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## **Committee for Veterinary Medicinal Products (CVMP)**

CVMP assessment report for a variation requiring  
assessment for Syvazul BTV 3 (EMEA/V/C/006623,  
EMA/VRA/0000269481)

Common name: Bluetongue virus vaccine (inactivated)

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

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# Introduction

## **Submission of the variation application**

In accordance with Article 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Laboratorios Syva S.A. (the applicant), submitted to the European Medicines Agency (the Agency) on 5 May 2025 an application for a variation requiring assessment for Syvazul BTV 3.

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## **Scope of the variation**

Syvazul BTV 3 (Bluetongue virus vaccine (inactivated)) is already authorised for use in Sheep for the following indications:

Sheep: for active immunisation of sheep to reduce viraemia, mortality, clinical signs and lesions caused by bluetongue serotype 3. Onset of immunity: 4 weeks after completion of the primary vaccination scheme. The duration of immunity has not been established.

Syvazul BTV 3 suspension for injection contains Bluetongue virus, serotype 3 (BTV-3), strain BTV-3/NET2023, inactivated.

<b>Variation requested</b>	
I.III.1.a.	Other changes specific to veterinary medicinal products to be administered to food-producing animals. Change or addition of target species.

This variation is to add cattle as target species, including an increase of the minimum specification for antigen content in the finished product.

Cattle:

For active immunisation of cattle to reduce viraemia caused by bluetongue serotype 3.

Onset of immunity: 3 weeks after completion of the primary vaccination scheme.

The duration of immunity has not been established.”

## **Changes to the dossier held by the European Medicines Agency**

This application relates to the following sections of the current dossier held by the Agency:

Part 1, part 2, and part 4.

It is noted by CVMP that an indication for use in cattle was sought as part of the original application for new marketing authorisation, but was not accepted because of inadequate data to support efficacy. Much of the cattle data submitted with the original application have been represented with this variation application under part 4 of the dossier, however has not been resubmitted in the case of part 3 of the dossier. This is considered acceptable since the part 3 data relating to cattle in the original application are not impacted by the current variation.

## **Part 2 - Quality**

Cross-reference is made to data already submitted and assessed for this marketing authorisation by the CVMP previously, and no new data on quality were submitted, except for data pertaining to the minimum concentration of the active substance used for the formulation of the vaccine. Only these new data have been assessed in the sections below.

### ***Quality documentation (physico-chemical, biological, and microbiological information)***

#### **Qualitative and quantitative composition**

The qualitative composition of the vaccine has been changed to increase the quantity of the active substance, inactivated Bluetongue virus (BTV) serotype 3 strain BTV-3/NET2023, from  $\geq 10^{6.9}$  CCID<sub>50</sub>/ml, to  $\geq 10^{7.2}$  CCID<sub>50</sub>/ml. The qualitative composition of all other constituents of the vaccine remains unchanged.

#### ***Description of the manufacturing method***

The manufacturing process remains unchanged, with the exception of the preparation of the vaccine bulk, which has been updated to amend the quantity of the active substance that will be used in the preparation of the vaccine. This value has increased from  $10^{13.2}$  CCID<sub>50</sub> to  $10^{13.5}$  CCID<sub>50</sub> to be added to a 2000 L batch. The volume of inactivated antigen and the manufacturing processes used to generate the inactivated antigen remain unchanged.

#### ***Control tests on the finished product***

The control tests on the finished product remain unchanged, however, the acceptance criteria for the interim RT-qPCR test used to quantify the active substance has been amended (increased) to take into account the increased minimum viral titre.

#### ***Batch-to-batch consistency***

Batch release protocols have been provided for two batches which are representative of the 40 dose and 100 dose presentations respectively. These batches were formulated to the proposed minimum viral titre of  $\geq 10^{7.2}$  CCID<sub>50</sub>/ml with quantification of the active substance within the specification proposed for the interim potency test.

#### ***Overall conclusions on quality***

Syvazul BTV3 was authorised under Article 25 'Applications in exceptional circumstances' and as such the minimum protective dose for BTV3 was based on the minimum protective dose confirmed for the three strains of BTV included in the BTV multi strain vaccine. As part of this variation, the applicant proposes to increase the minimum efficacious dose from  $\geq 10^{6.9}$  CCID<sub>50</sub>/ml, to  $\geq 10^{7.2}$  CCID<sub>50</sub>/ml. This change is considered acceptable, from a safety and efficacy perspective. Refer to comments under Part 3 and 4, respectively. Considering the interim potency test determines the number of genome copies per ml of BTV after inactivation, an increase in the minimum viral titre at formulation will result in an increase in the acceptance criteria of the potency test. Therefore, the acceptance criteria for the RT-qPCR based potency assay have been increased. This is considered acceptable based on the assumption that the updated acceptance criteria are correlated to the minimum viral titre, and considering the potency test currently utilised is an interim test that will be replaced in January 2026.

