Regulatory considerations for initiating paediatric trials with RSV antivirals

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European Medicines Agency

Expert meeting on RSV therapeutics
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In this talk...

- Overview PIPs for RSV-antivirals
- Challenges in evaluation of PIPs
- Current PDCO position
- Joining Enpr-EMA
- Conclusion

Disclaimer
Views expressed are personal, not to be understood or quoted as being made on behalf of the European Medicines Agency or its scientific Committees
## Overview: Antivirals in development

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Condition</th>
<th>Regulatory status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motavizumab</strong></td>
<td>Prevention of serious LRTI caused by RSV</td>
<td>PIP decision published</td>
</tr>
<tr>
<td><strong>Medi-8897</strong></td>
<td>Prevention of LRTI caused by RSV</td>
<td>Still under PDCO discussion</td>
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<tr>
<td><strong>ALX-0171</strong></td>
<td>Treatment of LRT disease caused by RSV</td>
<td>PIP decision published</td>
</tr>
<tr>
<td><strong>REGN-2222</strong></td>
<td>Prevention of LRT disease caused by RSV</td>
<td>PIP opinion adopted 12/2015</td>
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### Fusion inhibitors

| JNJ-53718678 | A Phase 1b, partially DB, PC study to assess the PK, safety, and tolerability of multiple doses of orally administered JNJ-53718678 in infants hospitalized with RSV infection. EudraCT number 2015-002003-28 |

### Nucleoside analogue

| ALS-008176 | Treatment of LRT disease caused by RSV       | PIP opinion adopted 1/2016                |
Challenges for PDCO in evaluating PIPs

- Defining the need - definition of condition:
  - Where is the highest need?
European Paediatric Regulation

Improve the health of children

- Increase high quality research into medicines for children
- Increase availability of authorised medicines for children
- Without unnecessary studies in children
Challenges for PDCO in evaluating PIPs

- Definition of condition:
  - Where is the highest need?
  - What do we want new RSV antivirals should achieve?
    - to decrease mortality?
    - to decrease severe disease?
    - to decrease disability?
Challenges for PDCO in evaluating PIPs

- Definition of condition:
  - Where is the highest need?
  - What do we want new RSV antivirals should achieve?
    - to decrease mortality? - likely not; mortality is low
    - to decrease severe disease? - yes - what is surrogate of severe disease?
Burden of Respiratory Syncytial Virus Infection in Young Children

Age-Specific Rates of Hospitalization for RSV Infection Among Children <24 Months of Age

<table>
<thead>
<tr>
<th>Age (in months)</th>
<th>n</th>
<th>Rate per 1000 Children</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>&lt;1</td>
<td>62</td>
<td>13.5</td>
<td>10.3-17.1</td>
</tr>
<tr>
<td>1</td>
<td>115</td>
<td>25.9</td>
<td>21.3-30.8</td>
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<tr>
<td>2</td>
<td>68</td>
<td>14.3</td>
<td>11.1-17.8</td>
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<tr>
<td>3</td>
<td>47</td>
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<td>7.7-13.5</td>
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<td>42</td>
<td>8.9</td>
<td>6.3-11.8</td>
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<td>5</td>
<td>22</td>
<td>4.8</td>
<td>2.9-7.0</td>
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<td>6</td>
<td>20</td>
<td>4.1</td>
<td>2.5-6.2</td>
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<td>26</td>
<td>5.6</td>
<td>3.6-8.0</td>
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<td>15</td>
<td>3.4</td>
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Hall et al, Pediatrics 2013
Definition of condition – PDCO position

Highest need: Prevention or Treatment of **LRTI** - not mild URTI

• **Target population:** children less than 1-2 (-3) years
  • Prophylaxis:
    - below 6 (12 months): healthy pre/full term infants
    - below 2 years: preterm infants/children with underlying chronic conditions putting them at high risk for serious RSV infection
  • Treatment:
    - below 3 years: preterm infants/children with underlying chronic conditions putting them at high risk for serious RSV infection

• **BUT**, need also in immunocompromised older children / adolescents
Challenges for PDCO in evaluating PIPs

- **Definition of condition:** Where is the highest need?
  
  PDCO position: prevention or treatment of LRT disease

- **How to define serious LRT disease?**
  - Absence of clear definitions
  - Considerable variability among physicians
Perspectives of paediatricians and general practitioners on key clinical findings in bronchiolitis

Fernandes et al, Pediatr Pulmonol 2015
Challenges for PDCO in evaluating PIPs

- **Definition of condition:** Where is the highest need?

