22 May 2019
EMA/290800/2019
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Nasym (EMEA/V/C/004897/0000)

Vaccine common name: Bovine respiratory syncytial virus vaccine live

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

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Introduction

The applicant LABORATORIOS HIPRA, S.A. submitted on 2 February 2018 an application for a marketing authorisation to the European Medicines Agency (the Agency) for Nasym, through the centralised procedure under Article 3(2)b of Regulation (EC) No 726/2004 (optional scope). The eligibility to the centralised procedure was agreed upon by the CVMP on 7 September 2017 as the applicant showed that the product constitutes a significant technical innovation.

The applicant applied for the following indication: Active immunisation of cattle from first days of life to reduce virus shedding, clinical signs and lung lesions caused by bovine respiratory syncytial virus infection.

The indication which was considered acceptable by CVMP is: Active immunisation of cattle to reduce virus shedding and respiratory clinical signs caused by bovine respiratory syncytial virus infection.

Onset of immunity:	21 days after administration of one dose by the nasal route.
	21 days after the second dose of the two dose intramuscular vaccination schedule.
Duration of immunity:	2 months after nasal vaccination.
	6 months after intramuscular vaccination.

The active substance of Nasym is a live attenuated Bovine Respiratory Syncytial Virus (BRSV), strain Lym-56. The final formulation of this immunological product is a lyophilisate and solvent for suspension, intended for the active immunisation of cattle by the intramuscular or nasal route.

Nasym is presented as a nasal spray or injection. The freeze-dried powder is contained in a type I glass vial of 10 ml and the solvent in polyethylene (PET) vials of 10 and 50 ml.

There are 4 proposed presentations containing a cardboard box with 1 freeze-dried powder vial of 5 doses and solvent vial of 10 ml, ii) a cardboard box with 1 freeze-dried powder vial of 25 doses and solvent vial of 50 ml, iii) a cardboard box with 10 freeze-dried powder vials of 5 doses and a cardboard box with 10 solvent vials of 10 ml and iv) a cardboard box with 10 freeze-dried powder vials of 25 doses and cardboard box with 10 solvent vials of 50 ml.

The rapporteur appointed is Jeremiah Gabriel Beechinor and the co-rapporteur is Katariina Kivilahti-Mäntylä.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC – full application.

On 22 May 2019, the CVMP adopted an opinion and CVMP assessment report.

On 29 July 2019, the European Commission adopted a Commission Decision granting the marketing authorisation for Nasym.

Marketing authorisation under exceptional circumstances

Not applicable.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Multi-strain dossier

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A detailed description of the pharmacovigilance system (dated 14/01/2019) which fulfils the requirements of Directive 2001/82/EC was provided. Based on the information provided the applicant has the services of a qualified person (QP) responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Appropriate and up to date certificates of Good Manufacturing Practices (GMP) compliance are provided for Laboratorios HIPRA S.A. for the site for manufacture of the active substance: Carretera C-63, 17170 Girona, Spain (dated 19/10/2016), and for the site of batch release: Avda., La Selva 135, Amer, 17170 Girona, Spain (dated 12/07/2016) by the Spanish competent authority (Agencia Española de Medicamentos y Productos Sanitarios).

The QP declaration states that the manufacture of the active substance at Laboratorios Hipra, S.A., Carretera C-63, Km 48.300 Poligono Industrial El rieral, Amer, 17170 Girona, Spain (audited 08/11/2017) is in accordance with the detailed guideline on good manufacturing practice for active substances used as starting materials as required by Article 46(f) of Directive 2001/83/EC and Article 50(f) of Directive 2001/82/EC.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

The GMP status of the active substance and of the finished product manufacturing sites has been satisfactorily established, and is in line with legal requirements.

Part 2 – Quality

Chemical, pharmaceutical and biological/microbiological information (quality)

Qualitative and quantitative particulars of the constituents

Qualitative and quantitative particulars

The finished product of the Nasym vaccine is presented as a lyophilisate and solvent for suspension for nasal spray or injection for cattle. Nasym contains the active substance Bovine Respiratory Syncytial Virus (BRSV), (strain Lym-56 live attenuated) at titre ≥ $10^{4.7 - 6.5}$ $CCID_{50}$ per dose of 2 ml. The requirements of the European Pharmacopeia (Ph. Eur.) monograph on vaccines for veterinary use against Bovine respiratory syncytial Virus (live) (Ph. Eur. 1177) are applicable. The vaccine does not contain an adjuvant.

The excipients in the freeze drying solution are Dextran, sucrose, gelatin, NZ amine, sorbitol, potassium dihydrogen phosphate, dipotassium phosphate in water for injection. The PBS solvent contains disodium phosphate dodecahydrate, potassium dihydrogen phosphate, sodium chloride, potassium chloride and water for injections.

The product is available as a freeze-dried powder in 10 ml type I glass vials. The vials are closed with a bromobutyl rubber stopper and aluminium cap. The solvent is available in PET vials of 10 and 50 ml. The vials are closed with a bromobutyl rubber stopper and aluminium cap as described in section 6.5 of the SPC.

Container and closure

The product is filled into 10 ml type I glass vials (in accordance with Ph. Eur. chapter 3.2.1 requirements) containing 5 and 25 doses. The solvent is available in PET vials (in accordance with Ph. Eur 3.2.2) of 10 and 50 ml. These are closed with bromobutyl rubber stoppers (in accordance with Ph. Eur. chapter 3.2.9) and aluminium seals.

The pack /container sizes are consistent with the vaccination schedule and intended use.

The containers and closures are in compliance with the pharmacopoeial requirements and their sterilisation is adequate.

Product development

An explanation and justification for the composition and presentation of the vaccine has been provided. BRSV is an enveloped, non-segmented negative stranded RNA virus described as a major cause of respiratory disease in young calves and as being responsible for economic losses to the farming industry throughout the world. The BRSV infection induces a fever (accompanied by depression, increased respiratory rate and anorexia), cough, and often a mucoid nasal discharge. It appears to cause little or no cytopathology in epithelial cell culture *in vitro*, suggesting that much of the pathology is due to the hosts response to the viral infection.

The vaccine was developed to protect calves from first days of age against BRSV. A live attenuated virus (Lym-56 live strain) was used in Nasym aiming to produce a stronger immune response more closely mimicking a natural infection. The first administration of Nasym is by intranasal route with the aim of imitating the most similar route to the real infection. From the literature the applicant considers that when the vaccine is transferred to the mucosal surface in the nostrils, the calf is able to develop an immune response at first days of life. The protection induced by BRSV vaccines at very young ages tends to be short lived (<4 months) particularly in calves with maternal derived antibodies (MDA), therefore the vaccine schedule for Nasym includes an administration at three months of age. The seroprevalence of BRSV infections varies greatly across different geographical regions.

Gene sequencing and phylogenic analysis revealed six genetic subgroups (I-VI) based on variation in the gene coding for the glycoprotein (G) protein. The G protein is responsible for virus binding to the cell surface receptor. The strain chosen for the vaccine is considered representative for all the genetic groups and subgroups. After an attenuation process the strain became the BRSV Lym-56 live attenuated strain. The strain was chosen due to its presence in different European countries (as is supported by the references provided) and the applicant highlights by using the Asquith strain (being very severe causing higher rates of mortality) the efficacy of Nasym was assessed in a worst-case and more demanding scenario (in presence of MDA and duration of immunity (DOI)), and this is considered acceptable. Acceptable information on the attenuation process of the original strain is provided.

The freeze drying excipient (SYVEL) was developed for Nasym in a number of trials and according to the applicant is not commonly used for other live vaccines. Each component was said to be selected to improve the survival of the virus in the nasal mucosa and to enhance product stability and is considered by the applicant as contributing to a significant technical innovation. The applicant has presented a summary of data which shows that SYVEL has shown better stability results for BRSV as compared to other excipients tested. The applicant has also provided vaccine stability data in support of the freeze drying excipient SYVEL (refer to Part 2G Stability).

The function of each excipient was detailed and the list of them is provided in section 6.1 of the SPC.

The manufacturing process of the antigen of Nasym was designed following the seed lot system, in accordance with the general Ph. Eur. monograph requirements on vaccines for veterinary use (Ph. Eur. 0062), on a Vero cell line. Vero cells are well known and extensively used and are handled according to the cell seed lot system in line with Ph. Eur. 5.2.4 (Cell cultures for the production of veterinary vaccines). All of the ingredients used are previously sterilised. There is no final terminal sterilisation of the vaccine however the freeze-drying excipient is sterilised before being mixed with the BRSV for the freeze-drying process under aseptic conditions. The solvent used to dilute the freeze-dried vaccine is sterile PBS. The method of sterilisation of the PBS in PET containers has been already authorised in other HIPRA vaccines. The viral harvest is produced in a bioreactor where microcarriers are used to grow the Vero cells. The blending phase comprises of 3 ml of antigen and 1 ml of freeze-drying excipient, the BRSV titre may be adjusted prior to blending in order to obtain the required virus concentration in the vaccine. The lyophilisation process is completed automatically.

Gentamycin and ampicillin are used as antibiotics, and nystatin as an antifungal in the infection culture medium of the virus strain and growth culture medium of the Vero cells. The amount of antibiotics remaining after the growth medium for Vero cells growth is removed or is considered negligible in the finished product; they are considered to have no pharmacological activity and are below the Maximum Residue Limits (MRL) established in the European Commission Regulation No 37/2010.

Description of the manufacturing method

An appropriate flowchart for the production of the antigen (live BRSV Lym 56 strain) in Vero cells was provided. The preparation of the pre-inoculum, the inoculum and the cell culture in the bioreactor were adequately described. Identity, titre, sterility, mycoplasma testing and extraneous agents testing are carried out on the BRSV master seed virus (MSV). Titre and sterility testing are carried out at the other stages of production (working seed virus (WSV), pre-inoculum, inoculum and cell culture in the bioreactor). The WSV is produced from the MSV by some passages in cell cultures in line with Ph. Eur. 0062 requirements. The culture from the bioreactor is concentrated, titre and sterility are performed again and the harvested virus is stored.