## Part 3 – Safety documentation (Safety and residues tests)

The applicant has not submitted any documentation related to Part 3 of the dossier in the current variation application to add cattle as a target species. Whilst not specifically justified, this approach is accepted noting that safety documentation relating to the target species cattle was assessed during the assessment of both the original application for the authorised multi-strain vaccine, 'Syvazul BTV suspension for injection for sheep and cattle' and the MAA procedure for Syvazul BTV 3. The available data were considered adequate to support safety of use in that species. Note that cattle as target species were withdrawn just prior to the end of the MAA procedure for Syvazul BTV3 due to outstanding concerns relating to the adequacy of available data to support efficacy. At that time, the safety aspects of the proposed SPC had been largely agreed. As such, relevant safety data have already been submitted and positively assessed by CVMP previously, however not formally adopted in a CVMP opinion. For completeness, a brief summary of the information which had been assessed for Syvazul BTV 3, updated as necessary, concerning the target species cattle, is presented below.

### **General requirements**

The MAA for Syvazul BTV 3 was submitted in accordance with Article 25 of Regulation 2019/6, that is, an application in exceptional circumstances.

In support of the safety of Syvazul BTV 3 for the target animal species sheep and cattle, users, consumers and the environment, the applicant has referred to those data that were submitted for the authorised multi-strain vaccine, 'Syvazul BTV suspension for injection for sheep and cattle' which contains a maximum of 2 of the following inactivated bluetongue virus serotypes: BTV serotype 1, 4, 8.

A similar regulatory approach to that taken for multi-strain dossiers was considered acceptable for the application, noting that Syvazul BTV 3 contains a single strain of BTV (serotype 3, BTV-3/NET2023 (inactivated)) and therefore a lower antigenic burden than the authorised multi-strain vaccine which can contain up to two BTV strains, and the same adjuvants and excipients in the same quantities as are included in the authorised multi-strain vaccine. Furthermore, Syvazul BTV 3 was originally proposed for use in the same target species according to the same vaccination schemes as the authorised multi-strain vaccine.

As the data concerned have been accepted by CVMP, reference was made to the summary of the CVMP's assessment as contained in the EPAR for 'Syvazul BTV suspension for injection for sheep and cattle' (EMA/802733/2018).

In addition to those data already accepted for the multi-strain dossier, the applicant has investigated safety of the candidate vaccine 'Syvazul BTV 3' in the context of a pre-clinical study performed in cattle that was primarily designed to investigate efficacy. Although the study in question was not designed as a safety study, this approach is foreseen in the relevant guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021): '*The safety and efficacy studies may be combined in the same pre-clinical (laboratory) study*'; and is considered acceptable.

Note that, as part of the current variation, the applicant proposes to increase the minimum titre from  $10^{6.9}$  CCID<sub>50</sub> per ml to  $10^{7.2}$  CCID<sub>50</sub> per ml. This is not considered to have any implications for safety in either sheep or cattle noting that:

- Syvazul BTV 3 contains a single strain of BTV (serotype 3) and therefore a lower antigenic burden than the authorised multi-strain vaccine which can contain up to two BTV strains,
- The vaccine batches use in the sheep preclinical studies contained inactivated virus at a concentration of  $10^{7.2}$  CCID<sub>50</sub>/mL, and
- Two batches of vaccine were used in the cattle pre-clinical laboratory study presented under Part 4, one containing inactivated virus at a concentration of  $10^{6.9}$  CCID<sub>50</sub>/ml, the other at a concentration of  $10^{7.2}$  CCID<sub>50</sub>/ml.

## ***Safety documentation***

### ***Pre-clinical studies***

#### **Safety of the administration of one dose**

See 'safety of one administration of an overdose' and 'safety of the repeated administration of one dose'.

#### **Safety of one administration of an overdose**

Administration of an overdose to cattle was not investigated in the context of the MAA for the authorised multi-strain vaccine 'Syvazul BTV'. In addition, the safety of administration of an overdose of Syvazul BTV3 was not investigated in cattle. Accordingly, the text that currently appears in section 3.10 of the SPC ("The safety of an overdose has not been established") is relevant to cattle and can be accepted.

#### **Safety of the repeated administration of one dose**

The conclusions reached by CVMP in respect of the safety of administration of a single and repeated dose of the authorised multi-strain vaccine 'Syvazul BTV-1+8' are noted and are considered relevant and applicable to the MAA for Syvazul BTV 3. Namely, this conclusion in respect of the target species cattle is:

Cattle: '...the results show that the administration of a single dose of 'Syvazul BTV-1+8' and of the repeated administration of two doses of the vaccine is considered safe. Adverse reactions such as local reactions and transient increase in temperature are adequately addressed in the SPC.'

