13 March 2024
EMA/129990/2024
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS (EMEA/V/C/005887/0000)

Vaccine common name: Avian metapneumovirus, avian infectious bronchitis, Newcastle disease, avian infectious bursal disease, avian reovirus and egg drop syndrome virus vaccine (inactivated)

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

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

© European Medicines Agency, 2024. Reproduction is authorised provided the source is acknowledged.

Introduction

The applicant Intervet International B.V. submitted on 3 November 2022 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS, through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (**optional scope**).

The eligibility to the centralised procedure was agreed upon by the CVMP on 9 September 2021 as no other marketing authorisation has been granted for the veterinary medicinal product within the Union.

Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS is an emulsion for injection for chickens containing inactivated avian metapneumovirus strain BUT1 #8544, inactivated avian infectious bronchitis virus strain M41, inactivated avian infectious bronchitis virus strain 4/91, inactivated Newcastle disease virus strain Ulster, inactivated avian infectious bursal disease virus strain GB02, inactivated avian infectious bursal disease virus strain 89/03, inactivated avian reovirus strain ARV-1, inactivated avian reovirus strain ARV-4 and inactivated eggdrop syndrome-1976 virus strain BC14, as active substances and light liquid paraffin as adjuvant.

The vaccine is presented in packs containing 1 bottle of 300 ml (1000 doses) or 600 ml (2000 doses).

The vaccine is to be administered intramuscularly as a single dose of 0.3 ml in the breast or thigh region from 8 weeks of age onwards, but no later than 3 weeks before the onset of lay.

At the time of submission, the applicant applied for the following indications:

For the active immunisation of chickens for:
- reduction of egg drop caused by avian metapneumovirus
- reduction of respiratory signs and egg drop caused by infectious bronchitis virus strains Massachusetts (GI-1 genotype), 4/91-793B (GI-13 genotype), QX – D388 (GI-19 genotype), Var2 (G1-23 genotype) and Q1 (GI-16 genotype)
- reduction of mortality and clinical signs caused by Newcastle disease virus
- passive immunisation of the progeny of the vaccinated chickens to:

  - reduce mortality and clinical signs of disease caused by very virulent (CS89), classical (STC) and antigenic variants (variant E and GLS) strains of infectious bursal disease virus
  - reduce viraemia and clinical signs of disease caused by avian reovirus (genotypes 1, 2, 3, 4 and 5)

- reduction of egg drop and eggshell defects caused by eggdrop syndrome-1976 virus

The rapporteur appointed is Jacqueline Poot and the co-rapporteur is Christine Miras.

The dossier has been submitted in line with the requirements for submissions under Article 8 of Regulation (EU) 2019/6 – full application.

On 13 March 2024, the CVMP adopted an opinion and CVMP assessment report.

On 6 May 2024, the European Commission adopted a Commission Decision granting the marketing authorisation for Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Vaccine Antigen Master file (VAMF)

A total of nine vaccine antigen master files were submitted with this application, as listed below. The VAMFs are considered approvable.

- EMEA/V/VAMF/0001 - Turkey rhinotracheitis virus, strain BUT1#8544, inactivated
- EMEA/V/VAMF/0002 - Avian infectious bronchitis virus, type Massachusetts, strain M41, inactivated
- EMEA/V/VAMF/0003 - Infectious bronchitis virus, strain 4/91, inactivated
- EMEA/V/VAMF/0004 - Newcastle disease virus, strain Ulster, inactivated
- EMEA/V/VAMF/0005 - Infectious bursal disease virus, strain GB02, inactivated
- EMEA/V/VAMF/0006 - Infectious bursal disease virus, strain 89/03, inactivated
- EMEA/V/VAMF/0007 - Reovirus, strain ARV-1, inactivated
- EMEA/V/VAMF/0008 - Reovirus, strain ARV-4, inactivated
- EMEA/V/VAMF/0009 – Egg drop syndrome-1976 virus, strain BC14, inactivated.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a summary of the pharmacovigilance system master file which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF) with the services of a qualified person responsible for pharmacovigilance and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Active substance

Refer to the respective vaccine antigen master files.

Finished product

Merck Sharp Dohme Animal Health S.L., Salamanca, Spain, performs the manufacturing of the finished product.
A manufacturing authorisation was issued on 24 November 2020 by the competent authority of Spain (AEMPS). A GMP certificate confirming compliance with the principles of GMP is provided. The certificate was issued on 16 February 2022, referencing an inspection on 16 December 2021, by the competent authority of Spain (AEMPS).
Intervet International B.V., Wim de Körverstraat 35 5831AN Boxmeer, the Netherlands, performs the batch release.

Proof of establishment in the EEA was provided.
A manufacturing authorisation was issued on 14 April 2022 by the Ministry of Agriculture, Nature and Food Quality of the Netherlands. A GMP certificate confirming compliance with the principles of GMP is provided. The certificate was issued on 23 July 2020, referencing an inspection on 16 July 2020, by the Ministry of Agriculture, Nature and Food Quality of the Netherlands.

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file is considered to be in line with legal requirements. The GMP status of the active substance(s) and of the finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

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

Qualitative and quantitative composition

Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS is an inactivated viral poultry vaccine presented in bottles containing 300 ml (1000 doses) or 600 ml (2000 doses).

The vaccine consists of nine antigens: inactivated avian metapneumovirus (AMPV) strain BUT1 #8544, inactivated avian infectious bronchitis virus (IB) strain M41, inactivated avian infectious bronchitis (IB) virus strain 4/91, inactivated Newcastle disease (ND) virus strain Ulster, inactivated avian infectious bursal disease (IBD) virus strain GB02, inactivated avian infectious bursal disease (IBD) virus strain 89/03, inactivated avian reovirus strain ARV-1, inactivated avian reovirus strain ARV-4 and inactivated eggdrop syndrome-1976 (EDS) virus strain BC14, as active substances and light liquid paraffin as adjuvant. Polysorbate 80, sorbitan oleate and PBS are included as excipients.

Container and closure system

The product is packed in polyethylene terephthalate (PET) containers (compliant with Ph. Eur. 3.2.2, USP 661, USP 87 and USP 88), closed with halogenated butyl rubber stoppers (Ph. Eur. 3.2.9) and aluminium caps. Containers and stoppers are sterilised by ionising radiation at a minimum of 25 kGy. Example certificates of analysis for the packaging materials are provided in the dossier.

Product development

The Nobilis Multriva inactivated vaccine range can be regarded as the successor of the Nobilis inactivated vaccine range containing the inactivated avian metapneumovirus (AMPV), infectious bronchitis virus (IBV), Newcastle disease virus (NDV), infectious bursal disease virus (IBDV), avian reovirus (ARV) and egg drop syndrome virus (EDSV) antigens.

The vaccine dose of Nobilis Multriva vaccine range is 0.3 ml, compared to the vaccine dose of 0.5

ml of the Nobilis inactivated vaccine range.

The AMPV, IBV M41 and EDSV antigens in the Nobilis Multriva vaccine range are the same as in the Nobilis inactivated vaccine range. The IBV D274 strain present in the Nobilis inactivated vaccine range was replaced in Nobilis Multriva by the IBV 4/91 strain, which is included to provide a broader protection and due to its globally more frequent presence. The NDV Clone 30 strain was replaced by the NDV Ulster strain, which is included to provide a broader protection in combination with live priming with NDV Clone 30. The IBDV D78 strain was replaced by the unique combination of IBDV GB02 (vIBDV) and IBDV 89-03 (VarE). This combination should provide protection against all classic, very virulent and different variant IBDV strains. The ARV 1733 and 2408 (both genetic class 1b) strains are replaced by the particular combination of two new strains (ARV-1 and ARV-4), originating from the genetic class 1b and 4, to provide protection against all described genotypes.

The adjuvant (oil phase of the emulsion) is the same as for the Nobilis inactivated vaccine range manufactured by the applicant.

The control tests were updated replacing animal testing where possible.

Description of the manufacturing method

Manufacturing of the vaccine

Active substances are manufactured as described in the respective vaccine antigen master files. For all of the antigens standard manufacturing methods are used. Virus strains are cultured mostly on primary chicken cells and subsequently inactivated and concentrated where appropriate. The processes were appropriately validated, control tests are adequate to assure the quality and consistency of the antigens.

The final product is manufactured by adding the inactivated antigen suspensions to PBS solution. Oil soluble constituents (sorbitan oleate and polysorbate 80) are dissolved in liquid paraffin and the solution is sterilised. The oil solution and the aqueous suspension are subsequently mixed and emulsified. An example formulation calculation is provided.

Bottles are filled and closed with a stopper and secured with a cap. The final product is stored at 2-8 °C.

The process is considered to be a standard manufacturing process for this type of vaccines. The major steps of the manufacturing process have been validated by three consecutive batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible and consistent manner. The in-process controls are adequate for this type of manufacturing process.

Production and control of starting materials

Starting materials listed in pharmacopoeias

Starting materials listed in pharmacopoeias and used for manufacturing of antigens are listed in the respective VAMFs. Certificates of analysis have been provided and all conform to the relevant specifications.

Starting materials listed in pharmacopoeias and used in the production of the finished product are:

Disodium phosphate dihydrate	Ph. Eur. Monograph 0602
Paraffin, light liquid	Ph. Eur. Monograph 0240
Polysorbate 80	Ph. Eur. Monograph 0428
Sodium chloride	Ph. Eur. Monograph 0193
Sodium dihydrogen phosphate dihydrate	Ph. Eur. Monograph 0194
Sorbitan oleate	Ph. Eur. Monograph 1041

Example certificates of analysis are provided for these starting materials and all materials comply with Ph. Eur. requirements.

Starting materials not listed in a pharmacopoeia

Starting materials of biological origin

Starting materials of biological origin not listed in pharmacopoeias and used in the manufacturing of the antigens are listed in the respective VAMFs. The seed materials are sufficiently characterised and appropriate tests have been performed to assure their quality. Other materials of biological origin conform to the in-house specifications as illustrated by certificates of analysis. The materials used conform to the requirements. No other starting materials of biological origin are used in the manufacturing of the finished product.

Starting materials of non-biological origin

Starting materials of non-biological origin, not listed in pharmacopoeias and used in the manufacturing of antigens are listed in the respective VAMFs. No other starting materials of non-biological origin are used in the manufacturing of the finished product.

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

Adequate information regarding the qualitative and quantitative composition of culture media used in the manufacturing of the antigens, their treatment processes and their storage conditions is provided in the respective VAMFs. The risk of contamination with extraneous agents was evaluated and considered negligible for each antigen.

Information regarding the qualitative and quantitative composition of solutions used in the manufacturing of the final product, their treatment processes and their storage conditions is provided in the dossier. All components are either tested for or treated to ensure that there are no contaminants. The evaluation of the risk of extraneous agents in the finished product is acceptable.

A TSE risk assessment on the finished product is provided in accordance with EMEA/410/01. The risk that the vaccine transmits TSE to chicken is estimated as practically zero.

Control tests during the manufacturing process

The control tests performed during the manufacture of the antigens are described in the respective VAMFs. These in-process control tests have been appropriately validated and are deemed to be sufficient to control all the critical steps in the manufacturing of the antigens.

The only control test performed during the manufacturing of the finished product is filling volume.

The relevant test method (weighing) is considered to fall under GMP. This in-process test is deemed to be sufficient to control the critical step in the manufacturing of the finished product.

Control tests on the finished product

A description of the methods used for the control of the finished product (appearance, viscosity, accelerated stability [stability of the emulsion], identity and potency, type of emulsion, free formaldehyde, sterility) and the respective specifications were provided.

The proposed tests are considered adequate to control the quality of the finished product. In general, the tests performed on the finished product were appropriately validated and limits have been set.

Batch-to-batch consistency

The results of in-process and finished product testing on 3 consecutive batches of finished product are presented. All batches conformed with all requirements and consistent results were obtained.

Stability

The stability of the bulk antigens is addressed in the respective VAMFs. From the data provided, the antigen's different storage periods have been adequately demonstrated.

The proposed shelf life of the product is 24 months at 2-8°C. A long-term stability study was performed, including 22 batches of finished product of which 3 were fall-out product batches. Batches were tested for appearance, viscosity, sterility (at the end of the storage period, to confirm integrity of closure) and potency for each of the 9 antigens. For most parameters, stability could be confirmed for at least 27 months of storage thereby supporting the proposed 24 months shelf life.

The data provided in support of a 10-hour in-use shelf life are considered adequate. The emulsion was stable at the higher temperature, as was the potency. The data is considered adequate to cover storage for 10 hours at room temperature.

Overall conclusions on quality

Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS is an emulsion for injection for chickens containing inactivated avian metapneumovirus strain BUT1 #8544, inactivated avian infectious bronchitis strain M41, inactivated avian infectious bronchitis strain 4/91, inactivated Newcastle disease virus strain Ulster, inactivated avian infectious bursal disease virus strain GB02, inactivated avian infectious bursal disease virus strain 89/03, inactivated avian reovirus strain ARV-1, inactivated avian reovirus strain ARV-4 and inactivated egg drop syndrome '76 virus strain BC14, as active substances and light liquid paraffin as adjuvant. The vaccine is presented in packs containing 1 bottle of 300 ml (1000 doses) or 600 ml (2000 doses).

The manufacturing method consists of blending of the different components followed by emulsification and can be considered as standard for this type of vaccine. For each of the antigen components a vaccine antigen master file is presented. For all of the antigens standard manufacturing methods are used. The processes were appropriately validated, control tests are adequate to assure the quality and consistency of the antigens.

Procedures have been implemented to ensure the absence of extraneous agents in the starting

materials of animal origin. A TSE risk assessment for the starting materials used is provided. The risk that the final product may transmit TSE to the target animal is considered negligible.

The production method, including appropriate in-process controls and quality controls on the finished product, together with control of the starting materials, generally ensure a consistent quality of batches of vaccine. The whole production process was evaluated at production scale and shown to be consistent.

The data provided support the proposed 24-month shelf life. Stability data of broached product kept at elevated temperatures show that the vaccine remains stable at 37°C for 3 days, so the proposed 10-hour in-use shelf life at room temperature is considered sufficiently supported.

In conclusion, the production process is adequately described and controls in place are appropriate to ensure the quality of the product at release and throughout the shelf life.

Part 3 – Safety documentation (safety and residues tests)

General requirements

Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS is presented as an emulsion for injection for chickens containing inactivated avian metapneumovirus, inactivated avian infectious bronchitis, inactivated Newcastle disease virus, inactivated avian infectious bursal disease virus and inactivated avian reovirus and egg drop syndrome virus, as active substances; and liquid paraffin (mineral oil) as adjuvant. The vaccine is to be administered to chickens intramuscularly as a single dose of 0.3 ml in the breast or thigh region from 8 weeks of age onwards, but no later than 3 weeks before the onset of lay.

A full safety file in accordance with Article 8(1)(b) has been provided.

Safety documentation

Five safety studies were conducted to investigate the safety of the product and included one pre-clinical study investigating the safety of the administration of one dose and four clinical trials.