Overall an adequate description of the antigen has been provided including validated storage periods and temperature ranges at different stages of the process. Production of the Vero cell line is adequately described. The preparation of the freeze drying excipient (SYVEL) is well described, including sterilisation and storage. Standard batches of solvent (sterile PBS) were prepared and the composition is presented. The bioburden of the PBS is measured and the integrity of the filters tested. An acceptable validation of the sterilisation process by filtration for the PBS is provided.

An acceptable flowchart for the production of the finished product (FP) was provided. Following viral harvest and addition of the excipient, stirring and homogenisation and then filling and freeze-drying the FP testing are carried out (including appearance, residual moistness, solubility, titre, sterility, mycoplasma absence and identity). Inclusion of the fill volume is included in part 2 D. Following the FP testing the product is labelled and packaged. During blending of the vaccine the titre of the virus is achieved by adjusting the amount of culture medium necessary to that required for release of the FP batches.

An acceptable validation of storage of the freeze drying excipient (SYVEL) is presented. The vaccine vials are stored in boxes at 2-8 °C. Stability data for batches to 18 months have been provided (refer to part 2.G).

Production and control of starting materials

Starting materials listed in pharmacopoeias

Appropriate Certificates of Analysis (CoA) are provided for each of the starting materials listed in the Pharmacopoeia. Appropriate CoAs and valid certificate of suitability (CEPs) are provided for Foetal bovine serum (FBS) and Adult bovine serum (ABS). Extraneous agents testing is carried out in line with Ph. Eur. 5.2.5 and shows negative results. Sterility is tested is in line with the relevant Ph. Eur. requirements. Appropriate certificates of irradiation are provided for FBS and ABS. Gelatin is a component used in the preparation of Nasym and appropriate CoAs and CEPs are provided from the two sites of manufacture.

Specific materials not listed in a pharmacopoeia

Starting materials of biological origin

The BRSV Lym-56 strain MSV and WSV preparation, control and storage are generally adequately presented. The MSV and WSV are manufactured and handled in a seed lot system in line with Ph. Eur. 0062. The WSV is produced from the MSV by passages in cell cultures again meeting the requirements of Ph. Eur. 0062. The origin of the BRSV antigen has been presented.

In-process controls were carried out on the MSV (titre, identity, sterility, mycoplasma testing, extraneous agents testing. The in-process controls carried out on the WSV include titre and sterility. Protein sequencing is carried out on the MSV to confirm the identity.

The MSV was tested for extraneous agents in line with the list for bovine species in EMA/CVMP/IWP/206555/2010-Rev.1 and found to be clear of the viruses tested. Where testing is not performed the applicant has provided appropriate justification. Overall acceptable validation of the PCR methods and other methods used to detect the extraneous agents was presented. Sterility is tested in line with the relevant Ph. Eur. 2.6.1. Mycoplasma testing is performed in line with the Ph. Eur. 2.6.7.

The Vero cell line used to grow the BRSV antigen is controlled by a cell seed system in line with Ph. Eur. 5.2.4 on cell cultures for the production of veterinary vaccines. The history of the cell line in terms of origin, number of passages, media used, storage conditions and preparation are adequately described. An adequate validation report on the identification of the species of origin (primate) by PCR is provided. Appropriate protocols for microscopic observation and viability are provided.

Acceptable validated PCR test methods for the detection of potential extraneous agents in line with EMA/CVMP/IWP/206555/2010 Rev 1 were provided. Where testing was not performed it was appropriately justified. Risk assessments for viral safety for biological materials used in cell culture were provided in line with Ph. Eur. 5.2.5 on substances of animal origin for the production of veterinary vaccines.

The materials of TSE-relevant animal species used in the culture of Nasym were shown to comply with the note for guidance for minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (NfG EMA/410/01 Rev 3). A valid CEP was provided for adult bovine serum used. Vero cells were also shown to comply with NfG EMA/410/01 Rev 3. Foetal bovine serum used also has a valid a CEP. Dextran also used in microcarriers is from an animal free origin. Overall the TSE risk of the materials used in the manufacturing is considered as negligible.

Starting materials of non-biological origin

Certificates of analysis have been provided for culture media and all conform to in-house specifications.

In-house preparation of media and solutions consisting of several components

Information regarding the qualitative and quantitative composition of all culture media, their treatment processes and their storage conditions is provided in the dossier. All components are tested for sterility and treated under aseptic processing where relevant.

Control tests during the manufacturing process

The applicant presented in-process data for the manufacture of three antigen bulks used to manufacture the consecutive Nasym vaccine batches referred to under 'batch to batch consistency' below. During the manufacture of the antigen the following tests are carried out: bacterial and fungal sterility and viral titre. Test descriptions and the limits of acceptance were presented and the test is satisfactorily validated. Sterility testing is according to Ph. Eur. 2.6.1 on sterility – data supporting the absence of inhibitory substances in the antigen bulk have been provided.

In-process testing of the SYVEL freeze-drying excipient involves tests for appearance, sterility, pH and density. The tests have been satisfactorily described.

Regular fill volume checks during filling of the freeze-dried vaccine are performed.

For the PBS solvent the in-process control tests are appearance, pH, bioburden and integrity of the sterilising filters before and after filtration. Test descriptions and the limits of acceptance were presented as well as satisfactory results for three consecutive batches. These in-process tests are deemed to be sufficient to control the solvent manufacturing process.

Control tests on the finished product

The description of the methods used for the control of the finished product (appearance, solubility, identity and viral titre, residual moisture, bacterial and fungal sterility, absence of mycoplasmas) and the specifications were provided. A satisfactory description of each test has been given. The acceptance criteria are supported by the results from the six consecutive vaccine batches (3 x 5 dose and 3 x 25 dose presentations) for which batch protocols were provided.

The titration test has been satisfactorily validated - satisfactory controls are applied to the titre of the reference standard batch in the test. The procedure for replacement of the reference standard and critical reagents are acceptable. The viral titration test was suitable as an identity test and met Ph. Eur. 1177 requirement.

The lower limit for the viral titration test is consistent with the minimum value recorded for the six consecutive vaccine batches for which batch protocols were provided and is higher than the minimum efficacious titre of $10^{4.7}$ $CCID_{50}$/dose determined from the studies in Part 4 of the dossier. The upper limit ($10^{6.5}$ $CCID_{50}$/dose) is consistent with the maximum titre shown to be safe in studies in Part 3 of the dossier.

The Ph. Eur. 1177 requirements on vaccines for veterinary use against 'Bovine respiratory syncytial virus vaccine –live' include a general test for absence of extraneous agents and a specific test for the absence of pestiviruses. As the seed materials have been tested for freedom from extraneous agents, the other starting materials are routinely checked for acceptable quality and the vaccine is manufactured under GMP conditions there is a negligible risk of extraneous agent contamination therefore a cell culture test to check for the absence of extraneous agents is not performed on Nasym batches.

Satisfactory validation data were presented for all of vaccine release tests.

The absence of a test for one or more of the components of the SYVEL freeze-drying excipient is justified on the basis that the in process control tests during production of this excipient (i.e. appearance, sterility, pH and density) and the residual moisture test done on the Nasym vaccine vial will alert to deviations in the composition of the excipient.

Tests for the PBS solvent (appearance, pH, volume control and bacterial and fungal sterility) and the limits applied are described and are acceptable.

Batch-to-batch consistency

The applicant presented data for the manufacture of three consecutive final product batches filled as 5 dose and 25 dose Nasym vaccine presentations. Three separate antigen bulks were used in the manufacture of these vaccine batches – data for the antigen bulks were given in addition to data from a fourth antigen bulk at a batch size close to that of the maximum size for routine batches. Data from three consecutive PBS solvent batches were also presented. All of the in process and finished product test results complied with the acceptance limits supporting the consistency of routine batches.

Stability

For the active ingredient:

Viral titration and sterility test data from two batches of the BRSV Lym-56 antigen (inoculum) stored at ≤-70°C were presented which support a 24 month storage period for the antigen (inoculum).

For the finished product:

The 3 x 5 dose and 3 x 25 dose Nasym consistency batches have been entered into a stability program. The batches were produced according to the procedure described in Part 2.B of the dossier and they have been filled into Type I glass vials which is the primary packaging proposed for marketing of the vaccine.

The batches are being evaluated at two stability conditions as follows:

a) vials stored at 2 - 8°C and tested months after manufacture for the control tests for release of the vaccine

b) vials stored at ≤-15°C for 6 months or 12 months followed by storage at 2 - 8°C. Prior to transfer to ≤-15°C the batches are tested for the control tests for release of the vaccine. On transfer to the 2 - 8°C months after transfer the vials are tested for the control tests for release of the vaccine.

The data provided are acceptable to support a 15 month shelf life at 2 - 8°C for the vaccine.

Limited stability data is available on vials stored at ≤ -15°C therefore the applicant proposes to continue these investigations to determine if prior storage at ≤-15°C is a viable storage condition for Nasym.

The control tests and acceptance limits proposed for stability testing are the same as those for release of routine batches with the exception of the limits for viral titre. The lower limit for stability testing is consistent with the titre shown to be efficacious in the efficacy trials in Part 4 of the dossier which is acceptable.

Stability of the reconstituted vaccine:

The applicant has clarified that an intranasal dose can be administered in approximately 1 minute per animal and indicates that in the clinical studies involving Nasym the average time to deliver 25 doses intranasally was approximately 30 minutes. On this basis there is no concern for the feasibility of administering the maximum 25 doses either by the intranasal or intramuscular routes therefore the recommendation that the vaccine is used immediately on reconstitution is supported and as such data on the stability of the reconstituted vaccine are not necessary.

Stability of the PBS solvent:

Stability data from three consecutive batches of the solvent filled in volumes of 10 ml, 25 ml and 250 ml in PET containers and stored at 5±3°C, 25 ± 2°C or at 40±2°C are presented. These presentations bracket the 10 ml and 50 ml presentations proposed for use with Nasym. The batches have been satisfactorily tested to 60 months at 5±3°C and 25 ± 2°C and to 6 months at 40±2°C for appearance, pH and sterility (Ph. Eur. 2.6.1). Based on these data the requested 5 year shelf life for the solvent when stored below 25°C is acceptable.