Information concerning adverse events in cattle in the proposed SPC is consistent with that proposed for the authorised multi-strain vaccine.

Syvazul BTV 3 has identical composition of adjuvants and excipients to the authorised multi-strain vaccine and differs only in the serotype of the inactivated BTV. As it is also noted that the inactivated BTV component is included at a lower antigenic load than that for which safety has been demonstrated for the multi-strain vaccine, it can be accepted that the data that were agreed by CVMP to demonstrate adequate safety of the multi-strain vaccine in cattle also fulfil the requirements to demonstrate safety of the candidate IVMP in this target species.

As stated above, the proposal to increase the minimum dose from  $10^{6.9}$  CCID<sub>50</sub> per ml to  $10^{7.2}$  CCID<sub>50</sub> per ml, is not considered to have implications for the conclusion on safety noting that:

- a dose of  $10^{7.2}$  CCID<sub>50</sub> per ml has been administered to both sheep and cattle in studies presented in the MAA for Syvazul BTV 3, and

- in respect of the multi-strain vaccine, 'Syvazul BTV-1+8', "*The safety studies have been carried out using batches of vaccine manufactured with the maximum number of strains (n=2) and containing at least the fixed target antigen amount ( $10^{6.9}$  TCID<sub>50</sub>/dose). Batches used contained standard amount of antigen or from 2 to 8 times the standard amount of antigen ( $10^{6.9}$  TCID<sub>50</sub>/ml) and the standardised final product.*"

Therefore, using the same principle of extrapolation of safety data generated with 'Syvazul BTV-1+8' to that of Syvazul BTV 3, it can be accepted that the increase of minimum titre to  $10^{7.2}$  CCID<sub>50</sub> per ml will not present an unacceptable risk to either of the target species, sheep or cattle.

## **Examination of reproductive performance**

The conclusions reached by CVMP in respect of examination of the effect on reproductive performance of the authorised multi-strain vaccine 'Syvazul BTV-1+8' were noted and were considered relevant and applicable during the assessment of the data presented in the MAA for Syvazul BTV 3. Namely, for cattle, this conclusion was:

Cattle: Laboratory studies examining reproductive performance in cattle were not performed, however the following conclusions concerning reproductive performance in cattle were reached based on the field studies submitted: '...the results show that the administration of two single doses of 'Syvazul BTV-1+8' administered 21 days apart is considered safe in pregnant (all trimesters) and lactating cows.'

It is concluded by CVMP that safety of administration of Syvazul BTV 3 to pregnant and lactating animals may be considered to have been adequately supported based on the data presented. Section 3.7 of the SPC for Syvazul BTV 3 contains the same information as that included in section 3.7 of the authorised SPC for the multi-strain vaccine, namely that the vaccine can be used during pregnancy and lactation, which is considered acceptable. It is also stated in section 3.7 that the safety and efficacy of the candidate vaccine has not been established in breeding male animals, which is consistent with the authorised multi-strain vaccine, and is also considered acceptable. No change to this section of the currently authorised SPC for Syvazul BTV 3 is proposed by the applicant. This is accepted.

## **Examination of immunological functions**

The conclusion reached by CVMP in respect of examination of immunological functions of the authorised multi-strain vaccine 'Syvazul BTV-1+8' (namely that no adverse effects on immunological function are anticipated), was noted and was also considered applicable to the application for Syvazul BTV 3, for both sheep and cattle.

## **User safety**

In respect of user safety, it was concluded by CVMP that for the multi-strain vaccine '...due to the nature and concentration of its active substances (inactivated bluetongue virus - maximum two of the following BTV serotypes: BTV-1, BTV-8 and BTV-4) and excipients (semi-purified saponin from Quillaja saponaria, aluminium hydroxide, silicon antifoaming agent, potassium chloride, potassium dihydrogen phosphate, disodium hydrogen phosphate anhydrous, sodium chloride and thiomersal), the vaccine does not pose any specific risk to the user when used as recommended.'

The user safety warnings agreed for Syvazul BTV 3 were based on the user safety warnings accepted by CVMP for Syvazul BTV-1+8, whereby it was concluded that the use of Syvazul BTV 3 will not pose a different risk to the user than that posed by the authorised vaccine. There is no adverse impact on user safety arising from this variation to include cattle as target species.