Pre-clinical studies

Safety of the administration of one dose

One pivotal GLP safety study was provided. Safety of a single dose and of a double dose of vaccine was studied in 7-week old SPF birds. In order to achieve the 200% antigen content multiple vaccine blends had to be used (not all components of the full combination can be blended at 200% in one preparation, due to space limitations). Groups of 11 birds received one of the following: a single dose of the complete vaccine (0.3 ml), a double dose of the complete vaccine (0.6 ml), a single dose of a vaccine containing AMPV and EDSV antigens blended at 200% (0.3 ml), a single dose of a vaccine containing IBV, NDV, IBDV and ARV antigens blended at 200% (0.3 ml) or a 1:1 mix of the two 200% antigen vaccines (0.6 ml).

During the 14-day observation period, birds were examined daily for clinical signs, intercurrent deaths and local reactions. None of the chickens showed abnormal signs of disease or died from

causes attributable to vaccination during the observation period. No palpable local reactions were found in any of the birds. Post-mortem macroscopic and microscopic examinations were not performed.

On the basis of the results no safety concerns arose following the administration of the recommended dose or the double dose to chickens slightly below the minimum recommended age, providing therefore a valid demonstration of the safety of a single dose of the product. The absence of post-mortem data is considered justified based on the high similarity of the composition of the product to the existing inactivated virus vaccines for poultry and the absence of palpable local reactions.

Safety of one administration of an overdose

No overdose studies are required for inactivated vaccines.

Safety of the repeated administration of one dose

The vaccine is to be given once during a lifetime. No repeated dose safety studies are therefore required.

Examination of reproductive performance

The vaccine is not intended for use during lay. As an inactivated vaccine, the product is not considered a risk to the developing reproductive system. No specific studies were performed. During field studies no differences were observed between vaccinated and control birds with respect to laying performance. A warning is included in the SPC to not use the product during lay or within 3 weeks before the onset of lay.

Examination of immunological functions

The product is an inactivated vaccine and none of the component are considered a risk for the immune system, therefore no studies were performed.

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 (and EMA/CVMP/543/03-Rev.01).

The main potential routes of accidental contact with the product have been considered and it was concluded that the most likely are those of accidental self-injection and dermal and/or oral exposure.

The active substances are inactivated viruses and not infectious to humans. The excipients, including adjuvants, are commonly used in other vaccines and do not present a safety concern. The light mineral oil included in the formulation is of concern since an accidental self-injection may have consequences that could, in the very worst-case, lead to loss of a digit due to blockage of blood vessels as a result of the pressure caused by inflammatory reactions.

As a result of the user safety assessment adequate information is included in section 3.5 of the SPC and since the product contains mineral oil, the standard warning for mineral oil-containing vaccines

is included in the product literature.

Based on the above risk assessment the CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Study of residues

No studies of residues were performed. This is considered acceptable.

MRLs

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, including adjuvants, listed in section 2 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.

The antimicrobial substances used in the manufacturing of the antigens are present at low residual levels in the finished product which is not considered to constitute a risk to the consumer.

Withdrawal period

The withdrawal period is set at zero days.

Interactions

The applicant has not provided data investigating interactions of the vaccine with any other veterinary medicinal product and therefore proposes to include a statement in Section 3.8 of the SPC that 'No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. 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.'

Clinical studies

Four single-centre, non-randomised, open, positive-controlled, two-armed GCP-compliant clinical studies with matched flocks were conducted to evaluate safety and efficacy in layer and broiler breeders. The studies were conducted in the Netherlands in well-managed farms.

All four studies were well designed and conducted and confirmed that the product is safe in both layer and broiler breeders when applied as part of the standard vaccination program.

Study 1: A field trial in the Netherlands to assess the safety and efficacy of a RT+IBm+ND+Gm+REOm+EDS vaccine in breeders	
Study sites	Broiler breeder farm in the Netherlands, matched houses.
Study design	Open, positive controlled, two armed (matched flocks).
Compliance with regulatory guidelines	GCP compliant

Animals	Conventional broiler breeders, originating from the same parent flocks and of the same age, were evenly distributed over the houses to obtain identical flocks of approximately 18,000 birds.
Test product	Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS, 0.3 ml, i.m.
Control product/ Placebo	Nobilis RT+IBmulti+G+ND 0.5 ml, i.m. plus Nobilis Reo inac. 0.5 ml i.m.
Vaccination scheme	Birds in the test group were vaccinated with the test product in the 14th week of life (right side breast muscle) while birds in the control group were vaccinated with the two control vaccines (in right and left side breast muscle). Prior to and after the 14th week, both flocks received all standard vaccinations for the farm.
Safety end points	Daily general health and feed intake for 2 weeks post vaccination (p.v.). Local reactions scored on 15 randomly selected birds in each group on days 1, 4, 7 and 14 p.v. and weekly thereafter until resolved. Egg production and hatchability was monitored for each group throughout the period of lay. Throughout the study, daily mortality, vaccinations and the use of medication was recorded.
Statistical method	Descriptive statistics (two groups)
Results	
Outcomes-Safety observations	General health and feed intake was scored as normal on all observation days. A local reaction was observed in one bird (out of 15 tested) of the control group on day 7. In the test group on day 4, one bird showed a subcutaneous haemorrhage of 2 cm long in the right breast, likely a result of mechanical trauma. On day 14 one bird had a large (10 x 3.5) subcutaneous reaction in the right breast. This concerned a hard swelling showing signs of inflammation (swollen and red). The bird was in good general condition. An additional scoring on Day 20 revealed no further local reactions. The mortality numbers were similar in both groups and comparable to normal mortality figures for this type of bird. Egg production was good and highly comparable between groups. Fluctuations were due to general causes and detectable in both groups. Hatchability was highly similar.
Adverse events	Local reactions were observed both in the test and control groups.
Discussion	
Discussion/conclusions further to assessment	*The study was appropriately designed and conducted to an acceptable standard (GCP). While some local reactions were observed in the test group (but also in the control group), this did not lead to any changes in the performance of the flock when compared to the positive control group.* *The study is considered to support the safety of the vaccine when*

	applied under field conditions.

Study 2: A field trial in the Netherlands to assess the safety and efficacy of the RT+IBm+ND+Gm+REOm+EDS vaccine in layers	
Study sites	Layer farm in the Netherlands, matched houses.
Study design	Open, positive controlled, two armed (matched flocks).
Compliance with regulatory guidelines	GCP compliant
Animals	Conventional layers, originating from the same parent flocks and of the same age, were evenly distributed to obtain identical groups. Groups were housed in different rows of the rearing house and later placed in two houses to obtain identical flocks of approximately 10,000 birds.
Test product	Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS, 0.3 ml, i.m.
Control product/ Placebo	Nobilis RT+IBmulti+G+ND 0.5 ml, i.m.
Vaccination scheme	Birds in the test group were vaccinated with the test product in the 12th week of life (right side breast muscle) while birds in the control group were vaccinated with the control vaccine (right side breast muscle). Nobilis Salenvac T was applied at the same time as the study products, in the left breast muscle. Prior to and after the 12th week, both flocks received all standard vaccinations for the farm.
Safety end points	Daily general health and feed intake for 2 weeks post vaccination (p.v.). Local reactions scored on 15 randomly selected birds in each group on days 1, 4, 7 and 14 p.v. and weekly thereafter until resolved. Egg production was monitored for each group throughout the period of lay. Throughout the study, daily mortality, vaccinations and the use of medication was recorded.
Statistical method	Descriptive statistics (two groups)
Results	
Outcomes-Safety observations	General health and feed intake was scored as normal on all observation days. Local reactions were not observed in control or test group. The mortality numbers were similar in both groups and comparable to normal mortality figures for this type of bird. Egg production was comparable between groups.
Adverse events	No immediate or local reactions observed.
Discussion	

Discussion/conclusions further to assessment	*The study was appropriately designed and conducted to an acceptable standard (GCP). No general or local reactions were observed, and performance of the test and control groups was highly similar and within normal ranges. The study is considered to support the safety of the vaccine when applied in layers under field conditions.*

Study 3: A field trial in the Netherlands to assess the safety and efficacy of the RT+IBm+ND+Gm+REOm+EDS vaccine in layers	
Study sites	Layer farm in the Netherlands, matched houses.
Study design	Open, positive controlled, two armed (matched flocks).
Compliance with regulatory guidelines	GCP compliant
Animals	Conventional layers, originating from the same parent flocks and of the same age, were evenly distributed to obtain identical groups. Groups were housed in different rows of the rearing house and later placed in two houses to obtain identical flocks of approximately 12,500 birds.
Test product	Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS , 0.3 ml, i.m.
Control product/ Placebo	Nobilis RT+IBmulti+G+ND 0.5 ml, i.m.
Vaccination scheme	Birds in the test group were vaccinated with the test product in the 12th week of life (right side breast muscle) while birds in the control group were vaccinated with the two control vaccines (in right and left side breast muscle). Avian Encephalomyelitis/fowl pox vaccine was applied via wing web and Nobilis ILT via ocular route as the same time as the test and control vaccines. Prior to and after the 12th week, both flocks received all standard vaccinations for the farm.
Safety end points	Daily general health and feed intake for 2 weeks post vaccination (p.v.). Local reactions scored on 15 randomly selected birds in each group on days 1, 4, 7 and 14 p.v. and weekly thereafter until resolved. Egg production was monitored for each group throughout the period of lay. Throughout the study, daily mortality, vaccinations and the use of medication was recorded.
Statistical method	Descriptive statistics (two groups)
Results	
Outcomes-Safety observations	General health and feed intake was scored as normal on all observation days. Local reactions were not observed in the test or control groups. Mortality was similar in both groups and somewhat higher than

	normal, which was attributed to feather pecking. Egg production was within normal ranges and comparable between groups.
Adverse events	Immediate or local reactions were not observed.
Discussion	
Discussion/conclusions further to assessment	*The study was appropriately designed and conducted to an acceptable standard (GCP). No general or local reactions were observed, and performance of the test and control groups was highly similar and within normal ranges. The study is considered to support the safety of the vaccine when applied in layers under field conditions.*

Study 4: A field trial in the Netherlands to assess the safety and efficacy of the RT+IBm+ND+Gm+REOm+EDS vaccine in broiler breeders primed with REOm	
Study sites	Broiler breeder farm in the Netherlands, matched houses.
Study design	Open, positive controlled, two armed (matched flocks).
Compliance with regulatory guidelines	GCP compliant
Animals	Conventional broiler breeders, originating from the same parent flocks and of the same age, were evenly distributed over the houses to obtain identical flocks of approximately 12,000 birds.
Test product	Nobilis REOm 0.3 ml, i.m. Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS, 0.3 ml, i.m.
Control product/ Placebo	Nobilis REO 1133 (0.2 ml) plus Nobilis RT+IBmulti+G+ND 0.5 ml, i.m. plus Nobilis Reo inac. 0.5 ml i.m.
Vaccination scheme	Birds in the test group were vaccinated with the test product in the 8th week of life (Nobilis Multriva REOm) and 12th week of life (Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS). Birds in the control group were vaccinated in the 8th week of life with Nobilis REO 1133 and in the 12th week with Nobilis RT+IBmulti+G+ND 0.5 ml, i.m. plus Nobilis Reo inac. Concurrent with the vaccination at 8 weeks of age, birds were vaccinated via wingweb with Tremvac. Prior to and after these vaccinations, both flocks received all standard vaccinations for the farm.
Safety end points	Daily general health and feed intake for 2 weeks post vaccination (p.v.). Local reactions scored on 15 randomly selected birds in each group on days 1, 4, 7 and 14 p.v. and weekly thereafter until resolved. Egg production and hatchability was monitored for each group throughout the period of lay. Throughout the study, daily

	mortality, vaccinations and the use of medication was recorded.
Statistical method	Descriptive statistics (two groups)
Results	
Outcomes-Safety observations	Some data could not be collected as planned due to COVID-19 restrictions (hatchability data) General health and feed intake was scored as normal on all observation days. A local reaction was observed in one bird (out of 15 tested) in the test group on day 7 (subcutaneous haemorrhage, Nobilis Multriva REOm) and in one bird on Day 15 (hard nodule in right breast 3x1 cm, Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS vaccination), the birds looked otherwise healthy. No local reactions were found one week later. Local reactions were found in one bird of the control group on Day 15 (mild subcutaneous inflammation in right breast: Nobilis RT+IB multi+G+ND vaccination). The mortality numbers were similar in both groups and comparable to normal mortality figures for this type of bird. Egg production was good and highly comparable between groups. Hatchability was tested once and was similar.
Adverse events	Local reactions were observed both in the test and control groups.
Discussion	
Discussion/conclusions further to assessment	*The study was appropriately designed and conducted to an acceptable standard (GCP). While some local reactions were observed in the test group (but also in the control group), this did not lead to any changes in the performance of the flock when compared to the positive control group.* *The study is considered to support the safety of the vaccine when applied to broiler breeders under field conditions.*

Environmental risk assessment

An environmental risk assessment has been performed in accordance with EMA Note for guidance on environmental risk assessment for immunological veterinary medicinal products (EMEA/CVMP/074/95-Final). The assessment can stop in phase one.

The product is an inactivated vaccine containing the inactivated viral poultry antigens and is adjuvanted with light liquid paraffin. Polysorbate 80, sorbitan oleate and PBS are included as excipients. The product is used in chickens and is administered intramuscularly. Therefore, direct exposure of the environment to the product does not take place. Any unused product or waste material does not pose an environmental risk. The product and waste should nevertheless be disposed by the appropriate channels and adequate advice is given in the product literature. As no live micro-organisms are present in the product, hazards and risks from the active ingredients are

considered negligible. Excretion of any of the active compounds of the product or their metabolites by vaccinated animals, if occurring at all, will only be in minute amounts and does not pose a risk to the environment. In conclusion, this veterinary medicinal product is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

The safety of a standard dose and a double dose of vaccine was tested in a GLP study. The vaccine is blended to contain a standard dose of each antigen and thus there are no minimum or maximum potency vaccine batches. From the results it can be concluded that the vaccine is safe in birds from 7 weeks of age, when applied in accordance with the SPC.

The vaccine is to be applied once during the production lifetime of the birds. No repeated dose safety studies are therefore required.

The vaccine is not intended for use during lay. As an inactivated vaccine, the product is not considered a risk to the developing reproductive system. No specific studies were performed, and this is acceptable. A warning is included in the SPC to not use the product during lay or within 3 weeks before the onset of lay.

The product is an inactivated vaccine and none of the components are considered a risk for the immune system, therefore no studies were performed. The absence of specific studies or data on immunological functions is adequately justified.

The results of four field safety and efficacy field trials indicated no safety issues. The data are considered to support the safety of the vaccine when used in field conditions. In the field trials, no differences were observed between vaccinated and control birds with respect to laying performance, supporting the notion that the product does not pose a risk to the developing reproductive system when used as recommended.

A comprehensive user safety assessment has been provided by the applicant. Mineral oil was pointed out as the major concern. The standard warning for mineral-oil containing vaccines is used, which is considered appropriate. The user safety has been adequately addressed and appropriate warnings are included in the SPC.

Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose a risk for the environment when used according to the SPC.

Residue studies are not required. The withdrawal period is set at zero days.

In conclusion, when used as recommended, the vaccine is considered to be generally safe for the target animal, the environment, the user and the consumer.

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

General requirements

Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS is to be administered to chickens intramuscularly as a single dose of 0.3 ml in the breast or thigh region from 8 weeks of age onwards, but no later than 3 weeks before the onset of lay.

The applicant applied for the following indications:

For the active immunisation of chickens for:

- reduction of egg drop caused by avian metapneumovirus.

- reduction of respiratory signs and egg drop caused by infectious bronchitis virus strains Massachusetts (GI-1 genotype), 4/91-793B (GI-13 genotype), QX – D388 (GI-19 genotype), Var2 (G1-23 genotype) and Q1 (GI-16 genotype).

- reduction of mortality and clinical signs caused by Newcastle disease virus.

- passive immunisation of the progeny of the vaccinated chickens to:

- reduce mortality and clinical signs of disease caused by very virulent (CS89), classical (STC) and antigenic variants (variant E and GLS) strains of infectious bursal disease virus
- reduce viraemia and clinical signs of disease caused by avian reovirus (genotypes 1, 2, 3, 4 and 5)

- reduction of egg drop and eggshell defects caused by egg drop syndrome ’76 virus.

The onset of immunity is 4 weeks post-vaccination, and a duration of immunity is 100 weeks of age for AMPV, IBV, NDV, IBDV, ARV and EDSV. In the progeny, the onset of immunity is 1 day of age, and a duration of immunity is 3 weeks of age for IBDV and ARV.

The vaccine was positioned for use in chickens that have received primary vaccinations with live or inactivated vaccines against infectious bronchitis virus (e.g. Nobilis IB 4-91, Nobilis IB Ma5), infectious bursal disease virus (e.g. Nobilis Gumboro D78, Innovax-ND-IBD) and avian reovirus (e.g. Nobilis Reo 1133, Nobilis Multriva REOm). This requirement is included in the SPC section 3.9. For IB, IBD and ARV therefore, data derived from studies in chickens that had received such prime-boost vaccinations were used to support onset and duration of efficacy. For AMPV, NDV and EDSV efficacy was determined in studies in non-primed birds, receiving only vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS.

Challenge model

The application of the AMPV-B 11/94 strain via the intravenous route did induce clinical signs of AMPV and the use of this challenge strain is considered sufficiently justified. There are several studies in public literature on avian and human metapneumoviruses which conclude that there is a relation between protection and antibody responses to the fusion protein (F-protein). Therefore, it can be accepted that antibody titres against F-protein are used as an indicator of immunity.

In order to demonstrate a broad protection against all genotype-I IBV strains, the following challenge strains were used: M41 (GI-1), 4/91 (GI-13), QX (GI-19), Var2 (GI-23) and Q1 (GI-16). These challenge strains cover the different viral lineages within the genotype I cluster. Vaccination challenge studies were set up in accordance with the Ph. Eur. Monographs 0959 and 5.2.7. Both the ocular and intratracheal routes of challenge were used to induce drop in egg production and eggshell defects. As IBV-specific antibodies are related to protection, serological analysis (HI assay) was performed in pre-clinical and clinical studies.

Efficacy studies for NDV were setup in accordance with Ph. Eur. 0870 and 5.2.7, using the Herts 33/56 challenge strain. As NDV-specific antibodies are related to protection, serological analysis (HI assay) was performed in vaccinated animals in both pre-clinical and clinical studies.

In order to demonstrate a broad protection against very virulent, classical and antigenic variant strains of IBDV, the following IBDV challenge strains were used: variant E challenge strain (antigenic variant), GLS challenge strain (antigenic variant), STC challenge strain (classical) and CS89 challenge strain (very virulent/hypervirulent). Efficacy studies were set up in accordance with Ph. Eur. 0960 and 5.2.7, in the progeny of vaccinated chickens. As IBDV-specific antibodies are related to protection against IBDV, serological analysis (virus neutralisation assay) was performed, in vaccinated animals as well as up to 21 days in the progeny of the vaccinated chickens, to demonstrate the efficacy of the vaccine.

In order to demonstrate a broad protection against all circulating ARV strains, the following ARV challenge strains were used to assess vaccine efficacy: GA 96139: ARV genotype 1 (ARV-1), SL11A0249-12_FR: ARV genotype 2 (ARV-2), SL10A1581-32_ES: ARV genotype 3 (ARV-3) and GA 94594: ARV genotype 5 (ARV-5). The challenge strains chosen are all different (heterologous) from the two strains in the vaccine. Efficacy studies were set up in accordance with Ph. Eur. 5.2.7 and were performed in the progeny of vaccinated chickens mostly at one day of age, when birds are most susceptible to ARV. Some of the strains (ARV-2 and ARV-5) are expected to cause clinical signs of ARV disease very soon (within 2 days) after challenge of one-day-old birds. For the other strains, the efficacy read-out parameter used was viraemia. As ARV-specific antibodies are related to protection against ARV-induced viraemia and clinical signs, serological analysis was performed in vaccinated chickens in both pre-clinical and clinical studies, as well as up to 21 days in the progeny of the vaccinated chickens, to demonstrate the efficacy of the vaccine. The serological test used to assess the antibody response is an antibody detection assay.

For EDS, vaccination challenge studies were set up in accordance with Ph. Eur. 5.2.7 and 1202 and using the EDSV M13 challenge strain. The main clinical parameter assessed was the percentage of egg drop and eggshell defects. Serological analysis (HI assay) was performed in vaccinated animals in both pre-clinical and clinical studies.

Efficacy documentation

A total of 56 studies were conducted to investigate the efficacy of the product and included 35 pre-clinical studies and 4 clinical trials that were further analysed in separately reported serological and challenge studies (17 in total). Laboratory studies were well documented and carried out in chickens of the minimum age recommended for vaccination, using pilot batches. Pilot batches were also used in the clinical trials.

Pre-clinical studies

Dose determination

Since Nobilis Multriva RT+Ibm+ND+Gm+REOm+EDS can be considered as an update of the existing range of Nobilis inactivated vaccines, the dose has been established based on prior experience.

Onset of immunity

AMPV

In one study, serological responses to IBV and AMPV after vaccination were analysed. Day-old

SPF laying hens were divided into 4 groups of 20 birds. One group was left untreated (control), one group was vaccinated at Day 0 with live AMPV vaccine (Nobilis Rhino CV) and at 15 weeks with the test vaccine (AMPV live), one group was vaccinated at Day 0 with live IB vaccines (Nobilis IB Ma5 and 4/91) and at 15 weeks with the test vaccine (IB live), and one group was vaccinated with the test vaccine at 15 weeks (Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS).

Blood samples were taken regularly from all treatment groups up to 99 weeks of age. AMPV antibody responses were analysed in a competitive ELISA using vaccine antigen. No AMPV-specific antibodies were detected after live AMPV vaccination (priming). Five weeks after vaccination with the test vaccine, AMPV antibodies were detected in vaccinates, with average titres in the live AMPV group much higher (6 $\log_2$) compared to the (non-primed) live IB and test vaccine groups (3.5 - 4 $\log_2$). In all vaccinated groups, titres persisted until 99 weeks of age with a slight decline. The control group remained negative throughout (3 $\log_2$).

The study was appropriately designed and executed to an acceptable standard. The study can be considered valid since controls remained AMPV seronegative. It can be concluded that (both with and without priming) antibodies against AMPV appeared 5 weeks after vaccination (first sampling) and persisted for up to 84 weeks after vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS.

Two challenge studies were performed, at 26 and 60 weeks of age, however the challenge was too weak, and no conclusions could be drawn. The decision not to repeat the studies and proceed with the results of study 2 only (DOI, challenge at 95 weeks of age) can be supported based on 3Rs considerations. The vaccine was shown to provide protection at 80 weeks post vaccination. Average antibody titres ≥ 3.6 $\log_2$ can be considered related to protection and serology can be used to support onset and duration of immunity. An additional serological study was performed in SPF birds vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 16 weeks of age and samples taken at 20 weeks of age. The average antibody titre at 4 weeks post vaccination was 3.2 $\log_2$ and thus lower than the minimum level associated with protection.

In conclusion, the originally claimed onset of immunity of 4 weeks for the AMPV component is not sufficiently supported by data. A protective serological response after vaccination (non-primed) was first detected at 5 weeks post vaccination and would be adequate to reduce clinical signs of AMPV. The OOI claim in the product information has been amended accordingly.

IBV

Serological responses to IBV and AMPV after vaccination were analysed in the same study described above for AMPV. Day-old SPF hens were divided into 4 groups of 20 birds. One group was left untreated (control), one group was vaccinated at Day 0 with live AMPV vaccine (Nobilis Rhino CV) and at 15 weeks with the test vaccine (AMPV live), one group was vaccinated at Day 0 with live IB vaccines (Nobilis IB Ma5 and 4/91) and at 15 weeks with the test vaccine (IB live), and one group was vaccinated with the test vaccine at 15 weeks (Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS).

Blood samples were taken regularly from all treatment groups up to 99 weeks of age. Antibodies to IBV M41 and IBV 4/91 were determined by HI test. Overall, similar serological profiles for both anti-IB M41 and anti-IB 4-91 antibodies were observed for each individual treatment group, albeit the average titres were higher for IB 4-91 antigen. From 20 weeks of age, birds in the non-vaccinated treatment group showed levels of non-specific reactivity for both anti-IB M41 antibodies and anti-IB 4-91 antibodies, typical of the age of the birds (≤ 5 $\log_2$). Priming with live Nobilis IB vaccines induced an initial IB antibody response peaking around 8 to 12 weeks of age at around 7-8 $\log_2$. Following boosting with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS the

antibody levels increased to around 11 log_2 and these levels persisted with a slight decline to at least 90 weeks of age. Non-IB primed birds showed a clear response following administration of the inactivated vaccine, but the titres achieved were lower than in the IB-primed birds (8-9 log_2). At the 99-week timepoint, titres had increased in all groups except the IB live group. This was likely an effect of IBV exposure so no conclusions can be drawn after week 90. It can be concluded that an antibody response was detectable from 5 weeks until 75 weeks post vaccination.

In another study, birds were vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 16 weeks of age. Some groups were primed, either with Innovax-ND-IBD at day of age or with Nobilis Gumboro D78 at 2 weeks of age. Serological responses to IBV M41 and IB 4-91 were determined 4 weeks after vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS. Altogether, these data support an onset of immunity of 4 weeks.

Several studies were performed to assess the protection of Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS against IBV challenge. In the first study, four groups of 40 day-old SPF birds were included. One group was left untreated (control), one group was vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 15 weeks of age, one group was vaccinated at day of age with live IB Ma5 and at 15 weeks with the test vaccine (prime-boost) and one group was vaccinated with live IB Ma5 at day of age (live IB). At 15 weeks of age each group was divided into 4 pens; egg production and quality were recorded per pen. At 26 weeks of age, birds were challenged with IBV M41 via ocular route and monitored for 4 weeks. In the controls, the maximum egg drop was 18.6% which is below the requirements for a valid test in Ph. Eur. 0959 (35%). The average post-challenge egg production in the vaccinated groups was higher by 10% (test vaccine), 12% (live IB) or 13% (prime-boost) compared to the controls. The study met the requirements of the OIE terrestrial manual for egg-drop in the controls (>15%) and the vaccinated (prime-boost) group experienced no drop in egg production, indicating complete protection. In other studies, with challenges at later stages after vaccination, a more pronounced drop in egg production was achieved in controls while again vaccinates were protected. It is agreed that in the interested of 3Rs, it is not desirable to repeat the study for protection at peak of lay.

The set-up of another study was similar to the previous one, however birds were challenged with IBV 4/91 strain. Egg drop in the controls was 5% at 2 weeks post challenge, the study was considered invalid.

Another study included 4 groups of 55 day-old SPF birds. One group was left untreated (control), one group was vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 16 weeks of age, one group was vaccinated at day of age with live IB 4/91 and at 16 weeks with the test vaccine (prime-boost) and one group was vaccinated with live IB 4/91 at day of age (live IB). At 18 weeks of age, 48 animals in each group were divided into 4 pens per group; egg production and quality were recorded per pen. At 27 weeks of age, birds were challenged with IBV 4/91 via intratracheal route and monitored for 4 weeks. The challenge did not result in a strong effect on average egg production (-13.8% in controls) and is not valid in accordance with Ph. Eur. 0959 requirements (at least 15% reduction). Moreover, it is noted that the vaccinated group with the lowest antibody response (live IB) had no drop in egg production whereas test vaccine and prime-boost groups did show a reduction in egg production that was small (5%) but statistically significant. It can be agreed that the reductions in the vaccinated groups after challenge are small and may not be biologically significant. Taken together, these data give only very limited support for the test vaccine efficacy against IB 4/91 challenge at peak of lay (11 weeks post vaccination). However, at 45 and 81 weeks post vaccination, full protection against drop in egg production due

to IBV 4/91 challenge was found in birds that were primed with live IB vaccines and boosted with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS. This is considered adequate to support efficacy against IBV 4/91.

A different study was performed where birds were primed with live IB vaccines (Nobilis IB Ma5 and Nobilis IB 4/91) at day of age and boosted with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 15 weeks. At 25 weeks post vaccination birds were challenged with IB-QX. Controls (unvaccinated birds) exhibited a clear drop in egg production which was prevented in the vaccinates. Another study had the same study design but for the challenge which was performed with IB variant2. Again, controls exhibited a clear drop in egg production which was prevented in the vaccinates. Finally, the applicant provided a new study in which birds that had received a priming and booster vaccination were challenged at 11 w.p.v. challenge with IB Q1. Full protection against egg-drop was observed in the vaccinates.

From the above data, it can be concluded that vaccination with a prime-boost scheme resulted in a reduction of coughing after challenge with IB strains. Thus, protection against respiratory signs caused by IB M41, IB 4-91, IB QX and IB Var2 can be considered adequately supported by data.

In conclusion, taking into account the positioning of the vaccine as a booster after live IB-vaccine priming, the claimed onset of immunity against IBV of 4 weeks is sufficiently supported by data. The serological response after the test vaccine vaccination (non-primed) was first detected at 4 weeks post vaccination and data supporting protection from egg drop at peak of lay is available for IBV M41, QX, Q1 and Var2 types.

NDV

In the first study, serological responses to NDV were evaluated. Seven groups of 34 to 38 day-old SPF chicks were included in the study: one group remained unvaccinated, two groups were vaccinated at day of age with Nobilis ND C2, two groups were vaccinated at day of age with Nobilis ND Clone 30, two groups were not vaccinated at Day 0. At 12 weeks of age, all vaccinated groups received Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS. Blood samples from 15 birds per group were collected at regular intervals. Antibody responses were evaluated by HI test using NDV La Sota and NDV Ulster antigens. Titres in the non-vaccinated controls remained at baseline levels throughout the study. No titres were observed in the non-primed birds prior to vaccination. Priming with live Nobilis ND vaccines induced an initial low anti-ND antibody response. Following boosting with inactivated vaccine, the antibody levels strongly increased, and these levels slowly declined by 30 weeks of age and remained stable up to 100 weeks of age. Titres after single vaccination were lower but clearly detectable from 4 weeks p.v. and decreased somewhat by 30 weeks of age to remain stable until 100 weeks of age. The study was appropriately designed and executed, and the results support an onset of immunity of 4 weeks post vaccination and a duration of immunity of 100 weeks of age (88 weeks post vaccination).

