9 July 2015
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Porcilis PCV ID (EMEA/V/C/003942/0000)

Common name: porcine circovirus vaccine (inactivated)

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

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Introduction

On 25 July 2014, the applicant Intervet International B.V. submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for Porcilis PCV ID through the centralised procedure, falling within Article 3(1) of Regulation (EC) No. 726/2004 (biotechnological veterinary medicinal product).

The eligibility to the centralised procedure was agreed upon by the Committee for Medicinal Products for Veterinary Use (CVMP) on 13 February 2014. The rapporteur appointed was Dr P. Hekman and the co-rapporteur was Dr M. Tollis.

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

Porcilis PCV ID contains inactivated porcine circovirus type 2 ORF2 subunit antigen as active substance adjuvanted by light liquid paraffin combined with dl-α-tocopheryl acetate and polysorbate 80. The proposed route of administration is intradermal and the recommended dose is 0.2 ml.

The applicant applied for the following indication:

For the active immunisation of pigs from 3 weeks of age to reduce viraemia, virus load in lungs and lymphoid tissues and virus shedding caused by porcine circovirus type 2 (PCV2) infection. In addition, to reduce daily weight loss and mortality associated with PCV2 infection.

The vaccine is presented as an emulsion for injection in type I glass vial of 10 ml with rubber stopper and in polyethylene terephthalate (PET) vial of 20 ml with rubber stopper, each in pack sizes of 1 and 10 vials.

On 9 July 2015, the CVMP adopted an opinion and CVMP assessment report.

On 28 August 2015, the European Commission adopted a Commission Decision granting the marketing authorisation for Porcilis PCV ID.

Scientific advice

Not applicable.

MUMS limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A detailed description of the pharmacovigilance system (dated 1 April 2014) which fulfils the requirements of Directive 2001/82/EC has been provided. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary

means for the notification of any adverse reaction occurring either in the European Union (EU) or in a third country.

Manufacturing authorisations and inspection status

The active substance as well as the finished product is manufactured by Intervet International B.V., Boxmeer, the Netherlands. Secondary packaging and batch release for the EU will be carried out by Intervet International B.V., Boxmeer, the Netherlands.

Manufacturing authorisation for the manufacturing site was issued on 17 June 2014 by the Ministry of Economic Affairs, the Netherlands. A valid Good Manufacturing Practice (GMP) compliance certificate was provided for the production site which was issued after inspection on 15-24 April 2014, by the Ministry of Economic Affairs, the Netherlands. A declaration by the qualified person of Intervet International B.V. confirming that active substance is manufactured in accordance with GMP was also provided.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing site were considered in line with legal requirements.

Part 2 – Quality

Composition

Porcilis PCV ID is an emulsion for injection for pigs, containing porcine circovirus type 2 ORF2 (PCV2 ORF2) recombinant antigen as the active substance at a quantity of at least 1,436 antigenic units (AU) per dose (as measured by the antigenic mass ELISA). The adjuvant system is based on oil in water emulsion of light liquid paraffin combined with dl-α-tocopheryl acetate. The product does not contain a preservative.

The product is to be administered using a needle-free intradermal injection device. In all safety and efficacy studies a specific device for intradermal application of liquids (IDAL) was used to administer the vaccine. Specifications of the IDAL are provided in the dossier.

Container

The vaccine is filled in 10 ml type I glass vials or 20 ml polyethylene terephthalate (PET) vials. Both types of containers are closed with a nitrile rubber stopper and sealed with an aluminium cap. Where appropriate, compliance with European Pharmacopoeia (Ph. Eur.) was demonstrated. Information on the sterilisation processes is provided.

Development pharmaceutics

The product was developed with the intention to achieve a single dose administration of the vaccine against PCV2. The single dose administration approach can improve animal welfare and reduce labour cost. The PCV2 ORF2 recombinant antigen is an established antigen also used in Porcilis PCV (EU/2/08/091/01-010). The dose for Porcilis PCV ID will contain at least 1,436 AU per dose (as measured

by the antigenic mass assay) in a 0.2 ml injection volume. The low injection volume is necessary because of the intended intradermal application route and therefore the concentration of antigen is increased. The product contains a known adjuvant, X-solve (a combination of two adjuvants: Diluvac Forte which is an adjuvant based on dl-α-tocopheryl acetate and Microsol, based on light liquid paraffin). The adjuvant is capable of stimulating a long lasting immune response. No preservative is added as the vaccine. Multiple broaching should be avoided.

The vaccine is to be applied intradermally using a suitable device. The IDAL device was used in all development studies.

Method of manufacture

Production of the vaccine is the result of a 2-phase process; production of PCV2 ORF2 antigen and subsequent manufacturing of the finished product. Following propagation of Sf-21-CB insect (Sf21) cells, antigen is produced by fermentation of Sf21 cells with PCV2 ORF2 baculovirus. Cells are harvested, concentrated and disrupted in order to free the virus-like particles (VLPs).

The harvest is subject to an inactivation procedure to ensure a product free from live viral contamination (recombinant baculovirus), this is performed by addition of binary ethylenimine (BEI). After inactivation, the residual BEI is neutralised by addition of sodium thiosulphate.

The adjuvant consists of Diluvac Forte concentrate and Microsol. Diluvac Forte concentrate contains dl-α-tocopheryl acetate. Microsol contains light liquid paraffin. Excipients are Polysorbate 80, Simethicone, Sodium chloride, Potassium chloride, Disodium phosphate dehydrate, Potassium dihydrogen phosphate, and water for injections. The finished product is prepared by mixing appropriate amounts of buffer solution, adjuvant and PCV2 ORF2 bulk antigen. The vaccine is formulated to contain a fixed amount of PCV ORF2 protein and a fixed amount of the 2 adjuvant components in each dose.

The final product is a sterile emulsion, not containing any toxic or live components and can thus be classified as an inactivated subunit vaccine.

The production process of Porcilis PCV ID was described with sufficient level of details and is considered acceptable.

Control of starting materials

Active substance

The origin, the production and the storage of the master cell seed and master seed are sufficiently described. The master cell seed (Sf21) was tested according to the European Pharmacopoeia (Ph. Eur.) monograph 5.2.4 on cell cultures for the production of veterinary vaccines, cell lines. The master seed was tested according to Ph. Eur. monograph 0062 on vaccines for veterinary use. For both seeds, testing for sterility, mycoplasma and extraneous agents was performed according to Note for Guidance (NfG) on extraneous agents (III/3427/93), Ph. Eur. monographs 2.6.1 and 2.6.7. Certificates of analysis were provided for starting materials used in the manufacture of active substance. In view of the type of materials of animal origin as well as the method of production and validated inactivation methods, the absence of extraneous agents testing on these starting materials is considered justified.

Excipients

The following materials were tested according to relevant Ph. Eur. monographs: paraffin light liquid, alpha-tocopheryl acetate, polysorbate 80, simethicone, gentamicin sulphate, sodium chloride, hydrochloric acid, potassium chloride, sodium hydrogen carbonate, disodium phosphate dihydrate, potassium dihydrogen phosphate, sodium thiosulphate, sodium hydroxide and water for injections. A deviation from Ph. Eur. requirements is present for light liquid paraffin. A lower viscosity than the one specified in Ph. Eur. monograph 0240 is considered acceptable and necessary in order to guarantee appropriate syringeability which paraffin of a higher, compliant, viscosity, would not achieve.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

All materials of animal origin used in the production of the final product were proven to comply with the current regulatory texts related to the NfG on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products *(*EMA/410/01 rev.3) and Commission Directive 1999/104/EEC. It can be concluded that the risk of transmission of animal spongiform encephalopathies (TSE) infectivity through the use of this vaccine is negligible.

Control tests during production

Descriptions and limits of acceptance of tests performed during production of the antigen and finished product were provided.

The number of infected cells is determined at the time of harvest by light microscopy. The number of disrupted cells is monitored by light microscopy. The baculovirus titre is determined by limiting dilution of cell culture after sonication and prior to inactivation. Inactivation control is performed on each antigen batch, after neutralisation, by culture. Testing for residual sodium thiosulphate is performed by titration. Antigen content of the antigen bulk is determined by antigenic mass ELISA on each batch. Sterility of the antigen bulk is determined using soy broth and thioglycollate media, alternatively an automated BacTec system (culture system) is used. During manufacturing of the final product, filling volume is checked.

All tests were appropriately validated and adequately control the production process. Results of tests on production runs indicate consistency of production.

