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

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

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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, including infants and toddlers (aged 28 days to 23 months) and older adults (e.g. aged  $\geq 60$  years). The guideline also addresses vaccination of pregnant women with the primary aim of preventing RSV disease in their infants while maternal antibody persists. The guidance provided is generally applicable to clinical development programmes in other populations such as neonates (aged  $<28$  days) or paediatric subjects aged from 24 months and adults of any age, with or without predisposition to develop severe RSV disease due to underlying conditions, including immunodeficiency.

### 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 can 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 and toddlers (aged 28 days 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  $\leq 35$  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 immunodeficiency. Long-term morbidity following RSV LRTI in early life may include asthma and recurrent 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. Older adults, with or without comorbid conditions (e.g. congestive heart failure, emphysema or asthma) are more likely than younger adults to develop LRTI requiring medical intervention.

A range of RSV vaccines is currently under development, including inactivated, live attenuated, subunit, 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 non-neutralising 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 RSV non-naïve populations, such as children aged from about 2 years and adults, including pregnant women.

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.

### 2.1. Vaccines

It is essential that this Guideline is read in conjunction with the *Guideline on clinical evaluation of new vaccines* (EMA/CHMP/VWP/164653/2005) and its future revisions. This Guideline is confined to issues that are most relevant for, or are 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.

Reflecting current clinical development programmes, the focus of the Guideline is on vaccines intended for the following groups:

- Infants and toddlers (aged 28 days to 23 months);
- Pregnant women, with intent to prevent RSV in their infants while protective levels of maternal antibody persist;
- Older adults (e.g. aged  $\geq 60$  years).

It is acknowledged that sponsors may wish to investigate the use of RSV vaccines in other populations (e.g. other age groups and/or subjects with co-morbidities or immunodeficiencies predisposing to development of RSV disease). Limited guidance is provided and consultation with EU competent authorities is strongly recommended.

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 the range of immunological parameters studies and choice of assay(s) that takes note of the most recent developments, including, if relevant, the use of International Standards in the assay development and validation processes.

### 2.2. Monoclonal antibodies

The focus is on the use of monoclonal antibodies that exert virus neutralisation activity for pre-exposure prophylaxis of RSV disease in neonates (age 0-27 days), infants and toddlers, including those with risk factors for developing RSV disease.

Although not specifically addressed, the principles discussed for the development of DAAs for treatment of RSV would be broadly applicable to the clinical evaluation of monoclonal antibodies for treatment of RSV.

### **2.3. Antiviral agents**

The focus is on evaluating DAAs for the treatment of RSV disease in infants and toddlers and in older adults, with or without co-morbidities or immunodeficiencies predisposing them to RSV disease. The guidance provided is generally applicable to clinical programmes that include other populations, such as subjects of any age who develop clinically apparent RSV infection.

The use of DAAs to prevent RSV disease is not considered but, depending on the preventive strategy, aspects of the guidance on design and analysis of efficacy trials with vaccines and/or monoclonal antibodies would be applicable. 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.

## **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)
- Guideline on strategies to identify and mitigate risks for first-in-humans and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev.1)
- Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010)
- 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 humoral and/or cell-mediated immune response can be achieved post-vaccination based on the immune parameter(s) most relevant to the vaccine construct and its route of administration.

Nonclinical studies may have limited capacity to evaluate effects in humans. Sponsors should consider the likely value of in-vivo nonclinical investigations before embarking on such studies. Considerations should include any available data relevant to the vaccine construct.

If conducted, nonclinical studies might be used to demonstrate that the vaccine protects RSV-naïve animals against development of RSV disease post-challenge. It may be of interest to challenge offspring born to vaccinated dams and/or to conduct passive antibody protection studies. Readouts may include effects of the intervention vs. placebo on viral loads in lower and upper respiratory tract tissues. The data from these experiments may be explored for correlations between immune responses and efficacy parameters.

For vaccines aimed at RSV-naïve subjects, 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. Studies could include large and small animal models and should include positive controls for enhanced RSV disease. 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 studies may be used to demonstrate that the monoclonal antibody protects RSV-naïve animals against development of RSV disease post-challenge.

### **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 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 some 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, body weight loss and pulmonary inflammation compared to untreated controls. Approaches to consider include the naïve bovine model (using bovine

RSV, which appears to have a similar pathogenesis to RSV in naïve humans) or ovine (using human RSV) model, to estimate the effect of the DAA on symptomatic illness and pathology.

## **5. Subject 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 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 initially from RSV non-naïve toddlers. Depending on the vaccine construct, the nonclinical data and accumulated scientific knowledge, it may be appropriate to consider conducting a safety and immunogenicity trial in RSV non-naïve infants before moving to RSV-naïve subjects.

