SCIENTIFIC DISCUSSION

1.1 Introduction

M-M-RVAXPRO is a trivalent vaccine containing the components of M-M-RII (more attenuated vaccine strain of measles virus (derived from Enders' attenuated Edmonston strain), the Jeryl Lynn strain of mumps virus, the Wistar RA 27/3 strain of live attenuated rubella virus). The only difference between M-M-RII and M-M-RVAXPRO resides in the replacement of human serum albumin (HSA) in M-M-R II with recombinant human albumin (rHA) during the manufacturing of measles, mumps, and rubella viral bulks. The rHA approved for use in the manufacture of M-M-RVAXPRO is Recombumin, a proprietary product manufactured by Delta Biotechnology Limited, UK, produced without the use of animal derived materials. The application for M-M-RVAXPRO also aims at harmonising the expiry titer for the mumps component of this combination vaccine to 4.1 $\log_{10}$ $TCID_{50}$/dose and harmonising the prescribing information across the EU. M-M-RVAXPRO is indicated for simultaneous vaccination against measles, mumps and rubella in individuals from 12 months of age.

Measles (rubeola) is caused by a paramyxovirus of the genus Morbillivirus and is transmitted from person to person via aerosolized or large respiratory infectious droplets. The clinical presentation consists of prodromal fever, conjunctivitis, coryza, and cough. In some cases, Koplik spots (an erythema with white spots in the buccal mucosa) can be observed. Subsequently, a maculopapular rash usually appears, spreads from the head to the entire body, and fades within 4 to 7 days. Measles can result in otitis media, pneumonia, encephalitis and death.

Mumps is caused by a paramyxovirus of the genus Rubulavirus and is spread by direct contact via the respiratory route. The clinical presentation is characterized by swelling of one or more salivary glands (usually the parotid glands) and may be preceded by several days of non-specific symptoms, including fever, lymphadenopathy, headache, malaise, myalgias, and anorexia. Mumps can result in deafness, orchitis, pancreatitis, meningitis, encephalitis and death.

Rubella is caused by a togavirus of the genus Rubivirus and is spread via infectious droplets shed from the respiratory secretions of infected persons to susceptible individuals. The clinical presentation is characterized by nonspecific signs and symptoms including transient erythematous and sometimes pruritic rash, postauricular or suboccipital lymphadenopathy, and low-grade fever. The most important consequences of rubella are the miscarriages, stillbirths, fetal anomalies, and therapeutic abortions, associated with Congenital Rubella Syndrome (CRS) that result when rubella infection occurs during early pregnancy. Anomalies associated with CRS include sensorineural deafness, cataracts, glaucoma, and other ophthalmic disorders, cardiac defects, microcephaly, meningoencephalitis and mental retardation.

1.2. Quality aspects

Introduction

The finished product is presented as a powder and solvent for suspension for subcutaneous injection in a single 0.5 ml dose. The lyophilised vaccine must be stored in the refrigerator. The lyophilised powder is presented in a vial (Type 1 glass) with a butyl rubber stopper and flip-off aluminium seal. The finished product contains the following excipients: sucrose, hydrolysed gelatin (porcine), sorbitol, monosodium glutamate, sodium phosphate, sodium bicarbonate, potassium phosphate, Medium 199

with Hanks' Salts, Minimum Essential Medium Eagle (MEM), neomycin, phenol red, hydrochloric acid and sodium hydroxide (pH adjustment).
Before use, each vial is to be reconstituted with water for injections supplied in either a vial (Type 1 glass) with a butyl rubber stopper or in a prefilled syringe (Type 1 glass) with plunger stopper and tip cap (chlorobutyl rubber), with or without needle(s).

After reconstitution, one dose (0.5 ml) contains:

Measles virus[1] Enders' Edmonston strain (live, attenuated) .....not less than $1x10^3$ $TCID_{50}$*
Mumps virus[1] Jeryl Lynn™ (Level B) strain (live, attenuated) .....not less than $12.5x10^3$ $TCID_{50}$
Rubella virus[2] Wistar RA 27/3 strain (live, attenuated) .....not less than $1x10^3$ $TCID_{50}$

* 50% tissue culture infectious dose

([1]) Produced in chick embryo cells.
([2]) Produced in WI-38 human diploid lung fibroblasts.

The product also contains traces of rHA, used in the bulk manufacturing process of the vaccine.

Active substance - measles

- ***Manufacture***

Seed lot system

The Enders' Edmonston strain of measles virus was isolated in primary human kidney cell tissue culture from the blood of a child (Edmonston) in the early acute phase of measles. The virus (10 ml) was received by Merck from Dr. John Enders at the Children's Hospital of Harvard Medical School in 1960. Further passages were performed at Merck to develop the Moraten (more attenuated Enders) strain that served as a pre-master seed from which the Master Seed was derived. The preparation of the Master Seed and the Stock Seed is appropriately described in the dossier.

Chicken embryo cells (CEC) as cell substrate

Chick embryo cells, the cell substrate for measles and mumps virus propagation, are sourced from eggs from a specific-pathogen-free (SPF) chicken flock. Embryos are removed from the eggs, dissociated with trypsin, clarified and centrifuged prior to virus infection.

Manufacture of measles harvested virus fluids (HVFs)

A virus propagator, a stainless steel tank, is planted with CEC suspension. The cells are infected with an appropriate volume of thawed measles stock seed, added to the seeding medium, stirred and incubated. The cell sheets are rinsed and refed several times, and the virus propagators are harvested. HVF is sampled for virus potency and sterility.

Manufacture of redispensed bulk

Harvests from one or more batches of HVF may be used to produce a single batch of measles vaccine bulk. The final bulk is dispensed in cans (*dispensed bulk*) and stored frozen. The dispensed bulk cans comprise a batch of drug substance. The dispensed bulk is thawed and used for filling or redispensed into aliquots appropriate for filling (*redispensed bulk*). The redispensed bulk is stored frozen until used in final product formulation. Samples for QC are drawn from the appropriate different bulk stages.

Control cell Cultures and Harvest Control Fluids (HCFs)

Uninfected harvested control fluids (HCF) are produced using the same cell substrate and culture media. Before the final collection of the HCF, control cell monolayers are examined microscopically throughout the harvest period.

Controls of materials and critical steps / process validation

The CEC substrate used in the manufacture of measles vaccine bulk is tested according to Ph. Eur. requirements.

Testing of the measles stock seed is consistent with the Ph. Eur., Section 2.6.16 and the monograph for Measles Vaccine (Live), with the exception of the virus identification test. Identity testing is instead performed post-clarification on the vaccine bulk, where antibody neutralization can be performed on a clarified bulk virus solution.

Critical process parameters (CPPs), critical quality attributes (CQAs), and their specifications/acceptance criteria are based on historical process capability, current manufacturing specifications, and the specifications defined in the company's monovalent measles vaccine license.

Process validation was both retrospective and prospective. Retrospective validation of measles vaccine manufactured with HSA was first used to determine acceptable ranges; a prospective validation of measles vaccine manufactured with rHA was then performed to demonstrate conformity of the processes to validation specifications. Within each manufacturing process step, goals, CPPs and CQAs were determined, along with appropriate specifications and acceptance criteria.

- ***Characterisation and specifications***

The complete nucleotide sequences for the Stock Seed (and a monovalent measles filled container vaccine lot and a clarified measles bulk lot manufactured with rHA have been determined. Nucleotide sequence alignment showed complete agreement.

Process-related impurities arising from the measles vaccine bulk manufacturing processes are classified as cell substrate- or cell culture-derived. Cell substrate-derived impurities may include proteins derived from the host organism, such as CECs used as substrate for measles vaccine bulk production. Cell culture-derived impurities may include antibiotics (e.g., neomycin), serum, or other media components. Also low levels of particle-associated reverse transcriptase activity are found; however, no signal of infectious retrovirus could be detected.

Since the measles process uses cell growth medium containing fetal bovine serum (FBS), measures have been taken to minimize the concentration of bovine serum proteins in the vaccine bulk. The concentration of bovine serum albumin (BSA) is used as a surrogate marker for other bovine serum proteins. Each measles final bulk is tested for BSA.

Measles vaccine bulk is an unpurified product whose potency was measured through a biological assay for the active substance rather than through evaluation of integrity of physical form. Degradation products are neither identified nor quantified.

Tests are performed at specified stages of vaccine bulk processing in order to confirm absence of extraneous agents, to verify potency and identity, and to provide a measure of quality and process consistency. Most assays performed on measles bulks are qualitative methods for which there are only two outcomes (growth or no growth, absence or presence, etc.). In many of these cases, the assay specifications are compendial.

The validation was performed using the assay procedure that was in place at the time the assays was validated. The parameters that were evaluated as part of the method validation for the assays have been provided for each analytical procedure. When applicable, the assay parameters addressed were specificity, inter-assay precision, limit of detection, limit of quantification, linearity, range, ruggedness, and robustness.

Batch analysis results have been provided for HVF/HCF lots and dispensed bulk lots; all results met specifications.

The reference standard used in potency testing is a monovalent measles vaccine lot manufactured using currently approved processes. The applicant committed to characterize the performance of the measles potency assay with international reference standards.

- ***Stability***

Formal stability studies were initiated on three lots of measles harvested virus fluids and three lots of pooled clarified bulk vaccine manufactured with rHA. These harvested virus fluids lots are considered representative of the individual harvests. The pooled clarified bulk vaccine is prepared from the pooled harvested virus fluids lots above.

Stability results for three lots of measles harvested virus fluids and three lots of measles pooled clarified bulk are available. All results to date meet the protocol acceptance criteria.

Active substance - mumps

- ***Manufacture***

Seed lot system

The Jeryl Lynn strain of mumps virus was isolated from a throat washing specimen collected in 1963 from a clinical case of mumps (Jeryl Lynn) by Dr. M. R. Hilleman, Merck Research Laboratories, Merck & Co., Inc. Virus strain isolation was performed at the Merck West Point, Pennsylvania facility. The preparation of the master seed and the stock seed is described in detail in the dossier.

Manufacture of mumps harvested virus fluids (HVFs) and redispensed bulk

CEC are planted in a similar manner to the process described for measles. Post-infection, the virus propagators are refed, the spent medium is drained and discarded; the virus harvest is collected. The HVFs are sampled for virus potency and sterility and shell frozen.

The redispensed bulk is manufactured in a similar manner to the process described for measles.

Control Cell Cultures and Harvest Control Fluids (HCFs)

The HCFs are manufactured in a similar manner to the process described for measles.

Controls of materials and critical steps / process validation

The seed testing is consistent with the Ph. Eur., Section 2.6.16 and monograph for Mumps Vaccine (Live), with the exception of the virus identification test. Identity testing is instead performed post-clarification on the vaccine bulk, where antibody neutralization can be performed on a clarified bulk virus solution.

Definition of CPPs and process validation were performed in a similar manner as for measles.

- ***Characterisation and specifications***

The complete consensus nucleotide sequence of the Stock Seed, and partial nucleotide sequences for an HSA-containing vaccine bulk lot and a rHA-containing bulk lot have been determined. To assess the population diversity of the stock seed and bulk product, the JL-strain specific nucleotide sequences were determined and results provided in the dossier.

Process-related impurities arising from the mumps bulk manufacturing processes may be classified as cell substrate-derived or cell culture-derived. Since the mumps process uses cell growth medium containing fetal bovine serum (FBS), mumps bulk lots were tested for BSA and the results for all of these lots were within the specification.

Mumps vaccine is an unpurified product whose potency is measured through a biological assay for the active substance rather than through evaluation of integrity of physical form. Degradation products are neither identified nor quantified.

The testing (and method validation) of the mumps bulk is essentially the same as for the measles bulk. Batch analysis results have been provided for HVF/HCF lots and dispensed bulk lots; all results met specifications.

The reference standard used in potency testing is a monovalent mumps vaccine lot manufactured using currently approved processes. The applicant committed to characterize the performance of the mumps potency assay with international reference standards.

- ***Stability***

Formal stability studies were initiated on three lots of mumps harvested virus fluids and three lots of pooled clarified bulk vaccine manufactured with rHA. For the mumps component, each harvested virus fluid lot placed on stability was produced by the pooling of three independent harvested virus fluid lots. These harvested virus fluid stability lots are considered representative of the individual harvests. The three pooled clarified bulk vaccine lots are prepared from the pooled harvested virus fluids lots above.

Stability results for three lots of mumps harvest fluids and three lots of pooled clarified bulk vaccine are available**.** All results to date meet the protocol acceptance criteria.

