of vamorolone at the time of vaccination.
Impact on risk-benefit balance of the product	If clinically relevant immunosuppressive actions would be confirmed by future data, it may significantly increase the risk particularly in immunocompromised patients, may reduce the effectiveness of vaccines and the risks associated with vaccination with live attenuated viruses. The impact on the benefit risk balance in DMD however would still be relatively low to modest as these risks in that case would be manageable in clinical practice by taking precautions measures. An EU PASS study will further characterise the risk of Infections due to immunosuppression in the post-marketing setting.
Public health impact	Not applicable. The DMD population is too small to have an impact on the safety and viral spread in the general population.

Important Potential risk: Hepatotoxicity	
MedDRA terms	SMQ: Drug related hepatic disorders
Potential mechanisms	The potential for glucocorticoids to exert hepatotoxic effects is thought to be due to their stimulation of the glucocorticoid receptors (GR) in the liver. This action is needed for the biological activity of the body cortisol related to gluconeogenesis and glycogen metabolism. Especially however when glucocorticoids are administered in overdose they can lead to hepatotoxic effects and liver steatosis (excess of glucocorticoids can due to their action on the GR lead to a constellation of metabolic abnormalities known as metabolic syndrome, which implies central obesity, hepatic hyperlipidemia, hypertension, and glucose intolerance). Because vamorolone exerts its pharmacological action in part also through an agonistic effect on the GR, hepatotoxic effects are considered as potential risks also for vamorolone, albeit to date the preclinical sign is weak and no clear valid clinical safety signal has been detected to date.
Evidence source and strength of evidence	Weak pre-clinical signal, nature of findings similar to those observed with other glucocorticoids. No valid safety signal in human data to date with vamorolone.
Characterisation of the risk	Clinically important hepatotoxicity can lead to medically severe increases of hepatic enzymes, primarily AST, ALT, GGT, GLDH and potentially also LDH and alkaline phosphatase. Potential development of organic alterations over time, primarily liver steatosis. Potential development of acute fulminant hepatitis as critical clinical condition. If it would be possibly occurring also with vamorolone, the frequency and severity are both expected to be low based on current product knowledge. Except in the case of fulminant hepatitis which may be a critical condition, the hepatotoxic effects are expected to be reversible at cessation of treatment and have a positive long-term outcome.
Risk groups or risk factors	Patients with existing hepatic impairment
Preventability	Use with caution in patients with existing hepatic impairment.
Impact on risk-benefit balance of the product	If confirmed for vamorolone, only a mild level of hepatotoxicity would be expected based on current product knowledge and the impact on the benefit-risk ratio would be low. If unexpectedly a significant level of hepatotoxicity would be detected from further use in clinical trials and in routine medical practice the impact on the benefit-risk ratio of course would be more significant. An EU PASS study will further characterise the risk of hepatotoxicity in the post-marketing setting.
Public health impact	None

Important Potential risk: Acute adrenal insufficiency (Adrenal crisis)	
MedDRA terms	PT: Adrenocortical insufficiency acute Searches at MedDRA HLGT level for following HLGTs: • HLGT Adrenal gland disorders
Potential mechanisms	Dose-dependent reduction in morning cortisol levels Sudden withdrawal of vamorolone treatment Acute stress situations (e.g. infection)
Evidence source and strength of evidence	This is a known effect of glucocorticoids, although TEAEs of adrenal suppression have been reported at 6mg/kg doses in the 2-4 year old age group in Study VBP15-006, events of acute adrenal insufficiency or adrenal crisis per se have not been fully characterised.
Characterisation of the risk	Based on current knowledge and low frequency of reported events of acute adrenal insufficiency (adrenal crisis) in the pivotal development programme to date, the overall expected frequency of acute adrenal insufficiency (adrenal crisis) events occurring with vamorolone is expected to be low particularly taking into consideration the risk minimisation measures that are in place. However, in younger patients (2-<4 years of age), who are more susceptible to significant stress situations e.g. due to an increased risk of infections the risk may be higher.
Risk factors and risk groups	Sudden withdrawal of vamorolone treatment in all age groups Acute stress situation (e.g. infection) in all age groups
Preventability	Gradually taper the dose when down-titrating or withdrawing vamorolone treatment Provision of a Patient Alert Card to patients to support early recognition and treatment of acute adrenal insufficiency (adrenal crisis).
Impact on risk-benefit balance of the product	The impact on the overall benefit risk balance in DMD is expected to be relatively low and manageable in clinical practice by employing preventability measures indicated above. An EU PASS study will further characterise the risk of acute adrenal insufficiency (adrenal crisis) in the post-marketing setting.
Public health impact	None

SVII.3.2. Presentation of the missing information

Missing information 1: Use in patients above 12 years of age
Evidence source: Age group that has not sufficiently been studied in clinical trials. The safety profile in patients above 12 years of age is expected to be similar to that observed in the pivotal trial population. Evidence will come from data obtained through organised systems for data collection and from spontaneous reporting during use in routine clinical practice.
Population in need of further characterisation: DMD patients above 12 years of age.

