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Guideline on the clinical evaluation of medicinal products indicated for the prophylaxis or treatment of respiratory syncytial virus (RSV) disease

Draft

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Executive summary

This guideline addresses clinical development programmes for medicinal products intended for the pre-exposure prophylaxis or treatment of disease due to respiratory syncytial virus (RSV). The guidance covers the development of vaccines and monoclonal antibodies for the prevention of RSV disease and direct acting antiviral agents (DAAs) for the treatment of RSV disease. The focus is on the assessment of safety and efficacy in populations most likely to develop RSV lower respiratory tract infection (LRTI) and severe RSV disease, in which a clinically important benefit of the intervention is most likely to be demonstrated. Depending on the type of intervention and product characteristics, these populations may include newborn infants (aged 0-27 days), infants (aged 28 days to 11 months), toddlers (aged 12-23 months), older paediatric subjects predisposed to develop severe RSV disease and the elderly (aged ≥ 65 years). The guideline also addresses vaccination of pregnant women with the aim of preventing RSV disease in their infants while protective maternal antibody levels persist.

At the time of preparing this guidance it is expected that efficacy trials will be designed to demonstrate superiority of the vaccine, monoclonal antibody or treatment over no active intervention. Consideration is given to clinical data that could support the use of preventive or therapeutic products in populations that were not included in efficacy trials (e.g. using immunological or pharmacokinetic data).

In efficacy trials of preventive and therapeutic products it is essential that there are clear age-specific definitions of RSV cases based on a combination of clinical and laboratory criteria. Sponsors are encouraged to take note of any available internationally-recommended and widely agreed age group-specific definitions.

Prior experience with a formalin-inactivated RSV vaccine led to concern regarding the potential for clinically severe vaccine-associated disease enhancement to occur after active immunisation of RSV-naïve paediatric subjects. To assess the risk, it is recommended that the duration of follow-up in each trial is sufficient to ensure that the majority of subjects have experienced natural exposure to RSV, with or without a clinically apparent illness. For vaccines intended for pregnant women, case ascertainment in infants should continue until anti-RSV antibody levels are similar between infants born to vaccinated and unvaccinated women. In the elderly, it is desirable that some data are available on the duration of protection, need for re-vaccination and the safety and immunogenicity of sequential doses at the time of licensure.

Issues for treatment trials include the basis for selection of the recommended dose regimen and the need to determine the maximum time from symptom onset to initiation of treatment that is associated with a clinically important benefit.

Other than addressing the risk of vaccine-associated disease enhancement after active immunisation the assessment of vaccine safety follows the same principles as for other vaccines. For monoclonal antibodies the safety database should suffice to identify any trends to increasing rates of local and systemic adverse reactions with sequential doses and/or with the first dose given in a second RSV season after a gap of several months. For antiviral agents for the treatment of RSV safety data should be collected in each target age group.

1. Introduction (background)

Respiratory syncytial virus (RSV) is an Orthopneumovirus of the family *Paramyxoviridae* with two major subtypes (A and B). The glycosylated F and G surface proteins in the RSV envelope are essential for pathogenesis and elicit neutralising antibodies in the host. Antigenic diversity between and within

RSV subtypes mainly reflects variations in the G glycoprotein, with low homology between G glycoproteins of A and B strains. After RSV infection via the human respiratory tract, the virus shows tropism for the ciliated epithelia in bronchioles and alveoli, where it elicits a local immune response leading to inflammation.

In Europe RSV disease is seasonal (e.g. typically November to April) with a peak in the mid-winter months. Most children have serological evidence of prior RSV infection by the age of 2-3 years and many have a primary infection during their first season. Primary RSV infections in newborn infants (aged 0-27 days), infants (aged 28 days to 11 months) and toddlers (aged 12 to 23 months) sometimes cause severe lower respiratory tract infection (LRTI), resulting in bronchiolitis, bronchitis and/or viral pneumonia. There is a higher risk of severe RSV disease associated with premature birth (at ≤ 35 weeks of gestation) and in children with a wide range of underlying conditions (e.g. bronchopulmonary dysplasia and haemodynamically significant congenital heart disease). Other underlying conditions that may predispose to severe RSV disease at any age include neuromuscular diseases, Down's syndrome, cystic fibrosis and some types of immunosuppression. Long-term morbidity following RSV LRTI in early life may include wheezing.

RSV infection in early life does not provide solid immunity so that individuals may be infected and may develop clinical manifestations of RSV multiple times during their life span. In healthy adults, adolescents and children who are RSV non-naïve, symptomatic RSV infection may be associated with mild upper respiratory tract infections and relatively few cases require medical intervention. Elderly subjects (aged ≥ 65 years) with or without comorbid conditions, such as congestive heart failure, emphysema or asthma, are more likely than younger adults to develop LRTI requiring medical intervention.

There is a very large range of RSV vaccines currently under development, including inactivated, live attenuated, chimeric, live viral vectored (some in a prime-boost regimen with two different constructs) and nucleic acid vaccines.

In the 1960s an alum-adjuvanted, formalin-inactivated, whole virion RSV vaccine was developed. When administered to RSV-naïve infants it was not protective and it was associated with a higher rate of severe RSV disease and some fatalities following subsequent natural infection compared to the unvaccinated control group. Whilst the exact mechanism of this vaccine-associated disease enhancement is not known, investigations indicated that the vaccine elicited mainly RSV binding antibody rather than virus neutralising antibody. Consequently, vaccine development for primary immunisation of RSV-naïve subjects has focussed on live attenuated or live viral vectored vaccines with the aim of eliciting high titres of RSV neutralising antibody and a Th-1 directed immune response.