- **How to define severe LRT disease?**
  - RSV-associated hospitalization used as surrogate for severe LRTI
  - Major limitations: criteria for hospitalisation highly variable within and across regions, dependent on local healthcare services, physicians perceptions, cultural, economic factors,...
  - Interpretability of study results diminished
How to define LRT disease?

**PDCO current position:**
In the absence of standardised and agreed definitions, Definition of LRTI should be based on

- clinical findings:
  - rales/crackles, lower chest-wall in-drawing
- objective measures of clinical severity:
  - increased respiratory rate, hypoxemia, inability to feed,...
Challenges for PDCO in evaluating PIPs

- **Definition of condition:** Where is the highest need?
- **How to define serious LRT disease?**
- **Lack of standardized outcome measures**
  - RSV-associated hospitalization used as a primary endpoint in RSV prophylaxis trials in infants
  - Major limitations: criteria for hospitalisation highly variable within and across regions, dependent on local healthcare services, physicians perceptions, cultural, economic factors
Clinical Endpoints for RSV Prophylaxis Trials

- Medically attended RSV illness in settings beyond RSV-associated hospitalizations alone:
  - composite reduction in hospitalization, emergency room or urgent care center visits because of an RSV respiratory infection
- Standardized definition of severe RSV LRI based on WHO definitions:
  - presence of lower chest wall in-drawing or hypoxemia ($\text{SpO}_2 \leq 95\%$ on room air at sea level, $\leq 92\%$ on room air at altitude > 1800m, or $\leq 5\%$ or lower in children with CLD or CHD with chronic underlying hypoxemia.
  - alternative definition of LRI: presence of lower chest wall in-drawing, OR wheezing OR crackles OR hypoxemia

Simoes et al, Pediatric Infectious Disease Journal 2015
Lack of standardised endpoints

Current PDCO position:

Clinically relevant outcome measures should meet the following requirements:

• endpoint to be specific and sensitive to capture LRTI

• Specificity: Virologic confirmation of presence of RSV

• Sensitivity: diagnosis of LRTI based on
  • clinical findings: rales/crackles, lower chest-wall in-drawing
  • objective measures of clinical severity: increased respiratory rate, hypoxemia, need for ventilator support in any form, inability to feed, ...
Challenges for PDCO in evaluating PIPs

- Definition of condition
- Definition of target population
- Lack of standardised, validated outcome measures
- Data generation in older children with underlying chronic conditions or who are immunocompromised
  - Population very heterogeneous
  - RSV infection in infants manifests as bronchiolitis
  - RSV infection in older immunocompromised children frequently manifests a RSV pneumonia
  - Dedicated clinical studies possible, feasible?
  - To what extent is extrapolation possible?
What are criteria for authorising a medicinal product in Europe?

EU pharmaceutical law

- To demonstrate the **quality, safety and efficacy**
- Based on objective criteria
- Balance of benefits and risks should be positive
**Agreed PIP for ALX-0171**

<table>
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<tr>
<th><strong>Quality</strong></th>
<th>Development of product- and age-specific nebuliser devices for paediatric populations requiring or not (non)-invasive ventilation as well as immunocompromised subjects.</th>
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| **Non-clinical studies (2)** | PK study in juvenile animals.  
| | In vivo efficacy testing in a neonatal lamb model. |
| **Clinical studies (9)** | DB, PC safety, tolerability and PK study in infants and toddlers hospitalised for RSV lower respiratory tract infection, aged 5 months to less than 24 months.  
| | DB, PC safety, tolerability and PK study in infants hospitalised for RSV lower respiratory tract infection, aged 28 days to less than 5 months.  
| | DB, PC efficacy, safety and PK study in infants and children hospitalised for RSV lower respiratory tract infection, including high-risk subjects, aged 28 days- <3 years  
| | DB, PC efficacy, safety and PK study in infants and children hospitalised for RSV lower respiratory tract infection and requiring invasive mechanical ventilation, including high-risk subjects, aged 28 days to < 3 years.  
| | 2-year long-term safety follow-up study in subjects who completed studies 6 and 7.  
| | DB, PC efficacy and safety study in infants and children hospitalised for RSV lower respiratory tract infection, including high-risk subjects, aged 28 days to less than 3 years.  
| | DB, PC efficacy and safety study in infants and children at risk of hospitalisation for RSV lower respiratory tract infection, including high-risk subjects, 28 days-<3 years.  
| | DB, PC efficacy and safety study in preterm and term newborn infants < 28days and infants with a history of prematurity, but currently aged 28 days to < 3 months.  
| | 2-year long-term safety follow-up study |
| **www.ema.europa.eu** | Modelling and simulation physiologically-based pharmacokinetic study for dose determination in all planned clinical studies.  
| | Extrapolation study to provide guidance on appropriate dosing regimens for immunocompromised subjects aged 0 to less than 18 years. |
Concept paper on extrapolation of efficacy and safety in medicine development