Control tests on the finished product

The description of the methods used for the control of the finished product (pH, appearance, viscosity, identity, in vitro potency, identity and assay of the adjuvants, sterility) and the limits of acceptance were provided.

Viscosity is determined using a rotating viscometer, the method was validated and an appropriate limit was set. Identification is performed in combination with potency. An antigenic mass assay is performed to confirm identity and content of antigen in each batch. The implementation of this in vitro method as an alternative to the usual in vivo methods is considered to be a positive development. The dl-alpha-tocopheryl concentration as well as the light liquid paraffin content is determined by high-performance liquid chromatography (HPLC).

The specifications proposed at release and at the end of shelf life are appropriate to control the quality of the finished product. The results of the analysis of production runs were presented which comply with the required specifications.

Stability

Stability was satisfactory for 3 batches of antigen.

Final product batches produced from 3 different antigen batches were tested for stability (potency, assay of the adjuvants, pH, viscosity, appearance and sterility) at regular intervals during a 27-month storage period at 2–8 °C. The data presented is considered to support the proposed shelf life of 24 months.

The transport stability at elevated temperatures and the in-use shelf life of 8 hours are substantiated by appropriate data.

Characteristics of the intradermal injection device

The product is administered using a multi-dose needle-free injection device IDAL. The following characteristics of the device are necessary to ensure correct administration of the vaccine.

The device should be capable of delivering a "jet stream" of vaccine (0.2 ml ± 10%) through the epidermal layers of the skin. For this purpose the device should give an initial peak force of 2.0- 4.2 N to penetrate the skin followed by a vaccine delivery phase with the force decreasing over time and a drop-off phase where the force goes to zero ("force curve").

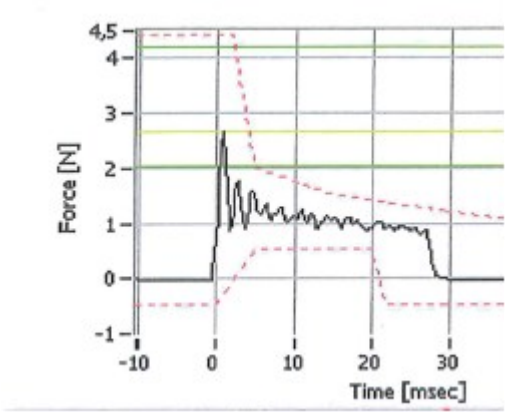

Figure 1 – The "force curve" required for the needle-free intradermal device to deliver the vaccine through the epidermal layers of the skin.

In figure 1 is shown an example of the "force curve" of the device where the dotted lines provide the boundaries of the force to be generated over time, the green lines indicate the boundaries of the peak force at start. In case a spring mechanism is used in the device the force of the "jet-stream" is determined by the strength of the spring and the size of the nozzle opening. In conclusion the most relevant characteristic for the device to deliver a 0.2 ml dose in an appropriate way is the "force curve".

Overall conclusions on quality

Porcilis PCV ID is a vaccine containing inactivated porcine circovirus type 2 ORF2 subunit antigen as active substance adjuvanted by light liquid paraffin combined with dl-α-tocopheryl acetate. The information provided is of sufficient detail and quality and indicate that Porcilis PCV ID can be produced with a proper and consistent quality. The respective certificates of suitability are provided. The control tests are properly validated and appropriate to control the production process. All starting materials are defined and comply with the provisions of Ph. Eur., where applicable.

The risk of transmission of TSE, infectivity through the use of this vaccine is negligible. The stability data presented support a shelf-life for the finished product of 24 months.

Specifications of the device to be used for application of the vaccine are provided.

Part 3 – Safety

Safety documentation

Laboratory and field safety studies were performed in accordance with Ph. Eur. monograph 0062 on vaccines for veterinary use and Ph. Eur. monograph 5.2.6 on evaluation of safety of veterinary vaccines and immunosera. Porcilis PCV ID is formulated to contain a fixed quantity of PCV2 ORF2 subunit antigen per dose; therefore, it was not required to use the maximum potency. Animals at minimum age were used, with variable levels of maternally derived antibodies (MDA). Animals were monitored for signs of disease, local inflammatory reactions (redness, size of swelling, temperature and pain), general health and rectal temperature.

Laboratory tests

One good laboratory practice (GLP)-compliant laboratory safety study was performed in animals at the minimum recommended age of 3 weeks. Safety and relevant performance measures were investigated in 4 field trials.

Safety of the administration of one dose

Piglets were randomly assigned to vaccine (n=20) or placebo (n=10) groups and received a single intradermal injection with one dose (0.2 ml) of vaccine or isotonic saline. Animals were observed daily for signs of disease including mortality, local reactions, body temperature (4 days) and general health until 42 days post vaccination. Histological evaluation of the site of administration was performed on randomly selected vaccinates on day 14 (n=5) and 28 (n=4) and on all remaining animals on day 42. No mortality occurred during the study and no signs of disease that could be attributed to vaccination were observed. Average rectal temperature did not increase after vaccination. Administration site reactions were observed in the majority of vaccinates and showed a biphasic pattern consisting of an increase (day 1) and decrease followed later by another increase (day 7-10) and decrease of the size. The extent of the local reactions was limited with a maximum size of 2.3 cm (day 12) and a maximum average of 1.1 cm (day 14) and had disappeared in all animals by day 28. Histologically, small application site reactions were found on study day 42 consisting of germinal centres indicative of a resolving active immune response. Based on this study the vaccine appears to be safe, with no systemic reactions and limited local reactions.

Examination of reproductive performance

Reproductive performance was not investigated, which is justified as the product is intended for finishing pigs.

Examination of immunological functions

Studies on the effect of the product on immunological performance were not reported, which is justified considering the nature and composition of the vaccine.

Study of residues

Not required.

The active ingredient being a substance of biological origin intended to produce active immunity does not fall within the scope of Regulation (EC) No. 470/2009 with regard to residues of veterinary medicinal products in foodstuffs of animal origin. In addition, the other components of the vaccine are either listed in table 1 of the annex of Commission Regulation (EU) No. 37/2010 or considered as not falling within the scope of Regulation (EC) No. 470/2009 when used as in this product.

The withdrawal period is set at zero days.

Interactions

The safety of the concurrent use (at the same time, at a different injection site) of Porcilis PCV ID and Porcilis M Hyo ID ONCE was investigated in a field trial, which is justified. Three (3) groups of 3-week old piglets were vaccinated with either Porcilis PCV ID (PCV) or Porcilis PCV ID and Porcilis M Hyo ID ONCE (PM) or were left untreated (control). Local and systemic reactions, rectal temperature and weight gain were monitored. Local reactions induced by Porcilis PCV ID were not enhanced by concurrent use with Porcilis M Hyo ID ONCE, while local reactions caused by vaccination with Porcilis M Hyo ID ONCE were in line with what is described in the summary of product characteristics (SPC) (transient swelling of up to 4 cm, biphasic pattern of reaction). Average rectal temperatures did not differ significantly between vaccinates and controls, while temperature increases in individual pigs in the PM group were in line with what is described in the Porcilis M Hyo ID ONCE SPC. Weight gain over the 3 weeks post vaccination was similar in all groups.

It can be concluded from the results of this study, and this is confirmed by safety data from 2 further field efficacy studies, that the concurrent use of Porcilis PCV ID and Porcilis M Hyo ID ONCE is safe in piglets from 3 weeks of age onwards. However, safety results from 1 field efficacy study indicate that for both vaccines concurrent use may slightly increase the incidence and severity of local reactions. An appropriate warning was included in section 4.8 of the SPC.

Field studies

Data from 4 good clinical practice (GCP) field studies are presented. The first study was performed in order to evaluate safety of the use of Porcilis PCV ID in the field, as well as the safety of concurrent use of Porcilis PCV ID and Porcilis M Hyo ID ONCE. The primary objective of the other 3 field studies was the collection of data on efficacy of vaccination, however during these studies pigs were also observed for

possible adverse events. Approximately 1,750 piglets were vaccinated in total, located on 6 farms in the Netherlands and Hungary.