Active substance - rubella

- ***Manufacture***

<u>Seed lot system</u>

The Wistar RA 27/3 strain of rubella virus was isolated in 1964 by Dr. Stanley Plotkin, Wistar Institute of Anatomy and Biology, Philadelphia, Pennsylvania, U.S., from a kidney explant obtained from a surgically aborted foetus. It was directly inoculated into WI-38 cells, and then attenuated.

The preparation of the Master Seed and the Stock Seed is appropriately described in the dossier. Release testing results were presented for both Virus Stock Seed Lots.

<u>Human diploid fibroblast cells (WI-38) as cell substrate</u>

The source of the cell substrate used in the manufacture of rubella vaccine is female, embryonic, human, lung tissue (WI-38) obtained from the Karolinska Institut, Stockholm, Sweden in 1962. Primary cells were isolated and a cell suspension was prepared at a population doubling level (PDL) of 8. Frozen ampoules of cells at PDL of 8 were sent to the American Type Culture Collection (ATCC) for storage.

WI-38 working cell banks (WCBs) are prepared using appropriate cells from the ATCC. WCB lots have been used in clinical trials; in the meantime, the stock for these two WCBs has been depleted and a new WCB lot was manufactured by the method described in the dossier and has passed all release testing.

Manufacture of rubella harvested virus fluids (HVFs)

An appropriate number of WCB ampoules are expanded to create a sufficient amount of cell substrate. Post-plant, the spent medium is removed and discarded. A sufficient quantity of rubella stock seed is added. Following virus adsorption, the infected cells are refed and incubated.

Post-infection, the spent medium is removed and discarded; the cell sheets are rinsed, refed and incubated.

The first HVF are collected, pooled and mixed with a stabilizer. The HVF is stored frozen and sampled for virus potency and sterility.

Manufacture of redispensed bulk

Harvests from one or more batches of HVF may be used to produce a single batch of rubella dispensed bulk which is redispensed into appropriate aliquots. The dispensed bulk cans comprise a batch of drug substance. The redispensed bulk is stored frozen until used in final product formulation. The redispensed bulk is diluted to target fill potency during the formulation of M-M-RVAXPRO.

Control Cell Cultures and Harvest Control Fluids (HCFs)

Control roller bottles and HCFs are prepared in analogy with the HVFs.

Controls of materials and critical steps / process validation

WI-38 cells from each WCB are passaged to the vaccine production PDL level or beyond to demonstrate safety and acceptable karyology at the PDL intended for use in harvested virus fluid (HVF) manufacturing. Release testing is described at appropriate process steps and will be performed in compliance with Ph. Eur 5.2.3.

Testing of the rubella stock seed is consistent with the Ph. Eur., Section 2.6.16 and the monograph for Rubella Vaccine (Live), with the exception of the virus identification test. Identity testing is instead performed post-clarification on the vaccine bulk, where antibody neutralization can be performed on a clarified bulk virus solution.

Definition of CPPs and process validation were performed in a similar manner as for measles.

- ***Characterisation and specifications***

Rubella virus stock seed and bulk vaccine product derived from each stock seed as well as bulk vaccine product derived from a clarified bulk lot manufactured with rHA showed complete agreement in the nucleotide sequence alignment.

Process-related impurities arising from the rubella vaccine bulk manufacturing processes are classified as cell substrate- or cell culture-derived. Since the rubella process uses cell growth medium containing fetal bovine serum (FBS), rubella bulk lots were tested for BSA and the results for all of these lots were within the specification.

Rubella vaccine bulk is an unpurified product whose potency is measured through a biological assay for the active substance rather than through evaluation of integrity of physical form. Degradation products have been neither identified nor quantified.

Tests are performed at specified stages of vaccine bulk processing in order to confirm absence of extraneous agents, to verify potency and identity, and to provide a measure of quality and process consistency. Most assays performed on rubella bulk are qualitative methods for which there are only two outcomes (growth or no growth, absence or presence, etc.). In many of these cases, the assay specifications are compendial.

The validation was performed using the assay procedure that was in place at the time the assays was validated. The parameters that were evaluated as part of the method validation for the assays were provided for each analytical procedure. A qualification of the test methods using rubella material manufactured with rHA has been conducted.

Batch analysis results have been provided for HVF/HCF lots and dispensed bulk lots; all results met specifications.

The reference standard used in potency testing is a monovalent rubella vaccine lot manufactured using the currently approved process. The applicant committed to characterize the performance of the rubella potency assay with international reference standards.

- ***Stability***

Formal stability studies were initiated on three lots of rubella harvested virus fluids and for three lots of pooled clarified bulk vaccine manufactured with rHA. For the rubella component, each harvested virus fluids lot placed on stability was produced from the pooling of a maximum of ten harvests. These harvested virus fluids lots are considered representative of the individual harvests. The pooled clarified bulk vaccine is prepared from the pooled harvested virus fluids lots above.

Stability results for three lots of rubella harvested virus fluids and three lots of pooled clarified bulk are available. All results to date meet the protocol acceptance criteria.

Recombumin 20% (rHA)

Recombumin 20% (w/v), a recombinant human albumin produced in *Saccharomyces cerevisiae*, is purchased from Delta Biotechnology Ltd. and is used as a component of the viral growth medium in the bulk manufacturing process of the M-M-VAXPRO antigens and may be present in the final presentation, as residual traces.

The preparation is sterile, endotoxin-free, contains no preservatives, the purity is not less than 99%. It is formulated with water for injection, sodium chloride, octanoic acid, sodium hydroxide and polysorbate 80. The product is filled in 50 ml Type II glass vials sealed with 20 mm siliconized chlorobutyl gray rubber stoppers secured with aluminium overseals with flip-off white plastic caps.

Recombumin 20% has been developed as replacement for human serum albumin for use in further manufacture of other pharmaceutical products or medical devices. It is equivalent to the native human serum albumin in primary, secondary and tertiary structure as well in binding capacity.

Manufacture

The fermentation and isolation processes have been adequately described in the dossier. Subsequently, the rHA is purified through a series of chromatographic and ultrafiltration steps. Validation data have been provided and critical parameters in the processes have been identified and investigated.
For stabilisation, sodium octanoate is added. For the final bulk, the purified rHA from one or two fermentation procedures can be used. After determination of albumin, octanoate and sodium concentrations in the unformulated bulk product, excipients (octanoate and polysorbate 80) and water for injection are added to achieve the bulk formulated product specification.
After sterile filtration, the formulated product is incubated for 15 days at 31±1°C, a visual inspection is performed post-incubation, followed by final labelling, storage and shipping.

Control of materials and critical steps / process validation

The host yeast strain and expression plasmid have been developed for expression of rHA. The sequence for the full length human albumin cDNA was obtained from published sources and the gene chemically synthesised.

Appropriate in-process controls and specifications for the MCB and WCB have been put in place.

All materials used in the manufacture of Recombumin are of non-human and non-animal origin.

Critical steps are appropriately controlled; process validation studies included process qualifications (including retrospective qualification for process changes, media fills and confirmation batches), impurity clearance studies (yeast DNA, antifoam, yeast antigens, albumin fragments, nickel, mannosylated rHA), hold time studies on intermediates and studies on chromatographic matrices used in the manufacturing process.

Characterisation and specifications

The identity with the native human albumin (commercially available) has been studied with various physicochemical techniques to demonstrate the equivalence of the primary, secondary and tertiary structure of the native human albumin and Recombumin rHA. Comparative binding studies showed the functional similarity.
The Ouchterlony test, competitive ELISA-methods and western blot assays with specific antibodies raised in rabbits demonstrated the absence of neoantigens in Recombumin rHA.

Product-related impurities have been identified as an rHA degradation product with MW of about 45kDa. The fragment comprises residues of the rHA molecule. A specific cleavage site could result from the action of certain yeast proteinases. Process development studies showed that the fragment is removed during purification.
It could be shown by GP-HPLC, that the main impurities in native albumin are polymers, whereas in contrast to the Recombumin rHA, there are no polymers, but dimers and trimers at the same level as in native albumin.

Process-related impurities are yeast DNA, antifoam, yeast antigens, albumin fragments, nickel and mannosylated rHA, which are removed to sufficiently low levels during the purification process

Specification tests include identity, purity, and impurity-testing, and quantity determination. Test parameters identical with HSA testing according Ph. Eur. monograph for HSA are: Octanoate, Protein, Purity, Sterility, polymers, pH and sodium. The levels are identical or lower (impurities and polymers).
With the exception of endotoxin testing and pH, all other tests are validated according to ICHQ2B. The specific parameters have been described in the method description.

Batch analysis data from 23 batches produced between May 1999 and October 2002 were provided and all test results are lower than the specification limits. The results demonstrated a reproducible and consistent production of Recombumin 20%.

The reference standard is in-house material, generated from released Recombumin 20% final batches.

Stability

Three batches were used for the original stability programme. The study was performed at three temperatures (5 °C, 25 °C and 40 °C) with time intervals of 2, 3, 6, 9, 12, 18 and 36 months. The statistical analysis of the data shows that a horizontal storage (worst case) at temperatures up to 27°C will not change the quality of the final product within a time frame of 36 months. Therefore initially a shelf life of 36 month at 2 – 25°C was defined. The stability study was extended with additional time intervals of 48 and 60 months at the 5 (2 – 8) ^{o}C and therefore the shelf life was modified to 60 months at 2 – 8 ^{o}C during the review process.

Critical process parameters (CPPs), critical quality attributes (CQAs), and their specifications/acceptance criteria are based on historical process capability, current manufacturing specifications, and the specifications defined in the company's monovalent measles vaccine license.

Process validation was both retrospective and prospective. Retrospective validation of measles vaccine manufactured with HSA was first used to determine acceptable ranges; a prospective validation of measles vaccine manufactured with rHA was then performed to demonstrate conformity of the processes to validation specifications. Within each manufacturing process step, goals, CPPs and CQAs were determined, along with appropriate specifications and acceptance criteria.

Medicinal Product

M-M-RVAXPRO is a sterile lyophilized vaccine preparation combining the 3 viruses used in the manufacture of the currently licensed M-M-RII vaccine from Merck. Sterile water for injections is provided for reconstitution. The product is intended for single-dose administration and contains no preservative.

- ***Pharmaceutical Development***

The formulation of M-M-RVAXPRO vaccine is appropriately described in the dossier. Four full-scale lots of M-M-RVAXPRO were manufactured for the purpose of evaluating clinical bio-equivalency, consistency of manufacture, and a new slotted stopper. In addition to the latex-free fluted stopper that

is currently used for the M-M-RII vaccine, a latex-free slotted stopper may also be used for the M-M-RVAXPRO vaccine. Stability results for the demonstration lots, including the process validation lot, clinical, and slotted stopper lots were satisfactory.

The diluent has a 0.2 mL overage to cover liquid losses to the inside of the vial when the vaccine is reconstituted.

- ***Manufacture of the Product***

All manufacturing operations for M-M-RVAXPRO are performed at Merck & Co., Inc, West Point, Pennsylvania, and USA.

The manufacture of M-M-RVAXPRO is essentially identical to the process used for the currently licensed M-M-RII with the following differences:

- The vaccine bulks contain rHA in replacement of HSA.
- The final formulated bulk is prepared using albumin-free diluents.
- Filled vaccine containers are sealed with a new slotted stopper in addition to the fluted stopper currently used for M-M-RII.

Batches of M-M-RVAXPRO vaccine are filled and lyophilized. Dilution of dispensed virus bulk with diluent, filling, and lyophilization takes place in a sterile suite under Class-100 laminar flow conditions. Each batch of bulk multivalent vaccine is prepared by aseptically combining aliquots of the three monovalent virus bulk components and their respective diluents to form the Final Formulated Bulk (FFB), which is maintained at 2-8 °C throughout the subsequent vial filling process. The volume of diluent added is dependent on the potency of the bulk virus component lot that is used and is determined by a formula that accounts for yields across processing steps. The virus concentrations in the FFB are controlled to ensure that the amount of virus in the filled container is within specifications at release and remains above the minimum expiry throughout the dating period.

In a Class 100,000 area, vendor-supplied glass vials and stoppers are washed with water for injection using a validated wash cycle. The washed vials are then sterilized in a qualified dry heat sterilizer. The stoppers are siliconized, steam-sterilized and vacuum-dried. The container and container closure system have been validated for compatibility and closure integrity.

Sterile vials are then filled with FFB, partially stoppered and frozen by passage through a qualified freezing tunnel. Trays of frozen product are then loaded onto shelves of a qualified lyophilization cabinet.

Critical process parameters during mixing, sterile filtration, filling and freezing/lyophilising are controlled by appropriate in-process controls.

The consistency of product manufacture for the formulation, filling, and lyophilization of M-M-RVAXPRO was demonstrated using three demonstration lots.