Protocols for safety and immunogenicity studies should provide criteria for defining RSV-naïve or non-naïve status at baseline. These criteria should reflect the limit of detection and lower limit of quantification for the assay(s) used. Since it is possible that some naturally primed subjects may not have measurable RSV neutralising antibody, sponsors are encouraged to apply other assays (e.g. that IgA or IgM or detect IgG against the F, G and/or other viral proteins) to assist in differentiating RSV-naïve and non-naïve subsets.

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

Vaccine efficacy trials may be confined 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 consideration should be given to stratification by age sub-group.

#### **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. A minimum gestational age for vaccination should be determined from safety and immunogenicity studies, depending on the number of doses and dose interval needed to optimise the immune response.

Protocols should state 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 fetus despite placental insufficiency, it may be appropriate to include these women.

#### **5.1.3. Older adults**

Trials that investigate administration of candidate vaccines to older adults should include adequate representation of age sub-groups (e.g. <65, 65-74, 75-84 and ≥ 85 years) to explore whether there is any effect of increasing age on safety, immunogenicity and efficacy. In vaccine efficacy trials, sponsors are encouraged to include a representative sample of subjects with conditions that may predispose

them to develop RSV disease but not expected to negatively impact on the immune response (e.g. underlying respiratory or cardiopulmonary disease).

#### **5.1.4. Other populations**

Before or after licensure sponsors may wish to investigate the use of RSV vaccines in populations other than those considered above. These may include, but are not limited to:

- Immunocompetent subjects of any age with protocol-specified conditions recognised to predispose them to RSV disease;
- Subjects of any age with selected types of immunodeficiency, which should be defined;
- 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 conduct separate trials in different population groups (e.g. infants born at  $\leq 35$  weeks of gestation, infants aged  $< 6$  months at enrolment and paediatric subjects with risk factors for severe RSV disease) or to stratify at the time of randomisation.

### **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 subgroups 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. Across the clinical trials, there should be adequate representation of subjects in all age subgroups within the targeted age range.

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

#### **5.3.1. Clinical criteria**

The list of clinical signs and symptoms and the number that should be met for eligibility should be tailored to the age range of the trial population. Sponsors are advised to consider proposals for classifying RSV disease severity in different age groups that come from well-recognised public health or professional bodies when developing subject selection criteria. The inclusion of at least one eligibility criterion that is an objective measure (e.g. oxygen saturation corrected for altitude and measured under standardised conditions and/or tachypnoea) is encouraged. Sponsors could also consider categorising subjects using published clinical scores and by type of ventilator support given, if applicable.

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. Efficacy trials may be confined to subjects who are hospitalised at the time of enrolment when treatment has to be given parenterally and/or to ensure that comprehensive data can be collected. When efficacy trials are conducted in non-hospitalised subjects or in both hospitalised and non-hospitalised subjects steps should be taken to ensure that data can be collected in a standardised fashion in both settings.

The maximum time elapsed that is allowed between symptom onset and randomisation should be stated in the protocol. Consideration may be given to stratification of subjects at randomisation by time intervals elapsed since onset of symptoms (e.g. using 12- or 24-hour intervals) up to the maximum allowed in the protocol.

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

### **5.3.2. Laboratory criteria**

Subject 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 minimise 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 subjects.

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). Subjects 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 aged from 28 days to ≤6 months or infants and toddlers aged from 28 days to 23 months at randomisation, pregnant women and older adults).

Following a demonstration of efficacy of a candidate vaccine in one or more populations and on a case by case basis, it may be possible to use an immunobridging approach to infer efficacy of the same vaccine in other populations (e.g. other age groups and populations with predisposition to RSV disease) to support a recommendation for use and inclusion of a posology (if different for different populations) in the Summary of Product Characteristics (SmPC).

In future, if the efficacy of a candidate vaccine can be inferred by interpreting the immune responses using a relevant immune correlate of protection, a demonstration of clinical efficacy against RSV disease would not be required. In the absence of a relevant immune correlate of protection, 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, may be considered on a case by case basis.

## **6.2. Monoclonal antibodies**

If the candidate monoclonal antibody is to be studied in a population for which there is no licensed and widely recommended monoclonal antibody directed at RSV, an efficacy trial should be conducted to demonstrate superiority of the intervention vs. an untreated control group. For example, such a trial may be conducted 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. Alternatively, trials may be designed to demonstrate that the efficacy of a candidate monoclonal antibody is non-inferior to that of a licensed product in a population for which the latter is indicated and widely recommended. It is recommended that superiority and non-inferiority trials use a double-blind design (i.e. with a placebo control) whenever this is feasible.