All studies had a similar design and were performed as controlled, randomised and blinded studies in which piglets were vaccinated at 3 weeks of age with 1 dose of Porcilis PCV ID either with or without 1 concurrent dose of Porcilis PCV M Hyo ID ONCE. Animals were monitored for local and systemic reactions for at least 4 weeks post vaccination, mortality and body weight gain at the end of the nursery period were collected as performance parameters indicative of safety. Additionally, in the field safety study rectal temperature was measured for 4 days post vaccination and piglets were individually observed for local and systemic reactions daily for 4 weeks post vaccination. The 3 farms involved in the efficacy field studies all had confirmed PCV2 infection, 2 farms also had confirmed *Mycoplasma hyopneumoniae* infections.

The administration of the vaccine was performed with the multi-dose needle-free specific injection device IDAL.

Field study 1:

A clinical study in the Netherlands was performed to assess the safety of a single vaccination with Porcilis PCV ID and of a concurrent vaccination with Porcilis PCV ID and Porcilis M Hyo ID ONCE in piglets at an age of 3 weeks.

The study was performed on 3 farms in the Netherlands with no particular disease problems in piglets between 18 and 48 days of age. Serological screening performed prior to the study indicated that antibodies against PCV2 were present in animals on all 3 farms. On each farm 90 healthy piglets of 18–20 days of age from 10 litters were included in the study and allocated to 1 of 3 treatment groups. Piglets in the test group (PCV) were vaccinated once with 1 dose of Porcilis PCV ID, in the other test group (PM) piglets were vaccinated with Porcilis PCV ID and concurrently with 1 dose of Porcilis M Hyo ID ONCE, in the control group piglets remained untreated.

Local reactions at the site of administration of Porcilis PCV ID showed a biphasic response, with a peak on day 2 (26% of animals) and day 12/13 (82%) in the PCV group and on day 1 (32%) and day 11 (75%) in the PM group. The maximum observed size of the local reaction was 3.0 cm (PCV group) and 2.5 cm (PM group) the majority (~75%) of animals had reactions of up to 1.0 cm. In the majority of animals the reaction had disappeared by day 21, it persisted in 3 animals but had disappeared by day 37 in all animals. Local reactions at the site of administration of Porcilis M Hyo ID ONCE showed a biphasic response, with a peak on day 2 (74% of animals) and on day 16 (78%), maximum observed size was 3.0 cm however most (~75%) of the animals had reactions of up to 1.0 cm. Local reactions could still be observed in 15 animals on day 28, in 4 animals it persisted and developed into a scar at 50 days after vaccination.

On all farms and in all groups occasional scores of 1 (less active) were recorded for general health (3% in all groups). Two (2) animals in the PM group died, both deaths appear unrelated to vaccination. Four (4) piglets were individually treated during the study period: 2 from the PCV group and 2 from the PM group, 1 for respiratory signs, 3 for lameness. Mean temperature profiles showed no differences between the groups. Individual temperatures above 40.5 °C were observed in 2 piglets from the PCV group (1 day and 3 days duration), 1 in the PM group (2 days) and 2 in the control group (3 days). No significant difference in average daily weight gain (ADWG) during the nursery period was found between the groups.

In conclusion, the field safety study confirmed results of the laboratory safety studies. The vaccine induced mild local reactions, no systemic reactions and no effect on ADWG was observed.

Field study 2:

A clinical study in the Netherlands was performed to assess the efficacy of a single vaccination of piglets at an age of 3 weeks with Porcilis PCV ID.

The study design is explained in field study 2 under the efficacy part. Outcomes from the observation for the safety of the product are described in the following paragraph. Safety parameters were systemic and local reactions as observed in the group (animals were not individually inspected/palpated), these were recorded on day 0, prior to and 4 hours after vaccination and on day 1, 4, 7, 14, 21 and 28. If abnormalities were noticed, animals were examined individually. Additionally, morbidity as well as ADWG and mortality during the nursery period were evaluated.

No immediate reactions were observed during or immediately after vaccination. Local reactions were observed in 2 animals, one in the PCV group (3 cm on day 14) and one in the control group (1 cm on day 1). Both were no longer noticed at the next observation. One general health score of 1 (less active) was recorded in the PCV group on day 1. Further general remarks were made by the investigator regarding wasting and arthritis; however, these could not be attributed to a specific animal or group. No significant differences in morbidity or mortality during the nursery period were observed between the groups. ADWG during the nursery period was very similar for both groups.

Field study 3:

A clinical study in Hungary was carried out to assess the efficacy of a single vaccination with Porcilis PCV ID given alone and concurrently with Porcilis M Hyo ID ONCE in piglets at an age of 3 weeks.

The study design is explained in field study 3 under the efficacy part. Outcomes from the observation for the safety of the product are described in the following paragraph. Safety parameters were systemic and local reactions as observed in the group (animals were not individually inspected/palpated), these were recorded on day 0, prior to and 4 hours after vaccination and on day 1, 4, 7, 14, 21 and 28. If abnormalities were noticed, animals were examined individually. Additionally, morbidity as well as ADWG and mortality during the nursery period were evaluated.

Immediate reactions were not observed. Local reactions were not observed for either of the vaccines. A general health score of 1 (less active) was recorded for one animal in the control group at day 7. No statistically significant difference in morbidity was observed between the groups. Mortality and ADWG during the nursery period was similar in all groups.

Field study 4:

A clinical study in Hungary was carried out to assess the efficacy of a single vaccination with Porcilis PCV ID given alone and concurrently with Porcilis M Hyo ID ONCE in piglets at an age of 3 weeks.

The study design is explained in field study 4 under the efficacy part. Outcomes from the observation for the safety of the product are described in the following paragraph. Safety parameters were systemic and local reactions as observed in the group (animals were not individually inspected/palpated), these were recorded on day 0, prior to and 4 hours after vaccination and on day 1, 4, 7, 14, 21 and 28. If abnormalities were noticed, animals were examined individually. Additionally, morbidity as well as ADWG and mortality during the nursery period were evaluated.

One hundred and six (106) animals were excluded from the final analysis as it was unclear whether they had received the correct vaccine dose. Immediate reactions were not observed. The incidence of local reactions at the site of Porcilis PCV ID administration at 14 days post vaccination was 2% in the PCV and 8% in the PM group; these had disappeared by day 28 and day 35 respectively. Maximum size was 3 cm in the PCV group and 4 cm in the PM group. The incidence of local reactions to Porcilis M Hyo ID ONCE was

8% in the M group and 11% in the PM group; these had disappeared by 35 days post vaccination. Maximum size was 6 cm in the PM group and 4 cm in the M group. A general health score of 3 (severe disease) was recorded for one animal in the M group at day 14; it was treated with antibiotics for respiratory disease and found healthy at the next time point. No statistically significant differences in morbidity or mortality during the nursery period were observed between the groups. ADWG during the nursery period was significantly higher in the PM group compared to the M and controls groups, also the PCV group performed somewhat better then the M group; this is indicative of a PCV field infection and not a safety issue.

In the field safety trial, local reactions with a biphasic pattern were observed in the majority of animals. The maximum observed size was 3.0 cm; the reactions had disappeared in all animals by day 37. No effects of vaccination were observed on morbidity, mortality, (mean) temperature profiles or ADWG during the nursery period. Safety data from the field efficacy trials generally confirmed these results.

In conclusion, the results from the above field studies support the overall safety profile of the vaccine under the expected conditions of use and this was further supported by the more general safety data gathered during 3 field efficacy studies.

Transient local reactions mostly consisting of hard non-painful swellings of a diameter of up to 2 cm are very common. A biphasic pattern of the local reactions, consisting of an increase and decrease followed by another increase and decrease of the size, is commonly observed. The local reactions disappear completely within approximately 5 weeks after vaccination. Adverse reactions are appropriately reflected in the SPC.

User safety

A user safety evaluation was performed in accordance with the CVMP Guideline on user safety for immunological veterinary medicinal products (EMEA/CVMP/IWP/54533/2006). Accidental self-administration was identified as the worst case scenario. The needle-free injection device has a safety mechanism to avoid self-injection and vaccination is performed only by professionals that have been instructed on how to use the device, the risk is therefore considered to be very low. Although the individual components of the vaccine are not considered toxic, accidental injection of the vaccine – particularly into a finger – may have serious consequences due to the presence of light liquid paraffin. Appropriate warnings are included in the SPC.

The CVMP therefore concluded that the user safety for this product is acceptable when used as recommended in the SPC.

Environmental risk assessment

An environmental risk assessment (ERA) was performed in accordance with the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) guideline and the CVMP Guideline on the environmental risk assessment of immunological veterinary medicinal products (EMEA/CVMP/074/95*)*. The overall risk to the environment was estimated as negligible and no Phase II assessment is required, which is considered justified based on the Phase I assessment provided.