The second study was designed fully in accordance with the Ph. Eur. 0870 test for immunogenicity. Three batches of Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS were included in the test: blended at 100%, 75% and 50% of the target NDV antigen quantity. For all three vaccine batches, three dilutions ($1/30^{th}$, $1/50^{th}$ and $1/120^{th}$ dose) were tested for protection against NDV Herts 33/56 challenge. The test can be considered valid since all control birds died within 6 days of challenge. The vaccine complied with the test since the smallest dose (minimum antigen content = 100% batch) corresponded to no less than 50 PD_{50} and the lower confidence limit is no less than 35 PD_{50}. The batches blended at 75% and 50% NDV antigen also complied with the test requirement.

In the third study, a total of 105 day-old SPF birds were included, divided into 7 groups. Groups were either not vaccinated (control), vaccinated at 12 weeks of age with Nobilis Multriva

RT+IBm+ND+Gm+REOm+EDS, primed with Nobilis ND C2 and boosted with the test vaccine or primed with Nobilis ND Clone 30 and boosted with the test vaccine. All groups were challenged at 16 weeks of age with NDV Herts 33/56 and birds were monitored for 21 days for clinical signs. All control birds were euthanised within 4 days after challenge due to signs of NDV. The results support an onset of immunity of 4 weeks, with 93.3%-100% protection against clinical signs and mortality after vaccination with Nobilis Multriva RT+IBm+ND+EDS+Gm+REOm with or without priming with Nobilis ND C2 or Nobilis ND Clone 30.

In conclusion, the claimed onset of immunity (reduction of mortality and clinical signs) against NDV of 4 weeks is considered sufficiently supported by the data provided.

IBDV

Study 1 investigated the serological response to IBDV and ARV. A total of 230 day-old SPF hens and 52 roosters were included in the study. These were divided into 6 groups and treated as summarised in the table below:

Treatment group	Number of birds	Prime vaccination at 1 day old	Prime vaccination at 2 weeks of age	Prime vaccination at 7 weeks of age	Boost vaccination at 16 weeks of age
1	45 hens 5 roosters	none	none	none	none
2	45 hens 5 roosters	none	none	none	Nobilis Multriva RT+IBm+ND+Gm + REOm+EDS
3	45 hens 5 roosters	Innovax-ND-IBD	None	Nobilis Reo 1133	Nobilis Multriva RT+IBm+ND+Gm + REOm+EDS
4	45 hens 5 roosters	None	Nobilis Gumboro D78	Nobilis Multriva REOm	Nobilis Multriva RT+IBm+ND+Gm + REOm+EDS
5	25 hens 3 roosters	Innovax-ND-IBD	None	Nobilis Reo 1133	Nobilis Multriva RT+IBm+ND+GB02 + REOm+EDS
6	25 hens 3 roosters	None	Nobilis Gumboro D78	Nobilis Multriva REOm	Nobilis Multriva RT+IBm+ND+Gm + REOm+EDS (25%)

Antibodies to IBDV GB02 and 89/03 antigen were determined by virus neutralisation (VN) assay. Eggs collected from these birds were used in studies on the protection of progeny.

Antibody titres to IBDV (GB02 and 89/03) in hatch mates at day of age were below the detection limit (<5 $\log_2$) of the VN test. IBDV responses were consistently lower in group 2 (test vaccine only) compared to primed groups, but in all groups a strong response (12-16 $\log_2$) was observed at 20 weeks of age (4 weeks post vaccination with the test vaccine) and titres were maintained at this level to the last sampling point at 51 weeks post vaccination.

Study 2 evaluated the serology for IBDV and ARV in progeny from vaccinated birds. Eggs were collected at 26 weeks of age (10 w.p.v.) from the 5 groups of vaccinated birds in study 1 (refer to the table above). After hatching, blood samples to determine MDA were taken at Day 0, 8, 15, 22 and 29. All offspring had detectable levels of MDAs to IBDV GB02 and 89/03 up to 29 days of age. At day 29 the titres were clearly higher in the primed groups (6-8 $\log_2$) compared to the non-primed group (3-4 $\log_2$).

In study 3, the efficacy against IBDV CS89 challenge was determined in the offspring of vaccinated birds. The study was designed in accordance with Ph. Eur. 0960 requirements. Eggs were taken at 10 weeks post vaccination from birds in study 1 (refer to the table above, groups 2, 3 and 4); groups of

25 hatched chicks were included in the study. In addition, a group of 10 MDA-chicks was included. At 21 days, all birds were challenged with IBDV CS89 and observed (scored) daily for 4 days. At Day 4 post challenge, birds were euthanised and bursa lesions were scored. The study can be considered valid since all controls were IBDV positive. Groups 2 and 3 complied with the test, for group 5 the requirement (not more than 3 birds IBDV positive) was not met. It can be concluded that at 10 weeks post vaccination, Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS provides adequate protection to offspring against vvIBDV challenge in accordance with Ph. Eur. 0960 requirements, either with or without prior priming with Innovax-ND-IBD, with a DOI of 21 days in progeny.

Several challenge studies were performed on offspring from birds in the field trials. These birds were all primed with Nobilis Gumboro D78 and boosted with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS. Protection against Variant E, STC and GLS strains was observed in offspring up to 21 days of age, when eggs were collected up to 66 weeks post vaccination.

In conclusion, based on the data provided, protection against vvIBDV is considered supported, with an OOI of 4 weeks. The claimed OOI in offspring of vaccinated birds (1 day of age) is considered supported for vvIBDV. Together the data is considered adequate to support the claimed protection against classical, very virulent and antigenic variant strains of IBDV, after vaccination according to a prime-boost schedule.

ARV

In study 1, described above in the section on IBDV, serological responses to ARV-1 and ARV-4 were determined by ELISA. The study can be considered valid, since control birds remained seronegative throughout the study. Birds vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 16 weeks of age developed detectable antibodies to ARV-1 and ARV-4 by 4 weeks post vaccination, which remained at similar levels (7-8 $\log_2$ for ARV-1 and 6-7 $\log_2$ for ARV-4) between 30 and 67 weeks of age (51 weeks post vaccination).

In study 2, described above in the section on IBDV, serological responses to ARV-1 and ARV-4 in progeny (eggs taken at peak of lay, 10 w.p.v.) of vaccinated birds were investigated. MDAs against ARV-1 were detectable in all chicks at day 1, however there were few birds (10-20%) with non-detectable antibodies to ARV-4. At 29 days, most of the MDA levels for ARV-1 and ARV-4 had decreased below the detection limit of their respective tests. In conclusion, since antibodies are required to confer protection to progeny, the serological studies support an onset of immunity of 4 weeks post vaccination in principle.

The actual protection of progeny after vaccination of parents with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS after priming with Nobilis REO 1133 or Nobilis Multriva REOm was shown in a number of studies. Chicks hatched from eggs taken at 44 weeks post vaccination were challenged at one day of age with ARV-1, ARV-2, ARV-3 and ARV-5 and were found to be protected from viraemia and clinical signs. In a second study in progeny taken at 63 weeks post vaccination, chicks were protected at day of age from ARV-5 challenge as detected by viraemia. In a further study in progeny taken at 35 weeks post vaccination, chicks were protected at day of age from ARV-2 and ARV-5 challenge as detected by viraemia and clinical signs. In a study in progeny taken at 63 weeks post vaccination, chicks at day of age had reduced clinical signs after ARV-2 challenge. Lastly, progeny taken at 70 weeks post vaccination had significantly reduced clinical signs after ARV-1 challenge at 14 days of age. Overall, based on the studies performed, it can be concluded that vaccination with the vaccine provides passive immunization of the progeny of vaccinated chickens to reduce mortality and clinical signs of disease caused by ARV with an onset of immunity of 4 weeks in the parent and 1-day-of-age in the offspring.

EDSV

Study 1 included a total of 216 three-week-old SPF hens assigned to two equally sized groups: group 1 was vaccinated at 16 weeks of age with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS vaccine. Group 2 served as nonvaccinated controls. At 16, 20, 30, 40, 50, 60, 70, 80 and 90 weeks of age, blood samples were collected from 20 chickens from each group. Sera were analysed using an EDSV HI assay. From 21 weeks of age to 90 weeks, egg production and quality were monitored daily. Titres in the non-vaccinated birds remained below the detection level of 4 $\log_2$ throughout the study. Group 1 seroconverted to give a mean titre of 7.7 $\log_2$ four weeks post-vaccination. Mean titres declined slowly to approximately 7.0 $\log_2$ by 50 weeks of age and were then maintained at this level until the end of the study at 90 weeks of age (74 weeks post vaccination). Egg production was consistent and comparable between groups.

In study 2, two groups of 35 SPF hens were included. Group 1 was vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 16 weeks of age, group 2 remained as non-vaccinated controls. After challenge at 30 weeks of age, the reduction in egg production in group 2 was not statistically significant, nor was the difference between the groups. No conclusions could be drawn.

In study 3, two groups of 36 day-old SPF hens were included. Group 1 was vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 16 weeks of age, group 2 remained unvaccinated. At 21 weeks of age, hens were housed in 3 pens of 10 animals per group. Egg production and quality was monitored daily from 19 to 36 weeks of age. Challenge was performed at 30 weeks of age. Blood samples were taken at 16, 20, 30 and 36 weeks. Titres in controls remained below detection levels up to week 30. In vaccinates average titres of 5.4 $\log_2$ and 5.2 $\log_2$ were found at 20 and 30 weeks of age, respectively. In the control group egg production was reduced significantly compared to pre-challenge baseline. On average, egg production in the vaccinated group was 50% higher than in the non-vaccinated control group. The percentage of abnormal eggs was low in both groups before and after challenge (<0.6%). The data support the presence of protective immunity at the peak of lay, 14 weeks after vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS.

In conclusion, the claimed onset of immunity of 4 weeks post vaccination for EDSV cannot be confirmed based on challenge due to the timing of the onset of lay. However, based on the serological response observed, it can be accepted that a response to vaccination develops by 4 weeks post vaccination which is to confer protection. At 4-weeks p.v. the average antibody response was highest. The first timepoint when challenge was performed and protection was shown was at peak of lay (14 weeks post vaccination), which is acceptable.

Duration of Immunity

AMPV

In study 1, serological responses to AMPV after vaccination were analysed up to 99 weeks of age (please refer to OOI, above).

In study 2, efficacy against AMPV challenge at 95 weeks of age was evaluated. Three groups of 30 day-old SPF layers were included in the study. One group remained untreated (control), one was vaccinated with live AMPV (Nobilis Rhino CV) at day old and with the test vaccine at 15 weeks of age, and one group was vaccinated at 15 weeks of age with the test vaccine. At 92 weeks of age, each group was divided into three pens (10 animals/pen) and egg production (and quality) was monitored daily. The daily mean for the number of eggs produced per day per hen was calculated for each treatment group from 92 weeks until the end of the study. At 95 weeks of age, a challenge was performed with AMPV. There was no serological evidence of previous exposure to AMPV. Upon challenge, the control birds exhibited a significant decrease in egg production and an increase in

abnormal eggs count was observed. The challenge can be considered as valid. None of the vaccinated groups showed any sign of egg production loss or reduced egg quality after challenge. It can be concluded that vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS either with or without prior priming with Nobilis Rhino CV protects birds against egg drop caused by AMPV up to 80 weeks post vaccination.

In conclusion, a serological response after vaccination with the test vaccine (non-primed) was observed until 84 weeks post vaccination and birds were shown to be protected from challenge until 80 weeks post vaccination, the claimed DOI of 80 weeks post vaccination for AMPV is therefore supported.

IBV

Serological responses to IBV and AMPV after vaccination were analysed (see OOI above). It can be concluded that an antibody response against IBV M41 and 4/91 was detectable at least until 75 weeks after vaccination (last reliable sample).

Seven studies were performed in which birds were vaccinated against IB using a priming vaccination with IB live vaccine(s) and a booster vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS, and subsequently challenged with IBV.

In the first study two groups of 20 day-old SPF hens were included. One group remained unvaccinated (control), the other was vaccinated at day of age with live IB Ma5 and IB 4-91 vaccines and at 15 weeks of age with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS. At 57 weeks of age each group was divided over three pens and egg production and quality were monitored. Challenge with IBV M41 was performed at 60 weeks of age and birds were monitored for 4 weeks. In the control group reductions in egg production up to 60.5% were observed. In the vaccinated group there was minimal effect of challenge (6.6% reduction). The study provides support for a duration of immunity of 45 weeks post vaccination in birds primed with live IB Ma5 and IB 4-91 vaccine and vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS against virulent challenge with IBV Massachusetts M41 strain.

Study 2 was set up identically to the study described above, but with challenge at 96 weeks of age. A significant reduction in egg production was observed in the control group (up to 50%) while in the vaccinated group a smaller effect (13%) was observed at 2 weeks post challenge. The study provides support for a duration of immunity of 81 weeks post vaccination in birds primed with live IBV Ma5 and IBV 4-91 vaccine and vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS, against virulent challenge with IBV Massachusetts M41 strain.

Study 3 was set up identically to the study 1, with the exception of the challenge that was performed (at 60 weeks of age) with IBV 4-91 strain. In the control group egg production decreased (up to 24% decrease) in the first two weeks after challenge. In the vaccinated group, egg production remained at pre-challenge level. The study provides support for a duration of immunity of 45 weeks post vaccination in birds primed with live IBV Ma5 and IBV 4-91 vaccine and vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS against challenge with variant IBV 4-91 strain.

Study 4 was set up identically to the study described above 3, but with challenge at 96 weeks of age. A significant reduction in egg production was observed in the control group (up to 42%), while in the vaccinated group egg production remained at pre-challenge level. The study provides support for a duration of immunity of 81 weeks post vaccination in birds primed with live IBV Ma5 and IBV 4-91 vaccine and vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS, against challenge with variant IBV 4-91 strain.

In study 5, two groups of 30 day-old SPF hens were included. One group remained unvaccinated (control), the other was vaccinated at day of age with Nobilis IB Ma5 and Nobilis IB 4-91 vaccines and at 15 weeks of age with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS. At 33 weeks of age each group was divided over three pens and egg production and quality were monitored. Challenge with IBV QX strain was performed at 40 weeks of age and birds were monitored for 4 weeks. In the control group, reductions in egg production up to 50.6% were observed. In the vaccinated group there was some effect of challenge (9.3% reduction). The study provides support for protection against egg drop caused by IBV QX strain at 25 weeks post vaccination in birds vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS, when primed with live IBV vaccines at one day of age.