## **Study of residues**

The conclusions reached by CVMP in respect of the risk posed to the consumer by the authorised multi-strain vaccine 'Syvazul BTV-1+8' are that 'Syvazul BTV' is expected to pose a negligible risk for the consumer; the withdrawal period is set at zero days.' As the active substance in Syvazul BTV 3 is of biological origin intended to produce active immunity, it is not within the scope of Regulation (EC) 470/2009. Furthermore, the excipients and adjuvants are the same as in the multi-strain vaccine. The same conclusion concerning consumer safety was reached for Syvazul BTV 3. The proposed addition of cattle as target species does not impact this conclusion; there is no change to the currently authorised withdrawal period of zero days.

## **Interactions**

Standard text is currently included in the SPC to section 3.8 to reflect that there are no data available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. No change to this information is required on the basis of the current variation.

## **Clinical studies**

Based on the clinical trials provided in support of the multi-strain dossier, the following conclusions concerning target animal safety were reached by CVMP, in respect of the target species cattle:

'...the administration of two single doses of 'Syvazul BTV-1+8' administered 21 days apart is considered safe in cattle of minimum age.'

'...the administration of two single doses of 'Syvazul BTV-1+8' administered 21 days apart is considered safe in pregnant (all trimesters) and lactating cows.'

A summary of pharmacovigilance data in ruminant species concerning the (then) candidate IVMP, now authorised as Syvazul BTV 3, which was authorised for emergency use in a number of MS during an ongoing BTV-3 outbreak was provided in the MAA for Syvazul BTV 3. These data were gathered between April and July 2024. Adverse events were reported and comprised both safety events and lack of expected efficacy (LEE) events.

Concerning cattle, the most commonly reported adverse events were lactation change, milk production decrease, hypersalivation, high somatic cell count, diarrhoea, anorexia, abortion, lethargy, and premature parturition. All adverse events were reported as 'very rare' with the exception of milk production decrease and anorexia which were 'rare'. In respect of very rare reports of diarrhoea, this was not included as an AE in section 3.6 since it was justified that causality was unclear/unlikely; in all reported cases there did not appear to be a temporal association with vaccination (reaction described as starting 4 – 7 days post-vaccination).

In section 3.6 of the proposed SPC in the current variation, the applicant has included a description of adverse events in the target species cattle which reflects the adverse event profile of Syvazul BTV 3 as used in the field. The proposed text in section 3.6 of the SPC is considered acceptable.

## **Environmental risk assessment**

The conclusions reached by CVMP in respect of the risk posed to the environment by the authorised multi-strain vaccine 'Syvazul BTV-1+8' are as follows: 'Syvazul BTV' is expected to pose a negligible risk for the environment when used according to the SPC.' The same conclusions were reached for Syvazul BTV 3 when considering the original application for authorisation. The current variation does not affect conclusions reached in respect of safety for the environment for Syvazul BTV 3.

## **Overall conclusions on the safety documentation**

It can be considered that the safety of administration of Syvazul BTV 3 to the target species cattle has been adequately demonstrated, and that the safety of administration of a minimum titre of  $10^{7.2}$  CCID<sub>50</sub>/ml is acceptable. The safety aspects of the proposed SPC are considered acceptable.

## **Part 4 – Efficacy documentation (pre-clinical studies and clinical trials)**

Syvazul BTV3 is an inactivated vaccine which was authorised for use in sheep in accordance with Article 25 of Regulation (EU) 2019/6, i.e., an application under exceptional circumstances. A positive opinion was adopted by CVMP on 15 January 2025 and on 20 February 2025, the European Commission adopted a Commission Decision granting the marketing authorisation for the product. The vaccine was developed under emergency circumstances due to the highly virulent BTV serotype 3 outbreaks in sheep reported from September 2023 in Europe.

It is noted that at the time of submission of the application for new product authorisation, the vaccine was proposed for use in sheep and cattle. Whilst the safety of vaccination of cattle was considered to have been adequately supported by the data presented, efficacy data were limited to the demonstration of the stimulation of neutralising antibodies following vaccination. In the absence of challenge data to confirm efficacy of Syvazul BTV 3 in cattle, CVMP considered that insufficient data were available to support the proposed indications for use; “active immunisation of cattle against bluetongue virus serotype 3”, therefore the applicant withdrew cattle as proposed target species.

In the current application, a new pre-clinical challenge study is provided in support of cattle as target species, with a proposed indication “for active immunization of cattle to reduce viraemia caused by bluetongue serotype 3.”

The vaccine is proposed for intramuscular use in cattle from 2 months of age (naïve animals) or from 3 months of age in calves born to immune cattle, with a primary vaccination schedule of two doses of 2 ml 3 weeks apart. The onset of immunity is claimed as 3 weeks after completion of the primary vaccination scheme. The duration of immunity has not been established, consequently, a revaccination schedule is not established.