A wider range of vaccine constructs is under consideration for children aged from about 2 years, adults and the elderly who have experienced prior natural infection(s) with RSV. In addition, some vaccines are under development for administration to pregnant women to increase the amount of RSV neutralising antibody passed to the foetus and reduce the risk of RSV disease in the first few months of life.

Concurrently, there are several directly acting antiviral agents (DAAs) for treatment of RSV disease as well as monoclonal antibodies with standard or prolonged plasma half-lives for prevention of RSV disease in clinical development.

2. Scope

The focus of the guideline is on the clinical evaluation of the safety and efficacy of vaccines, monoclonal antibodies or DAAs by direct comparison with control groups that do not receive an RSV-specific intervention. The guidance covers some nonclinical investigations of efficacy and risk of vaccine-associated enhanced disease to support clinical trials with preventive or therapeutic products directed at RSV.

Detailed guidance is not provided on the development of assays to measure virus neutralisation titres or other immune parameters. Currently much work is ongoing in this field and sponsors are expected to provide a justification for their choice of assay(s) that takes note of the most recent developments. As/when International Standards may be available these should be included in the assay development and validation processes. Some general considerations for the selection of assays to be used for the laboratory confirmation of clinical cases of RSV disease are included in the guidance.

The prevention and treatment of RSV disease is an area in which there is a wide range of ongoing and planned nonclinical and clinical activities with potential implications for future development programmes. Sponsors are encouraged to discuss their programmes with EU Competent Authorities even if their plans are generally in line with this guidance. Sponsors may wish to evaluate candidate products in target groups that are not addressed in detail in this guidance, in which case consultation with EU Competent Authorities is strongly recommended.

2.1. Vaccines

General requirements for the clinical development of new vaccines are provided in the *Guideline on clinical evaluation of new vaccines* (EMEA/CHMP/VWP/164653/05), which should be followed.

This guideline discusses issues that are most relevant or specific to RSV vaccines. Although the range of vaccine constructs currently in development is very wide, the general principles for clinical assessment are broadly applicable. The focus of the guidance is on vaccines intended for groups in which an important clinical benefit of vaccination is most likely to be demonstrated. These groups include, but are not limited to:

- Infants (aged 28 days to 11 months) and toddlers (aged 12-23 months), including those who were born prematurely and those who are at risk of severe RSV disease due to underlying conditions. Vaccination of newborn infants (aged 0-27 days) is a less likely strategy and it is not addressed, although the guidance provided would be broadly applicable;
- Pregnant women, with intent to prevent RSV in their infants while protective levels of maternal antibody persist; and
- Elderly subjects (aged ≥ 65 years).

2.2. Monoclonal antibodies

The focus of the guidance is on the use of monoclonal antibodies that exert virus neutralisation activity for pre-exposure prophylaxis of RSV disease in newborn infants, infants and toddlers, including those at risk of developing RSV LRTI and severe RSV disease.

Although not specifically addressed in this guidance the principles discussed for the development of direct acting antiviral agents for treatment of RSV are broadly applicable to the clinical evaluation of monoclonal antibodies for treatment of RSV and should be followed.

2.3. Antiviral agents

The focus of the guidance is on evaluating direct acting antiviral (DAA) agents for the treatment of RSV disease in newborn infants, infants, toddlers and the elderly. These are the groups especially at risk of developing RSV LRTI and severe RSV disease, in which a clinically important benefit of treatment is most likely to be demonstrated. The use of DAAs to prevent RSV is not considered. Pharmacokinetic trials, including drug-drug interaction trials, with new antiviral agents will be required but are not discussed since they are not specific to DAAs directed against RSV. Similarly, the development of appropriate formulations for paediatric use is not specific to DAAs directed at RSV and is not discussed. Available CHMP guidance should be consulted as appropriate.

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, and all other relevant EU and ICH guidelines. These include, but are not limited to:

- Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/2005) Rev 1
- Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines (EMA/CHMP/VWP/141697/2009)
- Pharmacokinetic trials in man (CHMP/EWP/147013/04)
- Evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function (CPMP/EWP/225/02)
- Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function (CPMP/EWP/2339/02)
- Investigation of drug interactions (CPMP/EWP/560/95)
- Reporting the Results of Population Pharmacokinetic Analyses (CHMP/EWP/185990/06)
- Clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99) (ICH11)
- Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population (CHMP/EWP/147013/04)
- Note for guidance on trials in support of special populations: Geriatrics (CPMP/ICH/379/95)
- Statistical principles for clinical trials (CPMP/ICH/363/96)
- Choice of a non-inferiority margin (CPMP/EWP/2158/99)

4. Nonclinical efficacy data to support clinical trials

4.1. Vaccines

Before commencing clinical trials with vaccines there should be nonclinical data to demonstrate that a functional immune response can be achieved post-vaccination based on the immune parameter(s) most relevant to the vaccine construct. Immunogenicity studies may be conducted in RSV-naïve and/or non-naïve animals depending on the human target population(s). Where relevant, studies may include

vaccination of RSV non-naïve dams followed by measurement of neutralising antibody in the offspring at birth.