Overall conclusions on quality

Appropriate information on the development, manufacture (including relevant process and finished product controls), and control of the starting materials has been provided to allow for a conclusion on the satisfactory consistency of the production of Nasym.

Appropriate CoAs were provided for each of the starting materials listed in the relevant Pharmacopoeia and valid CEPs are provided where relevant.

The MSV and WSV of the BRSV are manufactured and handled in a seed lot system in line with Ph. Eur. 0062. The WSV is produced from the MSV by several passages in cell culture in line with Ph. Eur. 0062. The Vero cell line used to grow the BRSV antigen, is controlled by a cell seed system in line with the requirements of Ph. Eur. 5.2.4. Overall the origin and history of the BRSV antigen and Vero cell line used for manufacture of the vaccine have been adequately described and overall appropriate controls have been implemented to ensure viral safety of these materials by validated PCR test methods.

The production and control of the PBS solvent is adequately described. The bioburden of the PBS is measured and the integrity of the filters tested. An acceptable validation of the sterilisation process by filtration for the PBS is provided and the storage period before filling is validated.

Satisfactory information has been presented to give reassurance on TSE safety.

The in-process tests performed during production of the antigen bulk and the SYVEL freeze-drying excipient are satisfactory. A fill volume check during filling of the freeze-dried vaccine is performed. In process testing of the PBS solvent (including bioburden) is satisfactory.

Overall a satisfactory description of each of the control tests for release of Nasym batches was given. The acceptance criteria for each test are supported by the six consistency batches (3 x 5 dose and 3 x 25 dose presentations). The lower limit for the viral titration test –potency test is based on the minimum value for the consistency batches and is higher than the minimum efficacious titre of $10^{4.7}$ $CCID_{50}$/dose. The upper limit ($10^{6.5}$ $CCID_{50}$/dose) is consistent with the maximum titre shown to be safe in studies in Part 3 of the dossier.

Considering the testing done on the starting materials for quality the manufacturing process is considered to be capable of routinely producing vaccine batches complying with Ph. Eur. 1177 (vaccines for veterinary use against 'Bovine respiratory syncytial virus vaccine –live), including extraneous agents testing required.

All of the other tests specified in Ph. Eur. 1177 are performed for vaccine release and acceptable validation data were provided.

Tests done on the PBS solvent and the limits applied were satisfactorily described and are acceptable.

Acceptable data from three consecutive vaccine batches each filled as 5 dose and 25 dose presentations and the antigen bulks used in their manufacture as well as data from three consecutive PBS solvent batches were provided.

Acceptable stability data for the storage of the BRSV Lym-56 antigen (inoculum) at ≤-70°C for 24 months were provided.

The stability data provided for batches at 2 - 8°C support a 15 months shelf life for the vaccine.

The recommendation in SPC section 6.3 is that the vaccine is used immediately on reconstitution is acceptable. The stability data for the PBS solvent support a 5 year shelf life for the solvent when stored below 25°C.

Part 3 – Safety

Introduction and general requirements

Nasym is a vaccine containing a live attenuated BRSV, strain Lym-56, intended for the active immunisation of cattle to reduce virus shedding and respiratory clinical signs caused by BRSV infection, for administration by either the nasal route or the intramuscular route. The proposed range of active substance included in each 2 ml dose is $10^{4.7}$ – $10^{6.5}$ $CCID_{50}$.

The proposed vaccination schedule and route of administration differs according to the age of animals intended for vaccination, as follows:

A single dose of the vaccine is intended for nasal use in calves from 9 days of age 'followed by a single intramuscular dose 2 months later. Thereafter, revaccination with a single dose by the intramuscular route is proposed every 6 months.

Two doses of the vaccine are intended for intramuscular use in calves from 10 weeks of age, separated by an interval of 4 weeks. Revaccination with a single dose by the intramuscular route is proposed 6 months after the 2nd dose of the primary vaccination scheme, and at 6 monthly intervals thereafter.

A full safety file in accordance with Article 12(3) has been provided. The safety of the immunological veterinary medicinal product has been investigated in accordance with the requirements of Directive 2001/82/EC, as amended. In addition, the Ph. Eur. monograph 5.2.6 'Evaluation of safety of veterinary vaccines and immunosera', and the specific requirements outlined in Ph. Eur. monograph 1177 'Bovine respiratory syncytial virus vaccine (live)' have been taken into account in order to demonstrate the safety of the vaccine.

Safety documentation

Three laboratory safety studies and two multi-centric field trials are presented to assess the safety of Nasym. The laboratory safety studies and the field studies were conducted according to Good Laboratory Practice (GLP) standards and Good Clinical Practice (GCP) guidelines, respectively.

Safety tests have been carried out for each recommended route and method of administration. Target animals of the youngest recommended age for vaccination for which the vaccine is intended for, were submitted to vaccination under both laboratory and field conditions.

In the pivotal safety study, the minimum age of animals included was 5 days of age, thus it has been demonstrated that it is safe to administer the vaccine to animals of this age (in accordance with the requirements of Ph. Eur. 1177). In addition, animals had been vaccinated from 2 days of age under field conditions. However, in the immunogenicity studies (refer to Part 4), the minimum age of animals included to investigate the onset of immunity (OOI) in accordance with the requirements of Ph. Eur. 1177 was 9 days of age for nasal vaccination, therefore it was considered appropriate to establish the minimum age for vaccination as 9 days of age. For the two dose basic intramuscular vaccination schedule, animals were vaccinated from 10 weeks of age.

The titre used in the laboratory safety studies corresponded to the maximum proposed range for the active substance, $10^{6.5}$ $CCID_{50}$/dose, or 10X the maximum proposed range, $10^{7.5}$ $CCID_{50}$/dose. A standard batch was used for the combined safety and efficacy field studies (CoA provided in Part 3C, titre: $10^{5.3}$ $CCID_{50}$/dose). The batches used in the safety trials were stated to have been manufactured in accordance with the manufacturing process described in Part 2.B of the dossier and at the same manufacturing facilities that will be used for future production batches.

Studies applicable to live vaccines were conducted to investigate the dissemination of a single dose of the vaccine strain, the spread from vaccinated animals to non-vaccinated contacts and reversion to virulence.

Study title	*Dose used*
Safety of the administration of the overdose and the repeated administration of a live BRSV vaccine.	maximum dose or 10X maximum dose
Dissemination of BRSV attenuated live strain in the vaccinated animal and spread to other unvaccinated animals.	Master seed virus, 10^7 $CCID_{50}$/animal
Reversion to virulence test of a BRSV vaccine strain with 10 animals.	Master seed virus, 1.3 x 10^7 $CCID_{50}$/animal
Clinical efficacy and safety evaluation of Nasym against BRSV under field conditions.	standard dose
Clinical efficacy and safety evaluation of Nasym against BRSV on unvaccinated 3 months-old calves under field conditions.	standard dose

Laboratory tests

Three GLP-compliant laboratory safety studies, conducted in seronegative calves younger than 2 weeks of age were presented. As stated in the introduction, two different vaccination schedules are recommended for Nasym depending on the age of animals. The applicant has investigated safety in the youngest category of target species under laboratory conditions, which is considered acceptable as young calves represent the most sensitive category of the target species. In addition, the safety of the vaccination schedule in calves from 3 months of age was investigated under field conditions.

Safety of the administration of one dose

Refer to 'Safety of the repeated administration of one dose'.

Safety of one administration of an overdose

Refer to 'Safety of the repeated administration of one dose'.

Safety of the repeated administration of one dose

One pivotal laboratory study was conducted to investigate the safety of the administration of a 10X overdose (nasal) and the repeated administration of a 10X dose (intramuscular) and a 1X dose (intramuscular) of Nasym, separated by intervals of 14 days. In this study, 6 seronegative calves were included in the test group and received the first dose of vaccine between the ages of 5 and 14 days old. Five calves were included in the control group that were mock-vaccinated with PBS. Follow-up consisted of observations until 21 days after the third administration, with monitoring of clinical signs, respiratory rate, rectal temperature and local reactions after intramuscular injection.

Results showed that no abnormal increases in temperature (>2°C from baseline), abnormal clinical signs or systemic effects were observed following the administration of a 10X nasal dose, a 10X intramuscular dose or a 1X intramuscular dose. However, there appeared to be a higher frequency of adverse reactions

in vaccinated animals compared to control animals with respect to alterations of faecal consistency and body temperature increases; a description of the observed reactions has been included in section 4.6 of the SPC.

The study was conducted in accordance with the requirements of the Ph. Eur. 1177 on vaccines for veterinary use against 'Bovine respiratory syncytial virus vaccine –live" for the evaluation of safety and demonstrated compliance with the requirement that no abnormal effect on body temperature occurs and no calf shows abnormal local or systemic reactions or dies from causes attributable to the vaccine virus. While the safety of the administration of three intramuscular doses has not been specifically evaluated (i.e., to investigate the basic vaccination scheme of two doses and the first revaccination dose in calves from 10 weeks of age), it can be accepted that a 'worst case' scenario for the evaluation of the safety of the administration of an overdose and the repeated administration of a dose has, in general, been implemented; calves were younger (approximately 19-28 days of age) than recommended (10 weeks) when first vaccinated intramuscularly with a 10X overdose followed by a 2 week interval until repeat administration with a 1X dose (also having received the 10X overdose by the intranasal route at the start of the study).

Therefore, while it may have been preferable if the study design had accommodated a third intramuscular dose, it can be accepted that, overall, the study conditions represented a worst case scenario for the evaluation of safety and that the safety of the administration of a single dose, overdose and repeated dose has been demonstrated.

Examination of reproductive performance

Reproductive performance has not been investigated for Nasym, this is considered acceptable considering that there are no data to suggest that the starting material is a risk factor and the vaccine is not recommended for use in pregnant animals. The standard statement 'The safety of the veterinary medicinal product has not been established during pregnancy and lactation' is included in section 4.7 of the SPC.