### **General requirements**

The vaccine strain included in Syvazul BTV 3, BTV-3/NET2023 (serotype BTV-3), was isolated from sheep during the recent outbreak in the Netherlands in September 2023. The choice of the vaccine strain is acceptable and is directly relevant to the current BTV epidemic in the EU.

As mentioned above, the application for Syvazul BTV 3 was submitted in accordance with Article 25 of Regulation (EU) 2019/6, i.e., an application under exceptional circumstances, which states “By way of derogation from point (b) of Article 8(1), in exceptional circumstances related to animal or public health, an applicant may submit an application which does not meet all requirements of that point, for which the benefit of the immediate availability on the market of the veterinary medicinal product concerned to the animal or public health outweighs the risk inherent in the fact that certain quality, safety or efficacy documentation has not been provided. In such a case, the applicant shall be required to demonstrate that for objective and verifiable reasons certain quality, safety or efficacy documentation required in accordance with Annex II cannot be provided.”

## **Challenge model**

The same challenge model and dose used in the challenge studies to demonstrate efficacy in sheep was used in the new challenge study in cattle.

## **Efficacy parameters and tests**

The efficacy parameters as evaluated in the new study provided were the same as those used in the studies presented in the dossier for Syvazul BTV 3 and are considered acceptable.

## **Efficacy documentation**

In addition to the data previously provided in the dossier for Syvazul BTV 3 (in which cattle were originally proposed as target species), one study is presented in the current application to investigate the efficacy of the product in cattle.

## **Pre-clinical studies**

### **Dose determination**

As currently authorised, the minimum amount of antigen in Syvazul BTV 3 is  $10^{6.9}$  CCID<sub>50</sub> per ml. However, in parallel with the proposal to add cattle as target species, the applicant proposes to increase the minimum amount of antigen to  $10^{7.2}$  CCID<sub>50</sub> per ml. The reason for this increase is because, in the challenge study conducted in cattle, the group of calves vaccinated with two doses of 2 ml with an antigen content of  $10^{7.2}$  CCID<sub>50</sub> per ml was considered by the applicant to yield more favourable efficacy results than the group of calves vaccinated with two doses of 4 ml with an antigen content of  $10^{6.9}$  CCID<sub>50</sub> per ml. See section 'Onset of immunity'.

In both challenge studies presented to support efficacy in sheep, test animals were vaccinated with a 2 ml dose of vaccine containing  $10^{7.2}$  TCID<sub>50</sub>/ml.

Noting that efficacy was evaluated in both sheep and cattle using vaccine with an antigen content of  $10^{7.2}$  CCID<sub>50</sub> per ml, the proposed increase of the minimum titre to  $10^{7.2}$  TCID<sub>50</sub>/ml can be accepted.

### **Onset of immunity**

#### **Study 10: Efficacy of a prime-boost administered BTV-3 vaccine against experimental BTV-3 infection in cattle**

Twenty-four healthy female calves, seronegative and free from BTV, of approximate minimum age on day of vaccination were randomly allocated to three treatment groups (n=8/group). On Study Day (D) 0 and D21, treatment group T01 received a placebo (saline) and T02 and T03 received two different formulations of Syvazul BTV 3 by intramuscular injection in the prescapular neck area (alternate sides for first and second vaccination); T02 were vaccinated with 2 ml of Syvazul BTV 3 containing  $10^{7.2}$  CCID<sub>50</sub>/ml, T03 were vaccinated with 4 ml of Syvazul BTV 3 containing  $10^{6.9}$  CCID<sub>50</sub>/ml. After vaccination, calves' rectal temperature and local reactions were monitored for five days and blood samples were collected to measure the serological response to vaccination (D14, D21 and D31). On D42, three weeks after the second vaccination, calves were challenged with virulent BTV-3 at a dose of  $4 \times 5.1 \log_{10}$  TCID<sub>50</sub>/animal by subcutaneous injection (BTV-3/Neth 2023).

During the follow-up period of 21 days post-challenge (D42 – D63), clinical observations and BTV specific signs, rectal temperature, viraemia and serology (BTV VP7 ELISA antibodies and BTV-3 specific neutralising antibodies) were evaluated. In addition, for blood samples positive for BTV-3, re-isolation

of BTV by culture was also conducted. The in-life phase of the study ended on D63, when calves were euthanised followed by gross and histopathological examination post-mortem. The study was partially blinded; the treatment groups were only blinded for the personnel performing the (histo)pathological examinations. Vaccine efficacy was evaluated by the assessment of viraemia as primary parameter. No specific pre-defined immunogenicity criteria were stated.

### Results:

Several animals were noted to have mild clinical signs before vaccination during acclimation, including mild respiratory symptoms and/or fever up to 39.8°C that resolved without treatment, however no animals were withdrawn from the study due to health deterioration/compromised welfare.