The product is inactivated and does not contain components at potentially toxic levels, moreover it is administered intradermally at low doses therefore exposure of the environment is negligible.

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

Safety of the product when used with intradermal injection device

The safety of the vaccine has been demonstrated using the multi-dose needle-free specific injection device IDAL. Specifications of the device are provided in the dossier. In addition, the safety profile of the product when administered using IDAL was confirmed by results from the field safety study.

Overall conclusions on the safety documentation

The safety of Porcilis PCV ID administered to pigs at the minimum recommended age of 3 weeks of vaccination was investigated in a well conducted, Ph. Eur. and GLP-compliant laboratory study and 4 field studies. Systemic reactions to vaccination were not observed, the extent of local reactions was limited. A biphasic pattern of local reaction appears to be very common and is properly addressed in the SPC.

The safety of the vaccine has been demonstrated using the multi-dose needle-free specific injection device IDAL. Specifications of the device are provided in the dossier. In addition, the safety profile of the product when administered using IDAL was confirmed by results from the field safety study.

Concurrent use of the vaccine with Porcilis M Hyo ID ONCE was investigated and data support the safety of concurrent use. However, results from one field (efficacy) trial indicated that such concurrent use may slightly enhance local reactions for both vaccines and an appropriate warning is included in the SPC.

A user safety evaluation was performed; the risk to the user is mainly caused by accidental injection due to the presence of mineral oil adjuvant. Appropriate precautions and warnings are included in the SPC.

In conclusion, the user safety for this product is acceptable when used as recommended in the SPC.

Based on the data provided the ERA can stop at Phase I. Porcilis PCV ID 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.

Part 4 – Efficacy

Introduction and general requirements

Porcilis PCV ID is formulated to contain a fixed quantity of PCV2 ORF2 subunit antigen per dose, therefore, a standard batch can be used in any efficacy trial and this is acceptable as no minimum (or maximum) potency is expected. The same holds true for Porcilis M Hyo ID ONCE, for which concurrent use was studied. In all safety and efficacy studies a needle-free intradermal injection device IDAL was used to administer the vaccine.

The efficacy of Porcilis PCV ID against PCV2 was evaluated in 6 laboratory challenge studies and 3 field trials. The effect of associated use of Porcilis M Hyo ID ONCE on efficacy of Porcilis PCV ID was investigated in 3 of these laboratory studies and 2 of the field studies. Additionally, for evaluation of the effect of associated use of Porcilis PCV ID on Porcilis M Hyo ID ONCE efficacy 2 laboratory challenge studies with *M. hyopneumoniae* (onset of immunity (OOI) and duration of immunity (DOI)) were performed. All studies were performed in the target animal at the minimum recommended age of 3 weeks

for vaccination, applying a single dose using the IDAL device. Information supporting the relevance of batches used for efficacy trials was provided. Challenge models for PCV2 and *M. hyopneumoniae* were in place as the applicant has already developed and licensed IVMP for both pathogens. All laboratory studies were in compliance with Ph. Eur. monograph 5.2.7, field studies were performed under GCP.

The proposed indications for use of the product are active immunisation of fattening pigs from 3 weeks of age to reduce PCV2 viraemia, reduce PCV2 load in lungs and lymphoid tissues, reduce shedding of PCV2 virus and to reduce daily weight gain loss and mortality associated with PCV2 infection. OOI of 2 weeks after vaccination and DOI of 23 weeks after vaccination is proposed. Associated use of the vaccine with Porcilis M Hyo ID ONCE is claimed to be effective when applied from 3 weeks of age onward. In order to support these claims, OOI and DOI studies for both single and concurrent use were performed, as well as field efficacy studies.

Laboratory trials

Six (6) laboratory challenge studies were performed in order to determine the vaccine dose and to determine OOI and DOI, these were designed as randomized, controlled and blinded vaccination-challenge studies. For PCV and *M.hyopneumoniae*, challenge models had been established previously for the development of previously authorised products. Conventional MDA+ piglets at the youngest age recommended for vaccination (3 weeks) were vaccinated with one intradermal dose. Primary parameters of efficacy were the amount of PCV2 in serum, tissues (lung, tonsil, inguinal lymphnodes (ILN)) and faeces. Secondary parameters included ADWG (for OOI studies) and serology.

Determination of the vaccine dose

Study 1:

This study was performed to investigate the dose-response relation of a single vaccination using the intradermal route with different antigen doses of Porcilis PCV ID when used to vaccinate piglets with antibodies against PCV2. Piglets were assigned randomly to the treatment groups (15 piglets per group); at 20-23 days of age, group 1 was vaccinated with a full dose (2,000 AU/dose of 0.2 ml), group 2 with a quarter dose (500 AU/dose of 0.2 ml) while group 3 was left untreated. Three (3) weeks after vaccination piglets were challenged and 3 weeks later all animals were necropsied. Main parameters of efficacy were the amount of PCV2 in serum, lung/lymphoid tissues and faeces. Clinical signs of post-weaning multisystemic wasting syndrome (PMWD) were not observed in any of the animals.

During the post-challenge period the viral load (log_{10} copies/µl DNA) in serum of the 2 vaccinated groups was ≥97% reduced compared to the control group. The difference with the control group was significant for both vaccinated groups, no statistically significant difference was found between the 2 vaccinated groups. A statistically significant reduction in faecal shedding was also observed in both vaccinated groups (≥84%) compared to the control group. Although virus excretion appeared to be somewhat higher in group 2, the difference between the 2 vaccinated groups was not significant. Viral load in lung and lymphoid tissues of the 2 vaccinated groups compared to the control group were significantly reduced by ≥76% (ILN), ≥83% (tonsil) and ≥84% (lung), no significant differences could be observed between the 2 vaccinated groups. Following vaccination and challenge the mean antibody level in the vaccinated groups was significantly higher than in the control group. The antibody profile in the vaccinated group 1 (full dose) was consistently higher than in the vaccinated group 2 (quarter dose), although the differences did not reach statistical significance. There was no statistically significant difference in bodyweight between the groups.

The chosen dose is considered appropriate based on the data provided.

Onset of immunity (OOI)

Study 2:

This study was performed to determine the OOI of a single vaccination using the intradermal route with Porcilis PCV ID, or with concurrent use of Porcilis M Hyo ID ONCE, when used to vaccinate piglets with antibodies against PCV2. Conventional piglets were randomly assigned to the treatment groups (15 piglets per group); at 18-21 days of age, group 1 (PCV) was vaccinated with a single dose of Porcilis PCV ID, group 2 (PM) was concurrently vaccinated with a single dose of Porcilis PCV ID and single dose of Porcilis M Hyo ID ONCE while group 3 was left as untreated controls. Two weeks after vaccination piglets were challenged and 3 weeks later all animals were necropsied. Main parameters of efficacy were the amount of PCV2 in serum, lung/lymphoid tissues and faeces.

In the 3 weeks post challenge, 4 animals from the PCV group, 1 animal from the PM group and 1 control were found dead or were euthanized. Additionally 1 animal from the PCV group and 3 controls were treated with antibiotics. Some of mortality and morbidity could be attributed to *Streptococcus suis* infections.

At 1 week post-challenge, the 2 vaccinated groups had higher viral loads in serum than the control group. This difference did not reach statistical significance. At 2 and 3 weeks post challenge the 2 vaccinated groups had significantly lower viral loads than the control group. No significant differences in the viral load were observed between the PCV and PM groups at any of the time points. Over the entire post-challenge period the area under the curve (AUC) for viral load in serum of each of the two vaccinated groups was ≥64% reduced compared to the control group, this apparent difference did not reach statistical significance. The faecal excretion showed a pattern similar to the virus load in serum. Over the entire post-challenge period the virus excretion was ≥65% reduced for both vaccinated groups (65% (non-significant) in PCV group, 100% (significant) in PM group). Differences between the vaccinated groups were not significant. Virus load was significantly reduced in both vaccinated groups for lymphoid tissues, reduction of virus load in lungs, was only statistically significant for the PM group compared to controls. There were no significant differences in ADWG between the groups. After challenge the mean antibody titre in both vaccinated groups were also significantly higher than in the control group. No significant differences in the mean antibody titre were observed between the two vaccinated groups.

In conclusion, virus load was reduced in lungs, lymphoid tissues and tonsils in the PCV group and in lymphoid tissues and tonsils in the PM group. Faecal excretion was reduced in the PM group only. The lack of significant differences for the other parameters was likely caused by the relatively low virus titres in all samples from the controls. An additional study was performed to support the claimed OOI at 2 weeks post vaccination.