Inspected unlabeled vials are placed in boxes labelled with the product name and number and the filled container lot number, and are stored at -20 °C or colder for up to 18 months until they are transferred for labelling and packaging. After labelling and packaging, the vaccine may be stored for up to 24 months at 2–8 °C.

Both, the sterile diluent in a syringe with fixed-needle and the diluent in a syringe without needle syringe are manufactured by an outside vendor. The diluent in a vial is manufactured by Merck & Co., Inc, West Point, Pennsylvania, USA.

At the outside vendor, Water for Injection (WFI), manufactured by distillation of purified water, is filled into glass syringes and sterilized. Each pre-filled, diluent syringe contains a target volume of 0.75 ml. Raw materials are in accordance with specifications. The manufacturing process is described

in detail and all relevant information regarding quality control, validation of the manufacturing process and stability of the diluent have been provided by the applicant.

At Merck, WFI, manufactured by distillation of purified water, is filled into glass vials and terminally sterilized. Each pre-filled diluent vial contains a target volume of 0.85 ml. The manufacturing process is described in detail and all relevant information regarding quality control, validation of the manufacturing process and stability of the diluent have been provided by the applicant

- ***Product Specification***

The FFB is tested for sterility and neomycin content.. The tests on the filled container include appearance, identity, potency, reconstitution time, pH, moisture, sterility, thermal stability and BSA content. Market containers are retested for viral identity prior to release.

Validation and qualification studies have been performed for assays that are used for routine batch release of M-M-RII and M-M-RVAXPRO final formulated bulk and filled container lots.

Each dose of the vaccine contains at the end of its shelf-life a minimum of 3.0 log $TCID_{50}$ measles virus, 4.1 log $TCID_{50}$ mumps virus and 3.0 log $TCID_{50}$ rubella virus. The release specifications have been selected to ensure that, at expiry, each dose will contain the aforementioned minimum potency for each virus when the vaccine is reconstituted and stored at 2–8 °C for up to 8 hours..

Results of batch release testing have been provided for three demonstration and the clinical trial lots; all lots fulfilled the pre-defined specifications.

All excipients are pharmacopoeial, except hydrolysed porcine gelatin, Medium 199 with Hanks' Salts, Minimum Essential Medium Eagle (MEM) which are controlled in-house.

Because M-M-RVAXPRO is a live virus vaccine composed of measles, mumps, and rubella input bulks prepared from cell culture fluids; it is not a highly purified product. To provide a marker for removal of fetal bovine serum used during the cell culture process, a quantitative test for residual BSA is conducted on the individual input virus bulks. The BSA content of the three input virus bulks is used to calculate the amount of BSA present in the filled container based on the dilution of each bulk during filling.

The reference standards used in measles, mumps, and rubella potency testing are monovalent, lyophilized measles, mumps, or rubella vaccine lots manufactured with HSA that are dedicated for use in potency testing.

The relative potency of test sample to standard is used to calibrate potency of the test material. However, the applicant commits to characterise the performance of the measles, mumps and rubella potency assays with Ph. Eur. Biological Reference Preparations.

- ***Viral Safety and TSE***

<u>Adventitious Agents</u>

The testing program for adventitious agents is described in detail in the chapters on the Measles, Mumps, and Rubella active substances. Where applicable, raw materials used in vaccine manufacturing are tested for adventitious agents prior to release and use in manufacturing. Validated processing steps that add additional levels of confidence for the absence of adventitious agents are filter sterilization and ultraviolet (UV)-irradiation.

<u>TSE</u>

The manufacturing process for M-M-RVAXPRO was evaluated for the theoretical risk of transmission of infectivity associated with BSE prions, with the conclusion that the risk of BSE transmission in M-M-RVAXPRO is exceedingly remote. The rationale and the calculation for the theoretical risk of transmission of infectivity associated with BSE prions were provided.

Biological reagents used in the manufacture of the vaccine or intermediates include fetal bovine serum (FBS), porcine pancreatic trypsin, porcine-derived hydrolyzed gelatine, choline chloride, bovine or porcine tallow-derived polysorbate 80, fish or sheep wool-derived cholesterol, and amino acids. Certificates of Suitability (CoS), which are granted by the European Directorate for the Quality of Medicines (EDQM), and the measures applied (e.g. regular audits of vendor facilities, testing to ensure that the appropriate quality standards are met, etc.) ensure that the ruminant-derived raw materials currently used in manufacturing are free of transmissible spongiform encephalopathy (TSE) or bovine spongiform encephalopathy (BSE) contamination.

- ***Stability of the Product***

Stability tests have been designed to measure product performance under anticipated handling and storage conditions and under stressed conditions that might be encountered after distribution. The anticipated conditions following lyophilization were studied. Upon use, the vaccine is reconstituted and may be stored for up to 8 hours at 2–8 °C prior to injection.

Stability studies were conducted on the demonstration, clinical, and slotted stopper lots at various temperatures to support the storage conditions of the vaccine. The presented data on the M-M-RVAXPRO stability lots showed that all three virus components are within the pre-determined specifications. Based on the presented stability data a shelf-life of 24 months at 2–8 °C can be granted.

Post-launch vaccine lots will be included in the annual stability program for the purpose of routine monitoring. A minimum of three lots per year of M-M-RVAXPRO or M-M-R II will be recruited as annual stability lots. Appropriate testing will be performed through product expiry.

For the diluent in a vial, the stability data support the product shelf life, routine handling, and an expiry of 36 months after storage at room temperature. For the diluent in a pre-filled syringe, the Applicant provided certificates of a stability study performed on the glass syringes.

Discussion on chemical, pharmaceutical and biological aspects

During the evaluation of M-M-RVAXPRO, a number of minor quality-related issues were identified. These related mainly to the qualification of the WI-38 cell substrate MCB/WCB for rubella, BSA testing and content, determination of the plasmid copy numbers in Recombumin cell banks, and the conduct of a rHA-specific release test for the M-M-RVAXPRO finished product. The applicant was also asked to characterize the performance of the measles, mumps and rubella potency assay with international reference standards. Regarding the calibration of potency results for measles, mumps and rubella, the demonstrated concordance between reference and test samples ensures that the calibration procedure does not shift sub-potent batches to comply with specifications. The data provided by the applicant satisfactorily address the concerns raised and support the view, that the calibration procedure is suitable and of significance to consistently manufacture vaccine of satisfactory quality.

It should also be noted that M-M-RVAXPRO, as other live attenuated vaccines, only has a few purification steps, resulting in residual traces of rHA in the vaccine. Based on this, the product information includes a statement on the theoretical risk of sensitization reactions to recombinant human albumin.

Several commitments are made by the applicant, and several follow-up measures are defined to provide further information post-approval. In conclusion, all quality issues are resolved.

1.2 Non-clinical aspects

M-M-RVAXPRO is a new vaccine based on well known trivalent measles, mumps, and rubella live attenuated combination vaccine which is currently manufactured using pooled serum-derived human serum albumin (HSA) as a component of the viral growth media in the bulk manufacturing process and as a component of the bulk diluents at formulation of the final product and authorised in many countries worldwide since 1978. The difference relates to the substitution of HSA by recombinant human albumin (rHA) in the bulk manufacturing process to address ongoing safety and sourcing concerns related to human blood-derived products. rHA is a recombinant protein produced in yeast and is structurally and analytically comparable to the unmodified monomeric population of HSA. Experimental data have confirmed that the substitution of rHA for HSA in the viral growth media result in satisfactory vaccine virus growth and product characteristics. Thus, rHA and HSA are considered functionally comparable for the production of viral bulks.

Pharmacology

Live virus vaccines require virus growth following vaccination in order to induce an immune response. Since measles, mumps, and rubella are the active pharmaceutical components, and since there is an obligate requirement, as biological agents, to replicate in order to induce immunity, direct pharmacodynamic assessment of the active components is not meaningful. For this reason traditional pharmacology studies were not conducted with measles, mumps, and rubella (live) vaccine with rHA, or its licensed vaccine components; however extensive safety testing was performed on cell cultures, cell banks, master and working seeds, and viral bulks to assure the safety of the final container vaccine. This was considered acceptable also supported by the Note for Guidance on the Preclinical Pharmacological and Toxicological testing of Vaccines (CPMP/SWP465/95) and by the CHMP scientific advice.

Pharmacokinetics

Experimental studies to demonstrate absorption, distribution, metabolism and excretion of the active ingredients in M-M-RVAXPRO have not been performed for any of the component viruses. These studies are not relevant for evaluation of live, attenuated viral vaccines, which induce their immunogenic response as a consequence of virus replication. Thus, it is known that a subcutaneous injection of either measles, mumps, and rubella (live) vaccine with rHA or measles, mumps, and rubella (live) vaccine with HSA results in limited virus replication. This is in line with the Note for Guidance on the Preclinical Pharmacological and Toxicological testing of Vaccines (CPMP/SWP465/95).

Toxicology

No toxicological studies have been performed for measles, mumps, and rubella (live) vaccine with with rHA, or for any of the vial components (measles, mumps, rubella).

Clinical experience with the existing measles, mumps, and rubella vaccine (live) has been accumulated over decades. In addition, for M-M-RVAXPRO extensive testing has been performed on material obtained at various steps in the manufacturing process to assure that each vaccine bulk and each finished product is free from adventitious agents that might be introduced during manufacturing. As described under the quality part of this document, testing includes analysis for absence of specific microbial contaminants (absence of mycoplasma, mycobacterium), microbial sterility, and absence of specific viral agents (ALV virus in measles and mumps bulk vaccine) and general viral adventitious agents (bulk vaccine). Absence of adventitious agents is determined using tissue culture safety tests, egg safety tests, animal safety tests (adult mice and suckling mice), and in general safety tests, (guinea pigs and mice).
It was therefore considered that toxicological testing would not provide additional information on the safety profile of this new vaccine, especially since rHA was subjected to separate toxico-pharmacological testing using concentrations by far exceeding those being present in the vaccine.
The absence of toxicological studies was therefore considered acceptable, also supported by the Note for Guidance on the Preclinical Pharmacological and Toxicological testing of Vaccines (CPMP/SWP465/95) and by the CHMP scientific advice.

Ecotoxicity/environmental risk assessment

An assessment of the risk was performed and no significant risk to the environment related to the use of this vaccine is anticipated.

1.3 Clinical aspects

Introduction

Measles, mumps, and rubella live attenuated vaccine has been authorised in all EU countries from 1978 to 1999 based on the results from several studies conducted comparing the immunogenicity, safety, and tolerability of different combinations (monovalent, bivalent, and trivalent) of measles, mumps and rubella vaccines. These trials were not conducted according to current Good Clinical Practices standards and therefore the results have been provided with this application only as supportive.

This new childhood vaccine has been developed:

- to harmonise the expiry titer for the mumps components of this combination vaccine to 4.1 log10 tissue culture infectious dose 50 (TCID50)/dose;
and
- to support the replacement of HSA with rHA in the manufacturing of the viral bulk.

The clinical development includes:
- a mumps end-expiry clinical study (Protocol 007)
- a rHA replacement clinical study (Protocol 009)
An overview of these studies is displayed in table 1.

Table 1: Summary of pivotal studies

Study	Study Title	Primary Study Objectives
007	A Study of measles, mumps, and rubella vaccine (live) at Mumps Expiry in healthy children 12 to 18 months of age	(1) To demonstrate a similar immune response to mumps virus by neutralization among subjects receiving measles, mumps, and rubella vaccine (live) containing an expiry dose of mumps virus concomitantly compared to subjects receiving measles, mumps, and rubella vaccine (live) containing a release dose of mumps virus, both used concomitantly with varicella vaccine live. (2) To demonstrate an adequate immune response among subjects receiving measles, mumps, and rubella vaccine (live) containing an expiry dose of mumps.
009	A Comparison of the Safety, Tolerability, and Immunogenicity of M-M-RVAXPRO manufactured with rHA Versus measles, mumps, and rubella vaccine (live) manufactured with HSA in Healthy Children 12 to 18 Months of Age	(1) To demonstrate that the antibody response rates to measles, mumps, and rubella among children who receive measles, mumps, and rubella virus vaccine live manufactured with rHA will be similar to the antibody response rates among children who received measles, mumps, and rubella vaccine (live) manufactured with HSA. (2) To demonstrate that who received measles, mumps, and rubella vaccine (live) manufactured with rHA will induce acceptable antibody response rates to measles, mumps, and rubella. *(3) To demonstrate that who received measles, mumps, and rubella vaccine (live) manufactured with rHA will be generally well tolerated.*

There are no fundamental changes proposed in the indication or dosing schedule of this new vaccine compared to the authorised one.