Nonclinical studies may be used to demonstrate that the vaccine protects against development of RSV disease post-challenge. If appropriate, studies may include challenge of offspring born to vaccinated dams. Readouts may include effects of the intervention vs. placebo on viral loads in lower and upper respiratory tract tissues. The data from these experiments should be explored for correlations between immune responses and efficacy parameters.

Nonclinical studies should provide a preliminary assessment of the risk that vaccine-associated enhanced RSV disease could occur. There are several issues that may impact on the ability of various animal models to evaluate the risk. This field is evolving and it is expected that sponsors will consider the scientific literature when designing the nonclinical programme to assess the potential risk of vaccine-associated RSV disease enhancement.

4.2. Monoclonal antibodies

Nonclinical studies should demonstrate that virus neutralisation is achieved *in vitro* and should describe the neutralising activity over a range of antibody concentrations and against a range of RSV isolates. Nonclinical efficacy studies may be conducted as described for vaccines.

4.3. Antiviral agents

Before commencing clinical trials, the antiviral activity of a DAA should be documented *in vitro* using a range of recent RSV clinical isolates. The DAA should also be investigated for activity against other viruses, including those known to cause respiratory disease.

The mechanism of action of the DAA should be investigated as well as the mechanism(s) of resistance in any RSV isolates that appear to have reduced susceptibility *in vitro*.

Nonclinical data may provide preliminary evidence of efficacy. In most of the in-vivo nonclinical models that have been used, RSV replication does not produce quantifiable symptoms so that the effect of a DAA is based on demonstrating effects on viral titres compared to untreated controls. One approach to consider is the naïve bovine model, which could be used to estimate the effect of the DAA on symptomatic illness caused by bovine RSV, which appears to have a similar pathogenesis to RSV in naïve humans.

5. Patient selection

5.1. Vaccines

Regardless of the target population(s) for a candidate vaccine, the first trials are expected to be conducted in healthy adults (e.g. aged 18 to <45 years) to provide data on safety and immunogenicity in RSV non-naïve male and non-pregnant female subjects.

5.1.1. Infants and toddlers

It is recommended that safety and immunogenicity data are obtained from RSV non-naive toddlers before moving to RSV non-naïve and naive infants. The serostatus of toddlers and infants aged > 6 months should be determined before they are vaccinated to ensure an adequate representation of

RSV-naïve and non-naïve subjects and to allow for dosing non-naïve subjects before moving to a naïve cohort.

The first safety and immunogenicity trial could be conducted in infants aged 6-12 months before progressing to infants aged < 6 months and infants aged < 6 months who were born prematurely (at ≤ 35 weeks of gestation). Generally, it would be reasonable to assume that most infants with remaining maternal anti-RSV neutralising antibody will be RSV-naïve unless they have had a documented prior illness due to the virus. For older infants with no remaining maternal anti-RSV neutralising antibody and for toddlers the protocol should provide criteria for defining RSV-naïve or non-naïve status at baseline that take into account the lower limits of detection and quantification of neutralising antibody for the assay used. Since it is possible that some naturally primed subjects may not have measurable neutralising antibody, sponsors are encouraged to apply other assays (e.g. that detect IgG against the F, G and/or other viral proteins) to assist in differentiating RSV-naive and non-naïve subsets.

Sponsors may confine vaccine efficacy trials to infants who commence vaccination within the first 6 months of life to provide an estimate of vaccine efficacy in a population that is predominantly RSV-naïve. If older infants and/or toddlers are to be enrolled it is recommended that there is stratification by age sub-group. The patient selection criteria should include the minimum gestational age at birth and the minimum and maximum ages required for enrolment. Stratification of infants by premature or non-premature birth could be considered if the trial includes infants born at ≤ 35 weeks of gestation.

It is not expected to be feasible to determine baseline serostatus prior to enrolment into efficacy trials.

5.1.2. Pregnant women

Pregnant women should be enrolled into safety, immunogenicity and efficacy trials based on their estimated duration of gestation. The method for estimating the gestational stage should be specified in the protocol and applied across all sites. It is expected that women will usually be vaccinated in the third trimester to maximize the amount of maternal antibody that is transferred to the foetus. If initial data on the immune response indicates that more than one dose is likely to be required, and depending on the dose interval needed to optimise the immune response to the second or further dose(s), it may be necessary that sequential trials enrol women at an earlier stage of pregnancy.

The protocol should give clear guidance on whether pregnant women with any evidence of placental insufficiency are eligible for enrolment. If there are cord blood data to suggest that vaccination increases the anti-RSV neutralising antibody transferred to the foetus despite placental insufficiency, it may be appropriate to include these women and to consider stratifying enrolment by the presence or absence of evidence of placental insufficiency at the time of randomisation.

5.1.3. Elderly

It is important that there is adequate representation of age sub-groups 65-74, 75-84 and ≥ 85 years across the safety and immunogenicity trials. Stratification by age sub-group at randomisation is recommended in efficacy trials. Sponsors are encouraged to include a representative sample of elderly subjects with conditions pre-disposing them to severe RSV disease but not expected to negatively impact on the immune response (e.g. with underlying respiratory or cardiopulmonary disease) in vaccine efficacy trials, with or without stratification.

5.1.4. Other populations

Before or after licensure, sponsors may wish to evaluate the safety and immunogenicity of RSV vaccines in populations other than those in which vaccine efficacy was demonstrated to support dose regimen recommendations. For example:

- Immunocompetent older paediatric subjects with conditions recognised to predispose them to RSV LRTI and severe RSV disease;
- Subjects with selected types of immunodeficiency;
- Subjects who have received a monoclonal antibody against RSV to investigate the minimum time interval that should elapse between the last dose of the monoclonal antibody and first dose of the vaccine.