Examination of immunological functions

No specific studies have been carried out to examine the potential for adverse effects on immunological function. This is considered acceptable; no negative influence on the immune response is anticipated after vaccination; the vaccine strain has lost its ability to replicate due to the attenuation process. No adverse reactions or increase of secondary infections were reported in the laboratory trials, and field trials confirmed the absence of adverse effects on the immunological functions. No hypersensitivity reactions were reported in either of the two field trials conducted on EU farms with historical records of BRSV infection. It is therefore unlikely that this vaccine will have an adverse effect on immunological functions due to the nature of the product (live vaccine without any known immunosuppressive effects).

Special requirements for live vaccines

Spread of the vaccine strain

Dissemination within the target species and spread of the vaccine strain to target and non-target species (sheep) were evaluated in one laboratory study. Although cattle are the principal reservoir of infection for BRSV, sheep can also become infected; therefore, the safety of spread to non-target susceptible species

has been studied by inclusion of a group of lambs, in addition to a group of calves, placed in contact with vaccinated calves.

In this study, 9 calves (2 – 14 days of age) were vaccinated with 10^7 $CCID_{50}$ of MSV and were used to study the dissemination of the vaccine virus in the vaccinated animal, while 4 non-vaccinated calves were placed in contact with the vaccinated group, as sentinels, to evaluate spread to other animals. In addition, a group of 3 lambs was placed in contact, as sentinels, to study the spread of the vaccine to non-target susceptible species. Animals were monitored for 21 days. Dissemination in vaccinated animals was evaluated by testing for the presence of BRSV in tissue samples with particular attention paid to the predilection sites for replication of the virus (on day 4, day 8 and day 12) and in secretions (urine, faeces, nasal and saliva). Justification for the selected sampling days was provided in accordance with the expected peak of virus replication in the upper respiratory tract (day 3 – 4 post-infection) and lower respiratory tract (day 7 – 8 post-infection). Clinical signs, nasal secretions and serology were evaluated in the groups of in-contact animals.

Within the target species, BRSV was detected in vaccinated animals at low levels in tissue samples associated with the respiratory tract in the three animals evaluated (n=3 subjected to necropsy) and in nasal secretions of 3/9 animals on day 4 post-vaccination. BRSV was not detected in tissues or secretions on day 8 or 12 post-vaccination. Therefore, it is accepted that dissemination in the target species is limited to the natural predilection sites of BRSV and the attenuation of the vaccine strain is supported by the fact that no virus could be detected on or after day 8 post-vaccination. Whilst BRSV was detected in nasal secretions of vaccinated calves, spread of the vaccine virus to non-vaccinated in-contact animals (target species and non-target species) did not occur under the conditions of the study; sentinel animals remained seronegative for BRSV antibodies, remained negative for presence of virus in nasal swabs, and did not present with clinical signs that could be attributed to spread of the vaccine virus.

It is therefore concluded that the vaccine virus does not spread to in-contact unvaccinated target species or non-target species (sheep).

Dissemination in the vaccinated animal

On the basis of the studies described in the previous section it is accepted that dissemination in vaccinated animals is limited to the natural predilection sites of BRSV (respiratory tract and nasal secretions), however this is for a short duration and no BRSV could be detected by day 8 post-vaccination in any tissues or secretions. While BRSV may be detected in nasal secretions following vaccination, there was no evidence of spread to non-vaccinated in-contact animals, which is considered acceptable.

Reversion to virulence of attenuated vaccines

Reversion to virulence was investigated in one laboratory study. A preliminary study, demonstrated that virus was not recovered after an initial passage in 2 calves, therefore in the reversion to virulence study the vaccine virus (master seed virus, 10^7 $CCID_{50}$/animal) was administered directly by the nasal route to 10 seronegative calves (3 – 7 days of age). Nasal swabs were collected for recovery of the virus and quantification by virus titration in cell culture from days 3 – 7 post-vaccination.

No live virus was recovered from nasal swabs following the administration of MSV at a dose higher than the maximum proposed range per dose. No clinical signs or alterations of body temperature were observed during the study. No subsequent passages were performed because the virus was not recovered from any of the 10 animals.

It is accepted that the absence of a potential for reversion to virulence for Nasym has been satisfactorily demonstrated, in accordance with the requirements of Ph. Eur. 1177, in which it is stated that the vaccine complies with the test for reversion to virulence if the virus is not recovered after an initial passage in 2 animals and a subsequent repeated passage in 10 animals.

Biological properties of the vaccine strain

No specific studies have been conducted to determine the intrinsic biological properties of the vaccine strain. However, as described in Part 2, the BRSV vaccinal strain Lym-56 was obtained by passage attenuation of a virulent strain of BRSV, which was isolated from a clinical case of bovine respiratory disease. The attenuation process used for the BRSV strain has been demonstrated to be adequate to produce a safe vaccine, since no adverse reactions due to the administration of the vaccine virus strain were observed. In addition, the absence of spread of the virus vaccine strain from vaccinated to non-vaccinated calves and spread to other susceptible non-target species has been demonstrated. Finally, no potential for reversion to or increase in virulence of the BRSV vaccine strain was observed following evaluation in accordance with Ph. Eur. requirements.

On the basis of the data presented the safety profile of the strain can be considered acceptable.

Recombination or genomic reassortment of the strains

No specific trials regarding the genomic reassortment or recombination/redistribution of the vaccine strain with other different strains of BRSV have been performed. The absence of such studies is considered acceptable; any resultant strains resulting from recombination with wild type strains would be likely to be less pathogenic than the wild type strain.

User safety

The applicant has presented a user safety risk assessment which has been conducted in accordance with CVMP guideline EMEA/CVMP/IWP/54533/2006.

The main potential routes of accidental contact with the product have been considered and it was concluded that the most likely exposure routes are those of accidental self-injection (intramuscular vaccination) and dermal or ocular exposure arising from accidental spray (nasal vaccination). BRSV is not pathogenic for humans and therefore does not pose a risk for the user. The excipients in the solvent (PBS) are commonly used in other vaccines and do not pose a risk for the user.

Based on the above risk assessment, it is concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC. As a result of the user safety assessment, the following precautions for the user are considered appropriate:

'In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.'

Study of residues

No studies on residues have been performed. The active substance being a principle of biological origin intended to produce active immunity is not within the scope of Regulation (EC) No 470/2009.

The excipients listed in section 6.1 of the SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Consequently, it is considered that there is no need to perform residue studies for Nasym and a withdrawal period of zero days is accepted.

Withdrawal period

The withdrawal period is set at zero days.

Interactions

The applicant has not provided data investigating interactions of Nasym with other veterinary immunological products and therefore a statement in Section 4.8 of the SPC that 'No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product has been included. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis.' This is considered acceptable.

Field studies

Two GCP, multicentre, randomised, double blind, placebo-controlled safety and efficacy field trials were carried out to investigate the safety and efficacy of Nasym under field conditions. Both of the two options for basic vaccination were evaluated.

In one study, the first dose was administered via the nasal route in calves from 2 – 21 days of age and the second dose was administered by the intramuscular route at around 3 months of age (test group; n=385, placebo group; n=375). Consequently, the interval between the first and second administration of product may have been slightly longer in some animals than the two months recommended in the proposed SPC.

In the other study, the first dose was administered at 3 – 4 months of age and the second dose was administered 1 month later, by the intramuscular route in the neck area (test group; n=174, placebo group; n=183). The SPC recommends that in cattle from 10 weeks of age, 2 ml of product should be administered intramuscularly followed by a second intramuscular injection 4 weeks later. In the field study, cattle aged 3-4 months old (older than the minimum age of cattle for which the primary vaccine course consists of two intramuscular injections) were included. The second injection was administered 4 weeks later in accordance with the recommendations included in the SPC. While it is noted that animals included in this field study were approximately 2 weeks older than the minimum age for intramuscular vaccination, this deviation may be accepted considering that the most sensitive category of target species can be accepted as neonatal calves, and that in laboratory safety studies animals were vaccinated from 10 weeks of age.

The total follow-up period of the first study in younger calves was 9 months after the first dose, and was 6 months after the second dose in calves vaccinated from 3 months of age (or until animals were slaughtered). In both studies, general safety evaluation with monitoring of adverse events was conducted in the 'overall safety population' (all animals that received at least one dose of the product), in addition to a subset of test and control animals subjected to closer monitoring for 'post-vaccine safety' prior to and after vaccination (79 animals in one study, 63 animals in the other study); rectal temperature, general and local reactions.

The results from both field trials have demonstrated that there were no mortalities, adverse reactions, changes in temperature or local reactions associated with test-article administration. Therefore, it is concluded that the safety of the product under field conditions of use in accordance with recommendations, has been satisfactorily supported.

Environmental risk assessment

An environmental risk assessment, conducted in accordance with requirements, was provided.

The applicant has considered the risks to the environment posed by the active ingredient. The likelihood of the active ingredient to cause hazards to the environment can be considered negligible, taking into account the following:

- The virus strain Lym-56 has been highly attenuated and has been shown to be safe and not to revert to virulence in the laboratory trials. Although human respiratory syncytial virus is closely related to BRSV, transmission to humans is not of concern since BRSV is not considered a zoonotic agent.
- The inability of the vaccine strain included in Nasym to transmit to non-target species (sheep) has been demonstrated.
- Infected animals are the main reservoir of BRSV, which is transmitted directly via aerosols droplets or direct contact with an infected animal, or indirectly through contaminated surfaces. However, the shedding ability of the live attenuated virus vaccine has been demonstrated to be negligible, the virus was not present in saliva, faeces or urine at any time point in vaccinated animals; the virus was only detected in the nasal secretion and in tracheal epithelium, bronchial epithelium and pharyngeal tonsil at day 4 post-vaccination, in some of the tested animals.
- The vaccine is intended to be administered individually and the risk of the product to be released into the environment is considered negligible.
- Apart from the antigen, the rest of the vaccine components are well-known excipients widely used in pharmaceutical formulations and are regarded as nontoxic at these low concentrations used.

It is concluded that the risk for the environment when using the vaccine Nasym can be considered as effectively nil. As the use of Nasym does not pose an environmental risk, no specific control measures are needed in addition to the general management recommendations and the precautions included in the SPC concerning the handling and disposal of unused veterinary medicinal product or waste materials derived from the use of such product.