The approved indication is:

"for simultaneous vaccination against measles, mumps and rubella in individuals 12 months or older. For use in measles outbreaks, or for post-exposure vaccination of non-pregnant adolescent and adult subjects, or, previously unvaccinated children older than 12 months who are in contact with susceptible pregnant women, and persons likely to be susceptible to mumps and rubella".

Pharmacokinetics

No pharmacokinetics studies have been conducted. Although live attenuated viral vaccines actively replicate in the vaccine, decades of experience with the pathology of wild-type measles, mumps and rubella viruses as well as with the corresponding live attenuated vaccines do not provide evidence that wild and vaccine viruses do persist for an extended period of time in the body nor that they do enrich in specific body tissues. In very rare exceptions measles wild-type virus (but not the attenuated vaccine virus) might persist in the body resulting in the clinical-pathological manifestation of Subacute Sclerotic Pan-Encephalitis (SSPE). Also in view of the limited number of doses administered (a maximum of two during lifetime) pharmacological studies with MMR vaccines are difficult if not impossible to conduct and results would not be suitable to add anything on our present knowledge on these vaccines.
The pharmacodynamic principles of vaccines can be described as the induction of a qualitative and quantitative acceptable immune response within an acceptable time frame suitable to protect from infection with the wild-type antigen. Successful achievement of protective immunity is controlled by measuring surrogate parameters present in the serum of vaccinees (in most instances antibody titers). Antibody concentrations (=titers) below or above a specific threshold might serve as generally accepted correlates for protection.
On this basis the absence of pharmacokinetic studies is considered acceptable.

Pharmacodynamics

No clinical pharmacology studies have been conducted. For similar reasons as above described, the absence of pharmacodynamics studies is considered acceptable

Clinical efficacy

- Dose response study (ies)

In view of the results of the pivotal clinical studies conducted with M-M-RVAXPRO discussed below and the exhaustive clinical experience accumulated with currently authorised measles, mumps, and rubella vaccine (live), dose finding/dose response studies using M-M-RVAXPRO were not considered necessary.

- Main study (ies)

Mumps End Expiry Clinical Trial (Protocol 007)

METHODS

This was a randomised, double blind, multicentre trial conducted in the United States.
It was conducted in response to changing test procedures for potency determination of the mumps component (from BSC-1 to Vero cells, resulting in increased titers/potencies) and in order to harmonize diverging specifications in individual countries where measles, mumps, and rubella vaccine (live) is authorised.
Study Participants

Infants 12 to 18 months of age were selected so as to follow the vaccination regimen recommended by the U.S. Advisory Committee on Immunization Practices (ACIP). Inclusion and exclusion criteria were applied in order to enroll healthy subjects without preexisting conditions that could confound the evaluation of the immunogenicity or safety profiles of the vaccine.

Treatments

Subjects were randomised to receive 1 of 3 sublots from 1 parent bulk lot of measles, mumps, and rubella vaccine (live):
Sublot 1, vaccine containing a mumps virus potency of no more than 3.8 log10 $TCID_{50}$/dose;
Sublot 2, vaccine containing a mumps virus potency of no more than 4.1 log10 $TCID_{50}$/dose;
Sublot 3, vaccine containing the current release potency for mumps (4.8 log10 $TCID_{50}$/dose).
Each dose of vaccine was administered concomitantly with one 0.5-ml subcutaneous dose of varicella vaccine, live in line with routine clinical practices in the United States.
Measles, mumps, and rubella vaccine (live) manufactured with an alternative stabilizer component called optimized Gelatin-medium O-Sorbitol was used in this study instead of Gelatin-medium O-Sorbitol (current formulation). Both formulations contain the same ingredients and are essentially equivalent except that the concentrations of the buffers and sugers vary slightly between the formulations. Equivalence in vaccine immunogenicity between measles, mumps, and rubella vaccine (live) manufactured with either formulation has been demonstrated and therefore the use of optimized Gelatin-medium O-Sorbitol for this study does not have an impact on the results of the study.

Table 2 summarises the vaccines, dosage schedule, and dose volume administered for subjects enrolled in each group. All vaccines were administered subcutaneously in the arm or thigh. If a subject remained seronegative to a particular vaccine viral component at 42 days postvaccination, that subject was given the option of being revaccinated with currently marketed measles, mumps, and rubella vaccine (live) or varicella vaccine, live.

Table 2: Vaccine Components, Dose, Vaccination Schedule, and Dose Volume Administered by Treatment Group

Sublot	Vaccine Component	Dose	Vaccination Schedule	Dose Volume Administered
1 (1)	Measles Mumps Rubella varicella vaccine, live **(2)**	3.1 log 10 TCID50 **3.8** log 10 TCID50 3.4 log 10 TCID50 ≥ 5974 PFU/ml	Day 0	0.5 ml
2 (1)	Measles Mumps Rubella varicella vaccine, live **(2)**	3.1 log 10 TCID50 **4.1** log 10 TCID50 3.4 log 10 TCID50 ≥ 5974 PFU/ml	Day 0	0.5 ml
3	Measles Mumps Rubella varicella vaccine, live **(2)**	3.1 log 10 TCID50 **4.8** log 10 TCID50 **(3)** 3.4 log 10 TCID50 ≥ 5974 PFU/ml	Day 0	0.5 ml

(1) Two sublots of measles, mumps, and rubella vaccine (live) derived from the same parent lot as the control lot were aged to target mumps virus potencies with a 95% upper confidence bound of no more than 3.7 and 4.0 log10 TCID50/dose. After reassignment of the mumps house standard (HS) potency to 4.3 log10 TCID50,/0.1 ml, the 95% upper confidence bound values were no more than 3.8 and 4.1 log10 TCID50, respectively. Final mumps virus potencies (95% upper confidence bound) were 3.76 (3.79) and 4.04 (4.08) log10 TCID50, respectively.
(2) Each 0.5-ml dose of varicella vaccine, live was given concomitantly with each sublot of measles, mumps, and rubella vaccine (live) at separate injection sites. Three separate lots of varicella vaccine, live were used for this study. Lot 1155H with a potency of 5974 PFU/ml; Lot 1013 J with a potency of 8577 PFU/ml; and Lot 1454J with a potency of 7458 PFU/ml.
(3) The mumps virus potency of 4.8 log10 TCID50/dose is the point estimate for the control group and is representative of a mumps potency within the release range for measles, mumps, and rubella vaccine (live).

Objectives

The primary objectives were:
1. To demonstrate a similar immune response to mumps virus by neutralization among subjects receiving measles, mumps, and rubella vaccine (live) containing an expiry dose of mumps virus compared to subjects receiving measles, mumps, and rubella vaccine (live) containing a release dose of mumps virus, given concomitantly with varicella vaccine live.

2. To demonstrate an adequate immune response among subjects receiving measles, mumps, and rubella vaccine (live) containing an expiry dose of mumps concomitantly with varicella vaccine live.

The secondary objectives were:
1. To demonstrate similar immune responses to measles, mumps, and rubella (seroconversion rates by ELISA) among children who receive measles, mumps, and rubella vaccine (live) containing an expiry dose of mumps virus compared to children who receive measles, mumps, and rubella vaccine (live) containing a release dose of mumps virus, given concomitantly with varicella vaccine, live.
2. To summarise the geometric mean titers (GMTs) to measles, mumps, and rubella (as measured by ELISA) and varicella (as measured by Varicella Antibody Enzymelinked immunoabsorbent assay [gpELISA]) 42 days postvaccination with measles, mumps, and rubella vaccine (live) given concomitantly with varicella vaccine live in both expiry groups and the release group.
3. To summarize the mumps neutralization GMTs and median titers in each treatment group.
4. To summarize the varicella immunogenicity (percent of subjects with titers ≥5 gp ELISA units by gpELISA) in subjects 6 weeks postvaccination.
5. To summarise the persistence of antibody to measles, mumps, and rubella (as measured by the mumps Plaque Reduction Neutralization (PRN) assay and by ELISA) 1 year postvaccination in each treatment group.
6. To describe the safety and tolerability of measles, mumps, and rubella vaccine (live) containing an expiry dose of mumps virus given concomitantly with varicella vaccine live.

Outcomes/endpoints

Critical timepoints to monitor subjects were day 0 (administration of study vaccine), day 42 or week 6 (blood draw to measure antibody titers to test vaccine) and day 365 or one year follow up (blood draw to monitor persistence of immunity).

For the primary objectives, the sera were tested for mumps antibody by a plaque reduction neutralization (PRN) assay. As per the amended protocol, a baseline antibody titer of <1:32 was considered seronegative and assigned a value of 1:16 for analysis. Seroconversion was defined as a 4-fold rise in antibody titers (1:16 to =1:64) between baseline and 6 weeks postvaccination. For the secondary objectives concerning measles, mumps, and rubella, the sera were tested for antibody to each viral component using an enzyme-linked immunosorbent assay (ELISA). For measles, a baseline antibody titer obtained at the starting dilution that was below the optical density (OD) cutoff for the assay (derived as a function of historical, known negative controls) was considered seronegative. At 6 weeks, an antibody titer (tested at a 1:10 dilution of the starting dilution) ≥21.3 measles Ab units (≥207.8mIU/ml) was considered seropositive. Seronegativity to mumps corresponded to an antibody titer <10 ELISA Ab units. Seropositivity to mumps corresponded to an antibody titer ≥10 ELISA Ab units. Seronegativity to rubella corresponded to an antibody titer <10 IU/ml. Seropositivity to rubella corresponded to an antibody titer ≥10 IU/ml.

Sample size

Considering the assumptions made, the planned total of healthy children to be randomised (1770 or 590/group) was considered acceptable.

Randomisation

Subjects were randomised 1:1:1 into 1 of 3 treatment groups according to a computer generated allocation.

Blinding (masking)

While varicella vaccine live was used in this trial under open-label conditions, measles, mumps, and rubella vaccine (live) was used under blinded conditions.

Statistical methods

The primary analyses of immunogenicity was performed based on the per protocol subjects. Per protocol subjects were defined as subjects who did not have major protocol violations, who had prevaccination and postvaccination serology results and who had baseline antibody titers below the seropositivity cut-off for the antigen being analysed (baseline measles antibody titers were <120 mIU/ml, whose baseline mumps antibody titers were <10.0 ELISA antibody units/ml, and whose baseline rubella antibody titers were <10.0 IU/ml).
The study was powered to establish non-inferiority (<5.0-percentage-point decrease in response rates for a test conducted at the one-sided 0.05 level) between the 4.1 log10 TCID50 and the 4.8 log10 TCID50 Mumps Virus Potency group, and to establish the acceptability of the immune response to mumps (lower bound of the 95% confidence interval >90%) for the 4.1 log10 TCID50 Mumps Virus Potency group. Only if the 4.1 log10 TCID50 dose was found to meet the criteria for an end-expiry mumps potency, the hypotheses to establish the suitability of the 3.8 log10 TCID50 dose as a mumps end-expiry potency would be tested.
There was one planned interim analysis of the immunogenicity for mumps on a randomly selected subset of ~600 subjects (~200 per group). The purpose of the preliminary subset analysis was to provide with an early read of the mumps immunogenicity data. At the time of the preliminary analysis, the study enrollment and the safety and immunogenicity follow-up had been completed. It was not planned to stop the trial based on interim results.

RESULTS

Participant flow
A total of 1997 healthy infants were enrolled and vaccinated. Table 3 summarises the number of subjects followed up through the end of the study:

Table 3: Summary of subjects excluded at critical time points post-vaccination from per-protocol immunogenicity analyses for measles, mumps (PRN and ELISA) and rubella

Treatment Groups of measles, mumps, and rubella vaccine (live)				
	3.8 log TCID50/dose Mumps Virus Potency	4.1 log TCID50/dose Mumps Virus Potency	4.8 log TCID50/dose Mumps Virus Potency	Main reason(s) for drop out
Entered	663	662	672	
Eligible at day 0	611	624	623	Deviation from protocol, Refused further participation/Lost to follow-up
Eligible at day 42 (week 6) Measles (ELISA) Mumps (PRN) Mumps (ELISA) Rubella (ELISA)	 562 459 577 590	 578 433 583 595	 572 437 588 602	**Seropositivity at baseline, Missing 6-week serology result**
Eligible at 182 to 546 days post vaccination	426	427	456	Lost to follow-up

No drop out due to adverse events was reported throughout the study period.

Recruitment
The study, conducted in 21 study centres in the United States was initiated on 26-Feb-1999 and was completed on 20-Jul-2001.

Conduct of the study
Two protocol amendments were made but none of these individual changes were considered to have a major impact as these were refinements of the originally describe methodology, clarifications on the original study and data analysis plan and improvements facilitating the conduct of the study.

Baseline data

The table 4 displays the subject characteristics by treatment group. The three groups were balanced with respect to gender, age, race and initial serostatus to each antigen.