5.2. Monoclonal antibodies

The first trials are usually conducted in healthy adults to provide preliminary data on safety and on the decay of RSV-specific antibody levels (i.e. total of pre-existing naturally-acquired neutralising antibody and exogenous neutralising antibody) over time.

In trials that evaluate safety, neutralising antibody levels and/or efficacy in paediatric subjects in whom a benefit may be anticipated, it may be appropriate to stratify at the time of randomisation (e.g. infants born at ≤ 35 weeks of gestation, infants aged < 6 months at the onset of the RSV season and paediatric subjects with risk factors for severe RSV disease). Older paediatric subjects with conditions recognised to predispose them to RSV LRTI and severe RSV disease may be included or studied separately.

5.3. Antiviral agents

The first trials to evaluate the safety and pharmacokinetics of DAAs for RSV are expected to be conducted in healthy adults. If potentially effective dose regimens for paediatric age sub-groups can be derived from modelling and simulation, and if the nonclinical and healthy adult safety data allow, it may be possible to proceed directly to trials in subjects who have RSV disease within the target paediatric age range for the product. Trials that evaluate safety, pharmacokinetics and/or efficacy in elderly patients should include representation from all age sub-groups. Stratification by age (e.g. 65-74, 75-84 and ≥ 85 years) should be considered in efficacy trials.

Patient selection in efficacy trials should be based on a case definition that combines clinical signs and symptoms with laboratory evidence of RSV.

5.3.1. Clinical criteria

The demonstration of a clinically important benefit of treatment is most likely to be possible in those with severe or very severe RSV disease. Furthermore, once a treatment has been licensed for RSV and is widely recommended, it may not be feasible to conduct further trials in which active treatment is withheld from patients with severe RSV disease (e.g. with RSV LRTI and severe LRTI). Therefore, it is recommended that efficacy trials with a new treatment for RSV should be confined to patients considered to be at the more severe end of the disease spectrum or should be stratified to ensure that a sufficient proportion of patients with severe disease are enrolled to be able to assess efficacy in this sub-group.

The list of clinical signs and symptoms and the number that should be met for eligibility must be tailored to the age range of the trial population. Sponsors are advised to take account of proposals for classifying RSV disease severity in different age groups that come from well-recognised public health or professional bodies, with or without some modification. The inclusion of at least one eligibility criterion that is an objective measure, such as oxygen saturation on room air corrected for altitude and measured under standardised conditions, is encouraged. Sponsors could also consider categorising patients using published clinical scores (e.g. Respiratory Distress Assessment Instrument [RDAI] and Respiratory Assessment Change Score [RACS] and by type of ventilator support given, if applicable.

Efficacy trials may be confined to hospitalised patients so that comprehensive data can be collected and/or if the treatment is administered each day by a healthcare professional. Due to variability in healthcare systems and thresholds for admission, it is not advisable to base a judgement of disease severity on the perceived need for hospitalisation.

A benefit of treatment may be detectable only if it is commenced within a defined time limit after symptom onset. Consideration may be given to stratification at randomisation by time intervals elapsed since onset of symptoms (e.g. using 12 hour intervals) up to the maximum allowed in the protocol. The maximum time elapsed that is allowed between symptom onset and randomisation should be balanced against the risk that the longer the duration the more likely it is that secondary bacterial infections may occur, which will impact on the assessment of the efficacy of the DAA.

Chest radiographs are not required to assess patient eligibility for treatment but may be obtained as a routine in elderly subjects, in which case the findings should be recorded.

5.3.2. Laboratory criteria

Patient enrolment may be based on a protocol-defined commercially available rapid diagnostic test (RDT) for RSV. It is recommended that the exact same RDT (e.g. a nucleic acid detection test [NAAT] from a single manufacturer that can detect low levels of virus) is used at all sites. If this is not feasible it is recommended that the protocol requires the use of RDTs that work on the same principle and have similar sensitivity and specificity to minimize the possibility that there is an imbalance across trial sites in baseline viral loads. The sponsor should justify the RDT(s) chosen based on their performance characteristics (sensitivity and specificity) and the ability of all trial sites to conduct the test(s) without delaying or hindering the randomisation and treatment of potentially eligible patients.

If the new DAA demonstrates different antiviral activity by RSV subtype the RDT(s) used should differentiate RSV A and B. Consideration should be given to using RDTs that also detect viruses that are recognised to co-exist in some RSV cases and have been reported to affect the severity and course of the disease (e.g. human metapneumovirus and influenza virus). Patients with RDT results indicating the presence of additional viruses that may be contributing to the clinical presentation should still be enrolled.

6. Assessment of efficacy

6.1. Vaccines

Currently there is no immune correlate of protection for RSV disease that could be used to infer protective efficacy based on immune responses and there is no vaccine licensed for the prevention of RSV. Therefore, vaccine efficacy trials in which candidate vaccines are compared with control groups that do not receive vaccination against RSV are required. At least one trial should be conducted in each

target population proposed for the candidate vaccine (e.g. in infants ± toddlers, in pregnant women and/or in the elderly).

Following a demonstration of vaccine efficacy in infants ± toddlers it may be possible to include dose regimens for older paediatric subjects who are at risk of developing severe RSV disease in the Summary of Product Characteristics (SmPC) based on demonstrating that the vaccine elicits immune responses comparable to those observed in the population in which efficacy was demonstrated.