Study 3:

This study was performed to determine the OOI of a single vaccination using the intradermal route with Porcilis PCV ID, or with concurrent use of Porcilis M Hyo ID ONCE, when used to vaccinate piglets with antibodies against PCV2.

The set up was the same as for study 2, only piglets were challenged at 3 weeks post vaccination.

After vaccination one animal from the PM group was euthanized as it could not walk. Additionally, one (1) animal from the PCV group was found dead; a *Streptococcus suis* infection was diagnosed at necropsy and confirmed by bacteriology. Serum samples of all animals were negative for PCV2 at the time of challenge. During the entire post-challenge period the viral load in the 2 vaccinated groups in serum was 100% reduced compared to the control group. This reduction was significant for each of the two vaccinated groups compared to the controls, no significant difference was found between the vaccinated

groups. Over the entire post-challenge period faecal shedding was ≥85% lower in the two vaccinated groups than in the control group, this difference was significant. Although the virus excretion in the PM group appeared to increase somewhat from 2 weeks post challenge, the difference between the two vaccinated groups was not statistically significant. Viral load in lymphoid tissues and lung was significantly lower in both vaccinated groups compared to the control group (≥76% (ILN), ≥84% (tonsil) and ≥84% (lung)). No significant differences were found between the two vaccinated groups. There were no significant differences in ADWG between the groups. At the time of challenge, as well as after challenge, the mean antibody titre of the 2 vaccinated groups was significantly higher than in the control group. No significant differences in the mean antibody titre were observed between the 2 vaccinated groups.

In conclusion, the main parameters of efficacy (virus load in serum, lymphoid tissues and lung, virus excretion in faeces) were all significantly improved in vaccinates, when challenged at three weeks post vaccination. Concurrent application of Porcilis M Hyo ID ONCE did not affect the efficacy of the product.

Study 4:

This study was performed to determine the OOI of a single shot intradermal vaccination with Porcilis PCV ID, or with concurrent use of Porcilis M Hyo ID ONCE, when used to vaccinate piglets.

The set up of the study was the same as for study 2, with challenge at 2 weeks post vaccination, however animals received a higher challenge dose (5.8 $\log_{10}$ $TCID_{50}$ vs 5.0 $\log_{10}$ $TCID_{50}$).

After vaccination, 1 control animal was slow and disoriented and 1 was found lame, both were treated with penicillin successfully.

One (1) vaccinated (PCV ID plus MHyo ID ONCE) animal was found lame on day 7 post challenge and was treated with penicillin, it was found lame again on day 12 post challenge and was then euthanized for welfare reasons. Post mortem did not reveal any abnormalities. Over the entire post-challenge period the viral load in the 2 vaccinated groups in serum was ≥70% reduced compared to the controls. Faecal shedding in vaccinates was ≥81% reduced (both groups) compared to controls. Viral load in lymphoid tissue and lung was reduced in the 2 vaccinated groups compared to the controls (≥62% (ILN), ≥61% (tonsil), ≥57% (lung)). All differences mentioned above were statistically significant compared to the control groups but not between vaccinated groups. At the time of challenge, as well as after challenge, the mean antibody titre of the 2 vaccinated groups, were significantly higher than in the control group. No significant differences in the mean antibody titre were observed between the 2 vaccinated groups.

In conclusion, the main parameters of efficacy (virus load in serum, lymphoid tissues and lung, virus excretion in faeces) were all significantly improved in vaccinates, when challenged at two weeks post vaccination. Concurrent application of Porcilis M Hyo ID ONCE did not affect the efficacy of the product.

Duration of immunity (DOI)

Two (2) laboratory challenge studies were performed to evaluate the DOI induced by Porcilis PCV ID. The set-up of both studies was identical but for the challenge which was given at 19 weeks post vaccination in the first study and at 23 weeks post vaccination in the second study. The main parameters of efficacy were the same as for the OOI studies described above, body weight was not recorded.

Study 5:

This study was performed to evaluate the DOI of a single vaccination using the intradermal route in piglets, following challenge at 19 weeks post-vaccination (22 weeks of age).

The experiment was performed according to a randomized, controlled design. Two (2) groups of 20 conventional PCV2 free piglets, 18-20 days of age, with low to moderate maternal antibody levels were included in the study. Group 1 was vaccinated with a single dose of Porcilis PCV ID; group 2 remained as untreated controls. At 19 weeks post vaccination 15 PCV2 free (low antibody, negative qPCR) piglets from each group were selected based on the order of inclusion and challenged. Necropsy was performed at 17-19 days post challenge.

Over the 17-19 days post challenge, virus load in serum was 100% reduced in vaccinates compared to the controls, this difference was statistically significant. The level of PCV2 in faecal swabs was also significantly lower in the vaccinates compared to the controls (AUC: 88% lower). At necropsy, virus load in tissues was lower in the vaccinated group (reduction ≥83% (ILN), ≥71% (tonsil) and ≥90% (lung)) and this difference was statistically significant. Following vaccination until the end of the study PCV2 antibody titres were significantly higher in the vaccinates compared to the control group.

In conclusion, the main parameters of efficacy (virus load in serum, lymphoid tissues and lung, virus excretion in faeces) were all significantly improved in vaccinates, when challenged at 19 weeks post vaccination.

Study 6:

This study was performed to evaluate the DOI of an intradermal one-shot PCV2 vaccine (Porcilis PCV ID) in piglets against PCV2, following challenge at 23 weeks post-vaccination (26 weeks of age).

The experiment was performed according to a randomized, controlled design. Two (2) groups of 20 conventional PCV2 free piglets, 17–21 days of age, with moderate maternal antibody levels were included in the study. Group 1 was vaccinated with a single dose of Porcilis PCV ID; group 2 remained as untreated controls. At 23 weeks post vaccination 15 PCV2 free (low antibody, negative qPCR) piglets from each group were challenged. Necropsy was performed at 19 days post challenge.

Over the 19 days post challenge, virus load in serum was 100% reduced in vaccinates compared to the controls, this difference was statistically significant. The level of PCV2 in faecal swabs was also significantly lower in the vaccinates compared to the controls (AUC: 90% lower). At necropsy, virus load in tissues was lower in the vaccinated group (reduction ≥88% (ILN), ≥75% (tonsil) and ≥82% (lung)) and this difference was statistically significant. Following vaccination until the end of the study PCV2 antibody titres were significantly higher in the vaccinates compared to the control group, except for the last time point (19 days post challenge) when titres were similar.

In conclusion, the main parameters of efficacy (virus load in serum, lymphoid tissues and lung, virus excretion in faeces) were all significantly improved in vaccinates, when challenged at 23 weeks post vaccination.

The influence of maternal derived antibodies (MDA) on the efficacy of the vaccine

Study 7:

This study was performed to evaluate the influence of PCV2 MDA on the efficacy of Porcilis PCV ID.

In order to determine the possible effect of MDA on vaccine efficacy a meta-analysis was performed on data from laboratory studies and data from field studies. Data from five vaccination-challenge laboratory studies and from DOI studies with field infections were combined into two data sets of respectively 90 vaccinated and 60 control pigs and 88 vaccinated and 44 control pigs. These data sets were analysed in detail for correlation between MDA titre and the effect of vaccination (PCV2 titre in serum, PCV2 excretion in faecal samples, PCV2 load in lymphoid and lung tissues).

For the field study data set of 233 vaccinated and 191 control pigs, data from three studies were combined, this data set was analysed for correlation between MDA and virus load in serum and faeces.

The set-up and performance of studies was sufficiently similar to allow combining of data. The area under the curve (AUC) for viral load (serum, faeces, tissue) was calculated for individual animals, correlation between PCV2 titre at the time of vaccination and the efficacy outcomes (AUC for serum, faeces and tissue PCV2 load) was calculated for vaccination and control groups separately and scatter plots were produced. Neither plots nor correlation coefficients gave any indication of a positive correlation between MDA and virus load in any of the groups either for laboratory studies or field studies.

Taken together with data already available in public literature about the lack of interference of MDA with other PCV2 vaccines, it can be concluded that there is at present no evidence of interference of MDA with efficacy of Porcilis PCV ID vaccination.

Prevention of transplacental transmission

Not applicable as the vaccine is intended to be used in pigs for fattening.