Table 4: Subjects baseline characteristics

	Treatment Groups of Measles, mumps, and rubella vaccine (live)							
	3.8 $\log_{10}$ $TCID_{50}$/dose Mumps Virus Potency[†]		4.1 $\log_{10}$ $TCID_{50}$/dose Mumps Virus Potency[‡]		4.8 $\log_{10}$ $TCID_{50}$/dose Mumps Virus Potency[§]		TOTAL	
	(N = 663)		(N = 662)		(N = 672)		(N = 1997)	
	n	(%)	n	(%)	n	(%)	n	(%)
Gender								
Male	323	(48.7)	340	(51.4)	339	(50.4)	1002	(50.2)
Female	340	(51.3)	322	(48.6)	333	(49.6)	995	(49.8)
Age (Months)								
Mean	12.5		12.5		12.5		12.5	
SD	1.0		1.0		1.0		1.0	
Median	12.0		12.0		12.0		12.0	
Range	11 to 24		11 to 18		11 to 17		11 to 24	
Male	11 to 24		12 to 17		11 to 17		11 to 24	
Female	12 to 18		11 to 18		11 to 17		11 to 18	
Race/Ethnicity								
Asian	12	(1.8)	7	(1.1)	12	(1.8)	31	(1.6)
Black	113	(17.0)	101	(15.3)	124	(18.5)	338	(16.9)
Caucasian	451	(68.0)	454	(68.6)	451	(67.1)	1356	(67.9)
Hispanic	43	(6.5)	41	(6.2)	44	(6.5)	128	(6.4)
Native American	8	(1.2)	15	(2.3)	7	(1.0)	30	(1.5)
Other	36	(5.4)	44	(6.6)	34	(5.1)	114	(5.7)
Initial Serostatus								
Mumps PRN								
Negative	471	(71.0)	443	(66.9)	450	(67.0)	1364	(68.3)
Positive	75	(11.3)	93	(14.0)	84	(12.5)	252	(12.6)
Unknown	117	(17.6)	126	(19.0)	138	(20.5)	381	(19.1)
Measles ELISA[%]								
Negative	624	(94.1)	629	(95.0)	632	(94.0)	1885	(94.4)
Positive	35	(5.3)	26	(3.9)	38	(5.7)	99	(5.0)
Unknown	4	(0.6)	7	(1.1)	2	(0.3)	13	(.65)
Mumps ELISA[¶]								
Negative	640	(96.5)	636	(96.1)	649	(96.6)	1925	(96.4)
Positive	19	(2.9)	19	(2.9)	21	(3.1)	59	(3.0)
Unknown	4	(0.6)	7	(1.1)	2	(0.3)	13	(.65)
Rubella ELISA[#]								
Negative	654	(98.6)	649	(98.0)	666	(99.1)	1969	(98.6)
Positive	5	(0.8)	4	(0.6)	4	(0.6)	13	(.65)
Unknown	4	(0.6)	9	(1.4)	2	(0.3)	15	(.75)

[†] Sublot 1 0.5-ml dose for subcutaneous injection in the arm contains: Measles—~3.0 (~1,000) $\log_{10}$ $TCID_{50}$, Mumps—3.8 (~6,300) $\log_{10}$ $TCID_{50}$ per dose, Rubella—3.4 (~2,500) $\log_{10}$ $TCID_{50}$. Mumps Expiry Group.

[‡] Sublot 2 5-ml dose for subcutaneous injection in the arm contains: Measles—~3.2 (~1,500) $\log_{10}$ $TCID_{50}$, Mumps—4.1(~12,500) $\log_{10}$ $TCID_{50}$ per dose, Rubella—3.4 (~2,500) $\log_{10}$ $TCID_{50}$. Intermediate Mumps Expiry Group.

[§] Sublot 3 0.5-ml dose for subcutaneous injection in the arm contains: Measles—3.8 (~6,000) $\log_{10}$ $TCID_{50}$, Mumps— 4.8 (~63,000) $\log_{10}$ $TCID_{50}$, Rubella—3.6 (~4,000) $\log_{10}$ $TCID_{50}$. Control Group.

[%] Serostatus cutoff: negative = ≤OD cutoff, positive = >OD cutoff

[¶] Serostatus cutoff: negative = <10 ELISA Ab units, positive = ≥10 ELISA Ab units

[#] Serostatus cutoff: negative = <10 IU ml, positive = ≥10 IU ml

N = Number of subjects vaccinated.

n = Number of subjects in each category.

SD = Standard deviation

The incidence of prior therapies appeared to be similar across the 3 treatment groups. Specifically, the use of anti-infective agents (amoxicillin), anti-inflammatory (ibuprofen), central nervous system agents (acetaminophen), vitamins and minerals was balanced across all treatment groups. The same applied for the incidence of concomitant therapies (mainly amoxicillin, ibuprofen and acetaminophen).

Outcomes and estimation

The study primarily focused on the identification of an acceptable end of expiry titer of the mumps component providing sufficient immunogenicity and inducing acceptable antibody titers to protect from measles, mumps and rubella. Two different log titer potencies (3.8 and 4.1) of the mumps component were compared to the current release potency of 4.8. A summary of antibody responses to

measles, mumps and rubella at 6 weeks post-vaccination for subjects initially seronegative to measles, mumps, or rubella is shown in table 5.

Table 5: Summary of antibody responses to measles, mumps and rubella at 6 weeks post-vaccination for subjects initially seronegative to measles, mumps, or rubella

		Treatment Groups of Measles, mumps, and rubella vaccine (live)					
		3.8 log 10 TCID 50/Dose Mumps Virus Potency (N=663)		4.1 log 10 TCID 50/Dose Mumps Virus Potency (N=662)		4.8 log 10 TCID 50/Dose Mumps Virus Potency (N=672)	
Antibody Assay	Parameter	Observed Response	95% CI	Observed Response	95% CI	Observed Response	95% CI
Mumps (PRN)	SCR (%)	89	(86,92)	93	(91,96)	92	(89,95)
	GMT	≥1118	(961,1301)	≥1285	(1124,1470)	≥1123	(976,1290)
	(%≥4096)	(33.8)		(34.4)		(31.6)	
	Median Titer	2048	(1694,2477)	2048	(1731,2443)	2048	(1719,2440)
Measles (ELISA)	SCR (%)	98	(97,99)	97	(95,98)	98	(97,99)
	GMT	1489	(1722,1986)	1710	(1587,1842)	1710	(1594,1833)
Mumps (ELISA)	SCR (%)	94	(92,96)	97	(96,99)	98	(97,99)
	GMT	84	(77,92)	85	(79,91)	85	(79,92)
Rubella (ELISA)	SCR (%)	94	(92,96)	94	(92,96)	95	(93,97)
	GMT	102	(93,111)	102	(93,111)	99.5	(92,108)

All values rounded

Abbreviations: N = Number of subjects vaccinated in each treatment group.; n = Number of subjects initially seronegative for mumps ; [PRN] contributing to the per-protocol analyses.; CI = Confidence interval; SCR = Seroconversion Rate.

Statistical analysis of non-inferiority and acceptability of mumps (PRN) seroconversion rates for the 3.8 log 10 TCID 50 mumps virus potency group and the 4.1 log 10 TCID 50 mumps virus potency group in comparison to the group receiving the 4.8 log 10 TCID 50 mumps virus potency (current release specification) are summarised below in table 6.

Table 6: Statistical Analysis of Non-Inferiority and Acceptability of Mumps [PRN] Seroconversion Rates

Mumps End Expiry Treatment Group	Observed SCR (95% CI) [†]	Acceptability Conclusion[†]	Estimated SCR[‡]	Estimated SCR[§] of M-M-R II – 4.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency (Control Group) [§] (N=672, n=437)	Estimated Differences[§%] (90% CI) [¶]	Non-inferiority Conclusion[¶]
M-M-R II – 4.1 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency (N=662, n=433)	93.3% (90.5%, 95.5%)	Acceptable (p-value = 0.010)	93.4%	92.2%	1.2 (-1.8,4.1)	Similar (p-value <0.001)
M-M-R II – 3.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency (N=663, n=459)	89.3% (86.1%, 92.0%)	Not Acceptable (p-value = 0.717)	89.4%	92.2%	-2.9 (-6.1,0.3)	Unable to Show Similarity (p-value = 0.140)

[†] The lower bound of the 95% CI being >90% implies that the value of the parameter is statistically significantly greater than the prespecified acceptability criterion (90%) and allows for a conclusion of acceptability. A 1-sided p-value ≤0.025 implies that the parameter is statistically significantly greater than the prespecified acceptability criterion of 90%.

[‡] Estimated SCRs and their differences were based on a statistical analysis model adjusting for study centers.

[§] The mumps virus potency of 4.8 $\log_{10}$ $TCID_{50}$/dose is the point estimate for the control group and is representative of a mumps potency within the release range for M-M-R II.

[%] [Treatment Group - Control Group].

[¶] A lower bound of 90% CI on the difference excluding -5.0 implies that the difference is statistically significantly less than the prespecified clinically relevant decrease of 5 percentage points and allows for a conclusion of similarity (non-inferiority). A 1-sided p-value ≤0.05 implies that the difference is statistically significantly less than the prespecified difference of 5 percentage points.

N = Number of subjects vaccinated in each treatment group.

n = Number of subjects initially seronegative for mumps [PRN] contributing to the per-protocol analyses.

CI = Confidence interval.

SCR = Seroconversion rate.

The study data showed that measles, mumps, and rubella vaccine (live) containing a mumps virus potency of no more than 4.1 $\log_{10}$ $TCID_{50}$ induced an acceptable immune response to measles, mumps and rubella that was similar to the measles, mumps, and rubella vaccine (live), containing the current release mumps virus potency of 4.8 $\log_{10}$ $TCID_{50}$. The data however failed to show either acceptability or similarity of the immune response to mumps induced by measles, mumps, and rubella vaccine (live), containing a mumps virus potency of no more than 3.8 $\log_{10}$.
Because of the choice of the selected level for the tests of non-inferiority (5 % one sided) the per-protocol non-inferiority test was repeated using a one-sided Type I error rate of 2.5%: to provide evidence that the experiment-wise error rate did not exceed 2.5% (one-sided), Repeating the non-inferiority analyses did not change the conclusions originally.

Secondary immunogenicity objectives included the observational comparison of GMTs and median titre measured by PRN (mumps) and GMTs by ELISA (measles, mumps, rubella) across the 3 treatment groups. Study results showed that the 3 groups were generally comparable with respect to median titres and GMTs for all antigens and assays utilized. The immune responses to measles, mumps, and rubella are summarised in table 7.

Table 7: Summary of Antibody Responses to Measles, Mumps, and Rubella at 6 Weeks Postvaccination for Subjects Initially Seronegative to Measles, Mumps, or Rubella (Per-Protocol Analysis)

		Treatment Groups of Treatment Groups of Measles, mumps, and rubella vaccine (live)					
		3.8 $\log_{10}$ $TCID_{50}$/dose Mumps Virus Potency (N=663)		4.1 $\log_{10}$ $TCID_{50}$/dose Mumps Virus Potency (N=662)		4.8 $\log_{10}$ $TCID_{50}$/dose Mumps Virus Potency (N=672)	
Antibody (Assay)	Parameter[†]	Observed Response	95% CI	Observed Response	95% CI	Observed Response	95% CI
Mumps (PRN)	SCR	89.3% (410/459)	(86.1%, 92.0%)	93.3% (404/433)	(90.5%, 95.5%)	92.2% (403/437)	(89.3, 94.6%)
	GMT	≥1117.7	(960.5, 1300.7)	≥1285.3	(1124.1, 1469.8)	≥1122.7	(976.3, 1290.9)
	(%≥4096)[‡]	(33.8%)		(34.4%)		(31.6%)	
	Median Titer	2048.0	(1693.6, 2476.6)	2048.0	(1731.2, 2422.7)	2048.0	(1719.2, 2439.7)
Measles (ELISA)	SCR	98.0% (551/562)	(96.5%, 99.0%)	96.9% (560/578)	(95.1%, 98.1%)	98.1% (561/572)	(96.6, 99.0%)
	GMT	1849.1	(1722.0, 1985.6)	1709.6	(1587.0, 1841.6)	1709.2	(1593.7, 1833.0)
Mumps (ELISA)	SCR	94.1% (543/577)	(91.9%, 95.9%)	97.4% (568/583)	(95.8%, 98.6%)	98.0% (576/588)	(96.5, 98.9%)
	GMT	83.8	(76.7, 91.6)	84.7	(78.5, 91.3)	85.2	(78.9, 92.0)
Rubella (ELISA)	SCR	94.2% (556/590)	(92.0%, 96.0%)	94.3% (561/595)	(92.1%, 96.0%)	95.0% (572/602)	(93.0, 96.6%)
	GMT	101.6	(93.2, 110.7)	101.5	(93.0, 110.8)	99.5	(91.8, 107.8)

[†] For measles, subjects whose prevaccination samples had optical density (OD) responses equal to or below the cutoff were considered seronegative at baseline, whereas subjects with a 6-week measles antibody titer ≥207.8 mIU/mL (≥21.3 measles Ab units) were considered seropositive postvaccination. For mumps, samples with mumps antibody titers ≥10 ELISA Ab units were considered seropositive, whereas samples with mumps antibody titers <10 ELISA Ab units were considered seronegative. For rubella, samples with rubella antibody titers ≥10 IU/mL were considered seropositive, whereas samples with rubella antibody titers <10 IU/mL were considered seronegative.