Study 6 was designed identically to study 5 described above, but for the challenge performed with Q1 strain. No effect of challenge was observed in either of the two groups and the study was considered invalid.

Study 7 was designed identically to study 5 (described above), except for the challenge strain used: IBV variant 2. Control birds exhibited significant reductions in egg production following challenge (max. 36.1%). In the vaccinated birds, mean weekly egg production was slightly reduced (< 10% of baseline). After challenge, the level of abnormal eggs was higher in the vaccinated group (8.5%) than the control group (3.9%). The effect on the egg production was re-evaluated by subtracting the abnormal eggs. The evaluation showed that the overall egg production using only well-formed eggs in the four-week period after challenge was significantly higher in the vaccinated birds compared to the non-vaccinated birds. The results are considered to support protection against egg drop caused by IBV variant 2 strain at 25 weeks post vaccination in birds vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS, when primed with live IBV vaccines at one day of age.

Finally, the applicant provided a study in which birds that had received a priming and booster vaccination were challenged at 11 w.p.v. with IB Q1. Full protection against egg-drop was observed in the vaccinates.

In conclusion, the serological response to IBV M41 and 4-91 antigens could be reliably detected until 75 weeks post vaccination (non-primed). Challenge data have been provided that support protection after a prime-boost schedule (live IBV vaccines followed by Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS). These data support efficacy against M41 and 4/91 challenge at up to 81 weeks post vaccination. Together the data are considered to support the claimed DOI for IBV of 80 weeks post vaccination.

In addition, efficacy of the prime-boost regimen against QX and Var2 challenge at 25 weeks, or against Q1 challenge at 11 weeks post vaccination was shown. Since it is accepted that antibodies are a correlate of protection for IBV, the serological OOI and DOI as determined for M41 and 4-91 strains is also valid for the variant strains that depend on cross reactivity of the antibodies generated against M41 and 4-91 antigens in the vaccine. A claim for cross-protection against QX, Var2 and Q1, separately included in the SPC, is therefore accepted.

NDV

The serological study (described above for OOI) provides support for an immune response that is maintained at a stable level until 100 weeks of age (88 weeks post vaccination).

Study 1 included a total of 126 day-old SPF chicks divided into 7 groups. Groups were either not vaccinated (control), vaccinated at 12 weeks of age with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS, primed with Nobilis ND C2 and boosted with the test vaccine or primed with Nobilis ND Clone 30 and boosted with the test vaccine. All groups were challenged at 60

weeks of age with NDV Herts 33/56, and birds were monitored for 21 days for clinical signs. Twelve out of thirteen control birds died of NDV. The vaccinated groups were significantly protected (80-100%). The results support a duration of immunity of 48 weeks, with protection against clinical signs and mortality after vaccination with Nobilis Multriva RT+IBm+ND+EDS+Gm+REOm with or without prior priming with Nobilis ND C2 or Nobilis ND Clone 30.

In study 2 and 3, the efficacy of the NDV component at 100 weeks of age was tested. A total of 126 day-old SPF chicks were divided into 6 groups. Groups were either not vaccinated (control), vaccinated at 12 weeks of age with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS, primed with Nobilis ND C2 and boosted with the test vaccine or primed with Nobilis ND Clone 30 and boosted with the test vaccine. All groups were challenged at 100 weeks of age with NDV Herts 33/56, and birds were monitored for 21 days for clinical signs. All controls died or were euthanised due to severe signs within 3 days. All vaccination regimes provided significant protection ($P<0.0001$) against NDV challenge at 100 weeks of age ranging from 80% to 93% protection from clinical signs and mortality.

In conclusion, the claimed DOI of 80 weeks post vaccination is considered sufficiently supported by data. Challenge at 88 weeks post vaccination showed significant protection, and serology indicates a stable response up to this date.

IBDV

Study 1 was set up similarly to study 3 above (section OOI, IBDV). However, eggs were collected when parents were 85 weeks old (69 weeks p.v.). All MDA- birds were found IBDV positive. None of the MDA+ chicks was IBDV positive. Based on these results, an average MDA HI titre of 6.3 $\log_2$ (IBDV GB02) and 6.2 $\log_2$ (IBDV 89/03) can be considered as a protective level. It can be concluded that Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS provides adequate protection of offspring against vvIBDV challenge either with or without prior priming with Innovax-ND-IBD or Nobilis Gumboro D78, with a duration of immunity of 85 weeks of age (69 weeks post vaccination) in the parent flock and 21 days in the progeny.

Study 2 was performed in SPF layers to evaluate the serological response to the IBDV component of Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS vaccine. The study involved a prime-boost vaccination schedule. The antibody titres for anti-IBDV GB02 and anti-IBDV 89/03 antibodies were measured up to 84 weeks post-vaccination and found to be very stable. Eggs were collected from chickens vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS alone or in combination with Innovax-ND-IBD or Nobilis Gumboro D78 when the chickens were 85 weeks of age. It was observed that all progeny derived from vaccinated chickens were 100% protected against vvIBDV (CS89) challenge at 3 weeks of age.

In conclusion, based on the data provided, in birds vaccinated according to a prime-boost schedule, a DOI of 80 weeks post vaccination against IBDV is considered supported. The claimed DOI in offspring of vaccinated birds (21 days of age) is considered supported.

ARV

In study 1, serological responses to ARV-1 and ARV-4 were determined. Birds vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 16 weeks of age developed detectable antibodies to ARV-1 and ARV-4 by 4 weeks post vaccination, which remained at similar levels between 30 and 100 weeks of age (84 weeks post vaccination).

Study 2 was performed in the progeny of birds vaccinated in study 1 (described above (section OOI, IBDV). Chicks were derived from eggs collected at 44 weeks of age from groups 1, 3 and 6 (MDA-, Nobilis Reo 1133 + test vaccine and Nobilis Multriva REOm +test vaccine at 25%, respectively), and assigned to groups of 10 chicks challenged at one day of age with ARV-1, ARV-2, ARV-3 or ARV-5.

Viraemia was tested at 3 days post challenge. In the control groups, 60, 90, 78 and 50% of birds were positive for ARV, respectively. In the vaccinated groups, all birds were protected, with the exception of one bird in the Nobilis Reo 1133+ Nobilis Multriva group challenged with ARV-5 (90% protection, non-significant difference with controls). It can be concluded that for prime-boost regimens protection of progeny at one day of age against viraemia after genotype 1, 2, 3 and 5 challenge was adequate for up to 44 weeks post vaccination.

In study 3, progeny from birds in study 1 (refer to table in section OOI, IBDV) was used to test efficacy against ARV-5 challenge. Eggs were collected at 63 weeks of age from groups 1, 2, 3 or 4 (MDA-; test vaccine; Nobilis Reo 1133+test vaccine; Nobilis Multriva REOm+test vaccine) and groups of 15 chicks were challenged at one day of age with ARV-5 virus. At day 3 post challenge, viraemia was determined in all birds. The study can be considered valid since, in the MDA- control birds, no antibodies were detected, and the level of infection was adequate (87%). A statistically significant reduction of the number of birds with viraemia after challenge was observed in all three vaccinated groups (protection 100%, 100% and 93%, respectively). A mean antibody titre of 5.9 $\log_2$ for ARV-1 and 4.7 $\log_2$ for ARV-4 was found in progeny of layer birds that were only vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS. It can be concluded that protection of progeny at one day of age against ARV genotype 5 challenge was adequate for up to 63 weeks post vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS with or without prior priming (Nobilis Reo 1133 or Nobilis Multriva REOm).

Study 4 included chicks derived from vaccinated parents (study 1, refer to table in section on OOI, IBDV). Eggs were collected at 51-52 weeks of age from birds in groups 1, 3 and 6 (MDA-, Nobilis Reo 1133 + test vaccine, Nobilis Multriva REOm + test vaccine at 25%). Per parent group, 30 chicks were assigned to each of two groups and challenged at one day of age with ARV-2 or ARV-5. Birds were observed for clinical signs twice daily until 21 days post-challenge. Efficacy evaluation was based on clinical signs until Day 21, body weight at Day 21 and macroscopic and histological examinations of the hocks. The study can be considered valid since no antibodies were detected in MDA- control birds and the level of infection in the control birds was adequate with clinical signs, reduced weight gain (ARV-2 only) and histopathological lesions in the hocks. Progeny from birds in group 3 (Nobilis Reo 1133 + test vaccine) showed a reduction of clinical signs caused by either ARV-2 or ARV-5 challenge. Progeny from birds in group 6 (Nobilis Multriva REOm + test vaccine at 25%) showed a reduction of clinical signs caused by ARV-5 challenge and had significantly lower histopathological lesion scores after ARV-5 challenge. No significant effects of vaccination were observed after ARV-2 challenge in this group. This appears to indicate that the protection induced by this vaccination schedule is lower than for the Nobilis Reo 1133 -+test vaccine combination, possibly due to the use of the 25% batch. The study provides support of efficacy, with a reduction of clinical signs due to ARV-2 and ARV-5 in progeny of birds primed with Nobilis Reo 1133 and boosted with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS with a DOI of 35 weeks post vaccination.

Study 5 was performed in progeny from parents vaccinated in study 1 (refer to table in section on OOI, IBV). Eggs were collected when parents were 62-62 weeks of age from groups 1 and 4. The parents were either non-vaccinated (offspring group A and C) or primed at 2 weeks of age with Nobilis Gumboro D78 and at 7 weeks of age with Nobilis Multriva REOm and vaccinated at 16 weeks of age with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS (offspring group B). Group A and B were challenged with ARV serotype 2, group C was mock-challenged. After challenge until the end of the study at 21 days post-challenge, birds were observed for clinical signs twice daily. Efficacy evaluation was based on weights, clinical signs (mortality and leg malfunction) and necropsy findings. Combined leg malfunctioning ARV scores were significantly lower in offspring from ARV vaccinated birds when compared to non-vaccinated birds: 73.3 % vs. 30%. The maximum clinical score observed was significantly lower in group B compared to group A. No difference in macroscopical necropsy scores of

histology scores was observed. No difference in survival was observed since few birds reached the humane endpoint. It can be concluded that protection of progeny at day of age against clinical signs induced by serotype 2 challenge was adequate for up to 63 weeks post vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS with prior priming with Nobilis Multriva REOm.

Study 6 was performed in progeny from parents vaccinated in study 1 (refer to table in section on OOI, IBDV). Eggs were collected when parents were 86-88 weeks of age from groups 1, 3 and 4 (MDA-; Reo 1133+test vaccine; REOm+test vaccine). Chicks (30 per group) were challenged with ARV-1 in the footpad at 14 days of age. An additional MDA- group was mock-challenged. Birds were weighed and footpad and tendon measurements were collected at the time of challenge. Footpads were scored at 5 days post-challenge. At 19 and 28 days of age, body weights and footpad/tendon measurements were conducted. The tendon or footpad to body weight ratios were calculated. At the end of the study, birds underwent post-mortem examination to evaluate macroscopical lesions on the legs, hock-joint, tendons and footpads. In addition, samples were collected for histology. None of the MDA- birds showed detectable ARV antibodies. All of the MDA- challenged birds had swollen or reddened footpads at day 5 post challenge; the score was significantly higher compared to the mock-challenged group. Vaccinated birds were significantly protected against ARV-1-induced footpad swelling/discoloration when compared to MDA- birds. The tendon/body weight ratio was lower in the REOm+test vaccine group compared to the MDA- group A, showing protection against tendon thickening. ARV-1 challenge did not lead to significant differences in macroscopic observations at necropsy compared to the mock-treated group. Thus, progeny from eggs collected at 70 weeks p.v. from birds primed with Nobilis Reo 1133 or Nobilis Multriva REOm and vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS showed a significant reduction of footpad swelling (and tendon swelling) caused by ARV-1 challenge at 14 days of age.

In study 7, offspring from birds in study 1 (primed with Nobilis REO 1133 or Nobilis Multriva REOm and boosted with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS) hatched from eggs taken at 76-78 w.p.v. was challenged with ARV-1 at 21 days of age. These chicks were found protected from footpad swelling.

In conclusion, birds vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 16 weeks of age developed detectable antibodies to ARV-1 and ARV-4 by 4 weeks post vaccination, which remained stable until 84 weeks post vaccination. Progeny from vaccinated birds were shown to be MDA+ until 21 days of age, which is considered adequate to support the claimed DOI in progeny. Protection against ARV challenge was investigated in the progeny of vaccinated birds at one day of age since this is the time of the highest susceptibility of the chicks, which is acceptable. The use of viraemia as a read-out in most of these studies is considered acceptable, considering the rather complicated nature of the clinical disease. Protection of progeny after vaccination of parents with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS after priming with Nobilis REO 1133 or Nobilis Multriva REOm was shown in a number of studies. Birds were challenged at one day of age with ARV-1, ARV-2, ARV-3 and ARV-5 and were found to be protected from viraemia and clinical signs.

EDSV

As observed in study 1 (refer to section on OOI for EDSV), a stable serological response to EDSV is observed until 74 weeks post vaccination.

In study 2, two groups of 30 16-week old SPF hens were included: one group was vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS vaccine and the other was not vaccinated. At the age of 53 weeks, hens were divided into 3 pens per group. Just before challenge, at 60 weeks of age, blood samples were collected. All hens were challenged with the EDSV M13 strain. Egg production and quality was monitored from 21 until 64 weeks of age. In the control group, egg production fell

consistently and significantly following challenge. On average, egg production in the vaccinated group was 45% higher compared to the control group and this difference was statistically significant. After challenge, the fraction of abnormal eggs in the control group was 6.8 times as high as in the vaccinated group and this difference was statistically significant. The study supports a duration of immunity of 44 weeks for protection against egg drop due to EDSV.

Study 3 was designed identically to study 2 described above, but for the timing of the challenge at 98 weeks of age. Vaccinated animals had an average of 6.8 $\log_2$ EDSV HI titre before challenge. After challenge, the egg production of the vaccinated group was not negatively affected. For the non-vaccinated treatment group, egg production went down following challenge and recovered towards the end of the observation period. On average, post-challenge egg production in the vaccinated group was 54% higher compared to the non-vaccinated control group and this difference was statistically significant. The percentage of abnormal eggs increased both in the vaccinated group and in the non-vaccinated group, no significant differences were observed between groups. The study supports a duration of immunity of 82 weeks post vaccination for protection against egg drop due to EDSV. It is noted that protection was not complete, since an increase in abnormal eggs was seen in the vaccinated group after challenge. This is however considered compatible with the claimed reduction in egg drop and eggshell defects.

In conclusion, the claimed DOI of 80 weeks post vaccination for EDSV is supported by the results of challenge at 82 weeks post vaccination and by serology up to 74 weeks post vaccination.

Maternally derived antibodies (MDA)

No studies were performed. This is accepted since at the age of vaccination MDAs are no longer relevant.

Interactions

The applicant has not provided data investigating interactions of the vaccine with any other veterinary medicinal product and therefore proposes to include a statement in Section 3.8 of the SPC that 'No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. 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.