Additional studies

Study 8:

This study was performed to evaluate the OOI of Porcilis M Hyo ID ONCE used in association with Porcilis PCV ID at separate application sites in specific pathogen free (SPF) pigs.

The objective of this study was to determine the effect of concurrent use of Porcilis PCV ID on the OOI of Porcilis M Hyo ID ONCE. Three (3) groups of 20 *M. hyopneumoniae* seronegative piglets (18-24 days of age) were used in the study, the first group was vaccinated with a single dose of Porcilis M Hyo ID ONCE, the second with a single dose of Porcilis M Hyo ID ONCE and a single dose of Porcilis PCV ID at the same time at a different location and the third group was left as untreated controls. All animals were challenged three weeks post vaccination and necropsy and lung lesion scoring was performed three weeks later (blinded). All animals were seropositive for PCV2 at the start of the study. Average lung lesion scores (LLS) were not significantly different between the vaccinated groups (Porcilis M Hyo: 3.6, Porcilis M Hyo ONCE and Porcilis PCV ID: 3.3, controls: 17.7) whereas for both groups scores were significantly lower compared to the controls.

In conclusion, concurrent use of the product with Porcilis M Hyo ID ONCE does not affect the OOI of Porcilis M Hyo ID ONCE.

Study 9:

The objective of this study was to determine the calculation of the required level of PCV2 antibodies correlating with efficacy of Porcilis PCV ID.

In order to determine the minimum Porcilis PCV ID induced antibody titre that still correlates with significant reduction of PCV2 viral load, data from five (5) studies with experimental challenge and two (2) studies with a field infection were analysed (in total data from 101 controls and 171 vaccinates). Based on antibody titres of control and vaccinated animals at the time of challenge the animals were grouped into categories. The majority of controls (84%) had a titre ≤2 log2, as a conservative approach all controls were grouped into 1 category. The reduction of viral load in serum, faecal swabs and tissues (tonsil, lymph node, lungs) was calculated for each category by comparing the AUC values to those of the controls. A detailed statistical analysis of the correlation between serum antibody titres (in vaccinates and controls from laboratory and field studies) and virus load was performed. A threshold for protection was established as evidenced by significant reduction in viral load in serum, faeces, lymphoid tissue and lung.

Study 10:

The objective of this study was to determine the DOI Porcilis PCV ID when used concurrently with Porcilis M Hyo ID ONCE.

In this study DOI against PCV2 after concurrent use of Porcilis PCV ID and Porcilis M Hyo ID ONCE was studied based on PCV2 serology. The use of serology as a correlate of protection is justified based on the results of the study described above as well as data from peer reviewed literature. This is in accordance with the CVMP Guideline on requirements for combined vaccines and associations of IVMPs. In order to increase the probability of a late onset of PCV2 infection the study was performed on 3 different farms with known late onset PCV2 infection.

In each of 4 studies (A, B, C, D), groups of 22 three-week-old piglets were vaccinated once with one dose of Porcilis PCV ID (PCV), or with one dose of Porcilis PCV ID and one dose of Porcilis M Hyo ID ONCE (PM), or left as untreated controls. Serum samples were collected from all animals at the time of vaccination and thereafter every other week until slaughter (at 23 to 25 weeks of age) for detection of PCV2 antibody titres. Serum samples were analysed for PCV2 nucleic acid if serological data indicated exposure to PCV2.

PCV2 antibody titres in the PM group were compared to the PCV group at the time of predicted OOI (week 2 post vaccination) and DOI (last sampling time point or last qPCR PCV2 negative sample). Statistical analysis was performed aiming to demonstrate the PCV2 antibody titre after concurrent used was not less than the pre-set margin of 2 $\log_2$ below the mean of the single use and at the same time still significantly higher than in the control group.

In 2 out of 4 studies (A, B), no PCV2 infection was detected and antibody titres between groups were compared at the time of slaughter (22 weeks post vaccination). PCV and PM groups were found to have comparable antibody profiles. The difference in PCV2 titres between the PM and PCV group was well within the non-inferiority margin at each time point tested (2 and 22 weeks post vaccination) in both studies. Mean serum antibody titres were above 3 $\log_2$ for all vaccinated groups at 22 weeks post vaccination. In study B however, individual antibody titres dropped below this threshold in 6/22 in the PCV group and 3/22 in the PM group by week 20-22 post vaccination. Animals with titers below the defined protective titer will be partially protected by challenge, albeit the reduction percentages are somewhat smaller and not always statistically significant. Based on these arguments, it is considered that the observed lower antibody titres in part of the herd at the end of fattening period will likely not influence the overall efficacy of the vaccine.

PCV2 infections were detected from 14 and 16 weeks post vaccination in study C and D respectively, therefore serological data at 14 and 16 weeks post vaccination was used for comparison. The antibody profiles were comparable between groups and the difference between PCV2 titres in the PM group and PCV was well within the pre-set non-inferiority margin. In both studies with PCV2 infection, the virus load (AUC) in serum of vaccinated groups was reduced by 100% compared to the control groups; this was a statistically significant difference.

It can be concluded from the results of this study that concurrent use of Porcilis PCV ID and Porcilis M Hyo ID ONCE has no impact on the efficacy of Porcilis PCV ID for up to 22 weeks post vaccination.

Study 11:

The objective of this study was to determine the DOI of Porcilis M Hyo ID ONCE used in association with Porcilis PCV ID at separate application sites in SPF pigs against *M. hyopneumoniae* challenge infection.

Two groups of 40 *M. hyopneumoniae* seronegative piglets were vaccinated at 17-24 days of age, group 1 (PM) was vaccinated with one dose of Porcilis M Hyo ID ONCE and one dose of Porcilis PCV ID at separate sites, group 2 (PCV) was vaccinated with Porcilis PCV ID only. At 25 weeks of age all animals were challenged with *M. hyopneumoniae*, lung lesions scoring was performed 3 weeks later. Serology for *M. hyopneumoniae* and PCV2 was performed at vaccination; 11 weeks post vaccination, prior to challenge and at necropsy.

No antibodies against *M. hyopneumoniae* were detected in PCV animals until after the challenge infection, indicating no field infection had occurred. At necropsy, a statistically significant reduction (-53%; $p<0.05$) in average lung lesion scores was observed in group 1 (PM), compared to group 2 (PCV). All animals were PCV2 serologically positive at the start of the study and at 11 weeks post vaccination titres had decreased slightly. Titres at 22 and 25 weeks post vaccination indicate a PCV field infection; titres at 11 weeks post vaccination were therefore used to evaluate the effect of associated use of Porcilis PCV ID and Porcilis M Hyo ID ONCE versus Porcilis PCV ID single use. The difference between the groups was -0.21 $\log_2$ and the 90% confidence interval was well within the pre-set limit of -2 $\log_2$, indicating no effect of concurrent use on PCV2 serum antibody titres at 11 weeks post vaccination.

Conclusion

Results of 3 OOI studies (2 studies with challenge at 2 weeks, 1 study at 3 weeks) with 15 piglets per group, support an OOI at 2 weeks. No difference in OOI was found between the single use of Porcilis PCV ID and concurrent use of PCV ID and Porcilis M Hyo ID ONCE.

Two (2) DOI studies with 20 piglets per group were performed with challenge at 19 and 23 weeks respectively, results indicate DOI of 23 weeks post vaccination with respect to viraemia, virus load and virus shedding.

A detailed statistical analysis of data from 10 laboratory and field studies was performed in order to establish whether MDA has an effect on vaccine efficacy; no correlation between serum antibody titre at the time of vaccination and virus load after challenge could be established.

An additional study was performed to evaluate the DOI of Porcilis PCV ID when used concurrently with Porcilis M Hyo ID ONCE. Efficacy was evaluated in a field study on 4 farms with known late onset PCV2 infection, this approach is considered acceptable. On 2 of the farms A PCV2 field infection was detected at 14 and 16 weeks post vaccination respectively. On the farms that did not experience a field infection, protection was evaluated serologically. For this purpose, a serum antibody threshold for protection was established through detailed statistical analysis of the correlation between serum antibody titres at the time of challenge (in vaccinates and controls from several laboratory and field studies) and virus load. This is considered an acceptable approach. Antibodies were above the threshold for up to 22 weeks post infection for all vaccinated groups. In conclusion no difference in efficacy was found for the single or concurrent use groups in any of the four farms.