[‡] Percentage of subjects with 6-week titer ≥4096.

N = Number of subjects vaccinated in each treatment group.
SCR = Seroconversion rate.
GMT = Geometric mean titer.
ELISA = Enzyme-linked immunosorbent assay.
PRN = Plaque reduction neutralization assay.
CI = Confidence interval.

Table 8 displays the 1-year postvaccination antibody persistence summaries for measles, mumps, and rubella. The antibody persistence rates are displayed for the subjects who were initially seronegative, who responded at 6 weeks postvaccination, and who had an evaluable antibody persistence blood sampling for the given antigen. GMTs at 6 weeks and 1-year postvaccination are displayed for this same cohort of subjects.

Table 8: Persistence of antibody responses to measles, mumps and rubella at 1 year post-vaccination in subjects initially seronegative to measles, mumps, or rubella who responded at 6 weeks post-vaccination

		Treatment Groups of Measles, mumps, and rubella vaccine (live)					
		3.8 log 10 TCID 50/Dose Mumps Virus Potency (N=663)		4.1 log 10 TCID 50/Dose Mumps Virus Potency (N=662)		4.8 log 10 TCID 50/Dose Mumps Virus Potency (N=672)	
Antibody Assay	Parameter	Observed Response n(%)[1]	95% CI	Observed Response n(%)[2]	95% CI	Observed Response n(%)[3]	95% CI
Measles (ELISA)	PR	99.8	(99,100)	99.8	(99,100)	99.6	(98,100)
	6-Week GMT	1936	(1800,2082)	1863	(1734,2002)	1829	(1705,1962)
	1-Year GMT	3848	(3508,4223)	3376	(3091,3687)	3266	(2990,3568)
Mumps (ELISA)	PR	96.7	(95,98)	95.4	(93,97)	95.7	(93,97)
	6-Week GMT	99.9	(93,108)	91.0	(84,98)	91.9	(85,99)
	1-Year GMT	80.7	(73,90)	79	(71,88)	74.9	(68,83)
Rubella (ELISA)	PR	100	(99,100)	100	(99,100)	99.6	(98,100)
	6-Week GMT	118	(110,127)	118	(109,128)	115	(108,124)
	1-Year GMT	159	(148.172)	155	(144,168)	154	(142,166)

Abbreviations: N = Number of subjects with persistence bleed.
n = Number of subjects in persistence analysis [1]n=.426, 423, 439 for measles, mumps, rubella; [2]n=.427, 437, 428 for measles, mumps, rubella; [3]n=.456, 466, 461 for measles, mumps, rubella
PR = Persistence rate (ratio)—proportion of subjects who maintained a positive response at 1 year among those who were initially seronegative and who responded at 6 weeks
postvaccination. A positive response for measles is antibody titer =207.8 mIU/mL, for mumps is antibody titer =10 ELISA Ab units, and for rubella is antibody titer =10 IU/mL.
GMT = Geometric mean titer.
ELISA = Enzyme-linked immunosorbent assay.
CI = Confidence interval.

rHA Replacement Trial (Protocol 009)

This was a double-blind, randomised, comparative, multicentre study designed to evaluate the immunogenicity, safety, and tolerability of M-M-RVAXPRO manufactured with recombinant human albumin (rHA) in comparison to currently authorised measles, mumps, and rubella vaccine (live) manufactured with human serum albumin (HSA) isolated from pooled-donor serum.

METHODS

Study participants

Infants 12 to 18 months of age were selected as to follow the vaccination regimen recommended by the U.S. Advisory Committee on Immunization Practices (ACIP). Inclusion and exclusion criteria were applied in order to enroll healthy subjects without preexisting conditions that could confound the evaluation of the immunogenicity or safety profiles of the vaccine.

Treatment

At Visit 1 (Day 1), subjects were randomly assigned to receive a single, 0.5-ml dose of either measles, mumps, and rubella vaccine (live) manufactured with rHA (M-M-RVAXPRO) or currently authorised measles, mumps, and rubella vaccine (live) manufactured with HSA.
All vaccines were administered via a subcutaneous injection either in the upper arm or in the antero-lateral thigh. No other vaccines were allowed to be given during the study period.
As specified in the protocol, if a subject did not have adequate antibody levels to one or more of the viral components of the vaccine at Visit 2 (Days 42 to 56 postvaccination), the subject's parent/guardian was offered the option of having the subject revaccinated with currently authorised vaccine. Subjects who were revaccinated were offered safety follow-up from Day 1 through Day 42 following revaccination and the appropriate serological evaluation at Day 42 following revaccination

Objectives

The primary objectives were to demonstrate that:
(1) the antibody response rates to measles, mumps, and rubella among children who receive M-M-RVAXPRO would be similar to the antibody response rates among children who receive measles, mumps, and rubella vaccine (live) manufactured with HSA
(2) M-M-RVAXPRO would induce acceptable antibody response rates to measles, mumps, and rubella.
(3) M-M-RVAXPRO would be generally well tolerated.

Secondary objectives were:
a. to summarise the geometric mean titers (GMTs) to measles, mumps, and rubella at 6 weeks postvaccination with either M-M-RVAXPRO manufactured with rHA or measles, mumps, and rubella vaccine (live) manufactured with HSA.
b. to summarise the incidence of antibodies to albumin in children who receive either M-M-RVAXPRO manufactured with rHA or measles, mumps, and rubella vaccine (live) manufactured with HSA.
c. to summarise the incidence of potentially allergic adverse experiences of special interest in children who receive either M-M-RVAXPRO manufactured with rHA or measles, mumps, and rubella vaccine (live) manufactured with HSA.
d. to explore the relationship between potentially allergic adverse experiences of special interest and antibodies to albumin.

Outcome/Endpoints

The primary endpoints were the antibody response rates to measles, mumps, and rubella measured 6 weeks postvaccination. The antibody response rates were defined as the percentage of subjects with measles antibody titers ≥120 mIU/ml in subjects whose baseline measles antibody titer was <120 mIU/ml, the percentage of subjects with mumps antibody (Ab) titers ≥10.0 ELISA Ab units/ml in subjects whose baseline mumps antibody titer was <10.0 ELISA Ab units/ml, and the percentage of subjects with rubella antibody titers ≥10.0 IU/ml in subjects whose baseline rubella antibody titer was <10.0 IU/ml. The secondary immunogenicity endpoints were measles, mumps, and rubella GMTs measured 6 weeks postvaccination.

Sample size

Considering the assumptions made, the planned total of healthy children to be randomised (515 evaluable subjects per group) was considered acceptable.

Randomisation

Patients were randomised in a 1:1 ratio to one of both treatment groups according to a computer generated allocation scheme.

Blinding (masking)

Appropriate blinding measures were taken.

Statistical methods

This study was powered for each of the three similarity comparisons (<5 percentage-point difference in rates for a test conducted at the 1-sided 0.05 level). For the second primary hypothesis regarding the acceptability of antibody responses to measles, mumps, and rubella for M-M-RVAXPRO with rHA, the response rates for each component in the M-M-RVAXPRO with rHA group was to be tested (1-sided <= 0.025 level) against a 90% lower bound.

Preplanned subgroup analyses were performed in the population of initially seronegative subjects, of initially seropositive subjects as well as in all subjects with sufficient serology.

RESULTS

Patients flow

A total of 1279 subjects were randomised. Participant flow was followed-up for 42 days and the summary of subjects excluded at 6 weeks post-vaccination from per-protocol immunogenicity analyses for measles, mumps and rubella is outlined below in table 9:

Table 9: Summary of subjects excluded at critical time points post-vaccination from per-protocol immunogenicity analyses for measles, mumps (PRN and ELISA) and rubella:

	M-M-RVAXPRO (with rHA)	Measles, mumps, and rubella vaccine (live) with HSA	Main reason(s) for drop out
Eligible at day 1 Measles Mumps Rubella	 641 641 641	 638 538 638	
Eligible at week 6 (day 42) Measles Mumps Rubella	 531 563 572	 498 533 543	Seropositivity at baseline, Missing or non evaluable 6-week serology results, Lost to follow-up, other technical difficulties

As in study 007 no subjects in study 009 discontinued due to an adverse experience.

Recruitment

The study conducted in 30 study centres in the United States was initiated on 5 December 2001 and was completed on 20 December 2002.

Conduct of the study

Two protocol amendments were made but none of these individual changes were considered to have a major impact as these were refinements of the originally describe methodology, clarifications on the original study and data analysis plan and improvements facilitating the conduct of the study.

Baseline data

The table 10 displays the subject characteristics by treatment group. The three groups were balanced with respect to gender, age, race and initial serostatus to each antigen.

Table 10: Distribution of subjects between the 2 treatment groups was well balanced with respect to gender, age, race, and initial serostatus to each antigen.

	M-M-RVAXPROwith rHA (N=641)		Measles, mumps, and rubella vaccine (live) with HSA (N=638)		Total (N=1279)	
	n	(%)	n	(%)	n	(%)
Gender						
Male	329	(51.3)	314	(49.2)	643	(50.3)
Female	312	(48.7)	324	(50.8)	636	(49.7)
Age (months)						
11 and Under	1	(0.2)	1	(0.2)	2	(0.2)
12 to 18	640	(99.8)	636	(99.7)	1276	(99.8)
Over 18	0	(0.0)	1	(0.2)	1	(0.1)
Mean	13.0		12.9		13.0	
SD	1.53		1.48		1.51	
Median	12.0		12.0		12.0	
Range	11 to 18		11 to 19		11 to 19	
Male	11 to 18		11 to 19		11 to 19	
Female	12 to 18		12 to 18		12 to 18	
Race						
Unknown	0	(0.0)	1	(0.2)	1	(0.1)
Asian	7	(1.1)	7	(1.1)	14	(1.1)
Black	108	(16.8)	116	(18.2)	224	(17.5)
European	0	(0.0)	1	(0.2)	1	(0.1)
Hispanic American	40	(6.2)	41	(6.4)	81	(6.3)
Indian	0	(0.0)	2	(0.3)	2	(0.2)
Multi-racial	16	(2.5)	26	(4.1)	42	(3.3)
Native American	14	(2.2)	13	(2.0)	27	(2.1)
White	456	(71.1)	431	(67.6)	887	(69.4)
Initial Serostatus						
Measles ELISA†						
Negative	567	(88.5)	553	(86.7)	1120	(87.6)
Positive	44	(6.9)	50	(7.8)	94	(7.3)
Unknown	30	(4.7)	35	(5.5)	65	(5.1)
Mumps ELISA‡						
Negative	602	(93.9)	591	(92.6)	1193	(93.3)
Positive	9	(1.4)	12	(1.9)	21	(1.6)
Unknown	30	(4.7)	35	(5.5)	65	(5.1)
Rubella ELISA§						
Negative	609	(95.0)	600	(94.0)	1209	(94.5)
Positive	2	(0.3)	3	(0.5)	5	(0.4)
Unknown	30	(4.7)	35	(5.5)	65	(5.1)

† Serostatus cutoff: negative = <120 mIU/ml, positive = ≥120 mIU/ml.
‡ Serostatus cutoff: negative = < 10 ELISA Ab units, positive = ≥10 ELISA Ab units.
§ Serostatus cutoff: negative = < 10 IU ml, positive = ≥10 IU ml.
N=Number of subjects vaccinated in each treatment group.
rHA=Recombinant human albumin.
HSA=Human serum albumin.

Fewer than half of the subjects in each treatment group received prior therapy within 14 days of study enrollment (40.9% of the recipients of M-M-RVAXPRO with rHA and 39.8% of the recipients of measles, mumps, and rubella vaccine (live) with HSA). The most commonly reported prior therapies were analgesics (10.5% and 13.0% respectively) and antibacterials for systemic use (12.2% and 10.7% respectively). Only 0.5% (3/641) of the recipients of M-M-RVAXPRO with rHA and 0.3% (2/638) of the recipients of measles, mumps, and rubella vaccine (live) with HSA received a prior vaccination within 14 days of study enrollment.