Clinical trials

Four clinical trials were performed in the Netherlands. In these experiments, the safety and efficacy of Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS was evaluated under clinical conditions. The general set-up of the studies is described in the dossier. In these four studies blood samples were collected and serological data were generated in six studies. In order to substantiate efficacy claims, 12 challenge experiments were performed in the laboratory with animals vaccinated in the field. The set-up of these studies and the results are discussed below for each virus.

AMPV

In study 1, serology was performed on samples taken during one field study. Commercial layers in the two groups were vaccinated with various vaccines as per the farm vaccination scheme.

Blood samples were collected from at least 20 birds per flock at 12, 16, 18 and 22 weeks of age

and then every 10 weeks until the end of the production period (approximately 86 weeks of age). Approximately 100 hens from the test flock were kept until 102 weeks of age and additional bleeds were taken from 20 birds at 92 and 102 weeks of age. Antibodies were detected against TRT (turkey rhinotracheitis). The test is considered valid since at 12 weeks of age (time of vaccination) all birds were seronegative for AMPV. The antibody profiles were similar for control and test groups.

In study 2 serology was performed on samples taken during another field study. Commercial layers in the two groups were vaccinated with various vaccines as per the farm vaccination scheme.

Blood samples were collected from 20 birds per flock at 12, 16, 18 and 22 weeks of age and then every 10 weeks until 92 weeks and at 100 weeks of age. Antibodies were detected against TRT. The test is considered valid since at 12 weeks of age (time of vaccination) all birds were seronegative for AMPV. It can be concluded that in the test flock antibodies were detected up to the end of the study whereas the control flock remained seronegative.

In study 3 serology was performed on samples taken during a third field study. Breeders in the two groups were vaccinated with various vaccines as per the farm vaccination scheme.

At 14, 19, 21, 25, 35, 45, 56, and 60 weeks of age blood samples were taken from 20 randomly selected hens in each group. Before the study, birds went to slaughter in week 60, approximately 100 birds from each flock were transferred to a research center and were kept until they were approximately 84 weeks of age. Blood sampling from 20 selected tagged hens per flock was carried out at approximately 5-week intervals. TRT antibodies were detected. Test and control birds were both primed with Nobilis Rhino CV at 5 weeks of age. This did not result in significant serological responses. After booster with either of the inactivated combination vaccines, responses to AMPV were similar in both groups and detectable up to 84 weeks of age. The data are however indicative of a field challenge between weeks 25 and 35 (and possibly between weeks 56 and 62). There was however no clinical signs of AMPV recorded nor was the performance of the birds affected in this study which is indicative of vaccine protection against AMPV. Little can be concluded on the OOI or DOI based on these data.

In study 4 serology was performed on samples taken during the fourth field study. Breeders in the two groups were vaccinated with various vaccines as per the farm vaccination scheme.

Test and control birds were both primed with Nobilis Rhino CV at 5 weeks of age. This did not result in significant serological responses. After booster with either of the inactivated combination vaccines, responses to AMPV were similar in both groups and detectable up to 55 weeks of age. The data are however indicative of a field challenge between weeks 35 and 55. Little can be concluded on the OOI or DOI.

Study 5 was performed using layers from the second field study, 30 from each group. At 94 weeks of age (82 weeks post vaccination) birds were challenged with AMPV and monitored for clinical signs. Average $\log_2$ anti-AMPV titres before and after challenge were 3.49 and 3.88 in the test group and 3.0 and 3.32 in the control group. Following challenge, egg production was stable at >80%, with no obvious differences between the test vaccinated and control groups. Further, no clinical signs of AMPV infection were observed and no virus was detected at any time point from any of the tracheal swabs from either experimental group. The study was considered invalid.

In conclusion, serology indicates a similar antibody response is achieved after vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS compared to licensed inactivated Nobilis vaccines containing a TRT component when applied in commercial vaccination schemes in layers or

breeders.

IBV

The set-up of studies 1-4 is described above for AMPV. IBV M41 and IBV 4/91 titres were also determined in these studies. Antibody profiles for test and control layer flocks were similar for both IBV antigens.

In conclusion, the antibody responses to IBV M41 and IBV 4/91 antigens were very similar after vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS compared to licensed inactivated Nobilis vaccines containing an IBV component when applied in commercial vaccination schemes in layers or breeders. It is noted that birds of test and control flocks were primed with various combinations of live IBV vaccines, in accordance with the proposed use of Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS as a booster vaccination.

NDV

The set-up of studies 1-4 is described above for AMPV. NDV La Sota and Ulster HI titres were also determined in these studies. Test and control birds were vaccinated with Innovax-ND-IBD and Nobilis ND C2 prior to the test vaccine or control vaccine. Antibody profiles for test and control layer flocks were similar for both NDV antigens.

In study 5, two groups of 15 test or control vaccinated layers from field study 1and 15 non-vaccinated SPF birds were included. Challenge was performed with NDV Herts 33/56 at 30 weeks of age. All SPF birds were affected with NDV and euthanised within 4 days. None of the vaccinated birds showed any symptoms of NDV. Vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS vaccine within the commercial vaccination scheme used, including prior vaccination with Innovax ND IBD and Nobilis ND C2, provided full protection against NDV challenge at 18 weeks post vaccination.

Study 6 was performed using fifteen 65-week-old commercial broiler breeders taken from field study 4. The hens had been vaccinated with Nobilis ND C2 at 2 weeks of age, Nobilis ND Clone 30 at 8 weeks of age and Nobilis Multriva RT+IBm+ND+EDS+Gm+REOm at 15 weeks of age. An additional group of 15 100-week-old SPF birds was used as unvaccinated controls. Challenge was performed at 65 weeks of age with NDV Herts 33/56, and birds were monitored for clinical signs for 21 days thereafter. All SPF birds were affected by NDV and euthanised within 4 days. None of the vaccinated birds showed any NDV-related symptoms during the observation period. Vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS vaccine within the commercial vaccination scheme used, including prior vaccination with Nobilis ND C2 and Nobilis ND Clone 30, provided full protection in breeders against NDV challenge at 50 weeks post vaccination.

Study 7 was set up as follows: fifteen 76-week-old commercial layers were taken from field study 2. The hens had been vaccinated with Innovax-ND-IBD at one day of age, Avinew NEO at 3 weeks of age, Nobilis ND Clone 30 at 7 weeks of age and Nobilis Multriva RT+IBm+ND+EDS+Gm+REOm at 12 weeks of age. An additional group of fifteen 60-week-old SPF birds was used as unvaccinated controls. Challenge was performed at 76 weeks of age with NDV Herts 33/56, and birds were monitored for clinical signs for 21 days thereafter. Twelve out of thirteen control birds were affected by the challenge and euthanised within 4 days (92%). One bird in this group was alive and healthy at day 3 post challenge and had to be euthanised on welfare ground and was scored as 'protected'. In the vaccinated group, one bird showed ND-related signs on day 13 post challenge and was euthanised, resulting in 93% protection. Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS vaccine and applied within the commercial vaccination scheme used, including prior vaccination with live NDV vaccines, provided full protection in layers

against NDV challenge at 50 weeks post vaccination.

In conclusion, the onset, duration and magnitude of the anti-NDV antibody response in the field trials cannot be attributed to vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS alone. A booster-effect was observed in the antibody titres from 4 weeks post vaccination with the test vaccine. Titres achieved were relatively stable up to 102 weeks of age and similar in flocks vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS or existing inactivated viral vaccines from the Nobilis range. Challenge studies show that birds vaccinated according to a commercial vaccination schedule, including various priming vaccinations for NDV and booster with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS, were significantly protected from velogenic NDV challenge until 76 weeks of age (64 weeks post vaccination).

IBDV

The set-up of study 1 is described above. AMPV, IBDV GB02 and IBDV 89/03 titres were also determined in this study. Test and control flocks were vaccinated at one day of age with Innovax ND-IBD. The controls received no booster vaccination with IBDV antigen. Average antibody titres for the test flock increased after booster with the test vaccine, for both IBDV antigens, compared to the control flock, and remained high up to 102 weeks of age.

The set-up of study 2 is described above. AMPV, IBDV GB02 and IBDV 89/03 titres were also determined in this study. Test and control flocks were vaccinated at one day of age with Innovax ND-IBD. The controls received no booster vaccination with IBDV antigen. Average antibody titres for the test flock increased after booster with the test vaccine, for both IBDV antigens, compared to the control flock, and remained high up to 100 weeks of age.

The set-up of study 3 is described above. AMPV, IBDV GB02 and IBDV 89/03 were also determined in this study. Test and control flocks were vaccinated at 27 days of age with Nobilis Gumboro D78. The controls received a booster vaccination with an inactivated vaccine containing IBDV antigen. Antibody profiles for test and control breeder flocks were similar for both IBDV antigens.

The set-up of study 4 is described above. AMPV, IBDV GB02 and IBDV 89/03 were also determined in this study. Test and control flocks were vaccinated at 27 days of age with Nobilis Gumboro D78. The controls received a booster vaccination with an inactivated vaccine containing IBDV antigen. Antibody profiles for test and control breeder flocks were similar for both IBDV antigens.

In study 5, IBDV and ARV MDA levels in progeny of broiler breeders were determined. The parents were vaccinated in field study 3 with priming live vaccines against ARV and IBDV and with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS vaccine or Nobilis RT+IBm+G+ND & Nobilis Reo inac vaccines (refer to study 3 in the AMPV section for the full vaccination schedule). When the vaccinated parent birds were 44.5 weeks of age, eggs were collected, and birds were hatched for evaluation of MDA levels. From both groups, 30 progeny were placed in isolators and blood samples were taken on Days 1, 7, 14, 21 and 28. Samples were analysed for ARV-1, ARV-4, REO, IBDV, IBDV 89/02 and IBDV GB02. MDA antibody titres to IBDV were substantial up to 14 days of age in both groups and declined gradually thereafter.

Study 6 included 135 one-day-old progeny from broiler breeders that were vaccinated in the field (study 3) with Nobilis Gumboro D78 at 27 days of age and with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 14 weeks of age. These chicks were hatched from eggs taken at 53 weeks of age. Control groups consisting of MDA- SPF layer chicks were also included. Birds were allocated to 8 challenge groups, 4 non-challenged pathology control groups and 4 serology groups.

Challenge was performed at 7 or 14 days of age, with IBDV variant E or IBDV CS89 via ocular route. At all three time points tested, the mean VN titres for both IBDV GB02 and IBDV 89/03 in the MDA- birds were below the detection limit of the assay. In MDA+ birds, anti-IBDV titres showed a steady reduction over time, with mean anti-IBDV GB02 VN titres of 9.4 $\log_2$ and 6.1 $\log_2$ and mean anti-IBDV 89/03 VN titres of 9.8 $\log_2$ and 6.3 $\log_2$ at 7 and 14 days of age, respectively. Controls were all IBDV positive after VarE or CS89 challenge. Vaccinated birds were 100% and 91.3% protected from VarE challenge and 96% and 100% protected from CS89 challenge at 7 and 14 days of age, respectively. The study was appropriately designed except for the timing of the challenges (at one and two weeks of age), which is not in accordance with Ph. Eur. 0960 (3 weeks of age). Adequate protection against both variant E and CS89 strains was observed when chicks were challenged at 14 days of age. This indicates a duration of immunity of 40 weeks post vaccination after priming with Nobilis Gumboro D78 and vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS in commercial breeders.

Study 7 included 80 one-day-old progeny from broiler breeders vaccinated in the field (study 3) with Nobilis Gumboro D78 at 27 days of age and with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 14 weeks of age. These chicks were hatched from eggs taken at 68 weeks of age. Control groups consisting of MDA- SPF layer chicks were also included. Birds were allocated to 6 challenge groups, 2 non-challenged pathology control groups and 4 serology groups. Challenge was performed at 21 days of age, with IBDV variant E or IBDV CS89 via ocular route. The VN titres in the MDA- animals were below the detection limit of both assays at all four time points. In MDA+ birds anti-IBDV titres showed a steady decline over time, with mean anti-IBDV GB02 VN titres gradually falling from a titre of 9.7 $\log_2$ at 1 day of age to 4.0 $\log_2$ at the time of challenge and the mean anti-IBDV 89/03 titres falling from 9.6 $\log_2$ at 1 day of age to 4.5 $\log_2$ at 21 days of age, with 3/10 birds having titres at or below the detection limit of the assay. All controls were IBDV positive, in the vaccinates 62.5% was protected from VarE and 100% from CS89 challenge. The study was appropriately designed, fully in accordance with Ph. Eur. 0960 requirements. Adequate protection against both variant E and CS89 strains was observed. This indicates a duration of immunity of 54 weeks post vaccination after priming with Nobilis Gumboro D78 before vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS.

Study 8 was performed using progeny of broiler breeders vaccinated in the field (study 3) with Nobilis Gumboro D78 at 27 days of age and with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 14 weeks of age. These chicks were hatched from eggs taken at 80 weeks of age. Control groups consisting of MDA- SPF layer chicks were also included. Birds were allocated to 4 challenge groups, 2 non-challenged pathology control groups and 4 serology groups. Challenge was performed at 21 days of age, with IBDV GLS strain or IBDV STC strain. At the time of challenge (21 days of age) the mean IBDV GB02 and IBDV 89/03 VN titres were 4.2 $\log_2$ and 5.4 $\log_2$, respectively for the MDA+ test group, whilst antibody levels were below the detection limit in the MDA- control group. All control birds were IBDV positive. Vaccinated birds were 8% protected from IBDV GLS challenge and 91.7% protected from IBDV STC challenge. The study was designed fully in accordance with Ph. Eur. 0960 requirements. Adequate protection against STC, but not GLS, strain was observed. This indicates a duration of immunity of 66 weeks post vaccination after priming with Nobilis Gumboro D78 before vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS.

Study 9 included progeny from broiler breeders vaccinated in the field (study 4) with Nobilis Gumboro D78 at 27 days of age and with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 15 weeks of age (test group) or with Nobilis Gumboro D78 at 27 days of age and with Nobilis RT+IBmulti+G+ND and Nobilis REO inac at 15 weeks of age (control group). Offspring were hatched from eggs taken at 71 weeks of age. A challenge control group consisting of MDA- SPF layer chicks was included. Birds were allocated to 3 challenge groups and 4 serology groups. Challenge was performed at 14 days of age,

with IBDV GLS strain via ocular route. In general, similar levels of anti-IBDV GB02 VN antibody were seen in the offspring of both vaccinated parent groups. The levels of anti-IBDV 89/03 VN antibodies tended to be slightly higher in the offspring of the test vaccine-vaccinated parents. At the time of challenge test vs control antibody levels were for anti-IBDV GB02: 7.3 log_2, vs 6.8 log_2; anti-IBDV 89/03: 5.4 log_2, vs 4.6 log_2. MDA- birds were seronegative at the time of challenge. All non-vaccinated control birds were IBDV positive. Test birds were 90% protected, control birds 100%. The study was appropriately designed, largely in accordance with Ph. Eur. 0960 requirements, except for the timing of the challenges. Adequate protection against IBDV GLS strain was observed when chicks were challenged at 14 days of age. This level of protection was achieved at 56 weeks post vaccination after priming with Nobilis Gumboro D78 before vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS.