Overall conclusions on the safety documentation

The applicant has provided three laboratory safety studies and two combined safety and efficacy field studies in support of the safety of Nasym.

The applicant has provided one pivotal laboratory study to investigate the safety of the administration of a 10X overdose (nasal) and the repeated administration of a 10X dose (intramuscular) and a 1X dose (intramuscular), separated by intervals of 14 days to target animal species vaccinated from 5 days of age.

On the basis of the results it was concluded that the safety of Nasym for the target animals when the vaccine is administered according to the recommended schedules and via the recommended routes has been adequately demonstrated. Whilst the safety of the vaccine was investigated in calves from 5 days of

age in the pivotal laboratory study, and from 2 days of age under field conditions, given that the efficacy of vaccination was demonstrated in calves from 9 days of age, the minimum age recommended for vaccination is established as 9 days of age. The SPC section 4.6 reflects the adverse reactions observed in the pivotal laboratory safety study (alterations of faecal consistency) and increases of body temperature observed in the field studies.

The examination of reproduction safety has not been investigated for Nasym, this is considered acceptable considering that there are no data to suggest that the starting material is a risk factor and the vaccine is not recommended for use in pregnant animals. The SPC section 4.7 include the statement that use is not recommended in pregnant or lactating animals.

The absence of spread of the virus vaccine strain from vaccinated to non-vaccinated calves and spread to other susceptible non-target species has been demonstrated. There was no risk of reversion to virulence when examined in accordance with requirements. The biological properties of the vaccine strain were described adequately and found to be acceptable.

The product is not expected to adversely affect the immune response of the target animals, and therefore no specific studies have been carried out to examine the potential for adverse effects on immunological function.

A user safety assessment conducted in accordance with the relevant guideline has been presented. Based on the assessment presented, it is accepted that the product does not pose an unacceptable risk to the user when used in accordance with the SPC. An appropriate warning for the user has been included in the product literature to seek medical advice in case of adverse reactions following accidental self-injection.

Two GCP safety and efficacy field trials were conducted, to investigate both of the proposed vaccination schedules. There were no test-article related mortalities, adverse reactions, local reactions or temperature increases reported in either of the studies. Therefore, it is accepted that the data provided support the safety of the product under field conditions of use, when used in accordance with recommendations.

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Introduction and general requirements

The originally proposed claims for the vaccine were for a reduction of virus shedding, clinical signs and lung lesions caused by BRSV infection when administered to cattle, from the 'first days of life' onwards. The OOI is claimed as 5 days after nasal vaccination and 21 days after intramuscular vaccination. The duration of immunity is claimed as 2 months after nasal vaccination and 6 months after intramuscular vaccination.

The vaccine is intended to be administered in young cattle, in order to protect calves from shortly after birth, especially during the susceptible period between the decrease of maternal antibodies and the onset of the acquired immunity in calves.

Efficacy was demonstrated in compliance with the European Directive 2001/82/EC (as amended by 2004/28/EC and Directive 2009/9/EC), and the European Pharmacopoeia (Ph. Eur.) chapter 5.2.7, as well as Ph. Eur. 1177 on vaccines for veterinary use against 'Bovine respiratory syncytial virus vaccine -live'.

Challenge model

One study is presented in which the pathogenicity of two different virulent BRSV strains (RB94 and DK9402022) was evaluated following aerosol administration to seronegative calves. The more virulent strain, BRSV strain DK9402022, was selected for use as challenge strain in the subsequent efficacy laboratory studies on the basis that this strain appeared to induce more severe respiratory signs in challenged animals and a higher incidence of detection of BRSV in nasal secretions than with the RB94 strain. No other general clinical signs or temperature increases were noted following challenge with either of the virulent BRSV strains tested. The route of challenge infection is considered appropriate and mimics the route of natural infection.

However, as will be discussed in the following sections, this challenge model was not capable of causing more severe signs of disease or lung lesions, and therefore is not considered appropriate for demonstrating a reduction of lung lesions.

In addition, this study was conducted over 10 years ago, with the two strains that were chosen to investigate pathogenicity dating from 2004/2005. One other study is presented, that is performed in a third country (Canada) in which a different challenge strain was used, the BRSV Asquith strain. This strain was originally isolated from a calf with severe respiratory tract disease and was capable of inducing severe respiratory signs of disease which led to euthanasia in some control animals. The applicant has satisfactorily justified the relevance of the BRSV strains DK9402022 and Asquith to the current epidemiological situation in the EU (with respect to the Asquith strain, it was noted that this strain clustered with a Spanish 2017 BRSV isolate following a phylogenetic analysis based on the amino acidsequence of protein G).

Efficacy parameters and tests

The efficacy parameters as provided in Ph. Eur. 1177 on vaccines for veterinary use against 'Bovine respiratory syncytial virus vaccine –live" are respiratory signs and viral shedding. In addition to general clinical signs, lung lesions and BRSV antibodies, were also investigated in the efficacy studies. The parameters chosen are considered appropriate for evaluating the efficacy of the product. The tests performed to evaluate viral shedding and the antibody response were PCR and ELISA, respectively. The scoring systems used for evaluation of general clinical signs, respiratory clinical signs and lung lesions were in-house developed methods and they can be accepted as covering a sufficiently broad range of clinical and pathological parameters to permit adequate assessment of infection with BRSV.

Efficacy documentation

The efficacy of Nasym was evaluated in seven laboratory studies, of which all but one was conducted in accordance with GLP, and two GCP-compliant field trials. Studies were conducted in accordance with Directive requirements, and in line with the immunogenicity requirements of the specific monograph Ph. Eur. 1177 on vaccines for veterinary use against 'Bovine respiratory syncytial virus vaccine –live". The efficacy of vaccination was investigated in laboratory challenge studies for each proposed route and method of administration, following vaccination of animals with the proposed minimum titre of active substance, $10^{4.7}$ $CCID_{50}$/dose.

Laboratory studies were well documented and carried out in target animals of the youngest age category recommended for nasal vaccination. The minimum age for calves vaccinated by this route is established as 9 days of age in accordance with the onset of immunity study in addition to animals from 10 weeks of age for the two dose basic intramuscular vaccination scheme, using batches manufactured according to the method proposed in Part 2 of the file.

Study title	Dose used
Efficacy of Nasym vaccine against a BRSV challenge in calves 21 days after intranasal vaccination.	Dose: $10^{4.7}$ $CCID_{50}$
Efficacy of Nasym vaccine against a BRSV challenge in calves 5 days after intranasal vaccination.	Dose: $10^{4.7}$ $CCID_{50}$
Efficacy of Nasym vaccine by intramuscular route against a BRSV challenge in young calves (3 months of age).	Dose: $10^{4.7}$ $CCID_{50}$
Study on the influence of MDA and the DOI of the Nasym vaccine in young calves after intranasal application.	Dose: $10^{4.7}$ $CCID_{50}$.
Study on the influence of MDA on Nasym vaccine efficacy after intramuscular administration in young calves (3 months of age).	Dose: $10^{4.7}$ $CCID_{50}$
Study on the DOI of the PB-179 vaccine in young calves after an intranasal and intramuscular administration.	Dose: $10^{5.3}$ $CCID_{50}$
Study on the DOI of the vaccine PB-179 in calves by intramuscular route (challenge at 4 months).	Dose: $10^{4.7}$ $CCID_{50}$
Study on the DOI of the vaccine PB-179 in calves by intramuscular route (challenge at 6 months).	Dose: $10^{4.7}$ $CCID_{50}$
Clinical efficacy and safety evaluation of Nasym against BRSV under field conditions.	Dose: $10^{5.3}$ $CCID_{50}$
Clinical efficacy and safety evaluation of Nasym against BRSV on unvaccinated 3 months-old calves under field conditions.	Dose. $10^{5.3}$ $CCID_{50}$

Laboratory trials

Throughout the laboratory trials, the methods for the evaluation of clinical signs, respiratory signs and lung pathology post-challenge was conducted according to the applicant's own scoring systems and was common to the laboratory studies (with the exception of the study performed in Canada).

Dose determination

The dose of $10^{4.7}$ – $10^{6.5}$ $CCID_{50}$ per dose (2 ml) was proposed in the absence of a specific dose determination study. This is acceptable considering that efficacy of the vaccine was investigated at the proposed minimum dose, $10^{4.7}$ $CCID_{50}$ (with the exception of one study).

Onset of immunity

Three laboratory studies were presented to investigate the OOI. The first two studies concern OOI following nasal vaccination of young calves at a maximum of 2 weeks of age, the third study investigates OOI following intramuscular vaccination in calves vaccinated at approximately 3 months of age.

Nasal administration

Intranasal administration of a single dose in seronegative calves 'less than 2 weeks of age' -OOI 21 days

The **OOI of 21 days** after the nasal administration of a single dose was investigated in seronegative calves vaccinated from the age of 9 days, in compliance with Ph. Eur. 1177 requirements to investigate the onset of protection.

On day 0 of the study, one group of 10 calves were vaccinated with Nasym by the nasal route (2 ml dose, 1 ml of vaccine administered in each nostril) and one group of 10 calves were mock-vaccinated with PBS.

At 21 days post-vaccination, all animals were experimentally infected by nasal inhalation of BRSV. General clinical signs, respiratory clinical signs, virus excretion (using nasal swabs) and antibody response were monitored for 14 days post-challenge. All animals were euthanised 14 days after challenge to evaluate lung lesions.

Results: A statistically significant difference in terms of reduction of mean titre of virus excreted ($p<0.001$) was observed in vaccinated calves at 21 days after nasal vaccination, compared to the control group. In addition, the mean duration of viral excretion was found to be statistically significantly shorter ($p<0.01$) in vaccinated animals compared with control animals (control animals excreted virus an average of 2.5 days longer than vaccinated animals). A statistically significant difference ($p<0.05$) in terms of reduction in respiratory clinical signs was observed in the vaccinated group compared to the control group at 28, 29, 30 and 32 days post vaccination; this was primarily attributable to the scores associated with respiratory rate, breathing effort and ocular discharge. General clinical signs observed post-challenge were mild (mainly slight depression), and it was not considered that these data provided sufficient support for a reduction of general clinical signs. No severe lung lesions were observed following this challenge, therefore it is not considered that this challenge model is suitable to support a claim for reduction of lung lesions.