Missing information 2: Safety on long-term use (in particular regarding bone fractures, weight gain, growth, hyperglycemia, dyslipidemia and hypertension).
Evidence source: The safety on long-term use (in particular regarding bone fractures, weight gain, growth, hyperglycemia, dyslipidemia and hypertension) of vamorolone has not been established.
Population in need of further characterisation: Patients on long-term treatment with vamorolone.

Part II: Module SVIII - Summary of the safety concerns

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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

The post-authorisation safety profile of vamorolone will be evaluated through routine pharmacovigilance activities. These activities are fully described in the Pharmacovigilance System Master File.

III.2 Additional pharmacovigilance activities

Two additional pharmacovigilance activities are described below:

A. Non-Interventional (Observational) Post Authorisation Safety Study Summary

Study short name and title:

A multi-registry non-interventional, post-authorization study to evaluate the safety in children 4 years and older with DMD treated with vamorolone suspension (AGAMREE) compared to standard of care.

Rationale and study objectives:

To investigate the long-term safety profile of vamorolone within the target age group. Specifically, the following important potential risks will be evaluated:

- Infections due to immunosuppression
- Hepatotoxicity
- Acute adrenal insufficiency (adrenal crisis)

Additionally, the following missing information will be evaluated:

- Use in patients above 12 years of age
- With respect to safety in long-term use:
    - Bone fractures
    - Weight gain
    - Growth
    - Hyperglycemia
    - Dyslipidemia
    - Hypertension

Study design:

This is a non-interventional cohort study that is based on secondary use of data from existing independent registries of patients aged ≥ 4 years with DMD in the real-world post marketing setting and compared to SOC.

Data will be collected as per local standard of care. Comparison groups will be defined, and analysis will be performed in respective subgroups.

Study population:

Patients aged ≥ 4 years with DMD and enrolled with one of the existing patient registries, who initiated vamorolone or are on Standard of Care, including steroids, and where patients, parents or legal representatives have provided informed consent.

Milestones:

Final Protocol: Q3 2024
Start of data collection Q1 2025
Estimated End of Data collection: Q1 2032

B. VBP15-006 Study

Study short name and title:

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).

Rationale and study objectives:

The VBP15-006 study has been initiated as part of a Paediatric Investigation Plan, in order to ensure that the necessary safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy data are collected to further characterise the benefit –risk in the target population (2 to below 4 years of age as steroid-naive subjects; 7 to below 18 years both steroid-treated and steroid-naive subjects).

The purpose of including the VBP15-006 study as part of this Pharmacovigilance plan is to generate and evaluate the missing information "use in patients above 12 years of age".

Study design:

This study is an open-label, multiple dose study to evaluate vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a treatment period of 3 months in steroid-naïve boys ages 2 to <4 years, and glucocorticoid-treated and currently untreated boys ages 7 to <18 years with DMD.

Study population:

Target population for the trial is DMD patients from 2 to <4 years who are steroid-naïve and 7 to <18 years of age, both glucocorticoid-treated and glucocorticoid-untreated subjects at time of study entry.

Milestones:

Last Patient Last Visit: 30 June 2024
Final Clinical Study Report: Q4 2024

III.3 Summary Table of additional Pharmacovigilance activities

Table III.1: On-going and planned additional PV activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
PASS Planned	Long term safety	Important potential risks: Infections due to immunosuppression Hepatotoxicity, acute adrenal insufficiency (adrenal crisis) Missing information "Safety on long-term use (in particular regarding bone fractures, weight gain, growth, hyperglycemia, dyslipidemia and hypertension)" Missing information "use in patients above 12 years of age"	Final protocol	Q3 2024
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

Part IV: Plans for post-authorisation efficacy studies

Table IV.1 Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific requirements

Study (Status)	Summary of objectives	Efficacy uncertainties addressed	Due date
Not applicable			

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important potential risk 1: Infections due to immunosuppression	**Routine risk communication:** SmPC section 4.4 Special Warnings and Precautions PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation for infections monitoring are included in SmPC section 4.4 and PL section 2. **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to medical prescription
Important potential risk 2: Hepatotoxicity	**Routine risk communication:** SmPC sections 4.2 Posology and method of Administration, 4.3 Contraindications and 4.4 Special Warnings and Precautions PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to medical prescription
Important potential risk 3: Acute adrenal insufficiency (adrenal crisis)	**Routine risk communication:** SmPC sections SmPC sections 4.2 Posology and method of Administration, 4.4 Special Warnings and Precautions and 4.8 Undesirable effects PL sections 2 and 4 **Additional risk minimisation measures to address the risk:** A Patient Alert Card to support early recognition and treatment of adrenal crisis **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to medical prescription
Missing information 1: Use in patients above 12 years of age	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to medical prescription

Safety concern	Routine risk minimisation activities
Missing information 2: Safety on long-term use (in particular regarding bone fractures, weight gain, growth, hyperglycemia, dyslipidemia and hypertension)	**Routine risk communication:** SmPC section 4.4 Special warnings and precautions for use SmPC section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** PL sections 2 and 4 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to medical prescription

V.2. Additional Risk Minimisation Measures

Additional risk minimisation measures are proposed to address the safety concern of acute adrenal insufficiency (adrenal crisis).