Most subjects received some concomitant therapy during the 42 days following vaccination (79.6% of the recipients of M-M-RVAXPRO with rHA and 78.2% of the recipients of measles, mumps, and rubella vaccine (live)). The most commonly reported concomitant therapies were analgesics (49.5% and 45.6% respectively), anti-inflammatories and antirheumatic products (31.4% and 24.3% respectively), and antibacterials for systemic use (26.2% and 22.6% respectively). Only 0.8% (5/641) of the recipients of M-M-RVAXPRO with rHA and 0.3% (2/638) of the recipients of measles, mumps,

and rubella vaccine (live) group received a concomitant vaccination within 42 days following the study vaccination.

Outcome and estimations

The analysis of the first primary immunogenicity hypothesis regarding the similarity of the antibody response rates to measles, mumps, and rubella among subjects receiving M-M-RVAXPRO with rHA compared with subjects receiving measles, mumps, and rubella vaccine (live) with HSA was based on 1-sided non-inferiority tests to exclude a decrease in response of more than 5% or more.

Table 11: Statistical Analysis of Similarity of Measles, Mumps, and Rubella Antibody Responses in Initially Seronegative Subjects (Per-Protocol Analysis)

		M-M-R-VAXPRO with rHA (N=641)		measles, mumps, and rubella vaccine (live) with HSA (N=638)		Estimated Difference (Percentage Points) (90% CI)[1,2]
Antibody (ELISA)	Parameter	n	Estimated Response	n	Estimated Response	
Measles	% ≥ 120 mIU/ml	531	98.3	498	98.8	-0.5 (-1.9,0.8)
Mumps	% ≥ 10 ELISA antibody units/ml	563	99.4	533	97.9	1.5 (0.4,2.8)
Rubella	% ≥ 10 mIU/ml	572	99.6	543	99.6	0.0 (-0.8,0.8)

Abbreviations: N=Number of subjects vaccinated in each treatment group.
n=Number of subjects initially seronegative for measles, mumps, and rubella contributing to the per-protocol analyses.
rHA=Recombinant human albumin.; HSA=Human serum albumin.; ELISA=Enzyme-linked immunosorbent assay.
Responses and their difference were based on a statistical analysis model adjusting for study centers.
[1][MMR II with rHA]-[MMR II with HSA].
[2]A lower bound of 90% confidence interval (CI) on the difference excluding a decrease of 5 percentage points or more implies the difference is statistically significantly less than the pre specified clinically relevant decrease of 5 percentage points and allows for a conclusion of similarity (non-inferiority). The associated 1-sided p-value for each test is <0.001.

For each antigen the (one-sided) p-value for the test was>0.001 supporting non-inferiority.

The analysis of the second primary immunogenicity hypothesis regarding the demonstration of an acceptable antibody response to measles, mumps, and rubella among subjects receiving M-M-RVAXPRO with rHA was based on 1-sided, 1-sample binomial tests (conducted at the ≤0.025 level). This is equivalent to requiring that the lower bound of the 1-sample 95% CI for the measles, mumps, or rubella response rate be above 90% in order to declare the response rate for the antigen acceptable. As shown in Table 12, the statistical criterion for acceptability of antibody response was met for each antigen.

Table 12: Statistical Analysis of Acceptability of Measles, Mumps, and Rubella Responses in Initially Seronegative Subjects (Per-Protocol Analysis):

	M-M-R-VAXPRO with rHA (N=641)		
Antibody (ELISA)	Parameter	n	Observed Response (95% CI)
Measles	% ≥ 120 mIU/ml	531	98.3 (96.8,99.2)
Mumps	% ≥ 10 ELISA antibody units/ml	563	99.4 (98.5,99.9)
Rubella	% ≥ 10 mIU/ml	572	99.6 (98.7,100)

The lower bound of the 95% confidence interval (CI) being >90% implies that the value of the parameter is statistically significantly greater than the prespecified acceptability criterion (90%) and allows for a conclusion of acceptability.

A summary of antibody responses to measles, mumps, and rubella among per-protocol subjects who had baseline measles antibody titers ≥120 mIU/ml, baseline mumps antibody titers ≥10.0 ELISA Ab

units/ml, or baseline rubella antibody titers ≥10.0 IU/ml is provided in Table 13. This assessment was made since maternal antibody to measles, mumps, and rubella can persist in children up to 12 months of age, which can diminish the antibody response to the viral components of this vaccine. This table include GMTs (as defined for the PRN assay and/or the ELISA assay) measured at baseline and ~42 days postvaccination, as well as the percentage of subjects with ≥4-fold rise in antibody level from baseline to ~42 days postvaccination, for each antigen, by treatment group.

Table 13: Summary of Measles, Mumps, and Rubella Antibody Responses in Initially Seropositive Subjects—Day 1 to Week 6 Postvaccination (Per-Protocol Analysis)

		M-M-R-VAXPRO with rHA (N=641)			measles, mumps, and rubella vaccine (live) with HSA (N=638)		
Antibody (ELISA)	Time Point	n	GMTs (95% CI)	% ≥4 Fold-Rise (95% CI)	n	GMTs (95% CI	% ≥4 Fold-Rise (95% CI)
Measles	Day 1	42	271.3 (209.1,352.1)		47	233.6 (194.7,280.3)	
	Week 6	42	1468 (971.4,2218.3)	76.2% (32/42) (60.5,87.9)	47	1762 (1288.1,2411.2)	85 (40/47) (71.7,93.8)
Mumps	Day 1	9	38.1 (NA)		11	23.7 (10.9,51.7)	
	Week 6	9	115.3 (NA)	55.6% (5/9) (NA)	11	65.8 (25.6,169.1)	63.6 (7/11) (30.8,89.1)
Rubella	Day 1	1	32 (NA)		2	111.0 (NA)	
	Week 6	1	71 (NA)	0.0 (0/1) 1.0 (NA)	2	5.0 (NA)	0.0 (0/2) 1.0 (NA)

Confidence intervals (CI) were only provided when n ≥10.

Abbreviations: N=Number of subjects vaccinated in each treatment group.
n=Number of subjects initially seropositive to given antigen (measles, mumps, and rubella).
rHA=Recombinant human albumin.
HSA=Human serum albumin.
GMT=Geometric mean titer.
ELISA=Enzyme-linked immunosorbent assay.
N/A=Not applicable.

While no formal statistical analyses were performed, 95% CIs on the observed rates were provided if there were at least 10 initially seropositive subjects within a treatment group for a given antigen. For measles, the 95% CIs on the observed rates in each group overlapped, suggesting that there was no evidence of a difference in the percentage of subjects with a ≥4-fold rise in measles antibody titer between the two treatment groups. For mumps, the 95% CI was not provided for the rHA group since the number of initially seropositive subjects was less than 10. However, the 95% CI for the HSA group did overlap the observed rate in the rHA group suggesting there were no differences between the groups.

Because of the choice of the selected level for the tests of non-inferiority (5 % one sided) the per-protocol non-inferiority test was repeated using a one-sided Type I error rate of 2.5%: to provide evidence that the experiment-wise error rate did not exceed 2.5% (one-sided). Repeating the non-inferiority analyses did not change the conclusions originally.

A subset of the participants of the study was included in an extension study to receive a second dose of either vaccines. As the non-inferiority in terms of immunogenicity had already been shown post dose 1, it was considered acceptable that no additional information post dose 2 (which is a catch up rather than a booster immunization) was necessary. Safety data were nonetheless provided as discussed further under the relevant section.

Clinical safety

The measles, mumps, rubella vaccine, live was first licensed in 1978 and since that time in many countries around the world. Extensive experience has been accumulated and is estimated that more than 400 million of doses have been administered during the last 25 years to infants in the age range of 12 to 24 months.

This new product related to a new formulation of measles, mumps, and rubella vaccine (live) replacing Human Serum Albumin (HSA) by recombinant Human Albumin (rHA) and adjusting the end of expiry potency of the mumps component to 4.1 log TCID 50.

- Patient exposure

In the mump end expiry clinical study 007 a total of 1997 subjects were vaccinated concomitantly with both measles, mumps, and rubella vaccine (live) with HSA and varicella live vaccine. Because study 007 was not conducted with the M-M-RVAXPRO, safety data are not so relevant. It showed however that adjusting the end of expiry potency of the mumps component to 4.1 log10 TCID50 would not have any effect on the safety of M-M-RVAXPRO.

Safety data presented derive therefore from the rHA replacement clinical study 009 in which 641 subjects were vaccinated with M-M-RVAXPRO with rHA and 638 subjects were vaccinated with measles, mumps, and rubella vaccine (live) with HSA. Subjects received a single dose of either study vaccine and were followed for adverse events for 42 days postvaccination.

- Adverse events

The safety analyses were based on comparisons (using risk differences and associated 95% CIs) of the incidence rates in each treatment group of local and systemic adverse experiences and of elevated temperatures (38.9°C, oral equivalent) that occurred within 42 days postvaccination.

Table 14 provides a summary of clinical adverse experiences by treatment group along with risk differences for comparisons of individual adverse experience between groups.

Table 14: Comparison of Treatment Groups With Respect to Clinical Adverse Experiences Reported in study 009 (Days 1 to 42 Following Vaccination)

	M-M-RVAXPROWith rHA (N=641)		Measles, mumps, rubella live vaccine With HSA (N=638)		Risk Difference ([M-M-RVAXPROWith rHA]-[Measles, mumps, rubella live vaccine With HSA]) Percentage Points (95% Confidence Interval)[†]
	n	(%)	n	(%)	
Number of subjects	641		638		
Subjects without follow-up	7		6		
Subjects with follow-up	634		632		
Number (%) of subjects:					
with no adverse experience	114	(18.0)	126	(19.9)	-2.0 (-6.3, 2.4)
with one or more adverse experiences	520	(82.0)	506	(80.1)	2.0 (-2.4, 6.3)
injection-site adverse experiences	227	(35.8)	188	(29.7)	6.1 (0.9, 11.2)
systemic adverse experiences	469	(74.0)	465	(73.6)	0.4 (-4.5, 5.2)
with vaccine-related adverse experiences[‡]	308	(48.6)	276	(43.7)	4.9 (-0.6, 10.4)
injection-site adverse experiences	226	(35.6)	187	(29.6)	6.1 (0.9, 11.2)
systemic adverse experiences	139	(21.9)	149	(23.6)	-1.7 (-6.3, 3.0)
with serious adverse experiences	3	(0.5)	5	(0.8)	-0.3 (-1.4, 0.7)
with serious vaccine-related[‡]adverse experiences	0	(0.0)	0	(0.0)	0.0 (-0.6, 0.6)
who died	0	(0.0)	0	(0.0)	N/A
discontinued due to an adverse experience	0	(0.0)	0	(0.0)	N/A
discontinued due to a vaccine-related[‡]adverse experience	0	(0.0)	0	(0.0)	N/A
discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)	N/A
discontinued due to a serious vaccine-related[‡]adverse experience	0	(0.0)	0	(0.0)	N/A

[†] Risk differences and confidence intervals are based on the pooled incidence rates across study centers.
[‡] Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
Percentages are calculated based on the number of subjects with follow-up.
N=Number of subjects vaccinated in each treatment group.
rHA=Recombinant human albumin.
HSA=Human serum albumin.
N/A=Not applicable.

The results showed a statistically significant increase in the proportion of subjects in the M-M-RVAXPRO group who experienced injection site reactions during Days 1-42 p.v. (35.8 % vs. 29.7 %). For Days 1 to 5 following vaccination, the rate of injection-site adverse reactions was significantly higher among recipients of M-M-RVAXPRO compared to recipients of measles, mumps, rubella live vaccine with HSA (35.6% versus 29.1%, 95% CI = 1.4% to 11.7%). The majority of the injection-site reactions were either injection site pain or injection-site swelling, which disappeared within 48 hours postvaccination. Among recipients of M-M-RVAXPRO, 27.3% reported injection-site pain, compared with 21.8% of recipients of measles, mumps, rubella live vaccine with HSA (risk difference = 5.5%, p-value = 0.024). The risk difference between the 2 groups for the incidence of injection-site swelling was 3.6% (p-value = 0.026), with 10.9% of subjects who received M-M-RVAXPRO and 7.3% of subjects who received measles, mumps, rubella live vaccine with HSA reporting this adverse experience. The overall incidence of injection site reactions in this study was within the range of other studies with M-M-R II. The reactions were generally mild and transient. There was no case of severe pain ever or large erythema or swelling in the test group. Therefore although there is no apparent explanation of the differences in injection site experiences between the two treatment groups, this difference is not considered to be clinically relevant.