Post-vaccination, there were no local reactions after the first or second dose of vaccine. After the 1st and 2<sup>nd</sup> dose of vaccine, fever for a duration of 1 – 3 days and fever for a duration of 1 day, respectively, was reported very commonly in vaccinated calves (not observed in the placebo group), however temperature increases were also observed prior to vaccination in both cases. The description of adverse events in section 3.6 of the SPC includes injection site reaction, injection site erythema, injection site nodule and elevated temperature as 'very common'. With respect to rectal temperature increases and description of local reactions, whilst the latter was not observed in the current study, it is considered appropriate to base the description of adverse events on the safety data from Syvazul BTV (refer to comments under Part 3). The text proposed for inclusion in section 3.6 is acceptable.

Post-challenge, one animal from group T03 died on 9 days post-challenge due to unrelated causes (clostridium toxemia) and was excluded from further analysis.

Clinical signs and lesions were observed post-challenge and were similar in all groups. Clinical signs were occasional and mild (dry to productive incidental cough, serous to mucoid nasal discharge and mildly to moderate increase of saliva production). Occasional lesions in the mouth mucosa were observed in the three groups, all were observed at a single timepoint with the exception of 1 calf in Group T01 (duration 9 days) and 1 calf in Group T02 (duration of 5 days). After clinical assessment, these lesions were not considered BTV related. The statistical comparison of the clinical scores across the three groups revealed inconsistent patterns, with significant differences shifting between groups over time. In the CVMP view, although the applicant claims that some clinical signs were unrelated to BTV-3 challenge, and while this can be accepted in some cases, the challenge appeared to have induced mild clinical signs to a certain degree. It should also be highlighted that the non-blinded nature of clinical observations may have biased the results. Under the conditions of this study, a beneficial effect of vaccination on clinical signs of BTV 3 infection in cattle could not be demonstrated.

Between days 1 and 9 post-challenge, rectal temperatures higher than 39.5 °C were observed in calves from all groups. The maximum number of animals with hyperthermia occurred at 7 days post-challenge for Group T01 (5 calves) and Group T03 (7 calves), and at 4 days post-challenge for Group T02 (6 calves). No positive impact of vaccination on fever was observed; increases in temperature were observed in all groups and rectal temperatures were significantly higher in each of the two vaccinated groups in one out of the two measurements performed on days 7, 8 and 9 post challenge compared to the control group.

Concerning viraemia, from day 5 post-challenge all animals developed viraemia and tested positive until the end of the study, with peak levels on day 10 post-challenge. Statistically significant differences were reported in the mean BTV RT-qPCR Ct values at day 7, 10, 12, 14, 17, 19 and 21 post-challenge for Group T02 compared to the placebo group, and on days 7, 12, 14, 17, 19 and 21 for Group T03 compared to the placebo group, with higher viraemia in the control group compared to the two vaccinated groups at these timepoints. Peak levels in BTV genome were observed at 10 days

post-challenge with a group average of Ct 23.1 for calves in T01, Ct 23.7 for calves in T03 and Ct 25.9 for calves in T02.

A reduction of maximum 0.8 log<sub>10</sub> TCID<sub>50</sub> was demonstrated for calves in Group T02 at 10 and 12 days post-challenge, when the group average of the placebo-vaccinated calves was 4.0 and 3.9 log<sub>10</sub> TCID<sub>50</sub> respectively, compared to 3.2 and 3.1 log<sub>10</sub> TCID<sub>50</sub> in T02, respectively. A reduction of maximum 0.5 log<sub>10</sub> TCID<sub>50</sub> was demonstrated in Group T03 at 17 days post-challenge, average in Group T01 was 3.5 log<sub>10</sub> TCID<sub>50</sub> compared to 3.0 log<sub>10</sub> TCID<sub>50</sub> in Group T03.

The AUC was 59.3, 48.8 and 53.8 TCID<sub>50</sub>/ml in Group T01, T02 and T03, respectively. The difference between Group T01 and T02 was statistically significant (p=0.008), but not between Group T01 and T03 (p=0.119). Thus, it can be accepted that there is a slightly greater reduction of viraemia in Group T02 than Group T03, and therefore the choice of the administration of two doses, each consisting of a 2 ml dose with a minimum antigen content of 10<sup>7.2</sup> CCID<sub>50</sub>/ml appears justified. However, noting that the actual dose administered in the other vaccinated group was the same, but with a larger volume and therefore twice the adjuvant content, it cannot be excluded that these results represent biological variation. That said, the proposed dose volume and active substance concentration for cattle can be accepted. Furthermore, it should be highlighted that the reduction of viraemia following vaccination is considered modest. However, whilst the clinical relevance of the magnitude of the reduction could be questioned further, it is noted that a statistically significant reduction was demonstrated and that this vaccine has been developed in the framework of an Article 25 application ('exceptional circumstances'). Thus, this point will not be pursued.