Subject to a demonstration of efficacy in infants and/or toddlers, together with an adequate assessment of safety, it may be possible to include dose regimens for older paediatric subjects considered to be at risk of severe RSV disease and/or with certain types of immunodeficiency 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 approved in some EU member states for treatment of RSV bronchiolitis in infants and toddlers via inhalation but it is not recommended for use in previously healthy subjects in treatment guidelines. There is no DAA approved for treatment of RSV in other age groups. Therefore, it is expected to be feasible to conduct double-blind trials to demonstrate that candidate DAAs are superior to untreated control groups based on clinically relevant primary endpoints in the all treated population. The feasibility of superiority trials may have to be reconsidered once new DAAs for treatment of RSV have been licensed and have entered widespread use.

The clinical effect of a DAA and the most appropriate primary efficacy endpoint may be different in subjects presenting with mild RSV disease compared to those presenting with severe RSV disease and it is recommended that separate efficacy trials are conducted in populations defined by the clinical presentation. Furthermore, the conduct of post-approval placebo-controlled trials in subjects with severe RSV disease may prove difficult if the DAA is already being used widely outside of the indicated population. For this reason, sponsors should consider evaluating the DAA in subjects with mild and severe disease in parallel or evaluating efficacy in the more severely ill population first.

If a DAA has shown convincing efficacy in one population, it may be possible to recommend use of the same or an alternative posology in another population based on safety and on pharmacokinetic data showing comparable plasma exposures. These safety and pharmacokinetic data could be collected in an uncontrolled trial in a specific population (e.g. defined by age or by specific type of immunodeficiency).

## 7. Trial design

### 7.1. Vaccines

General recommendations for the design of clinical trials that aim to i) evaluate the safety and immunogenicity of a candidate vaccine against RSV, ii) support the dose regimen(s) to be taken forward into confirmatory studies, iii) and demonstrate vaccine efficacy are the same as those for other types of vaccines (see EMA/CHMP/VWP/164653/2005).

#### 7.1.1. Safety and immunogenicity trials

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 there could be a negative effect on its protective efficacy and that the severity of clinically apparent RSV could be enhanced in some subjects. In such cases, consideration should be given to conducting additional in vitro and/or in vivo nonclinical studies before deciding whether to proceed with clinical development.

##### Infants and toddlers

Safety and immunogenicity trials with candidate vaccines in infants and toddlers should include a thorough investigation of immune responses 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 or equivalent in non-seasonal regions before proceeding to the next trial. 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 infant immune response to a candidate vaccine should be assessed by exploring whether there is an inverse relationship between the pre-vaccination maternal antibody level and the infant immune response to vaccination. 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 maximising 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.

The RSV neutralising antibody decay curve should be documented in vaccinated women during and for a period of time (e.g. 3-6 months) following delivery. It is recommended that revaccination of women during their next pregnancy should be investigated whenever the opportunity arises in the post-approval period. If initial vaccination was with more than one dose it would be appropriate to investigate whether a single dose could suffice in subsequent pregnancies.

Unless otherwise justified, trials should follow-up infants for RSV disease until it is predicted that they will have no or negligible maternal antibody before initiating the next trial. This will allow for data on RSV disease and its severity to be collected and reviewed to assess whether there is any signal for enhanced disease in infants born to vaccinated vs. unvaccinated mothers.

### Older adults

Trials to support dose regimen selection should include an exploration of immune responses in age subgroups across the targeted age range.

Immune responses to vaccination should be analysed according to the pre-vaccination levels of the relevant immune parameters.

Unless there are data available indicating that re-vaccination is not necessary, plans should be in place to assess the safety and immunogenicity of further doses after various time intervals. 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**

This section addresses some special considerations for efficacy trials with RSV vaccines.

#### Primary endpoint

The primary efficacy endpoint should be based on cases of laboratory-proven RSV disease that meet the clinical criteria (i.e. cases that meet the primary case definition). Considerations for defining cases of RSV disease and their severity are those applicable to subject selection criteria in treatment trials as described in section 6.3. The primary endpoint could be based on any clinically apparent laboratory-proven RSV disease or against one or more of RSV LRTI and severe RSV disease.

#### Secondary and other endpoints

If the primary endpoint is all laboratory-proven cases of RSV disease (i.e. regardless of severity) then secondary endpoints should include 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 (i.e. to detect a difference in the severity of RSV cases that occur in vaccinated vs. unvaccinated subjects).

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

Other secondary endpoints could include the type of healthcare interaction for each case (e.g. home visit by a doctor, emergency room visit, hospitalisation and need for intensive care).