There were relatively few reports of morbilliform rash (3.2% of subjects vaccinated with M-M-RVAXPRO and 1.7% of subjects vaccinated measles, mumps, rubella live vaccine with HSA) or rubelliform rash (0% of subjects and 0.2% respectively), and the differences in incidence rates between the 2 treatment groups were not statistically significant for either type of rash (p-value = 0.104 and 0.317, respectively). No cases of mumps-like symptoms were reported in either treatment group.

Although a greater proportion of subjects who received M-M-RVAXPRO (17.6%) than subjects who received measles, mumps, rubella live vaccine with HSA (14.6%) experienced an elevated temperature (38.9°C), oral equivalent during Days 1 to 42 postvaccination, the difference between the 2 treatment groups was not statistically significant (risk difference = 3.0%, p-value = 0.159). The fevers were generally mild and short of duration.

One of the main purposes of conducting Protocol 009 was to explore the possibility that the rHA present as a manufacturing residual could provoke an immune reaction. These potentially allergic reactions, defined as "adverse experiences of special interest" in the protocol included urticaria, angioedema, non-injection-site rash (including maculopapular and generalized erythematous rashes, but excluding eczematous and other simple, localized rashes [e.g., diaper rash]), wheezing, collapse or shock-like state (onset within 48 hours of vaccination), and unexpected serious adverse experiences that were potentially allergic reactions.
The proportion of subjects who experienced any of these reactions was similar in both treatment groups: 87 out of 634 subjects (13.7%) vaccinated with M-M-RVAXPRO and 87 out of 632 subjects (13.8%) vaccinated with measles, mumps, rubella live vaccine with HSA. The most commonly reported was non-injection-site rash, observed in 9.9% of the subjects in the M-M-RVAXPRO and in 9.8% of subjects in the measles, mumps, rubella live vaccine with HSA group. The incidence rates of wheezing, urticaria, and angioedema were low (<3%) and well balanced between the 2 treatment groups. No statistical difference was observed when comparing the incidence rates of these adverse experiences of special interest between the 2 treatment groups (95% CI risk difference for each comparison contains 0). These adverse experiences of special interest were generally mild or moderate. No subjects from either treatment group experienced collapse or shock-like state (onset within 48 hours of vaccination) or unexpected serious adverse experiences that were potentially allergic reactions.

To further address the potential allerginicity, the applicant provided the results of an extension to the previously mentioned safety and immunogenicity study (Protocol 009 Extension Study). This study was conducted in 373 healthy, 3- to 5-year-old children who were previously enrolled in the Protocol 009 Base Study and who were vaccinated with a second dose of either v (194 subjects) or measles, mumps, rubella live vaccine with HSA (179 subjects). This study was conducted in the U.S., where the second dose of measles, mumps and rubella vaccine is recommended routinely at 4 to 6 years of age but can be administered at any visit provided at least 4 weeks have elapsed since the first vaccination given at or after 12 months of age. The primary objective of the study was to demonstrate that a second dose of M-M-RVAXPRO was generally well tolerated.
Numerous analyses were made showing that a second dose of M-M-RVAXPRO was not associated with an increase in the incidence and severity of clinical symptoms, including those suggestive of hypersensitivity reaction.

From experience gained with measles, mumps, and rubella vaccine (live) over decades it is unlikely that identical gelatine contained in M-M-RVAXPRO will cause an increase in gelatine specific allergic reactions.

The safety database is still limited (642 subjects who received a primary dose of M-M-RVAXPRO and 194 subjects who received a second dose). The applicant committed to perform a post-authorisation safety study to collect additional safety data on approximately 3000 subjects receiving 2 doses of M-M-RVAXPRO a few months apart.

Although no rHA specific antibodies have been detected so far, the potential risk of allergic reaction sensitization due rHA, triggered by a first dose of M-M-RVAXPRO followed potentially by more severe allergic reactions upon administration of a second dose cannot be excluded. As well as the Protocol 009 extension study in which a subset of original recipients received a second dose of M-M-RVAXPRO, the effect of repeat exposure to Recombumin® 20% has been tested in a large Phase 1 clinical trial specifically designed to solicit a maximum immunological response. Nevertheless appropriate pharmacovigilance activities described under the risk management programme section have been proposed to address this potential risk.

The risk of allergic reactions to the yeast impurities present in M-M-RVAXPRO was considered unlikely in view of the calculated maximum yeast antigen content per dose of vaccine.

- Serious adverse event/deaths/other significant events

In protocol 009 only 8 subjects (3 recipients of M-M-RVAXPRO and 5 recipients of measles, mumps and rubella live vaccine with HSA) experienced serious adverse experiences, none of which were determined to be vaccine-related. There were no deaths in the study.

- Laboratory findings

No specific laboratory analyses other than vaccine specific serology (immunogenicity and anti rHA antibodies) were performed.

- Safety in special populations

No safety studies in special populations are required for this type of vaccine**.**

- Safety related to drug-drug interactions and other interactions

Since a similar safety (and efficacy) profile was demonstrated for M-M-RVAXPRO compared to MMR II it is acceptable to extrapolate the safety data from concomitant use of measles, mumps, and rubella vaccine (live) with these vaccines.

- Discontinuation due to adverse events

There were no discontinuations due to AES in pivotal studies 007 and 009.

- Post marketing experience

Since equivalence (non-inferiority) was demonstrated for M-M-RVAXPRO compared to measles, mumps, and rubella vaccine (live) it is not expected that post marketing experiences for M-M-RVAXPRO will differ from those made with measles, mumps, and rubella vaccine (live). This data have therefore been included in the SPC.

1.4 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The description of the Pharmacovigilance system of the applicant was provided during the procedure.

Risk Management Plan

The MAA submitted a risk management plan.

Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk

		minimisation activities
Potential risk of rHA-related hypersensitivity reactions especially after the second dose	Post-marketing surveillance using pre-specified quantitative analysis of spontaneous reporting	Warning in the SPC to exercise caution when using any product containing recombinant human albumin in individuals who previously showed signs of hypersensitivity to rHA
Limited safety database	Safety study to collect additional safety data on approximately 3000 subjects receiving 2 doses of M-M-RVAXPRO a few months apart	

There will be a transition period where both M-M-RVAXPRO vaccine and measles, mumps, rubella (live) vaccine containing HSA will be on the market.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

1.5 Overall conclusions, benefit/risk assessment and recommendation

Quality

M-M-RVAXPRO is a trivalent live vaccine for immunisation against measles, mumps and rubella. The three virus components are: the more attenuated vaccine strain of measles virus (derived from Enders' attenuated Edmonston strain), the Jeryl Lynn strain of mumps virus, and the Wistar RA 27/3 strain of live attenuated rubella virus. The one of the difference between the existing measles, mumps and rubella vaccine (live) and M-M-RVAXPRO resides in the replacement of human serum albumin (HSA) with recombinant human albumin (rHA) during the manufacturing of measles, mumps, and rubella viral bulks. The quality aspects of the vaccine have been adequately addressed.
M-M-RVAXPRO, as other live attenuated vaccines, has only a few purification steps, resulting in a residual traces of rHA remaining in the vaccine. Based on this, the product information includes a statement on the theoretical risk of sensitization reactions to recombinant human albumin. The applicant committed to fulfil several follow-up measures to provide further information post-approval. There are no unresolved quality issues, which have a negative impact on the benefit-risk ratio.

Non-clinical pharmacology and toxicology

Clinical experience with the existing measles, mumps, and rubella vaccine (live) has been accumulated over decades. In addition, for M-M-RVAXPRO extensive testing has been performed on material obtained at various steps in the manufacturing process to assure that each vaccine bulk and each finished product is free from adventitious agents that might be introduced during manufacturing. It was considered that new toxico-pharmacological testing would not provide additional information on the safety profile of this new vaccine in comparison with the existing one, as supported by with the CHMP scientific advice. This is also in line with the Note for Guidance on the Preclinical Pharmacological and Toxicological testing of Vaccines (CPMP/SWP465/95).

Efficacy

M-M-RVAXPRO contains the same vaccine virus strains as currently authorised trivalent measles, mumps, and rubella vaccine. Two changes have been introduced regarding the formulation of M-M-RVAXPRO:

- A fixed end of expiry potency of the mumps component (4.1 instead of 4.8 log TCID 50 per dose)

- And Human Serum Albumin (HSA) was replaced by recombinant Human Albumin (rHA), as an excipient in the growth media.

In the double-blind, randomised, multicenter study 007**,** a total of 1997 subjects were vaccinated concomitantly with both measles, mumps and rubella live vaccine and varicella live vaccine. Results supported the claim that the end of expiry potency of the mumps component is non-inferior to the current release specification for that vaccine component (4.1 log Tissue Culture Infectious Dose 50 instead of the current 4.8 log TCID 50).

In the l double-blind, randomized, multicentre study 009, 641 subjects were vaccinated with M-M-RVAXPRO and 638 subjects were vaccinated with measles, mumps, and rubella vaccine (live) with HSA. Results showed that M-M-RVAXPRO is equivalent (non-inferior) to the currently licensed measles, mumps, and rubella vaccine (live) vaccine in terms of immunogenicity, i.e. response (seroconversion) rates and GMTs.

At present no data are available on the intramuscularly administration, thus M-M-RVAXPRO should only be used subcutaneously as be stated in the Summary of Product Characteristics. A study has recently been initiated to evaluate the safety and immunogenicity of M-M-RVAXPRO when administered via the subcutaneous or the intramuscular route, respectively, the results of which will be provided as part of the follow-up measures to be submitted post-authorisation.

Safety

The safety database derives mainly from study 009 in which 642 subjects received a primary dose of M-M-RVAXPRO and 640 received a primary dose of measles, mumps, and rubella vaccine (live) vaccine with HSA. For the majority of clinical adverse experiences reported no significant difference could be observed for M-M-RVAXPRO compared to measles, mumps, and rubella vaccine (live) vaccine. In this study, there were higher frequencies of injection site reactions with M-M-RVAXPRO nonetheless in retrospective comparison showed that these were within the rate observed in previous studies with measles, mumps, and rubella vaccine (live) vaccine. These reactions were mild and transient. The numerically higher fever rate was considered to be also within the range observed in previous studies and of no clinical importance.

The effect of a second dose of M-M-RVAXPRO were evaluated in an extension study, involving participants from study 009 who received either a 2nd dose of M-M-RVAXPRO (n = 194) or measles, mumps, and rubella vaccine (live) vaccine (n = 179). Adverse reactions of special interest, i.e. those being indicative for an allergic reaction were specifically monitored. Numerous analyses were made and no differences between the two groups were detected, including no increase in potential allergic reactions is observed after a second dose of M-M-RVAXPRO. Moreover, all adverse reactions (severe or not including those signaling potential allergic reactions) decreased after the second dose of M-M-RVAXPRO or measles, mumps, and rubella vaccine (live) vaccine indicating the absence of any re-exposure effects mediated by rHA or any other vaccine component. Antibodies against rHA were not detectable in sera of individuals vaccinated with M-M-RVAXPRO at day 42 following first and second dose injection as evidenced by an anti rHA antibody ELISA.

All the adverse reactions reported in clinical trials and post-marketing with the current formulation of measles, mumps, and rubella vaccine (live) vaccine have been included in the Summary of Product Characteristics.

Benefit/risk assessment

M-M-RVAXPRO, a childhood vaccine which has been developed to harmonise the expiry titer for the mumps components of this combination vaccine and to support the replacement of human serum albumin with recombinant human albumin in the manufacturing of measles, mumps and rubella viral bulks. There are no fundamental changes proposed in the indication or dosing schedule of this new vaccine compared to the authorised one using human serum albumin.

M-M-RVAXPRO has been demonstrated to be non-inferior in terms of immunogenicity and also in terms of safety compared to measles, mumps, and rubella vaccine (live) vaccine.

A risk management plan was submitted and includes pharmacovigilance activities to further monitor potential change in the safety profile related to the replacement of HSA with rHA. Although no rHA specific antibodies have been detected so far in the clinical studies, even after administration of a second dose, a theoretical risk of hypersensitivity to rHA cannot be ruled out.
In addition the applicant will perform a post-marketing safety study to increase the safety database in particular after second dose of vaccine.
The CHMP, having considered the data submitted, was of the opinion that no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of M-M-RVAXPRO in the prophylaxis of "simultaneous vaccination against measles, mumps, and rubella in individuals 12 months or older. For use in measles outbreaks, or for post-exposure vaccination of non-pregnant adolescent and adult subjects, or, previously unvaccinated children older than 12 months who are in contact with susceptible pregnant women, and persons likely to be susceptible to mumps and rubella" was favourable and therefore recommended the granting of the marketing authorisation.