Once a vaccine against RSV has been shown to be efficacious and has been licensed for use in a specific population, it may not be considered appropriate to withhold a licensed RSV vaccine from the control group in a vaccine efficacy trial with a candidate vaccine, in which case trials should demonstrate that the efficacy of a candidate vaccine is at least non-inferior to that of a licensed vaccine. Alternatively, a demonstration of efficacy against RSV disease may not be required for candidate vaccines if efficacy can be inferred by interpreting the immune response to the candidate vaccine using a widely accepted immune correlate of protection that was established in a prior efficacy trial with another RSV vaccine. Nevertheless, even if an immune correlate of protection has been identified from an efficacy trial with one vaccine it may not be widely applicable across candidate vaccine constructs and in different populations.

If there is no established immune correlate of protection that can be applied to immune responses against a candidate vaccine, the possibility of inferring efficacy using an immunobridging approach, whereby the candidate vaccine is shown to elicit a comparable immune response to a licensed vaccine for which efficacy has been demonstrated, would have to be discussed with EU Competent Authorities on a case by case basis. Immunobridging between a candidate vaccine and a licensed vaccine will not be possible if different parameters are required to describe the immune response.

6.2. Monoclonal antibodies

If possible, an efficacy trial should be conducted to compare a candidate monoclonal antibody with a group that does not receive a licensed anti-RSV monoclonal antibody. Such a trial may be possible in populations that are considered at risk of developing severe RSV disease but are not eligible to receive a licensed product according to national recommendations. If this design is not possible, an efficacy trial may be designed to demonstrate that the efficacy of a candidate monoclonal antibody is at least non-inferior to that of a licensed product.

Subject to a demonstration of efficacy in infants and/or toddlers, together with an adequate assessment of safety, dose regimens for older paediatric subjects considered to be at risk of severe RSV disease and/or with certain types of immunodeficiency could be included in the SmPC based on achieving similar neutralising antibody titres and decay curves.

6.3. Antiviral agents

At the time of preparing this guidance inhaled ribavirin is still approved in some EU member states for treatment of RSV bronchiolitis in infants and toddlers via inhalation but it is not actually recommended in treatment guidelines. There is no approved DAA for RSV in other age groups. Therefore, a candidate DAA should be shown to be superior to a control group that receives placebo in the all treated population based on a clinically relevant primary endpoint.

It is recognised that the feasibility of placebo-controlled trials may have to be reconsidered once new DAAs for treatment of RSV have been licensed and have entered widespread use. In this setting it is recommended that sponsors discuss the design of pivotal efficacy trials with EU Competent Authorities.

If a DAA has shown convincing efficacy in infants (± toddlers), it may be possible to base a recommendation for use of the same or an alternative posology in the SmPC for older paediatric subjects who have severe RSV disease based on safety and pharmacokinetic data. The proposed dose regimen(s) should achieve plasma exposures similar to those documented in the population in which efficacy was demonstrated.

Immunodeficient persons may require a different dose regimen to combat high viral loads and/or a longer duration of treatment to clear replicating virus. Analyses of efficacy according to baseline viral load using data collected during an efficacy trial in subjects treated for their first RSV infection may assist in determining the need for a different dose. Nonclinical data may provide some indication of the need for a longer duration of treatment. Sponsors could consider conducting an exploratory trial in immunodeficient subjects with severe RSV disease using a dose regimen based on previous clinical experience. If necessary, additional trials could be conducted using alternative regimens. The data may suffice to support a recommended posology in the SmPC.

7. Trial design

7.1. Vaccines

General recommendations for the design of clinical trials that aim to:

- evaluate the safety and immunogenicity of a candidate vaccine against RSV,
- support the dose regimen(s) to be taken forward into confirmatory studies,
- demonstrate vaccine efficacy,

are the same as those for other types of vaccines (see Guideline on clinical evaluation of new vaccines, EMEA/CHMP/VWP/164653/05).

7.1.1. Safety and immunogenicity trials

Infants and toddlers

Safety and immunogenicity trials with candidate vaccines in infants and toddlers should include a thorough investigation of the immune response as relevant to the vaccine construct. It is recommended that trials that include RSV-naïve subjects should require follow-up for RSV disease for at least one season before moving to the next trial in this population. This cautious approach allows for very preliminary assessments of any risk of enhanced disease to be made before exposing additional subjects, and likely larger numbers, in the next trial.

The potential for maternal antibody to interfere with the immune response to active immunisation of infants should be assessed. If the presence of maternal antibody has a blunting effect on the infant immune response, it is recommended that the immune response to a further dose after several months have elapsed should be evaluated to determine whether the first dose primed the infant immune system.

Pregnant women

The protective titre of RSV neutralising antibody in infants is not known. Dose regimen selection for pregnant women may be based on maximizing the difference in neutralising antibody titres in cord blood between infants born to vaccinated and unvaccinated mothers whilst maintaining an acceptable safety profile. Cord blood antibody levels in infants delivered over a range of weeks elapsed from the

time of maternal vaccination (only or last dose, as applicable) may assist in determining the timing of maternal vaccination. The RSV neutralising antibody decay curves in infants should be documented. If trials are conducted in areas with variable rates and durations of breastfeeding sponsors may consider exploring the antibody decay curves accordingly.