Infectious virus was demonstrated in at least 7/8 calves in Group T01, on an average of 2.75 timepoints; in 6/7 calves in Group T03, on an average of 2.42 timepoints; and in 6/8 calves in Group T02 on an average of 1.25 timepoints. No statistical difference was found between groups for the number of timepoints in which virus was isolated in calves of the 3 groups, although a trend (p=0.09) was observed for the difference between Group T01 and Group T02. Overall, a statistically significant effect of vaccination on virus isolation was not confirmed in this study.

Serological analysis (anti-BTV VP7 antibodies) demonstrated a similar response to vaccination in Groups T02 and T03; none of the vaccinated calves were shown to seroconvert by 3 weeks after the first dose, whereas by ten days after the second dose (subsequent sampling timepoint), all but one calf (group T02) was positive for BTV VP7 ELISA antibodies. This latter calf seroconverted post-challenge. The control group calves remained seronegative until after challenge. No significant differences were reported in the antibody titres between the two vaccinated groups.

All calves in each group were seronegative to BTV3 neutralising antibodies until after challenge. Data regarding neutralising antibodies were incomplete, with valid data available for Day 42 and Day 63. Samples from Day 42 (3 weeks after the second dose) showed absence of neutralising antibodies in all study animals, and on Day 63 (3 weeks post-challenge), 1/8, 4/8 and 5/7 calves in groups T01, T02 and T03, respectively, were positive for BTV neutralising antibodies. In the CVMP view, it is somewhat surprising that virus neutralising antibodies were not detectable at 3 weeks after the 2nd dose (in line with the claimed onset of immunity), also taking into account data provided for cattle in the original submission for Syvazul BTV 3 (in which neutralising antibodies were detected 3 weeks after the second dose in the study presented). However, following challenge in the current study, virus neutralising antibodies were observed in 50% or more of vaccinated calves.

Post-mortem evaluation results indicated that scar tissue of small mucocutaneous lesions in the mouth was observed in one calf in T01 and two calves in T02. Histological examination revealed mild inflammatory reactions at the mucocutaneous junction. No macroscopic changes were observed in the heart; however, histological examination showed a mild myocarditis in one calf in T01 and three calves

vaccinated respectively in T03 and T02. BTV-3 infection could not be excluded as a cause of the lesions in the mouth mucosa and heart.

Overall, it can be concluded that the efficacy data provided in this challenge study in cattle are modest, noting that mild clinical signs to some degree and notably fever are evident in vaccinated calves, in addition while a serological response as measured by ELISA is detected, a virus neutralising antibody response is not observed at 3 weeks after completion of primary vaccination. However, the applicant adequately demonstrated a statistically significant reduction of viraemia in calves vaccinated twice with a 2 ml vaccine dose containing  $10^{7.2}$  CCID<sub>50</sub>/ml.

Therefore, the proposed indication for use in cattle 'for active immunisation of cattle to reduce viraemia caused by bluetongue serotype 3', with an onset of immunity of 3 weeks after completion of the primary vaccination scheme, can be accepted.

### ***Duration of immunity***

No data provided. Refer to introductory comments. The lack of data to support a duration of immunity (DOI) was considered an acceptable data gap for an Article 25 application for Syvazul BTV 3. However, the applicant was requested by CVMP to investigate the DOI in sheep as a post-authorisation measure. The specific obligations are therefore updated to include reference the investigation of the DOI in cattle.

### ***Maternally derived antibodies (MDA)***

No data provided. It is proposed that section 3.4 of the SPC will include the statement: "No information is available on the use of the vaccine in sheep and cattle with maternally-derived antibodies." This is acceptable.

### ***Clinical trials***

No data provided. As accepted for the target species sheep in the MAA for Syvazul BTV 3, the absence of clinical trials for the target species cattle is acceptable, provided that adequate reassurances are available from pre-clinical studies to support that a reasonable level of efficacy will be achieved, in line with relevant guidance for applications under exceptional circumstances.

### ***Overall conclusion on efficacy***

Overall, the data provided in the pre-clinical laboratory challenge study conducted in cattle, which investigated efficacy following challenge at 21 days after the completion of primary vaccination (2 doses, separated by 3 weeks) is considered to adequately support a positive effect of vaccination in the target species cattle for a reduction of viraemia.

Thus, taking into account acceptable derogations in data requirements for a vaccine authorised in accordance with Article 25 ("exceptional circumstances"), whilst the benefit of vaccination may be considered modest in cattle, adequate data are provided in support of the addition of the target species cattle.