Nasal vaccination with Nasym did not induce an antibody response in serum; at day of challenge all animals in both groups were negative for BRSV antibodies. At day 35, 14 days after challenge, 9/10 vaccinated animals and 8/10 control animals were seropositive with a significantly greater average titre of antibodies in the vaccinated group compared to the control group.

It was concluded that the data from this study support a reduction in viral shedding and a reduction in respiratory clinical signs at 21 days after administration of a single dose of the vaccine by the nasal route with the minimum recommended dose.

Intranasal administration of a single dose in seronegative calves vaccinated between 7 and 14 days of age.-OOI 5 days

The **OOI of 5** days after the nasal administration of a single dose was investigated in seronegative calves vaccinated between 7 and 14 days of age. On day 0 of the study, one group of 10 calves were vaccinated with Nasym by the nasal route (2 ml dose, 1 ml of vaccine administered in each nostril) and one group of 10 calves were mock-vaccinated with PBS. At 5 days post-vaccination, all animals were experimentally infected by nasal inhalation of BRSV (at the age of 12 – 19 days). General clinical signs, respiratory clinical signs, virus excretion (using nasal swabs) and antibody response were monitored for 14 days post-challenge. All animals were euthanised 14 days after challenge to evaluate lung lesions.

Results: Virus was excreted in both groups following challenge, however there were no differences between the vaccinated and control groups for either the amount of virus excreted or the mean duration of viral excretion. A statistically significant difference ($p<0.05$) in terms of reduction in respiratory clinical signs was observed in the vaccinated group compared to the control group at 9, 10, 12, 13, 15 and 16 days post-vaccination (based upon total respiratory scores); this was primarily attributable to the scores associated with respiratory rate and breathing effort. General clinical signs observed post-challenge were mild (and related to either slight depression or slight alteration of general clinical signs). No severe lung lesions were observed at 14 days post-challenge (the total percentage of lung lobes affected in both groups was <2%).

Nasal vaccination with Nasym did not induce an antibody response in serum; all animals in both groups remained negative for BRSV antibodies by day of challenge (day 5). At day 19, 5/10 animals in the control group were seropositive, however only 2/10 vaccinated animals were seropositive. There were no significant differences between groups for average titres on day 19.

It was concluded that, while data from this study support a reduction in respiratory clinical signs at 5 days post-vaccination, a reduction in viral excretion was not demonstrated at this time-point. Therefore, given that a reduction of viral excretion is a requirement of Ph. Eur. 1177 for the demonstration of immunogenicity, the onset of immunity after nasal vaccination is established as 21 days. However, it was considered acceptable to include information in section 5 of the SPC that a reduction of respiratory clinical signs (but not a reduction of virus shedding) is observed at 5 days after nasal vaccination, but that full immunity is not established until 21 days post-vaccination.

Intramuscular administration

Intramuscular administration of two doses, separated by an interval of 28 days, in seronegative calves vaccinated from 3 months of age -OOI 20 days

The **OOI of 20 days** after the intramuscular administration of two doses, separated by an interval of 28 days, was investigated in seronegative calves vaccinated from 10 weeks of age. On day 0 of the study, one group of 5 calves were vaccinated with Nasym by the intramuscular route in the neck (2 ml dose) and revaccinated 28 days later, and one group of 5 calves were mock-vaccinated with PBS following the same schedule. At 20 days after the second vaccination, all animals were experimentally infected by nasal inhalation of BRSV. General clinical signs, respiratory clinical signs, virus excretion (using nasal swabs) and antibody response were monitored for 14 days post-challenge. All animals were euthanised 14 days after challenge to evaluate lung lesions.

Results: A statistically significant difference in terms of reduction in mean titre of virus excreted ($p<0.05$) was observed at 51, 52, 54 and 55 days post initial vaccination and a statistically significant difference ($p<0.05$) in terms of the mean duration of excretion from challenge to 14 days post-challenge was observed in vaccinated calves compared to the control group. A statistically significant reduction ($p<0.05$) in terms of respiratory clinical signs was observed in the vaccinated group compared to the control group at 52, 55, 56 and 62 days post initial vaccination (based upon total respiratory scores); this was primarily attributable to the scores associated with respiratory rate and nasal discharge. A statistically significant difference ($p<0.05$) between treated and control groups in terms of the average total respiratory clinical signs score from challenge to 14 days post-challenge was also reported. However, this challenge did not induce general clinical signs at a frequency or severity that would allow for a valid comparison between groups; 1/5 vaccinated animals and 2/5 control animals were reported with slight depression on at least one day in the post-challenge period. The CVMP concluded that the data provided inadequate support for a claim for a reduction of (general) clinical signs.

No severe lung lesions were observed in this study, and, while the overall percentage of lung affected was numerically lower in the vaccinated group (6.14%) compared to the control group (9.55%), there were no statistically significant differences reported between the groups. Thus, it is not considered that the data provided support a reduction in lung lesions following intramuscular vaccination of calves from 3 months of age. All animals were seronegative on day 0 and day 28. On day 35 (1 week after the 2nd vaccination), 4/5 vaccinated animals seroconverted, while the control group animals remained seronegative. On day 62, 2 weeks post-challenge, all animals were seropositive. The average ELISA titre was significantly greater in vaccinated animals compared to the mock-vaccinated group on day 35, 42, 48 (pre-challenge) and 62.

It was concluded that the data from this study supports a reduction in viral shedding and a reduction in respiratory signs of disease at 20 days after completion of the 2 dose vaccination schedule in calves from 10 weeks of age vaccinated by the intramuscular route with a minimum recommended dose.

Duration of immunity

The DOI of 2 months after the first nasal dose was investigated in a study which was also carried out to investigate the influence of MDAs on the response to vaccination (refer to following section for study design). Taking into account the data from the vaccinated and control animals that were seronegative at study start, challenge at 8 weeks after a single nasal dose supported a statistically significant reduction ($p<0.05$) in respiratory clinical signs; 5/9 animals in the control group compared to 0/9 animals in the vaccinated group were euthanised due to severity of respiratory signs of disease. In addition, a reduction in viral shedding was observed in both the vaccinated MDA-positive (at 4, 6 and 8 days post-challenge) and vaccinated MDA-negative groups (at 6 and 8 days post-challenge), compared to the MDA-negative control group. The AUC of mean titre of virus excretion from days 2 to 8 post-challenge of vaccinated animals was significantly lower compared to the MDA-negative control group. (No significant differences were observed between the MDA-positive and MDA-negative vaccinated groups for viral excretion). Overall, these data support the proposed first intramuscular administration of vaccine at 8 weeks after the first nasal dose.

Three studies are presented in support of the DOI for a) 6 months after the first intramuscular revaccination in animals vaccinated by the nasal route, b) 4 months after the completion of the two dose basic intramuscular vaccination scheme, and c) 6 months after the completion of the two dose basic intramuscular vaccination scheme.

Study on the DOI of the vaccine PB-179 in calves by intranasal and intramuscular route

This study investigated the **DOI of 6 months after the first intramuscular revaccination** in animals vaccinated by the nasal route. The study was performed by selecting animals from one of the farms of the field study, for which it is accepted that no intercurrent infection with BRSV occurred in the period between vaccination/mock-vaccination under field conditions and challenge in laboratory facilities.

Two groups of 6 calves, vaccinated or mock-vaccinated, respectively, under field conditions by the nasal route between 2 and 14 days of age were included. At approximately 3 months of age, animals were vaccinated or mock-vaccinated by the intramuscular route. At 6 months after the intramuscular vaccination, animals were transported to laboratory facilities for BRSV challenge (BRSV strain DK9402022), having been screened 2 weeks prior to transport for BRSV antibodies to confirm that animals were seronegative (note; vaccinated animals were seronegative also at this stage) and presence of BRSV in nasal swabs to confirm the absence of field infection. On the day of challenge, animals were again screened, however 2 of 6 animals in the control group had very low levels of BRSV antibodies and were excluded from the study. Further reassurances were provided by the applicant to exclude possible BRSV infection on the farm; the levels of antibodies in the two animals were either very low or on the threshold of seropositivity. The two animals remained negative for BRSV in nasal samples, and of the 31 animals on the site which were appropriately screened for potential inclusion in the study, all were negative for BRSV in nasal samples and seronegative.

Following challenge, virus excretion, general and respiratory clinical signs and antibody response were measured, with euthanasia and evaluation of lung lesions at 16 days post-challenge. The results demonstrated a statistically significant difference in the overall mean titre of virus excretion in the 14 days after challenge, and in the mean duration of virus excretion. General clinical signs were limited to mild depression in both groups (in keeping with the findings from the previously conducted laboratory studies) and were not clinically relevant. There was a numerical reduction in the respiratory signs total score, and a statistically significant difference between groups for score of nasal discharge, which was lower in the vaccinated group compared to the mock-vaccinated group on day 7 post-challenge. A reduction of lung lesions was not supported by the data provided; there were no statistically significant differences in the mean percentage of total lung affected by challenge between the vaccinated (2.56%)

and mock-vaccinated groups (5.89%), or in the mean percentage of individual lobes affected. Furthermore, histopathological analysis of the samples suggested that BRSV may not have been the sole agent contributing to the lesions observed.

Given that animals had been vaccinated under field conditions for a combined safety and efficacy clinical trial, an intermediate titre batch, rather than the required minimum titre for evaluation of efficacy parameters had been used. The deviation from the general requirements to demonstrate efficacy parameters with a minimum titre batch, was appropriately justified by the applicant. Taking into account a) that a longer gap between nasal vaccination and the first intramuscular dose occurred (approximately one month longer than that recommended in the SPC, i.e. less favourable scenario for efficacy evaluation), b) that the minimum dose has been used for investigation of OOI and for DOI of 6 months after the IM-IM schedule with similar results obtained (new study presented in the response to list of outstanding issues), and c) that there are no other data available which would call into question the adequacy of the proposed minimum dose, it was concluded that this deviation from requirements could be accepted.

Overall, the DOI of 6 months after a single intramuscular 'booster' dose, after initial vaccination by the nasal route, was considered to be adequately supported.