The RSV neutralising antibody decay curve should be documented in vaccinated women during and following the pregnancy and the time taken to return to pre-vaccination levels should be determined. It is recommended that revaccination strategies that include administration of further doses to women during their next pregnancy should be investigated. These data may be generated in the post-approval period. If initial vaccination was with more than one dose it would be appropriate to re-vaccinate subgroups with a single dose or a repeat course to assess whether a reduction in doses is possible.

It is recommended that trials should require follow-up of infants for RSV disease for at least one season before moving to the next trial. This cautious approach allows for very preliminary assessments of any risk of enhanced disease to be made in infants born to vaccinated vs. unvaccinated mothers before exposing additional subjects, and likely larger numbers, in the next trial.

Elderly

Trials should be conducted to support selection of the dose regimen(s) for age sub-groups 65-74 years, 75-84 years and 85 years and older.

In this RSV non-naïve population there is evidence that pre-existing neutralising antibody is protective and that high titres are associated with lower risk of severe RSV LRTI. It is particularly important in this age group that the neutralising antibody response to vaccination is analysed by pre-vaccination serostatus.

It is likely that further doses of efficacious vaccines will be required at intervals. The safety and immunogenicity of revaccination after various time intervals should be documented and the ability of the vaccine to elicit an anamnestic immune response should be assessed. Since the ageing process could itself have a negative impact on immune responses to revaccination, a comparison could be made with responses to a single dose in a control group that is age-matched to the re-vaccinated cohort.

7.1.2. Efficacy trials

The design of vaccine efficacy trials is described in the Guideline on clinical evaluation of new vaccines (EMEA/CHMP/VWP/164653/05), which includes considerations for using data on post-vaccination immune responses and efficacy to investigate possible immune correlates of protection. This section addresses some special considerations for efficacy trials with RSV vaccines.

If a candidate vaccine elicits a large increment in non-neutralising antibody in one or more subsets of subjects in safety and immunogenicity trials, there is concern that this could potentially interfere with the protection afforded by neutralising antibody. In such a case, it is possible that not only would the vaccine have poor or no efficacy but also that the severity of clinically apparent RSV could be enhanced at least in some subsets of subjects. Therefore, if such a finding is apparent in the immunogenicity trials with a candidate vaccine it is recommended that additional in-vitro and/or in-vivo nonclinical studies are conducted before deciding whether to proceed to a vaccine efficacy trial.

Furthermore, not all RSV vaccines under development may elicit neutralising antibody. Depending on the vaccine construct and route of administration the primary interest may be mucosal antibody levels (e.g. IgA levels in nasal secretions) or cell-mediated immune responses. In these cases, the clinical

data, supported by appropriate nonclinical studies, should demonstrate that there are no anticipated negative effects of vaccination on pre-existing neutralising antibody titres before proceeding to vaccine efficacy trials.

Primary endpoint

The primary efficacy endpoint should be based on cases of RSV disease meeting the primary case definition. Considerations for defining cases of RSV disease and their severity are those applicable to patient selection in treatment trials described in section 5.3 (Patient selection, Antiviral agents).

The primary endpoint could be based on any clinically apparent laboratory-proven RSV disease or against one or more of RSV LRTI and severe/very severe RSV disease.

Secondary endpoints

If the primary analysis is to be based on all RSV disease (i.e. regardless of severity) then secondary analyses should be conducted based on RSV LRTI, severe RSV disease and/or other case definitions. This is essential in all vaccine efficacy trials, regardless of the trial population, to assess the risk of vaccine-associated enhanced disease.

If the primary analysis is to be based on RSV LRTI or severe RSV disease the method of case ascertainment may mean that other clinical presentations are not captured in the database. If they are, a secondary analysis should assess whether there is any difference in the proportion of cases that are severe between the group that receives the active intervention and the control group.

In trials in which pregnant women are randomised to the vaccine or control group, the time between birth and the first clinically apparent RSV infection meeting the case definition should be included as a secondary endpoint. In trials in which infants or toddlers are randomised to the vaccine or control group the time between last vaccination and the first clinically apparent RSV infection (any and/or meeting the case definition) should be included as a secondary endpoint.

Although it is recommended that the perceived need for and type of healthcare interaction (e.g. home visit, emergency room visit or hospitalisation) should not be part of the case definition for the primary analysis, the information should be collected and included in the secondary analyses.

An assessment of whether a vaccine has an impact on any possible sequelae of RSV disease is not required for licensure. There is interest in evaluating whether vaccination impacts on the rate of symptomatic wheezing in children, which could be investigated in the post-licensure period. This would require a clear definition of symptomatic wheezing along with long-term structured follow-up to maintain high retention of the original clinical trial population to determine whether there is any detectable benefit and its duration.

Case ascertainment

It is generally recommended that active surveillance is used for case ascertainment in efficacy trials with candidate RSV vaccines. The exact method of case ascertainment will depend on the primary endpoint (i.e. all RSV disease or severe/very severe RSV disease) and, to some extent, the secondary endpoints. Subjects or their care-givers should receive instructions on trigger signs and symptoms for possible RSV and whether they should in the first instance contact site staff and/or present to participating local healthcare facilities. On occasion, subjects or their care-givers may present or be taken to healthcare facilities not participating in the trial so they are not captured as cases in the database. Active surveillance could include regular contact by site staff to elicit any missed cases and

to obtain permission to obtain the relevant data to categorise the case, if adequate data have been collected.