Study 10 included progeny from broiler breeders vaccinated in the field (study 4) with Nobilis Gumboro D78 at 27 days of age and with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 15 weeks of age. Offspring were hatched from eggs taken at 63 weeks of age. A challenge control group consisting of MDA- SPF layer chicks was included. Challenge was performed at 21 days of age, with IBDV GLS strain via ocular route. In MDA- animals, VN neutralisation levels were below detection levels. In the MDA+ group, a mean VN titre of 5.4 log_2 IBDV GB02 was found, whereas 6/10 birds were seronegative for IBDV 89/03 VN with a mean titre of 2.2. log_2. All MDA- birds were IBDV positive. The test group was 42% protected; this was statistically significant. The study was appropriately designed, fully in accordance with Ph. Eur. 0960 requirements. Protection against GLS strain was observed at 48 weeks post vaccination after priming with Nobilis Gumboro D78 before vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS.

In conclusion, high antibody titres to IBDV GB02 and IBDV 89/03 were found up to 102 weeks of age in layers and breeders vaccinated in the frame of a commercial vaccination programme, including Innovax ND-IBD or Gumboro D78 priming. Protection was observed in progeny of such (primed) birds, against variant E and CS89 strains at 54 weeks post vaccination, against STC strain at 66 weeks post vaccination and against GLS strain at up to 56 weeks post vaccination. Since no clear decrease of antibody titres was observed in the serological studies, these prime-boost regimes are considered to provide protection of progeny against IBDV for the claimed 80 weeks post vaccination.

ARV

Study 1: birds in the field study 1 were treated as summarised above for AMPV. Serological evaluation was performed to detect ARV-1 and ARV-4. Birds were not primed with ARV antigen. In the test group (very) low titres specific for ARV-4 were observed. ARV-1 specific titres were medium already before vaccination, which is indicative of a field infection. After vaccination, ARV-1 titres increased to high in the vaccinated birds: a booster effect appears to have occurred. No conclusion can be drawn on ARV-1 titres in birds vaccinated with the test vaccine without priming vaccination. The results indicate very little effect of vaccination with the test vaccine alone on ARV-4 titres.

Study 2: birds in the field study 2 were treated as summarised above for AMPV. Serological evaluation was performed to detect ARV-1 and ARV-4. Birds were not primed with ARV antigen. In the test group, titres specific for ARV-4 increased after vaccination and remained at medium levels until 100 weeks. ARV-1 specific titres were medium already before vaccination, which is indicative of a field infection. After vaccination, ARV-1 titres increased to high in the vaccinated birds: a booster effect appears to have occurred. No conclusion can be drawn on ARV-1 titres in birds vaccinated with the test vaccine without priming vaccination. The results indicate some effect of vaccination with the test vaccine alone on ARV-4 titres.

Study 3: birds in the field study 3 were treated as summarised above for AMPV. As part of the routine vaccination schedule for the farm, all birds had been primed against ARV using Nobilis Reo 1133 (genotype ARV-1-like) at 8 weeks of age. Serological evaluation was performed to detect ARV-1 and ARV-4. In the test group, low titres specific for ARV-4 were initially observed after priming, which increased after vaccination with the test vaccine to medium-high and remained until 84 weeks of age. However, ARV-4 titres increased steeply between 56 and 62 weeks of age, which is suggestive of a field challenge and may well have helped maintain titres against ARV-4. ARV-1 specific titres were medium after priming and increased to high after vaccination with the test vaccine. The ARV-1-specific titres remained high for up to 84 weeks, however also here a (small) increase in titre was observed between weeks 56 and 62, suggestive of a field challenge.

Study 4: birds in the field study 4 were treated as summarised above for AMPV. Birds in the test group had been primed against ARV using Nobilis Multriva REOm, while the control flock had been primed with Nobilis Reo 1133 (genotype ARV-1-like) at 8 weeks of age. Serological evaluation was performed to detect ARV-1 and ARV-4. In the test group low titres specific for ARV-4 were initially observed; after priming the titre increased to medium high and after vaccination with the test vaccine these remained at medium high to medium levels until 100 weeks. ARV-1-specific titres were medium after priming and increased to high after vaccination with the test vaccine. The ARV-1-specific titres gradually decreased to medium levels at 100 weeks of age. Data are supportive of a DOI of 100 weeks of age, after priming with Nobilis Multriva REOm.

In study 5 the levels of maternal derived antibodies (MDA) in the progeny of vaccinated broiler breeders from field study 3 were studied. The broiler breeders were vaccinated with live prime vaccines against Reo and Gumboro and with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS vaccine or Nobilis RT+IBm+G+ND and Nobilis Reo inac vaccines at 15 weeks of age. When the vaccinated parent birds were 44.5 week of age, eggs were collected, and birds were hatched for evaluation of MDA levels. After hatching the progeny had substantial antibody titers for ARV1 and ARV4. These titres remained high until 7 days of age (doa) and decreased gradually over time; the detection limit was reached at 28 doa.

In study 6 progeny from broiler breeders in the test group in field study 3 was taken at 53 weeks of age to determine levels of MDA (for set-up refer section on IBDV above). The test group had been vaccinated with Nobilis Reo 1133 at 8 weeks and Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 14 weeks of age. The day-1 titre for ARV-1 was 5.6, decreasing to 2.2 Log2 at 14 doa, and for ARV-4 this was 2.3 and 1.7 Log2 at 1 and 14 doa, respectively.

In study 7 progeny from broiler breeders in the test group in field study 3 was taken at 68 weeks of age to determine levels of MDA (for set-up refer section on IBDV above). The test group had been vaccinated with Nobilis Reo 1133 at 8 weeks and Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 14 weeks of age. Moderate levels of anti-ARV antibodies were seen in day-old birds which showed a steady reduction over time, with mean anti ARV-1 titres decreased to 1.43 Log2 at 21 days-of-age and mean anti ARV-4 ELISA titres falling below the detection limit at 21 days-of-age.

Study 8: progeny from broiler breeders vaccinated in the field (study 3) with Nobilis Reo 1133 at 8 weeks of age and with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 14 weeks of age were hatched from eggs taken at 80 weeks of age (n=80). Blood samples were taken at 1, 7, 15 and 21 days of age and analysed for ARV-1 and ARV-4 antibodies. Anti-ARV titres showed a steady reduction over time, with mean anti ARV-1 titres decreased from 4.3 (day 1) to 1.6 log2 at 21 days-of-age and mean anti ARV-4 ELISA titres falling from 2.9 (day 1) to 1,0 log2 at 21 days-of-

age (titers at day 14 and 21 were below the detection limit of the assay).

Study 9: progeny from broiler breeders vaccinated in the field (study 4) with Nobilis Multriva REOm at 8 weeks of age and with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 15 weeks of age (test group) or with Nobilis Reo 1133 at 8 weeks of age and with Nobilis RT+IBmulti+G+ND and Nobilis REO inac at 15 weeks of age (control group) were hatched from eggs taken at 71 weeks of age. Blood samples were taken at 1, 7 and 14 days of age and analysed for ARV-1 and ARV-4 antibodies to determine MDAs. Antibody titres to ARV-1 were of similar, moderate levels at day-of-age, in progeny of control or test birds, gradually declining to non-detectable levels at 21 days of age. Anti-ARV-4 titres were only detected in progeny from test birds, falling below detection level between day 14 and 21.

In study 10, progeny from broiler breeders in field study 4 was challenged with ARV strains. The test group was vaccinated with Nobilis Multriva REOm vaccine at 8 weeks of age followed by a booster vaccination at 14 weeks of age with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS vaccine. The control group was vaccinated with live Nobilis Reo 1133 at 8 weeks of age followed by booster vaccination at 14 weeks of age with Nobilis Reo inac. Eggs were collected when birds were 44 weeks of age, MDA- control groups consisted of day-old SPF chicks. Challenge was performed at day of age with ARV-1, ARV-2, ARV-3 or ARV-5 challenge strain (i.m.). After challenge birds were scored for clinical signs twice daily. Blood was collected from hatch mates at t=0 and at t=3 all birds were euthanised and blood was collected to screen for ARV viraemia. The MDA+ test group showed mean antibody titers for ARV-1 of 5.7 $\log_2$ and ARV-4 of 3.2 $\log_2$. The MDA+ control group showed an antibody titre for ARV-1 of 4.9 $\log_2$ but no ARV-4 titre was observed. After challenge with 4 different ARV genotype (ARV-1, -2, -3 and -5) strains there was no viraemia detected in any of the progeny of both vaccinated MDA+ broiler groups. On the other hand, the majority of progeny of the MDA- control group (70-100%) were tested positive for the presence of viraemia. It is noted that it is unclear whether broilers and (SPF) layers have the same susceptibility to viraemia, MDA- broilers were not available. Based on the data, protection against clinical signs and viraemia after ARV-1, -2, -3 and -5 challenge can be expected in the progeny of vaccinated birds at day-of-age.

In study 11 progeny from broiler breeders included in field trial 3 was challenged with ARV strains. The test group was vaccinated with Nobilis Multriva REOm vaccine at 8 weeks of age followed by a booster vaccination at 15 weeks of age with inactivated Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS vaccine. Eggs were collected when birds were 61 weeks of age, MDA- control groups consisted of day-old SPF chicks. Challenge was performed at day of age with ARV-1 or ARV-2 challenge strain (i.m.) or mock-challenge with PBS was given. After challenge birds were scored for clinical signs for 21 days. Cloacal swabs were taken daily from day 1 to 6 and on day 10, to determine shedding. Blood was collected from hatch mates at t=0 and at t=3 blood was collected in the viraemia groups to screen for ARV viraemia. Macroscopic and histopathological changes in hock joints were evaluation at necropsy (21 days p.c.), bodyweight was recorded on day 1 and 21. Shedding in MDA+ was significantly lower at day 1 and 2 after ARV-1 challenge and on days 3 to 5 after ARV-2 challenge. It is possible that this could be due to different infection dynamics in broilers versus layers rather than an effect of MDA. After ARV-2 challenge, clinical signs occurred in both MDA+ and MDA- birds, these were significantly higher compared to non-challenged birds. The results of the study appear to support the notion that broilers are more susceptible to clinicals signs of ARV (except effects on growth) compared to layer type birds. The absence of an MDA- broiler group makes it difficult to draw (any) conclusions from the study.

In conclusion, efficacy against challenge with ARV-1, 2, 3 and 5 strains was shown in progeny from birds at 30 weeks post vaccination. A reduction of clinical signs (ARV-2 and ARV-3) and

viraemia was achieved.

EDSV

The set-up of study 1 including the vaccination schedule for field study 1 is described above for AMPV. Evaluation of EDSV titres was performed. Antibody titres for test and control flocks were similar. An average titre of 6.7 log_2 at 4 w.p.v. and 3.6 log_2 at 90 w.p.v. was detected in the test flock.

The set-up of study 2 including the vaccination schedule for field study 2 is described above for AMPV. Evaluation of EDSV titres was performed. The non-vaccinated control flock remained seronegative. An average titre of 7.0 log_2 at 4 w.p.v. and 5.4 log_2 at 88 w.p.v. was detected in the test flock.

The set-up of study 3 including the vaccination schedule for field study 3 is described above for AMPV. Evaluation of EDSV titres was performed. The non-vaccinated control flock remained seronegative. An average titre of 3.9 log_2 at 5 w.p.v. and 3.4 log_2 at 70 w.p.v. was detected in the test flock.

The set-up of study 4 including the vaccination schedule for field study 4 is described above for AMPV. Evaluation of EDSV titres was performed. Antibody titres in the control group remained close to the detection limit throughout the study. In the test group a response to vaccination is observed, albeit low. Antibodies remained detectable until 40 weeks post vaccination.

In study 5 commercial layer hens from field trial 1, vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at the age of 12 weeks were included when they were 69 weeks of age (n=30). Unvaccinated commercial layer hens were also obtained from the field (16 week of age) as non-vaccinated challenge controls (n=30). Birds were housed in 3 pens of 10 animals per group. Egg production and egg quality was monitored. All birds were challenged with the EDS M13 strain; the vaccinated group was 74 weeks of age and the control group 21 weeks of age. The study is considered valid since a clear effect on egg production and quality was observed in non-vaccinated birds after challenge. The use of younger birds as control group is considered justified, this can be viewed as a worst-case scenario since these birds have a higher laying percentage compared to birds at 74 weeks of age. The laying percentage after challenge was significantly higher in the vaccinated birds. The results support efficacy of the vaccine in commercial layer birds, with a duration of immunity of 62 weeks after vaccination.

Overall conclusion on efficacy

AMPV

The proposed indication for AMPV is reduction of egg drop caused by avian metapneumovirus. The claimed onset of immunity is 4 weeks post vaccination and the duration of immunity 80 weeks post-vaccination. In total, four studies were performed to determine onset and duration of immunity against AMPV. After vaccination, antibodies to AMPV were detected from 5 weeks after vaccination (first sample) and persisted at consistent level for up to 84 weeks after vaccination. The AMPV titres after vaccination with Nobilis Multriva were notably higher in birds primed with Nobilis Rhino CV, compared to titres in non-primed birds. The conclusion for the first two experiments in which birds were challenged at 26 or 60 weeks of age was that the challenge was too weak, and the studies were invalid. The applicant's reasoning not to repeat the challenge studies for the 26 and 60 weeks timepoints is accepted. The vaccine was shown to provide protection at 80 weeks post vaccination. Average antibody titres ≥ 3.6 log_2 can be considered related to protection and serology can be used to support onset and duration of immunity. The totality of data is considered to support the claim for

reduction of egg drop caused by avian metapneumovirus, with an onset of immunity of 5 weeks post vaccination and a duration of immunity of 80 weeks.

In the four clinical trials, layer pullets and broiler breeders were vaccinated under field conditions (receiving the standard vaccination program, with or without the test vaccine). AMPV serology indicates a similar antibody response is achieved after vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS compared to licensed inactivated Nobilis vaccines containing an TRT component. A challenge study with AMPV was performed on birds derived from one of the clinical studies but the study was invalid, and no conclusions could be drawn.

IBV

The proposed indication for IBV is reduction of respiratory signs and egg drop caused by infectious bronchitis virus, strains Massachusetts (GI-1 genotype), 4/91-793B (GI-13 genotype), QX – D388 (GI-19 genotype), var2 (G1-23 genotype) and Q1 (GI-16 genotype). The vaccine is to be used as a booster vaccination following priming with live vaccines against Infectious Bronchitis virus (e.g. Nobilis IB 4/91, Nobilis IB Ma5). The claimed onset of immunity is 4 weeks post vaccination and the duration of immunity 80 weeks post-vaccination. A serological response was observed from 5 weeks post vaccination and can be reliably concluded to last for 75 weeks post vaccination.

Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS is positioned as a booster vaccine to be administered after priming vaccination with live IBV vaccines.