V.3. Summary of risk minimisation measures

Table Part V.3 1: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk 1: Infections due to immunosuppression	**Routine risk minimisation measures:** SmPC section 4.4 PL section 2 **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 **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, 4.4 and 4.8 PL sections 2 and 4 **Additional risk minimisation measures:** A patient alert card to support early recognition and treatment of adrenal crisis	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** An observational PASS to further characterise and quantify long-term safety profile of AGAMREE
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, hyperglycemia, dyslipidemia and hypertension).	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8 PL sections 2 and 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • An observational PASS to further characterise and quantify long-term safety profile of AGAMREE

Part VI: Summary of the risk management plan

This is a summary of the risk management plan (RMP) for AGAMREE. The RMP details important risks of AGAMREE, how these risks can be minimised, and how more information will be obtained about AGAMREE's risks and uncertainties (missing information).

AGAMREE's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how AGAMREE should be used.

This summary of the RMP for AGAMREE should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of AGAMREE's RMP.

I. The medicine and what it is used for

AGAMREE is indicated for the treatment of Duchenne Muscular Dystrophy (DMD) (see SmPC for the full indication). It contains vamorolone as the active substance and it is given by oral route.

Further information about the evaluation of AGAMREE's benefits can be found in AGAMREE's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage *https://www.ema.europa.eu/en/medicines/human/EPAR/agamree*.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of AGAMREE, together with measures to minimise such risks and the proposed studies for learning more about AGAMREE's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of AGAMREE is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of AGAMREE are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of AGAMREE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	Infections due to immunosuppression, hepatotoxicity, acute adrenal insufficiency (adrenal crisis)
Missing information	Use in patients above 12 years of age Safety on long-term use (in particular regarding bone fractures, weight gain, growth, hyperglycemia, dyslipidemia and hypertension).

II.B Summary of important risks

Potential risk: Infections due to immunosuppression	
Evidence for linking the risk to the medicine	This is a known effect of glucocorticoids but clinically relevant infections due to immunosuppression trend has not been yet detected with vamorolone. Part of the vamorolone pharmacological activity is also based on agonistic effect on Glucocorticoid Receptor (GR).
Risk factors and risk groups	Immunocompromised patients Use in combination with live attenuated vaccines Duration of treatment and dose
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 Patient information leaflet section 2 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** An observational Post Authorisation Safety Study (PASS)* to further characterise and quantify long-term safety profile of AGAMREE

*A PASS is a study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk management measures.

Potential risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Weak pre-clinical signal, nature of findings similar to those observed with other glucocorticoids. No valid safety signal in human data to date with vamorolone.
Risk groups or risk factors	Patients with existing hepatic impairment
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.2, 4.3 and 4.4 Patient information leaflet section 2 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**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

Potential risk: Acute adrenal insufficiency (Adrenal crisis)	
Evidence for linking the risk to the medicine	This is a known effect of glucocorticoids, however events of acute adrenal insufficiency or adrenal crisis per se have not been fully characterised for vamorolone.
Risk groups or risk factors	Sudden withdrawal of vamorolone treatment in all age groups Acute stress situation (e.g. infection) in all age groups
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4 and 4.8 Patient information leaflet sections 2 and 4 **Additional risk minimisation measures to address the risk:** A Patient Alert Card to support early recognition and treatment of adrenal crisis **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to medical prescription
Additional pharmacovigilance activities	**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

Missing information 1: Use in patients above 12 years of age	
Risk minimisation measures	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 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) 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, hyperglycemia, dyslipidemia and hypertension)	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4, 4.8 PL sections 2 and 4 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**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

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of AGAMREE.

II.C.2 Other studies in post-authorisation development plan

A. Post Authorisation Safety Study

A multi-registry non-interventional, post-authorization study to evaluate the safety in children 2 years and older with DMD treated with vamorolone suspension (AGAMREE) compared to standard of care.

Purpose of the study:

To investigate the long-term safety profile of vamorolone within the target age group. Specifically, the following important potential risks will be evaluated:

- Infections due to immunosuppression
- Hepatotoxicity
- Acute adrenal insufficiency (adrenal crisis).

Additionally, the following missing information will be evaluated:

- Use in patients above 12 years of age
- With respect to safety in long-term use:
    - Bone fractures
    - Weight gain
    - Growth
    - Hyperglycemia,
    - Dyslipidemia.
    - Hypertension

B. Study VBP15-006

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).

Purpose of the study:

The VBP15-006 study has been initiated as part of a Paediatric Investigation Plan, in order to ensure that the necessary safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy data are collected to further characterise the benefit –risk in the target population (2 to below 4 years of age as steroid-naive subjects; 7 to below 18 years both steroid-treated and steroid-naive subjects).

The purpose of including the VBP15-006 study as part of this Pharmacovigilance plan is to generate and evaluate assess the missing information "use in patients above 12 years of age".

Part VII: Annexes

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Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

A patient alert card (see details below) to support early recognition and treatment of adrenal crisis is proposed:

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.