Thus, the variation proposal can be accepted.

## Part 5 – Benefit-risk assessment

### ***Introduction***

Syvazul BTV 3 is already authorised for the active immunization of sheep to reduce viraemia, mortality, clinical signs and lesions caused by bluetongue serotype 3. Onset of immunity: 4 weeks after completion of the primary vaccination scheme. The duration of immunity has not been established.

Syvazul BTV 3 suspension for injection contains Bluetongue virus, serotype 3 (BTV-3), strain BTV-3/NET2023, inactivated and is presented in packs containing.

The proposed variation is to add cattle as target species, including an increase of the minimum specification for antigen content in the finished product.

### ***Benefit assessment***

#### **Direct benefit**

For the target species cattle, the direct benefit of use of Syvazul BTV 3 is its efficacy for the claim: active immunisation of cattle to reduce viraemia caused by bluetongue serotype 3.

#### **Additional benefits**

The addition of the target species cattle increases the range of available treatment possibilities for vaccination against BTV serotype 3 in this target species.

### **Risk assessment**

#### Quality

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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. Within the current variation, the qualitative composition of the vaccine has been changed to increase the quantity of the active substance, inactivated BTV serotype 3, strain BTV-3/NET2023, from  $\geq 10^{6.9}$  CCID<sub>50</sub>/ml, to  $\geq 10^{7.2}$  CCID<sub>50</sub>/ml. This is considered acceptable.

#### Safety

##### Risks for the target animal

Administration of Syvazul BTV-3 in accordance with SPC recommendations is generally well tolerated in cattle. The main reported adverse reactions include an increase in temperature and injection site reactions.

##### Risk for the user

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations. Standard safety advice is included in the SPC. This conclusion remains unaffected by this variation.

##### Risk for the environment

Syvazul BTV 3 is not expected to pose a risk for the environment when used according to the SPC

recommendations. Standard advice on waste disposal is included in the SPC. This conclusion remains unaffected by this variation.

Risk for the consumer:

Syvazul BTV 3 is not expected to pose a risk for the consumer. The withdrawal period is zero days. This conclusion remains unaffected by this variation.

## **Risk management or mitigation measures**

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user, environment and consumer, and to provide advice on how to prevent or reduce these risks. Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target species cattle. There are no changes to the potential risks of this product to the user, environment and consumer, for which the currently authorised information in the SPC remains appropriate.

Post-authorisation measures

Three specific obligations to complete the post-marketing authorisation measures for the marketing authorisation under exceptional circumstances are detailed in Annex II of the currently authorised product information and mentioned below.

For consistency, this should be amended to include a specific obligation to investigate the duration of immunity in cattle, with a proposed due date to be included in line with a suitable time period from the completion date of this variation application, as follows:

<b>Description</b>	<b>Due date</b>
Completion of the development of the potency test for the BTV 3 antigen.	January 2026
Data from the completed stability study should be provided to confirm the proposed shelf life and the recommended storage conditions for the inactivated BTV 3 antigen and the Syvazul BTV 3 finished product.	January 2027
A study on duration of immunity in sheep should be conducted and data should be provided as soon as available.	February 2026
A study on duration of immunity in cattle should be conducted and data should be provided as soon as available.	March 2026

## **Evaluation of the benefit-risk balance**

The changes described in this variation are not envisaged to impact on the following aspects: user safety, environmental safety, consumer safety.

At the time of submission of the variation application, the applicant applied for the following indication: "Cattle: For active immunization of cattle to reduce viraemia caused by bluetongue serotype 3.

Onset of immunity: 3 weeks after completion of the primary vaccination scheme.

The duration of immunity has not been established."

Based on the data presented to date, the overall benefit-risk balance for the variation is considered positive.

The product has been shown to be efficacious in cattle for the indication to reduce viraemia caused by bluetongue virus serotype 3.

The increase of the minimum antigen content in the finished product: from  $\geq 10^{6.9}$  CCID<sub>50</sub> to  $\geq 10^{7.2}$  CCID<sub>50</sub>.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target species cattle and presents an acceptable risk for users, the environment and consumers, when used as recommended. Appropriate precautionary measures, including withdrawal period, have been included in the SPC and other product information.

Based on the data presented to date, the overall benefit-risk balance for the product is considered to remain positive.

The product information has been reviewed and is considered to be satisfactory and in line with the assessment.

## Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for a variation to the terms of the marketing authorisation for Syvazul BTV 3 is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) 2019/6).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the approval of the variation for the above mentioned veterinary medicinal product.

Changes are required in the following Annexes to the Union marketing authorisation:

I, II, IIIA and IIIB

As a consequence of this variation, several sections of the SPC are updated. The corresponding sections of the Package Leaflet are updated accordingly.