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 and asthma in children, which could be investigated in the post-licensure period. This would require a clear definition of symptomatic wheezing (vs. asthma) and 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 RSV disease) and, to some extent, the secondary endpoints. Subjects or their caregivers 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 caregivers 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

The primary analysis may be conducted as soon as the total (i.e. blinded to treatment assignment) predefined number of cases of RSV that meet the case definition has been accrued. Depending on where the trial is conducted, this may mean that the target number of cases for triggering the primary analysis is achieved after one RSV season or an equivalent period in non-seasonal settings. This is acceptable.

If there is any vaccine-associated disease enhancement, it is expected to occur with the first natural RSV infection after completion of vaccination. The total post-vaccination follow-up period, which may need to continue beyond the time at which the primary analysis is conducted, should ensure that a sufficient number of trial subjects have been exposed to circulating RSV to be able to assess the potential risk. To support the adequacy of follow-up, the proportion of subjects in the placebo group who have serological evidence of RSV infection, with or without symptoms, could be assessed. Follow-up may need to be continued in the post-approval period to describe the duration of protection after a primary series.

#### Pregnant women

The level of protective efficacy of a candidate vaccine may reflect maternal and placental health and other potential factors such as the rate and duration of breastfeeding and 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. Therefore, the primary analysis could reflect a large contribution of cases from one or a few region(s), especially if it is case-driven (i.e. enrolment ceases once a minimum total number of cases has been accrued). Due to these issues, efficacy by region should be explored and consideration may be given to stratification of randomisation by geographical region as well as exploring efficacy by potential contributing factors, such as breastfeeding.

It is recommended that infants born to trial participants are followed for safety and efficacy up to the time at which it is predicted that no or negligible amounts of maternal antibody will remain.

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.

## Older adults

As described for trials in infants, the target number of cases for triggering the primary analysis may be achieved after one RSV season or an equivalent period in non-seasonal settings. This is acceptable. Unless otherwise justified, the duration of protection should be documented by follow-up beyond the time of the primary analysis and, as necessary, continuing into the post-approval period so that data are accumulated to assess the possible need for re-vaccination to maintain protection. If waning efficacy is documented, subjects could be re-randomised to receive a further dose or no dose and followed thereafter for RSV disease.

### **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 (e.g. in non-pregnant women to inform on concomitant administration of vaccines during pregnancy) or may evaluate the effects of co-administration in subsets during efficacy trials.

## **7.2. Monoclonal antibodies**

### **7.2.1. Dose-finding trials**

While standard humanised monoclonal antibodies are likely to be given at 3 to 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 that cases are collected for at least 6 months or until the required number of cases for the primary analysis have 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 and asthma, 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. 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 in healthy adults. Such studies may be able to show a relationship between dose, plasma exposure, effect on clinical signs and symptoms and reductions in post-challenge viral loads in respiratory samples that could assist in selecting regimen(s) for further trials. 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.

### **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 is not currently possible due to lack of information on the clinical benefit that may be achieved by DAAs against RSV. It is recommended that proposals for primary endpoints in confirmatory trials should be discussed with EU Regulators on a case by case basis considering potentially clinically important effects in the target population(s). 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 and management that occurs for each case (e.g. hospitalisation) and details such as the need for and duration of assisted ventilation should be captured and reported in secondary analyses.

In preliminary and confirmatory efficacy trials, it is recommended that the effect of treatment on viral loads and the risk of selecting for RSV resistant to the DAA is assessed. Appropriate respiratory samples should be collected at baseline from all subjects. Additional samples should be collected at post-baseline intervals at least in a randomised subset of subjects and from all subjects who appear not to be responding to treatment (e.g. who fail to meet pre-defined improvement criteria after a specified number of days). 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 respiratory tract specimens. Whenever possible, baseline and post-baseline samples should be used for genotypic studies to assess selection of resistance to the DAA.

## **8. Safety aspects**

### **8.1. Vaccines**

The general principles for the assessment of the safety of vaccines in clinical trials are described in EMEA/CHMP/VWP/164653/2005 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 regardless of the intended use. This is expected to be assessed by comparing the severity of RSV cases that occur in previously vaccinated and unvaccinated subjects. The level of risk that should be ruled out should be discussed and agreed with EU Competent Authorities on a case by case basis. This requirement may change in future if experience indicates that one or more vaccine constructs similar to the candidate vaccine pose no or a negligible risk in RSV non-naïve and/or naïve subjects.

#### **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 if the vaccine is primarily intended for RSV-naïve subjects.

#### **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. Older adults**

Older adults may require repeated dosing, perhaps annually, to maintain protection against RSV disease, in which case the safety profile of re-vaccination should be assessed 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 courses. 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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