Final

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<th>Event</th>
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<tbody>
<tr>
<td>Agreed by Scientific Advice Working Party</td>
<td>25 April 2012</td>
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<tr>
<td>Agreed by Biostatistic Working Party</td>
<td>15 May 2012</td>
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<td>Agreed by PK Working Party</td>
<td>30 May 2012</td>
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<td>10 May 2012</td>
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<td>Adoption by PDCO</td>
<td>16 May 2012</td>
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<td>Adoption by CHMP</td>
<td>24 May 2012</td>
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<td>Start of public consultation</td>
<td>29 June 2012</td>
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<tr>
<td>End of consultation (deadline for comments)</td>
<td>30 September 2012</td>
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Keywords: extrapolation, medicine development, biostatistics, modelling and simulation

Agreed PIP for ALX-0171

- Development of product- and age-specific nebuliser devices for paediatric populations requiring or not (non)-invasive ventilation as well as immunocompromised subjects.

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<td>Randomised, double-blind, placebo-controlled efficacy and safety study in infants and children hospitalised for RSV lower respiratory tract infection, including high-risk subjects, aged 28 days to less than 3 years.</td>
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P/0246/2014
www.ema.europa.eu

- Modelling and simulation physiologically-based pharmacokinetic study for dose determination in all planned clinical studies.
- Extrapolation study to provide guidance on appropriate dosing regimens for immunocompromised subjects aged 0 to less than 18 years.
Additional challenge: clinical trial in community setting

When to start treatment?

- Identified need: **treatment of LRTI**
- URTI not major problem, not necessitating antiviral treatment

BUT

- Antiviral treatment in children at high risk for severe LRTI early in course of RSV infection
  - before major tissue injury in the lower airways has occurred
  - to prevent development of severe LRTI
- Thin line between early treatment to avoid LRTI and prevention
The Disease Pyramid & the Trial Trapezoid

More severe LRTI

Moderate LRTI

Mild URTI

Minimal/subclinical
The Disease Pyramid & the Trial Trapezoid

Too severe

Meet entry criteria

Too mild

More likely to get funded by payer

Easier to recruit

Result

– too many trial patients at bottom of trapezoid
– lumping URTIs with LRTIs may diminish effect on preventing LRTI
– insufficient evidence for efficacy in more severe patients
Additional challenge: clinical trial in community setting

- When to start treatment?

- How to evaluate treatment effect in community setting?
  - Caregiver ratings to document evolution of severity of signs of acute respiratory tract infection over time – no validated rating scales available

- How to evaluate long-term effect on wheezing and asthma?
  - How many years should children be followed-up?
  - What could be the endpoint(s)?
  - To be evaluated in the post-authorisation period
Summary

• Competitive clinical trial landscape
• Several paediatric developments for new antivirals ongoing
• No agreed definition of severe RSV LRTI
• Lack of standardised and validated outcome measures
• Heterogeneous choice of outcome measures in clinical trials
• How to evaluate long-term effect on wheezing and asthma?
• Uncertainty to what extent extrapolation of efficacy possible
Conclusions

• **Urgent need**
  
  • To agree on standardised definition for severe RSV LRTI
  
  • To establish clinically relevant endpoints to assess efficacy of RSV antivirals
  
  • For consensus definition of core outcome measures to be measured and reported in all clinical trials to allow comparability of trial results ([www.comet-initiative.org](http://www.comet-initiative.org))
Conclusions

- **Urgent need**
  - To agree on standardised definition for severe RSV LRTI
  - To establish clinically relevant endpoints
  - For definition of core outcome measures
- EMA Guideline on medicines for treatment and prevention of RSV infections: planned to release draft concept paper by Q2 2016
- Regulatory requirements should be up to date with progress in science
- This goal only to be achieved through close cooperation between academia, regulators, industry and parent/patient organisations
- Joining the European Network of Paediatric Research at EMA (Enpr-EMA)
Enpr-EMA
Key operational goals

Platform for close interactions of all stakeholders necessary to facilitate the conduct of (large) studies in children

- To link together existing networks EU and extra-EU
- To offer single point of contact for (European) networks enprema@ema.europa.eu
- To define strategies for resolving major challenges
- To offer access to academic partners through collaboration with EMA SME office
- Enpr-EMA does not fund / conduct clinical trials

http://enprema.ema.europa.eu/enprema
Thank you

Contact me at: irmgard.eichler@ema.europa.eu
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