For the use of Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS as a booster, after priming with live IB Ma5 and IB 4/91 vaccines (at day of age), the efficacy against IBV M41 and 4/91 challenge is supported by data at 45 and 81 weeks post vaccination. In addition, efficacy of the prime-boost regimen against QX and var2 challenge at 25 weeks post vaccination was shown. Efficacy against IBV Q1 was shown at 11 weeks post vaccination.

The applicant has provided an overview of all the clinical data recorded in the IB vaccination-challenge studies. From this data it can be concluded that vaccination with a prime-boost scheme resulted in a reduction of coughing and respiratory clinical signs. Thus, protection against respiratory signs caused by IB M41, IB 4-91, IB QX and IB Var2 is considered adequately supported by data.

Serological analysis of the clinical trials shows that the antibody responses to both IBV M41 and 4/91 were very similar in vaccinated groups compared to control vaccinated groups. It is noted that in all four clinical studies, birds of both test and control flocks were primed with various combinations of live IB vaccines at more than one timepoint prior to vaccination with the inactivated vaccine.

NDV

The proposed indication for NDV is reduction of mortality and clinical signs caused by NDV. The claimed onset of immunity is 4 weeks post vaccination and the duration of immunity 80 weeks post-vaccination. One serological study and four vaccination-challenge studies were performed in order to support OOI and DOI against NDV. Serology showed a response to vaccination from 4 weeks with measurable titres lasting at least until 88 weeks post vaccination. Priming with live ND vaccines resulted in consistently higher antibody titres. A challenge study performed in accordance with Ph. Eur. 0870 requirements showed that the vaccine blended at 100%, 75% or 50% complies with the test. Further challenge studies support the claimed OOI of 4 weeks and good levels of protection at 48 and 88 weeks post vaccination. This protection was achieved both with and without priming of birds with live ND vaccines.

In the four clinical trials birds were primed with various combinations of ND vaccines at more than one timepoint prior to vaccination with the test or control vaccine. Therefore, the onset, duration and magnitude of the anti-NDV antibody response cannot be attributed to vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS alone. A booster-effect was observed in the antibody titres from 4 weeks post vaccination with test or control vaccines. Titres achieved were relatively stable up to 102 weeks of age and similar in test and control groups. Challenge studies in birds derived from the clinical trials showed that birds vaccinated according to a commercial schedule were significantly protected from velogenic NDV challenge at 30, 65 and 76 weeks of age (i.e. up to 64 weeks post booster vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS).

IBDV

The proposed indication for IBDV is passive immunisation of the progeny of the vaccinated chickens to reduce mortality and clinical signs of disease caused by very virulent (CS89), classical (STC) and antigenic variants (variant E and GLS) strains of infectious bursal disease virus. The vaccine is to be used as a booster vaccination following priming with live or inactivated vaccines against infectious bursal disease virus (e.g. Nobilis Gumboro D78, Innovax-ND-IBD). The claimed onset of immunity 4 weeks post vaccination and the duration of immunity 80 weeks post-vaccination. In progeny, an OOI of 1 day of age and a DOI of 3 weeks of age is claimed. A total of 4 studies was performed in support of the efficacy against IBDV: a serological study in vaccinated birds, a serological study in progeny and two challenge studies in progeny.

Birds vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 16 weeks of age developed detectable antibodies to IBDV GB02 and IBDV 89/03 by 4 weeks post vaccination, which remained at similar levels until 67 weeks of age (51 weeks post vaccination). Antibodies in progeny of vaccinated birds (MDA) could be detected at least up to 15 days of age. Eggs were collected at 10 weeks and at 69 weeks post vaccination. When challenged with vvIBDV at 21 days of age, the progeny was adequately protected. This result was achieved with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS vaccination either with or without prior priming with Innovax-ND-IBD. In another study, birds were primed with Nobilis Gumboro D78 or Innovax-ND-IBD and boostered with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS. The antibody titres for anti-IBDV GB02 and anti-IBDV 89/03 antibodies were measured up to 84 weeks post-vaccination and found to be very stable. Eggs were collected from vaccinates at 85 weeks of age. It was observed that all progeny derived from vaccinated chickens were 100% protected against vvIBDV (CS89) challenge at 3 weeks of age.

Based on the data provided, protection against vvIBDV is considered supported, with an OOI of 4 weeks and a DOI of 80 weeks post vaccination. The claimed onset (1 day of age) and duration (21 days of age) of immunity in offspring of vaccinated birds is considered supported for vvIBDV.

Five serological studies were performed to evaluate IBDV efficacy in the field studies. IBDV antibodies were detected by Gumboro GB02 and Gumboro 89/03 virus neutralisation assay. Average titres in test and control flocks were similar. In addition, five laboratory challenge studies were performed using birds derived from the clinical trials. In one study the MDA titres in progeny from test and control group broiler breeders were determined at 30 weeks post vaccination. IBDV MDA titres were substantial until 14 days of age. Several challenge studies were performed on offspring from birds in the field trials. These birds were all primed with Nobilis Gumboro D78 and boostered with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS. Protection against Variant E, STC and GLS strains was observed in offspring up to 21 days of age, when eggs were collected up to 66 weeks post vaccination. These studies support the claimed DOI of 21 days in progeny of birds vaccinated according to a prime-boost schedule.

ARV

The vaccine is intended to induce passive immunity in the progeny of vaccinated chickens, to reduce viraemia and clinical signs of disease caused by Avian Reovirus (genotypes 1, 2, 3, 4 and 5). The vaccine is to be used as a booster vaccination following priming with either live or inactivated vaccines (Nobilis Reo 1133, Nobilis Multriva REOm). The claimed onset of immunity is 4 weeks post-vaccination and 1 day of age in the progeny, the duration of immunity is 80 weeks post-vaccination in the vaccinated chickens and 3 weeks in the progeny. A total of 6 studies were performed in support of the efficacy against ARV: a serological study in vaccinated birds, a serological study in progeny and four challenge studies in progeny.

Birds vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS at 16 weeks of age developed detectable antibodies to ARV-1 and ARV-4 by 4 weeks post vaccination which remained at similar levels until 67 weeks of age (51 weeks post vaccination). Offspring of SPF birds vaccinated with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS alone or after priming with Reo vaccines showed levels of MDA that persisted until 28 days of age. Protection of progeny after vaccination of parents with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS after priming with Nobilis REO 1133 or Nobilis Multriva REOm was shown in a number of studies. Birds were challenged at one day of age with ARV-1, ARV-2, ARV-3 and ARV-5 and were found to be protected from viraemia and clinical signs.

The onset of immunity of 4 weeks p.v. is considered sufficiently supported by the serological data. Cross-protection against serotype 2, 3 and 5 is considered sufficiently supported by the data provided. The claimed DOI of 80 weeks post vaccination is sufficiently supported by the data.

For ARV, four serological studies were performed on sera taken from the clinical trials. In addition, five serological studies in progeny of vaccinated birds were performed, as well as two (laboratory) challenge studies in progeny from field-vaccinated animals. Antibody titres to ARV-1 and ARV-4 were of similar, moderate levels at day-of-age, in progeny of birds primed using Nobilis Reo 1133 or Nobilis Multriva REOm and boostered using Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS, in the different field studies. In the progeny the antibody titres gradually declined, disappearing by 21 days post vaccination. Antibody levels were similar in progeny from eggs collected at 68, 71 or 80 weeks of age of the parent flock. A challenge study was performed in progeny (broilers) derived from eggs collected at 30 weeks post vaccination from birds vaccinated with Nobilis Multriva REOm and Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS. An MDA- control groups consisted of day-old SPF chicks. Challenge was performed at day of age with ARV-1, ARV-2, ARV-3 or ARV-5 challenge strains. The results support protection against clinical signs (ARV-2 and ARV-3) and viraemia for all challenge strains. A second study in progeny derived from eggs taken at 46 weeks post vaccination from breeders vaccinated in the field with Nobilis Multriva REOm and Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS suggests a reduction of viraemia but not clinical signs after ARV-1 or ARV-2 challenge. In general, results from clinical trials support the efficacy of the prime-boost regimens against ARV-1, 2, 3, 4 and 5.

EDSV

The proposed indication for EDSV is reduction of egg drop and eggshell defects caused by egg drop syndrome ’76 virus, with an onset of immunity of 4 weeks post vaccination and a duration of immunity of 80 weeks post-vaccination. In total 5 studies were performed, one serological study and 4 challenge studies.

While there is no direct evidence for the claimed onset of immunity of 4 weeks post vaccination for EDSV, based on the serological response observed it can be accepted that a response to vaccination has developed by 4 weeks post vaccination that is likely to confer protection. Duration of immunity is supported by the results of challenge at 82 weeks post vaccination and by serology up to 74

weeks post vaccination. The claimed duration of immunity to EDSV of 80 weeks post vaccination is supported by data.

In the clinical trials EDSV HI antibody titres were induced by vaccination with Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS and these remained detectable for up to 87 weeks post vaccination in layer type birds and up to 73 weeks post vaccination in broiler breeders. Laboratory challenge of commercial layer birds at 62 weeks post vaccination confirms protection as observed in pre-clinical studies.

Part 5 – Benefit-risk assessment

Introduction

Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS is an inactivated vaccine for chickens containing avian metapneumovirus strain BUT1 #8544, avian infectious bronchitis virus strain M41, avian infectious bronchitis virus strain 4/91, Newcastle disease virus strain Ulster, avian infectious bursal disease virus strain GB02, avian infectious bursal disease virus strain 89/03, avian reovirus strain ARV-1, avian reovirus strain ARV-4 and eggdrop syndrome ’1976 virus strain BC14 as active substances and light liquid paraffin as adjuvant. The active substances are known.

The vaccine is presented as an emulsion for injection in packs containing 1 bottle of 300 ml (1000 doses) or 600 ml (2000 doses) and is to be administered intramuscularly as a single dose of 0.3 ml in the breast or thigh region from 8 weeks of age onwards, but no later than 3 weeks before the onset of lay.

At the time of submission, the applicant applied for the following indications:

For the active immunisation of chickens for:
- reduction of egg drop caused by avian metapneumovirus
- reduction of respiratory signs and egg drop caused by infectious bronchitis virus strains Massachusetts (GI-1 genotype), 4/91-793B (GI-13 genotype), QX – D388 (GI-19 genotype), Var2 (G1-23 genotype) and Q1 (GI-16 genotype)
- reduction of mortality and clinical signs caused by Newcastle disease virus
- passive immunisation of the progeny of the vaccinated chickens to:

  - reduce mortality and clinical signs of disease caused by very virulent (CS89), classical (STC) and antigenic variants (variant E and GLS) strains of infectious bursal disease virus
  - reduce viraemia and clinical signs of disease caused by avian reovirus (genotypes 1, 2, 3, 4 and 5)

- reduction of egg drop and eggshell defects caused by egg Drop Syndrome ’76 virus

The dossier has been submitted in line with the requirements for submissions under Article 8 of Regulation (EU) 2019/6 – full application.

Benefit assessment

Direct benefit

The proposed benefit of Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS is its efficacy against AMPV, IBV, NDV, IBDV, ART and EDSV, which was investigated in a large number of well-designed pre-

clinical and clinical studies conducted to an acceptable standard.

Additional benefits

Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS is a comparatively large combination of inactivated viral components, reducing the need for the application (injection) of different vaccines within a short timeframe. Compared to existing inactivated viral vaccine combinations, the dose volume is smaller which is an advantage with respect to injection-site safety and animal welfare.

Risk assessment

Quality

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. Quality data for each of the antigens is included in the respective vaccine antigen master files. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The whole production process was evaluated at production scale and shown to be consistent. The stability data provided support the proposed 24-month shelf life.

Safety

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal

Administration of Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS in accordance with SPC recommendations is generally well tolerated.

The safety of the vaccine in chickens at 7 weeks of age was confirmed in a GLP safety study and four clinical trials. The main reported adverse reaction is injection site swelling that was observed in some animals after being administered the standard dose. However, the effects were mild and transient.

Risk for the user

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations. Standard safety advice for veterinary medicinal products containing mineral oil is included in the SPC.

Risk for the environment

Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk for the consumer

The product is not considered to pose a risk to consumer safety. Based on the components, residue studies are not required. The withdrawal period is set at zero days.

Special risks

None identified.

Risk management or mitigation measures

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

User safety

User safety risks have been identified. These risks have been addressed by the safety warnings included in the SPC.

Environmental safety

No specific environmental safety risks have been identified. Standard advice on waste disposal is included in the SPC.

Conditions or restrictions as regards the supply or safe and effective use of the VMP concerned, including the classification (prescription status)

The veterinary medicinal product is subject to a veterinary prescription.

Official control authority batch release may be required for this product.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication:

For the active immunisation of chickens for:
- reduction of egg drop caused by avian metapneumovirus.
- reduction of respiratory signs and egg drop caused by infectious bronchitis virus strains Massachusetts (GI-1 genotype), 4/91-793B (GI-13 genotype), QX – D388 (GI-19 genotype), Var2 (G1-23 genotype) and Q1 (GI-16 genotype).
- reduction of mortality and clinical signs caused by Newcastle disease virus.
- passive immunisation of the progeny of the vaccinated chickens to:
    - reduce mortality and clinical signs of disease caused by very virulent (CS89), classical (STC) and antigenic variants (Variant E and GLS) strains of infectious bursal disease virus.
    - reduce viraemia and clinical signs of disease caused by avian reovirus (genotypes 1, 2, 3, 4 and 5).
- reduction of egg drop and eggshell defects caused by egg drop syndrome ’76 virus.

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

The product has been shown to be efficacious for the active immunisation of chickens for:

- reduction of egg drop caused by avian metapneumovirus (AMPV).
- reduction of respiratory signs and egg drop caused by infectious bronchitis virus (IBV) strains Massachusetts (GI-1 genotype) and 4/91-793B (GI-13 genotype).
- reduction of mortality and clinical signs caused by Newcastle disease virus (NDV).
- passive immunisation of the progeny of the vaccinated chickens to
    - reduce mortality and clinical signs of disease caused by very virulent (CS89) and classical (STC) strains of infectious bursal disease virus (IBDV).
    - reduce viraemia and clinical signs of disease caused by avian reovirus (ARV) genotypes 1 and 4.
- reduction of egg drop and eggshell defects caused by egg drop syndrome-1976 virus (EDSV).

Onset of immunity:

- IBV, NDV, IBDV, ARV and EDSV: 4 weeks post-vaccination.
- AMPV: 5 weeks post-vaccination
- IBDV and ARV in progeny: 1 day of age

Duration of immunity:

- AMPV, IBV, NDV, IBDV, ARV and EDSV: 80 weeks post-vaccination
- IBDV and ARV in progeny: 3 weeks of age

Cross protection has been established for IBV strains QX-D388 (GI-19 genotype), Var2 (GI-23 genotype) and Q1 (GI-16 genotype).

Cross protection has been established for IBDV antigenic variant strains (variant E and GLS).

Cross protection has been established for ARV genotypes 2, 3 and 5.

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, including withdrawal period, have been included in the SPC and other product information.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) considers that the application for Nobilis Multriva RT+IBm+ND+Gm+REOm+EDS is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) 2019/6).

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