Infants and toddlers

At trial sites in regions where RSV is seasonal the recruitment period should be timed such that the last assigned dose is given no more than a specified number of weeks before the usual season start month. If the trial includes sites in seasonal and non-seasonal regions it may be useful to stratify enrolment accordingly.

If the total (i.e. blinded to treatment assignment) number of cases of RSV accrued that meet the case definition fulfils the requirements of the statistical analysis plan, the primary analysis may be conducted after the end of the first season or after an equivalent time period post-vaccination if sites in non-seasonal regions are included.

If there is any vaccine-associated disease enhancement, it is expected to occur with the first natural RSV infection after completion of vaccination. During follow-up for 2-3 seasons or an equivalent time period in non-seasonal regions the majority of trial subjects should have been exposed to circulating virus. To support this assumption, the proportion of subjects in the placebo group who have serological evidence of RSV infection, with or without symptoms, could be assessed. If RSV enhanced disease has not been observed in the vaccinated group after 2-3 seasons of follow-up despite serological evidence of a high natural exposure rate in the unvaccinated control group, it is very unlikely that it would be detected during additional follow-up. Follow-up for 2-3 seasons is also sufficient to describe the duration of protection after a primary series without further vaccine doses.

Pregnant women

The level of protective efficacy of a candidate vaccine may reflect maternal and placental health as well as the rate of decline in neutralising antibody in infants, which may not be constant in all settings. In addition, the risk of infants encountering RSV may vary across sites so that the attack rate and the median time to RSV disease could differ by region. Furthermore, if immunogenicity trials suggested an effect of breastfeeding on infant neutralising antibody levels it is possible that regional differences in the rates and durations of breastfeeding could affect the efficacy observed. Therefore, the primary analysis could reflect a large contribution of cases from one or a few region(s), especially if the primary analysis is case-driven (i.e. enrolment will cease once a minimum total number of cases has been accrued). Due to these issues, it may be appropriate to stratify by geographical region at the time of randomisation.

Recruitment of pregnant women and completion of vaccination should be timed so that their infants are at risk of RSV exposure at least throughout the first 3-6 months of life. It is recommended that infants are followed up to the time at which prior data indicate that geometric mean neutralising antibody titres are similar for infants born to vaccinated and unvaccinated mothers.

If the primary analysis is confined to infants born a minimum number of weeks after their mothers were vaccinated, a sensitivity analysis should be conducted in all infants regardless of the time elapsed between maternal vaccination and delivery. If more than one dose of the vaccine is to be given to pregnant women and if the primary analysis is confined to infants born to mothers who received all assigned doses, a sensitivity analysis should be conducted using data from infants born to mothers who received at least one dose.

Some infants may be eligible for routine use of an anti-RSV monoclonal antibody according to local guidance, in which case it would be appropriate to exclude them from the primary analysis of efficacy although cases of RSV disease should be captured and reported.

Elderly

At trial sites in regions where RSV is seasonal the recruitment period should be timed such that the last doses are given no more than a specified number of weeks before the expected start of the RSV season. Depending on the site distribution and seasonality the sponsor should consider stratification by region.

There may be sufficient cases accrued during the first RSV season to be able to conduct the primary analysis. In all cases, subjects should be followed through 2 or 3 seasons with re-randomisation of the initial vaccinated group to be re-vaccinated or not in the sequential years so that advice on the need for re-vaccination to maintain protection can be given at the time of licensure. This advice can be modified in the post-approval period as additional data emerge (e.g. if data suggest that vaccination every 2-3 years is sufficient to maintain protection).

7.1.3. Trials to support co-administration with other vaccines

It is not required that vaccine co-administration trials are conducted before licensure. Nevertheless, the routine use of RSV vaccines may be limited until there are data available on co-administration with the types of vaccines most likely to be given concomitantly in each target population group. Sponsors may conduct separate co-administration trials or may evaluate the effects of co-administration in subsets during efficacy trials. General guidance on trials to evaluate the effects of co-administration of vaccines is provided in the Guideline on clinical evaluation of new vaccines (EMEA/CHMP/VWP/164653/05).

7.2. Monoclonal antibodies

7.2.1. Dose-finding trials

While standard humanised monoclonal antibodies are likely to be given at 3-4 week intervals, modified monoclonal antibodies with long serum half-lives are under investigation to allow for less frequent administration. The peak neutralising antibody activity and the activity decay curve should be described in trials in the target population to support dose selection. These clinical data, combined with nonclinical data, should be used to determine the most appropriate dose interval for further evaluation.

7.2.2. Efficacy trials

General considerations for the design of efficacy trials are the same as those for vaccine efficacy trials. At trial sites in regions where RSV is seasonal the recruitment period should be timed such that subjects receive the first dose of the monoclonal antibody no more than a specified number of weeks before the usual start month. Subsequent doses should be given throughout the RSV season depending on the serum half-life of RSV neutralising activity. In non-seasonal regions, it is suggested that dosing is continued and cases are collected for at least 6 months or until the required number of cases for the primary analysis has been accumulated.

In efficacy trials in infants and toddlers it is recommended that there is stratification by age and/or by broad category of underlying factors predisposing subjects to develop severe RSV disease (e.g.

prematurity, time of birth in relation to peak RSV season, type of co-morbidity). As for vaccines, an assessment of effects on sequelae, such as symptomatic wheezing, is of interest.