Study on the DOI of the vaccine PB-179 in calves by intramuscular route

In this study, the **duration of immunity of 4 months** after completion of the two dose basic intramuscular vaccination scheme was investigated. Seronegative calves were initially vaccinated intramuscularly from the age of 10 weeks, and administered the 2nd dose intramuscularly 28 days later, in accordance with the recommended schedule. A minimum titre batch was used for vaccination, and challenge was conducted using the DK9402022 BRSV challenge strain. Follow-up was similar to the other laboratory challenge studies, with evaluation of virus excretion, general and respiratory clinical signs, lung lesions at 14 days post-challenge and the antibody response.

The results of this study demonstrate a statistically significant difference in terms of reduction in mean titre of virus excreted and in mean duration of excretion from challenge to 14 days post-challenge in vaccinated calves compared to the control group. Thus, a claim for a reduction of viral shedding at 4 months after completion of the two dose intramuscular vaccination scheme is supported. While a reduction in general clinical signs was not supported, a reduction in respiratory clinical signs was accepted. On this latter point, a statistically significant difference in the total respiratory clinical signs score or in individual parameters was not demonstrated, however there were numerical reductions in the scores for dyspnoea, and in the average daily scores for total respiratory signs on days 7, 8, 9, 10, 11, 12, 13 and 14 (period when challenge-related respiratory signs were observed). Furthermore, 1/6 control animals in the mock-vaccinated group developed severe dyspnoea in the post-challenge period (day 7), accompanied by depression, and this animal was euthanised on day 8 post-challenge.

Regarding lung lesions, there were no statistically significant differences in the mean percentage of total lung affected by challenge between the vaccinated and mock-vaccinated groups (the overall percentage of lung affected in the vaccinated group was 3.63% and 7.69% in the control group), or in the mean percentage of individual lobes affected.

In summary, the data from this study support a reduction of virus excretion and respiratory clinical signs at 4 months after the 2nd dose of the two dose intramuscular vaccination schedule.

Study on the DOI of the vaccine PB-179 in calves by intramuscular route

In this study, the **DOI of 6 months** after completion of the two dose basic intramuscular vaccination scheme was investigated. Seronegative calves were initially vaccinated intramuscularly from the age of 10 weeks, and administered the 2nd dose intramuscularly 25 days later, rather than the recommended 28

days later. However, it is not considered that this minor deviation (considering that challenge was not conducted until 6 months later), will have had any relevant impact on the study data. A minimum titre batch was used for vaccination, and challenge was conducted using the DK9402022 BRSV challenge strain. Follow-up was similar to the other laboratory challenge studies, with evaluation of virus excretion, general and respiratory clinical signs, lung lesions at 14 days post-challenge and the antibody response.

The results of this study demonstrate a statistically significant difference in terms of reduction in mean titre of virus excreted and in mean duration of excretion from challenge to 14 days post-challenge in vaccinated calves compared to the mock-vaccinated group. Thus, a claim for a reduction of viral shedding at 6 months after completion of the two dose intramuscular vaccination scheme is supported. While a reduction in general clinical signs was not supported, a reduction in respiratory clinical signs was demonstrated. A statistically significant difference in the total respiratory clinical signs score between groups was observed on days 8, 9 and 11 post-challenge, with higher scores in the control group. In addition, concerning the comparison of respiratory parameters individually assessed, statistically significant differences between groups for the average score for respiratory rate score was observed on day 8 post-challenge, for breathing effort on days 8, 9 and 10 and for nasal discharge on days 9, 11 and 12 post-challenge ($p<0.05$).

Regarding lung lesions, there were no statistically significant differences in the mean percentage of total lung affected by challenge between the vaccinated and mock-vaccinated groups (the overall percentage of lung affected in the vaccinated group was 6.22% and 5.7% in the control group), or in the mean percentage of individual lobes affected.

In summary, the data from this study support a reduction of virus excretion and respiratory clinical signs at 6 months after the 2nd dose of the two doses intramuscular vaccination schedule.

Efficacy of revaccination schedule

The revaccination schedule comprises of the administration of a single dose of vaccine, administered by the intramuscular route at intervals of every 6 months. While a study has not been presented to investigate the efficacy of the first 6 monthly 'booster' after completion of the two dose basic intramuscular vaccination scheme, the study provided in support of the DOI of 6 months after the first intramuscular dose following nasal vaccination is intended to support the efficacy of the revaccination scheme. While it was noted that there were no data presented to support that a single intramuscular dose of vaccine would be capable of protecting until the time of the proposed subsequent 6 monthly booster, it was accepted that the investigation of the DOI of 6 months after the administration of the first IM 'booster' after initial nasal vaccination represents a worst case scenario for the demonstration of a 6 month DOI after a single IM dose.

Therefore, the efficacy of the 6 monthly revaccination schedule is accepted.

Maternally derived antibodies (MDA)

Two studies were presented to investigate the possible interference of MDAs on the response to vaccination.

For **calves vaccinated from 7 days of age with a single nasal dose**, efficacy of vaccination, in the presence of MDAs was investigated in a non-GLP study conducted outside the EU. Calves were obtained from local farms (in Canada), removed from their dams at birth and were fed either 1.5 litres of negative to BRSV antibodies pooled dairy colostrum or positive to BRSV antibodies colostrum. The average MDA level of animals in this study was 4.7 $\log_2$. On day 0 of the study, two group of calves (MDA+, MDA-, n=9/group) were vaccinated by the nasal route with Nasym in accordance with recommendations.

Two groups of calves (MDA+, MDA-, n=9/group) were mock-vaccinated with PBS according to the same vaccination schedule. On day 58, 8 weeks post-vaccination, all animals were aerosol challenged with BRSV (Asquith strain). Clinical signs, virus excretion, partial pressure of oxygen in arterial blood (PaO_2), BRSV antibodies and lung lesions at necropsy (8 days after-challenge) were evaluated. The decision to challenge animals at 8 weeks post-vaccination was based on the proposed DOI of 2 months of a single nasal dose in minimum age calves, at which time the first intramuscular dose is proposed to be administered.

Results: Protection from severe respiratory signs of disease from a virulent challenge at 8 weeks post-vaccination was high in both MDA+ vaccinated calves (8/9 calves protected) and MDA- vaccinated calves (9/9 calves protected), while in the mock-vaccinated groups, 9/18 animals were euthanised due to severity of signs; 5/9 MDA- animals and 4/9 MDA+ animals. Both the MDA- vaccinated animals and the MDA+ vaccinated animals had a significantly lower number of euthanised animals than the mock-vaccinated groups ($p<0.05$, both cases), and no significant differences were observed among the vaccinated groups.

This is the only study presented in which more severe lung lesions were observed in the control groups, and whilst statistically significant differences are claimed between the vaccinated vs control groups for the overall percentage of lung affected, there would appear to be statistically significant differences between groups for 3/8 lung lobes only. However, it is noted that similar lung lesions were observed between MDA+ and MDA- vaccinated groups, indicating no adverse impact of MDAs on vaccine efficacy. The applicant provided data to support that this study could be considered representative of EU conditions, with respect to MDA levels in comparison with MDA titres in animals in the EU safety and efficacy field trial.

The CVMP concluded that there are sufficient data available to demonstrate that MDAs are unlikely to adversely affect the response to vaccination of calves of approximately one week old when administered a single nasal dose of Nasym.

For **calves vaccinated from approximately 3 months of age by the intramuscular route**, with a second dose administered one month later, efficacy of vaccination, in the presence of MDAs was investigated in a study. On day 0 of the study, two group of calves (n=7 each) of 3 months of age were vaccinated, differing in the presence or absence of MDAs. Both groups were intramuscularly vaccinated with Nasym and a second dose administered 28 days later. A mock-vaccinated MDA+ group (n=7) received PBS as placebo according to the same vaccination schedule. The MDA titres were representative of the titres found in animals of the minimum age to be intramuscularly vaccinated under field circumstances (MDA levels in the preclinical study were 1.4 log2, while in the field the mean level of antibodies against BRSV at day of vaccination was 0.94 log2. At the time when MDAs disappeared in the MDA+ non-vaccinated control group, all animals were challenged with BRSV (strain DK9402022) by aerosol (19 days after the 2nd vaccination).

General clinical signs, respiratory clinical signs, virus excretion and antibody response were monitored for 14 days post-challenge. All animals were euthanised 14 days after challenge to evaluate lung lesions.

Results: it was demonstrated that there were no relevant differences in MDA- vs MDA+ vaccinated group following a challenge at 19 days after the 2nd dose. No relevant differences in the respiratory clinical signs were observed in MDA+ compared to MDA- animals; the total score of respiratory clinical signs was statistically significantly greater in the control group than in the MDA+ vaccinated group ($p<0.05$, ANOVA test) at 7, 8, 10, 11, 12 & 13 days post-challenge. The average of total respiratory signs score was statistically significantly greater in the control group than in both vaccinated groups ($p<0.001$, ANOVA test) from days 0-14 post-challenge but was not reported to be statistically significantly different between

the MDA- vs the MDA+ vaccinated groups. Clinical signs were absent in both of the vaccinated groups, while slight depression was reported in the control group in 5/7 animals.

Regarding the serological profile observed in animals in this study, after day 0 (vaccination / mock-vaccination), BRSV antibody levels continued to decline in MDA+ calves, with animals becoming seronegative by day 28 (day of 2nd administration of vaccine), and in the MDA+ non-vaccinated calves, all animals were seronegative by day 35. The decline of MDAs was similar in both the MDA+ vaccinated animals and the MDA+ control animals. One week after the 2nd dose of vaccine, antibody levels increased similarly in MDA+ animals and the MDA- animals.

In summary, it can be accepted that the presence of MDAs in calves from 3 months of age does not interfere with the response to vaccination. While it was noted that in this study, also conducted in compliance with the requirements of Ph. Eur. 1177 (and very similar therefore to the OOI study in 3 month old calves), there was no statistically significant difference in viral shedding between any of the study groups (MDA- vaccinated, MDA+ vaccinated, MDA+ non-vaccinated animals) after challenge, the applicant justified that these data were not contradictory to the data obtained in seronegative calves at OOI, and was due to the different characteristics of the control groups in each study (i.e. MDA negative in the OOI study and MDA positive in the latter study at study start), which makes it not a 'like for like' comparison.