OOI and DOI of Porcilis M Hyo ID ONCE were evaluated in two laboratory challenge studies, in accordance with Ph. Eur. monograph 2448. No effect of concurrent use of the product with Porcilis M Hyo ID ONCE on OOI against *M. hyopneumoniae* was detected. The DOI study results showed a significant reduction of lung lesions in concurrently vaccinated pigs and non-inferiority to the single vaccine was confirmed using historical data, which is an acceptable approach.

Field trials

Three (3) GCP-compliant field trials were performed on farms in the Netherlands and Hungary.

Field study 1:

The first study investigated the efficacy of a single vaccination of Porcilis PCV ID, the other 2 trials compared the single vaccination with Porcilis PCV ID with the concurrent use of Porcilis PCV ID and Porcilis M Hyo ID ONCE. In all 3 farms an active PCV2 infection was present while in 2 farms evidence for *M. hyopneumoniae* active infection was found. In all trials approximately 300 piglets were included per group, primary efficacy parameters were ADWG in the finishing period and PCV2 viraemia. Secondary parameters of efficacy were overall ADWG, mortality, morbidity and PCV2 faecal shedding, as well a lung lesion scores. One (1) study was designed to evaluate mortality in addition to the parameters above; approximately 600 piglets were included per group for this purpose.

The efficacy of Porcilis PCV ID in the following studies has been demonstrated using the IDAL multi-dose needle-free injection device.

Field study 2:

A clinical study in the Netherlands was conducted to assess the efficacy of a single vaccination of piglets at an age of 3 weeks with Porcilis PCV ID.

This field study was performed on a Dutch herd with confirmed PCV2 infection but no routine vaccination against PCV2 according to a randomised, blinded (laboratory) and controlled design. Piglets (*n*=567) from three production batches, 18-24 days of age, were allocated to one of two groups. One group (PCV) was vaccinated intradermally, using the IDAL injector, with one dose of Porcilis PCV ID and the control group remained untreated. Primary efficacy parameters were ADWG in the finishing period and PCV2 viraemia. Secondary parameters were overall ADWG, mortality, morbidity and PCV2 faecal shedding. Pigs were weighed individually at the start of the study, at transfer to the finishing unit and prior to slaughter. Serum samples and rectal swabs were taken from 30 animals per group at regular intervals for PCV2 serology and qPCR.

The ADWG during finishing was 31.6 g/day higher in the PCV group compared to the controls, this difference was statistically significant. The overall ADWG was 20.2 g/day higher in the PCV group, which was also significant. Mortality was not significantly different between the groups (controls 6.7%, PCV 8.5%), and neither was morbidity (7% in both groups). PCV2 viraemia (mean AUC) was 2.94 for the PCV group and 29.70 $\log_{10}$ copies/µl DNA*week for the controls, a difference that was found to be statistically significant. PCV2 excretion (PCV2 in rectal swabs, AUC) was 7.28 for the PCV group and 19.91 $\log_{10}$ copies/µl DNA*week for the controls, which was a statistically significant difference. Results of PCV2 serology (IgG and IgM) indicated both groups had comparable levels of MDA, in the PCV group a response to vaccination (week 4) and in the controls a response to a field infection (from week 7) could be observed.

In conclusion the study confirms reduction of virus load and excretion in vaccinates, as determined in the laboratory studies. In addition the ADWG was improved in vaccinates. A difference in mortality was not observed.

Field study 3:

A clinical study in Hungary was conducted to assess the efficacy of a single vaccination with Porcilis PCV ID given alone and concurrently with Porcilis M Hyo ID ONCE in piglets at an age of 3 weeks.

This GCP-compliant study was performed in a Hungarian pig herd with confirmed PCV2 and *M. hyopneumoniae* infections, according to a randomized, blinded and controlled design. Piglets (n=1,810) of 18-24 days of age were allocated randomly to one of three groups: the first group (PCV) was vaccinated with one dose of Porcilis PCV ID, the second (PM) with one dose of Porcilis PCV ID and

concurrently one dose of Porcilis M Hyo ID ONCE at the same time at different sites, the third group (controls) remained untreated. Both vaccines were administered by IDAL injection device. All included animals were used to assess an effect on mortality. The first 940 animals included were used to assess an effect on ADWG and morbidity while approximately 40 animals in each group were used to assess PCV2 viraemia and faecal shedding. The primary efficacy parameters were ADWG during finishing, PCV2 viraemia and mortality, secondary efficacy parameters were overall ADWG, PCV2 faecal shedding and morbidity. Pigs were weighed individually at the start of the study, at transfer to the finishing unit and prior to slaughter. Serum samples and rectal swabs were taken from 40 animals per group at regular intervals for PCV2 and M Hyo serology and PCV2 qPCR. Lung lesion scoring for M Hyo could not be performed as pigs were routinely slaughtered outside Hungary.

The ADWG during finishing was 44.5 g/day higher in the PCV group and 50.9 g/day higher in the PM group compared to the controls; these differences were statistically significant. The ADWG in PCV and PM groups was not significantly different. Overall ADWG was 25.0 g/day higher in the PCV group and 29.7 g/day in the PM group compared to the controls, this difference was statistically significant while the difference between PCV and PM groups was not. PCV2 viraemia (AUC) was 0.66 in the PCV group, 0.00 in the PM group and 23.85 $\log_{10}$ copies/µl DNA*week, which was found to be a statistically significant difference. The difference between the PCV and PM groups was not significant. Surprisingly, PCV2 Faecal shedding (AUC) was highly similar for all three groups (PCV: 23.04, PM: 23.55, controls: 23.86 $\log_{10}$ copies/µl DNA*week), for which no explanation was found. Retesting of some of the serum and faecal samples in the qPCR revealed no laboratory errors. Morbidity was not significantly different between the 3 groups. Mortality was 9% for the PCV group, 9% for the PM group and 14% for the control group, the differences between PCV and controls and between PM and controls were statistically significant while there was no significant difference between the PCV and the PM group. Due to errors in the performance of the trial, lymphnodes from dead pigs were not all collected and tested for PCV2 (137 tested, 55 missing), data were therefore not analysed statistically albeit the average viral load and percentage positive samples was lower in both vaccinated groups compared to the controls. Results of PCV2 serology (IgG and IgM) indicated the three groups had comparable levels of MDA, in the PCV and PM groups a response to vaccination (week 4) and in the controls a response to a field infection (from week 10) could be observed. Results of M Hyo serology indicated a response to vaccination in the PM group only and a response to a field infection in all groups from week 10 onward.

In conclusion the study confirms reduction of virus load and excretion in vaccinates, as determined in the laboratory studies. The ADWG was improved and a significant reduction in mortality was observed in vaccinates. In addition, the results confirm that concurrent use with Porcilis M Hyo ID ONCE does not affect the efficacy of the product.

Field study 4:

A clinical study was conducted in Hungary to assess the efficacy of a single vaccination with Porcilis PCV ID given alone and concurrently with Porcilis M Hyo ID ONCE in piglets at an age of 3 weeks.

This GCP-compliant study was performed in a Hungarian pig herd with confirmed PCV2 and *M. hyopneumoniae* infections, according to a randomized, blinded and controlled design. Piglets (n=1322) of 18-24 days of age were allocated randomly to 1 of 4 groups. In total 106 animals did not receive the correct dose of vaccine, these animals were excluded and only the per-protocol;-population was used for evaluation of efficacy parameters. The first group (PCV) was vaccinated with 1 dose of Porcilis PCV ID, the second (PM) with 1 dose of Porcilis PCV ID and concurrently 1 dose of Porcilis M Hyo ID ONCE at the same time at different sites, the third group (M) was vaccinated with 1 dose of Porcilis M Hyo ID ONCE and the fourth group (controls) remained untreated. Both vaccines were administered by IDAL injection device. Primary efficacy parameters were ADWG in the finishing period, PCV2 viraemia and lung lesion scores at

slaughter (M Hyo). Secondary parameters were overall ADWG, mortality, morbidity, PCV2 faecal shedding and pleurisy lesions (M Hyo). Pigs were weighed individually at the start of the study, at transfer to the finishing unit and prior to slaughter. At slaughter all lungs were examined individually and scored for lung lesions and pleurisy. Serum samples and rectal swabs were taken from 60 animals per group at regular intervals for PCV2 serology and qPCR.