7.3. Antiviral agents

7.3.1. Exploratory trials

Exploratory trials should characterise the safety and pharmacokinetics of DAAs and determine whether there are dose-limiting safety issues. Taken together with nonclinical data, potentially effective dose regimens for specific age groups may be derived from modelling and simulation.

Sponsors may consider conducting a human challenge trial. Such trials are usually conducted in healthy adults, aged from 18 to about 45 years, in whom it is not usually possible to trigger a clinically apparent infection with a challenge strain. It may be possible to show a relationship between dose and effect on post-challenge viral loads in respiratory samples that could provide some preliminary information on a possible effective dose range. Information may also be generated on the time window after inoculation within which the DAA should be given to achieve the maximum effect on viral load. Such trials could also be used to assess co-administration of DAAs vs. each given alone to support the development of combination regimens.

A preliminary efficacy trial may be used to select a final dose regimen for a confirmatory trial and document the effect of time elapsed between first symptoms and starting treatment on outcomes. Preliminary efficacy trials may be used to explore the benefit of the DAA based on a range of clinically relevant endpoints (e.g. time to resolution of clinical signs and symptoms and time to recovery of normal oxygen saturation) to select primary and secondary endpoints for confirmatory trials.

7.3.2. Confirmatory trials

Confirmatory trials should demonstrate superiority of the treatment over the untreated control group (i.e. in which subjects receive no specific anti-RSV treatment) in the target population based on a clinically relevant endpoint, which could be a composite endpoint.

Definitive guidance on the preferred primary endpoint, which may be a composite, is not currently possible due to lack of information on the clinical benefit that may be achieved by DAAs against RSV. Any clinically relevant endpoints that are not included in the final selected primary endpoint should be designated as secondary endpoints. Although not appropriate for the primary endpoint, the type of healthcare contact that occurs for each case and details such as the need for and duration of assisted ventilation should be captured and reported in secondary analyses.

It is recommended that efficacy trials should assess the effect of treatment on viral loads in appropriate respiratory samples collected at baseline and at intervals during treatment at least in a randomised subset of treated and untreated patients to permit analyses of response by baseline load. Protocols should specify the quantitative RSV RNA test to be used at local laboratories of the participating sites and/or at a central laboratory using frozen shipped specimens.

8. Safety aspects

8.1. Vaccines

The general principles for the assessment of the safety of vaccines in clinical trials are described in the Guideline on clinical evaluation of new vaccines (EMEA/CHMP/VWP/164653/05) and should be followed.

Currently, it is considered essential to assess the risk of vaccine-associated disease enhancement in the clinical programme for each candidate vaccine and regardless of the intended target population for use. The requirements for such an assessment for a specific type of candidate vaccine may change in future if extensive experience indicates that similar vaccine constructs pose a negligible risk.

Section 7.1 (Trial design, Vaccines) provides guidance on the recommended duration of follow-up of vaccinated subjects and infants born to vaccinated mothers to assess this risk. The level of risk that should be ruled out should be discussed and agreed with EU Competent Authorities on a case by case basis. Depending on the vaccine construct and the available nonclinical and clinical data it may be necessary to conduct additional trials to adequately assess the risk.

8.1.1. Infants and toddlers

Safety data obtained from trials in RSV non-naïve subjects may be poorly predictive of the safety profile in RSV-naïve subjects. Therefore, a cautious approach is recommended for the commencement of trials in infants and toddlers. The potential risk of vaccine-associated disease enhancement may be higher in RSV-naïve infants in the first six months of life compared to RSV-naïve infants aged 7-12 months, RSV-naïve toddlers and non-naïve infants and toddlers. Therefore, it is particularly important that there is a large representation of infants aged < 6 months in the safety database.

8.1.2. Pregnant women

The risk of local and systemic reactions to vaccination should be assessed in detail before proceeding to vaccinate large numbers of pregnant women in efficacy trials. The rates of premature delivery, complications of pregnancy or labour and the condition of infants at birth should be compared between the vaccinated and unvaccinated groups.

If re-vaccination is required in subsequent pregnancies the safety profile should be documented and compared with the first pregnancy in which the woman was vaccinated to determine whether the risk of significant adverse reactions is different. These data may be obtained in post-licensure studies.

There would be considerable concern regarding the use of any live vaccine construct (live attenuated or live viral vectored vaccine) during pregnancy. If sponsors are proposing to use a live construct there should be early discussions with EU Competent Authorities.

8.1.3. Elderly

It is expected that elderly subjects will likely require repeated dosing, perhaps annually, to maintain protection against RSV disease. The safety profile of repeated dosing over 2-3 seasons should be fully documented and compared with that of the first dose(s).

8.2. Monoclonal antibodies

Although there is already considerable experience with the use of monoclonal antibodies in infants and toddlers, it is essential that local and systemic reactions to the first and all sequential doses are fully captured to document any trends there may be to increasing rates of adverse reactions with sequential doses and/or in sequential seasons. Subjects should be followed for safety after the last dose is administered for a period determined by the half-life of the RSV neutralising activity.

8.3. Antiviral agents

Safety data should be collected in each target age group as for any new active substance. The acceptable size of the pre-licensure safety database in each of the target groups will depend on the actual safety profile that is observed and, to some extent, on the magnitude of efficacy that is demonstrated against RSV disease at the more severe end of the disease spectrum. If there are any particular concerns raised by the safety data generated in pre-licensure trials in any target population it is possible that additional data may be required pre-licensure and/or by means of a post-authorisation safety study.

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