The presence of immunomodulatory molecules, other than immunoglobulins, that would have been present in MDA positive groups, may have conferred a protective effect in the control group. Nevertheless, while a SSD was not achieved, the mean total virus excretion and the mean duration of virus excretion were numerically lower in the vaccinated groups (MDA positive and MDA negative at study start) compared to the control group, in addition a statistically significant difference in the daily group average of virus excretion was demonstrated between groups at day 7 post-challenge, with a significantly lower daily average virus excretion in the vaccinated groups compared to the mock-vaccinated group.

A reduction in viral shedding has been demonstrated in accordance with the Ph. Eur. 1177 requirements in the OOI study. Furthermore, it is accepted that the MDA interference study satisfactorily demonstrates that there are no relevant differences in the response to vaccination depending on MDA status at time of vaccination. Therefore, it can be accepted that a reduction in virus excretion has been established following the two dose intramuscular vaccination schedule.

Field trials

Two multicentre, randomised, double blinded and placebo-controlled clinical field trials were carried out to assess both the safety and efficacy of Nasym in controlling BRSV infections in calves under field conditions. Both studies started in March 2017 and finished in February 2018. In both field studies mentioned above, animals were randomly allocated to two treatment groups that were administered either the vaccine Nasym or a placebo (PBS).

In both studies, the vaccination schedule consisted of two doses of 2 ml. In each study, one of the two options of primary vaccination was studied. In one study**,** animals received the first dose via the nasal route from the first few days of age and revaccination was administered by the intramuscular route in the neck at approximately 3 months of age. In the other study**,** the first dose was administered at 3 months of age and the second dose was administered 1 month later, both by the intramuscular route.

For both studies, the primary efficacy variable was the incidence of respiratory episodes positive to BRSV infection. Secondary variables included the incidence of affected animals and severity of respiratory clinical signs in case of an outbreak of BRSV, antibiotic treatments against respiratory disease, average daily weight gain and mortality due to respiratory disease.

In the first study (calves from 2 – 21 days of age), one small 'outbreak' of clinical BRSV infection has been reported (17 days post-vaccination, on one of the largest participating farms). The main clinical sign was dyspnoea. However, according to the study protocol, an outbreak of respiratory disease should have been considered when the cumulated percentage of animals with clinical signs compatible with BRSV during 3 days was ≥10%. However, the investigator on the respective farm did not follow this criteria and after collecting 4 animals with signs compatible with BRSV on the same day (1st day), the investigator considered it as the onset of the outbreak (reported as deviation #4). Consequently, this infection should have not been considered as an outbreak according to the study plan. Secondly, the investigator started a metaphylactic treatment with antibiotics (doxycycline 20% in water) in all animals in the farm (mass medication), instead of doing it only on the animals of the affected pen, as stated in the protocol. Hence, this mass medication could eradicate the concomitant infection and the outbreak evolution could be attenuated.

No further outbreaks of BRSV were reported during the trial. Overall, in the absence of any other'outbreaks' of BRSV, it is considered that this field trial is not informative in terms of the ability to investigate the efficacy of vaccination under field conditions.

In the other study (calves from 3 months of age), no outbreaks of BRSV on the farms included in this field trial were reported, therefore this study does not provide any informative data regarding the efficacy of vaccination of calves from 3 months of age by the intramuscular route under field conditions.

Overall conclusion on efficacy

The efficacy of Nasym was evaluated in eight laboratory studies and two safety and efficacy field trials.

The investigation of the OOI of 21 days after the nasal administration of a single dose in calves vaccinated from 9 days of age demonstrated a statistically significant reduction in viral shedding and a statistically significant reduction in respiratory clinical signs in vaccinated calves compared to the control group. A reduction of general clinical signs or lung lesions was not considered to have been adequately supported.

The investigation of the OOI of 5 days after the nasal administration of a single dose in calves vaccinated between 7 and 14 days of age demonstrated a statistically significant reduction in respiratory clinical signs, however, a reduction in viral shedding, general clinical signs or lung lesions was not demonstrated.

The investigation of the OOI of 20 days after the intramuscular administration of two doses, separated by an interval of 28 days, in calves vaccinated from 3 months of age demonstrated a statistically significant reduction in viral shedding and a statistically significant reduction in respiratory clinical signs. A reduction of general clinical signs or lung lesions was not considered to have been adequately supported.

In conclusion, the OOI of Nasym is established as 21 days, following either a) a single nasal dose in the youngest age category of the target species or b) completion of the two dose basic vaccination scheme when administered by the intramuscular route in cattle from 10 weeks of age.

The DOI of 2 months after the first nasal dose was adequately supported on the basis of a statistically significant reduction in viral shedding and in respiratory clinical signs in vaccinated animals compared to the control group at 8 weeks after a single nasal dose. These data support the proposed first intramuscular administration of vaccine at 8 weeks after the first nasal dose.

The DOI of 6 months after the first intramuscular dose in animals previously vaccinated by the nasal route, was adequately supported for the claims for a reduction of viral shedding and respiratory clinical signs.

The DOI of 6 months after completion of the 2 dose intramuscular vaccination schedule in animals vaccinated from 10 weeks of age was satisfactorily supported for the claims for a reduction of viral shedding and respiratory clinical signs.

The efficacy of the revaccination schedule, which comprises the administration of a single dose by the intramuscular route every 6 months, has been satisfactorily demonstrated. While the efficacy of the first single 'booster' dose after the two dose basic intramuscular vaccination scheme was not investigated, it was accepted that the study provided to demonstrate a DOI of 6 months after the first intramuscular 'booster' dose, after nasal vaccination, represents a 'worst case scenario' for the evaluation of the DOI of the proposed single dose revaccination.

Two studies were presented to investigate the possible interference of MDAs on the response to vaccination, and the data provided indicate that for both vaccination schedules, the presence of MDAs is unlikely to interfere with the response to vaccination.

The efficacy of vaccination of Nasym under field conditions was investigated in two multi-centre, randomised, blinded, negatively-controlled field trials in farms included on the basis of historical records of clinical or sub-clinical BRSV infection. However, in the absence of any BRSV outbreaks that could be considered suitable for the evaluation of efficacy, no conclusions can be reached regarding the efficacy of Nasym under field conditions. However, this is not an uncommon situation for field trials for veterinary vaccines, and it is considered that there are adequate data provided in the laboratory efficacy studies to support the efficacy of vaccination, with an indication for a reduction of viral shedding and respiratory clinical signs.

Overall, the product has been satisfactorily demonstrated to be efficacious for the claims for a reduction of viral shedding and a reduction of respiratory clinical signs. These two parameters are supported with an OOI of 21 days (after single nasal dose, and after completion of the two dose intramuscular basic vaccination schedule), and with a DOI of 2 months after single nasal vaccination and at 6 months after completion of the two dose basic intramuscular vaccination schedule. The first intramuscular revaccination (single dose) in animals vaccinated by the nasal route is to be administered at 2 months after nasal vaccination. The first intramuscular revaccination (single dose) in animals vaccinated via the two dose intramuscular scheme is to be administered 6 months after the 2nd dose of the basic vaccination scheme. Thereafter, in both situations, the revaccination schedule consists of the administration of a single intramuscular dose at intervals of every 6 months.

Part 5 – Benefit-risk assessment

Introduction

Nasym is a live attenuated BRSV vaccine, proposed for the active immunisation of cattle to reduce virus shedding and respiratory clinical signs caused by BRSV infection. The vaccine is presented as a lyophilisate for suspension with the provided solvent, PBS, for nasal administration to calves from 9 days of age or for intramuscular injection to calves from 10 weeks of age.

The application has been submitted in accordance with Article 12(3) of Directive 2001/82/EC (full application).

Benefit assessment

Direct therapeutic benefit

The benefit of Nasym is its efficacy in the reduction of viral excretion and respiratory clinical signs in calves vaccinated from 9 days of age with a single dose administered by the nasal route. A reduction of viral excretion and a reduction in respiratory clinical signs is supported for calves vaccinated from 10 weeks of age by the intramuscular route. Efficacy was shown in a number of laboratory studies.

The OOI is 21 days after vaccination after a single nasal dose, and 21 days after completion of the two dose basic intramuscular vaccination scheme. The DOI is 2 months after nasal vaccination and 6 months after completion of the two dose basic intramuscular vaccination scheme.

The presence of MDAs in calves vaccinated at 7 days of age did not adversely affect the response to nasal vaccination, this ability to provide protection from BRSV infection in very young calves is claimed as a significant benefit of vaccination with Nasym.

Additional benefits

Nasym increases the range of available vaccines for the control of BRSV infection and, as a consequence, would reduce the need for antimicrobial treatment due to secondary bacterial infections which are commonly associated with the bovine respiratory disease complex.

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 appear to support the 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. Based on the stability data provided a 15 month shelf life can be assigned to the finished product.

Safety

Risks for the target animal and non-target animals:

The product is generally well tolerated in the target animals. The mild adverse reactions observed following vaccination are included in the SPC (slight alteration of faecal consistency, transient temperature increases). No adverse reactions were observed after a tenfold overdose of Nasym. The vaccine strain has been demonstrated to be stably attenuated and is not expected to revert to a virulent form, in addition the absence of spread of the virus vaccine strain from vaccinated to non-vaccinated calves and spread to other susceptible non-target species has been demonstrated.

Risk for the user:

The use of Nasym does not pose a risk to the user, when used in accordance with recommendations.

Risk for the consumer:

There are no risks identified for consumers of animals vaccinated with Nasym. All components included in the product are either allowed substances according to Table 1 of Regulation (EC) No. 37/2010, or are

substances considered as not falling within the scope of Regulation (EC) No. 470/2009, therefore a withdrawal period of zero days is considered acceptable.

Risk for the environment:

It is accepted that the vaccine does not pose a risk to the environment when used in accordance with recommendations.

Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, user, and the environment, and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

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 animals and presents an acceptable risk for users, the environment and consumers, when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) considers that the application for Nasym is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.