Weight gain during the finishing period in the PCV group was significantly larger compared to control and M groups (48.7 and 37.3 g/day respectively), overall ADWG was also significantly larger in the PCV group compared to controls and M group (30.8 and 24.7 g/day respectively). The ADWG for the PM group was significantly higher compared to the M and control groups for all phases; for nursery, finishing and overall the difference was 19.4, 58.3 and 41.9 g/day compared to the controls and 23.0, 46.9 and 35.7 g/day compared to the M group. ADWG in PM and PCV groups were not significantly different. Average lung lesion scores were 3.4 and 4.2 in the PM and M groups compared to 7.7 and 6.4 in the control and PCV groups, this difference was statistically significant. A difference in pleurisy scores between the groups was not observed. Mortality was 8% in the PCV, 5% in the PM, 10% in the M and 11% in the control group, these differences were not statistically significant. Morbidity was similar in all groups (PCV: 3%, PM: 3%, M: 3%, controls: 2%). PCV2 viraemia (AUC) was 2.15 in the PCV group and 2.88 in the PM group, which was significantly lower then in the control (23.77) and M groups (25.50 $\log_{10}$ copies/µl DNA*week). Faecal shedding (AUC) was 9.75 in the PCV group, 9.25 in the PM group and this was significantly lower compared to the control (16.17) and M groups (25.50 $\log_{10}$ copies/µl DNA*week). PCV2 serology (IgG and IgM) indicated all groups had comparable levels of MDA, in the PCV and PM group a response to vaccination (week 4) and in the control and M groups a response to a field infection (from week 7) could be observed. Results of M Hyo serology indicated all groups had comparable MDA titres, a response to vaccination was observed in the PM and M groups and a response indicative of a field infection was seen in all groups after week 16.

In conclusion the study confirms reduction of virus load and excretion in vaccinates, as determined in the laboratory studies. In addition the ADWG was improved in vaccinates. A difference in mortality was not observed. The study confirms that concurrent use of the product with Porcilis M Hyo ID ONCE does not negatively affect the efficacy of the product or the protection achieved by vaccination with Porcilis M Hyo ID ONCE.

Conclusion

In all 3 field efficacy studies ADWG during the finishing period was significantly higher in the vaccinates compared to the controls, as was overall ADWG. PCV2 viraemia was significantly lower in the vaccinates compared to the controls. PCV2 faecal shedding was significantly lower in the vaccinates in 2 field studies, although in one study results were very similar for all groups which was unexpected (based on viraemia) and could not be explained. In the study designed to detect differences in mortality, mortality was found to be significantly lower in the vaccinates (field study 3). Morbidity was not significantly different between vaccinates and controls in any of the studies.

Results from the field studies confirmed the observations in the laboratory studies with regard to reduction of viraemia and virus shedding. Additionally a reduction in the loss of ADWG and a reduction of mortality were found.

Concurrent use of Porcilis PCV2 ID with Porcilis M Hyo ID ONCE did not affect any of the outcomes for the efficacy parameters. Efficacy of Porcilis M Hyo ID ONCE when used concurrently with Porcilis PCV ID was evaluated in one field study; concurrent use did not affect the efficacy of the vaccine.

Intradermal injection device IDAL

The efficacy of the vaccine has been demonstrated using the multi-dose needle-free specific injection device IDAL. Specifications of the device are provided in the dossier.

Overall conclusion on efficacy

The efficacy claims were evaluated in a number of laboratory and field efficacy studies. All laboratory studies were in compliance with Ph. Eur. monograph 5.2.7, field studies were performed under GCP.

No statistically significant differences in efficacy were found between a full and a quarter dose of vaccine (antigen), however, as vaccines with a quarter dose of antigen would be rejected in the finished product potency test, a sufficient antigen overage is applied which provides additional assurance that only protective batches will be released. A detailed analysis of data from several studies showed that MDA at levels routinely found in conventional piglets do not hinder development of immunity after vaccination.

Based on the results of laboratory challenge studies, OOI is considered supported at 2 weeks post vaccination; this includes reduction of viraemia, reduction of virus load in lung and lymphoid tissues and reduction of virus shedding.

Laboratory study results indicate that protective immunity lasts for 23 weeks post vaccination. The claim for reduction of ADWG losses was adequately supported by results of the field studies. Results of field trials confirmed the reduction of PCV2 viraemia and faecal shedding as observed in the laboratory trials. The claim for reduction of mortality is supported by results from one field trial specifically designed to detect differences in mortality rate.

Evidence was provided for efficacy of Porcilis PCV ID when used concurrently with Porcilis M Hyo ID ONCE. Based on the data provided, the following indications can be accepted:

For the active immunisation of pigs to reduce viraemia, virus load in lung and lymphoid tissues and virus shedding caused by PCV2 infection. To reduce loss of daily weight gain and mortality associated with PCV2 infection.

The efficacy of the vaccine has been demonstrated using the multi-dose needle-free specific injection device IDAL. Specifications of the device were adequately provided.

Part 5 – Benefit-risk assessment

Introduction

Porcilis PCV ID is a ready to use liquid adjuvanted vaccine containing baculovirus-expressed PCV2 ORF2 subunit antigen. It is intended for intradermal use, in finishing pigs from 3 weeks of age. The intradermal application route was developed with the aim to reduce the basic vaccination schedule to a single dose. Porcine circo virus disease (PCVD) is a disease associated with production losses, affecting the global swine industry. Economic loss associated with PCVD is often the result of a complex interaction between, circovirus, mycoplasma and other infections, poor management and poor environmental conditions.

The dossier was submitted in line with requirements of Article 12(3) of Directive 2001/82/EC.

Benefit assessment

Direct therapeutic benefit

Well conducted controlled clinical trials demonstrated that Porcilis PCV ID is efficacious for the active immunisation of fattening pigs with a minimum age of 3 weeks to reduce viraemia, virus load in lungs and lymphoid tissues and virus shedding caused by PCV2 infection during the finishing period. Therapeutic benefit was further demonstrated by reduction of loss of daily weight gain and mortality associated with PCV2 infection in vaccinated pigs during the finishing period.

OOI was satisfactorily demonstrated at 2 weeks (14 days) post vaccination and DOI was shown to last for 23 weeks (161 days) post vaccination.

The efficacy of the vaccine was adequately confirmed in the presence of MDA.

Additional benefits

Porcilis PCV ID requires a single dose administration of the vaccine to piglets which, in addition to the intradermal injection with a needle-free application device, improves animal welfare.

The efficacy of Porcilis PCV ID when used concurrently with Porcilis M Hyo ID ONCE on the same day, at a different application site is comparable to single use of both vaccines. Concurrent use further reduces the number of times piglets are handled and thereby improves animal welfare.

Risk assessment

Main potential risks have been identified as follows:

Quality:

The formulation and manufacture of Porcilis PCV ID is well described and specifications set will ensure that product of consistent quality will be produced provided that conditions are fulfilled.

For the target animal:

The product is generally well tolerated in the target animal. Safety trials performed in the most sensitive category (3 week old piglets) show that transient local reactions at the injection site are very common consisting of a biphasic pattern and occur in the form of soft or hard, warm swellings of up to 2 cm diameter that disappear within 5 weeks. Systemic reactions to vaccination were not observed. The adverse reactions are appropriately reflected in the SPC. Safety of concurrent use of the product with Porcilis M Hyo ID ONCE was demonstrated; however, there was some indication for enhanced local reactions, which is adequately reflected in the SPC. No specific safety studies have been performed to assess the impact of vaccination on reproductive performance, this is justified as the vaccine is intended for finishing pigs and a warning is included in the SPC.

All safety and efficacy studies were performed using a specific needle-free intradermal injection device IDAL, it is unclear how the vaccine would perform when applied with any other device. The recommended use of the IDAL is adequately reflected in the SPC.

For the user:

Risk to the user can occur after accidental injection also considering that the product contains a mineral oil adjuvant. The user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

For the environment:

The product is not expected to pose any risk to the environment when used as recommended.

For the consumer:

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

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, consumer, and the environment and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

The product has been shown to effectively induce active immunity in finishing pigs to reduce viraemia, virus load in lungs and lymphoid tissues and virus shedding caused by PCV2 infection. The formulation and manufacture of Porcilis PCV ID is adequately described and set specifications will ensure that a finished product of consistent quality will be produced. Porcilis PCV ID is well tolerated by the target animals and presents an acceptable risk for users when used as recommended and the environment and appropriate warnings have been included in the SPC. The withdrawal period is set at zero days.

The product has been shown to have a positive benefit-risk balance overall.

Conclusion on benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete SPC and product literature.

Conclusion

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

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP recommends the granting of the marketing authorisation for Porcilis PCV ID.