Human metapneumovirus (hMPV) and para-influenza virus 3 (PIV3) vaccine (mRNA-1653)

Conference Call February 12, 2019
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Human metapneumovirus (hMPV) and parainfluenza virus 3 (PIV3) vaccine (mRNA-1653)

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## Prophylactic vaccines pipeline

<table>
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<th>Modality</th>
<th>Program #</th>
<th>Program</th>
<th>Preclinical development</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3 and commercial</th>
<th>Moderna rights</th>
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<td><strong>Prophylactic vaccines – Commercial programs</strong></td>
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<td>RSV vaccine</td>
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<td>Merck to pay milestones and royalties</td>
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<td></td>
<td>mRNA-1647</td>
<td>CMV vaccine</td>
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<td></td>
<td>mRNA-1653</td>
<td>hMPV+PIV3 vaccine</td>
<td>Phase 1b (pediatrics)</td>
<td>Phase 1 (adults)</td>
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<td>mRNA-1278</td>
<td>VZV vaccine</td>
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<td>Merck to pay milestones &amp; royalties</td>
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<tr>
<td><strong>Prophylactic vaccines – Global health programs</strong></td>
<td>mRNA-1440</td>
<td>Influenza H10N8 vaccine</td>
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<td>Worldwide Advancing subject to funding</td>
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<td>mRNA-1851</td>
<td>Influenza H7N9 vaccine</td>
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<td>Worldwide Advancing subject to funding</td>
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<td>mRNA-1325</td>
<td>Zika vaccine</td>
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<td>mRNA-1893</td>
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<td>mRNA-1388</td>
<td>Chikungunya vaccine</td>
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<td>Worldwide Advancing subject to funding</td>
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</table>

Abbreviations: CMV, cytomegalovirus; hMPV, human metapneumovirus; PIV3, human parainfluenza 3; RSV, respiratory syncytial virus; VZV, varicella zoster virus
**RSV, hMPV, and PIV3 are leading causes of respiratory illness**

| Influenza | RSV  
| Respiratory syncytial virus | hMPV  
| Human metapneumovirus | PIV3  
| Parainfluenza virus type 3 |

**Epidemiology, disease burden**
- 12,000-56,000 deaths per year in the U.S.\(^1\)
- Hospitalization rate in children < 5 years old in the U.S.: 0.9:1000\(^2\)
- > 177,000 older adults hospitalized due to RSV associated respiratory infections each year in the U.S.; 14,000 deaths as a result\(^3\)
- Hospitalization rate in children < 5 years old in the U.S.: 3:1000\(^2\)
- Hospitalization rate in children < 5 years old in the U.S.: 1.2:1000\(^2\)
- Associated with an estimated 1 million outpatient clinic visits and > 250k ED visits annually among U.S. children < 5 years old\(^4\)
- Hospitalization rate in children < 5 years old in the U.S.: 0.5:1000\(^2\)
- Of 4 PIV types, PIV3 results more frequently and in more serious lower respiratory tract infections\(^5\)

**Clinical signs & symptoms**
- Upper and lower respiratory tract infection

**Target population for current development**
- Older adults
- Infants

**Partnership status**
- Merck to pay milestones and royalties
- Moderna ran Phase 1 trial; Merck to lead rest of clinical development
- Wholly-owned by Moderna

**Moderna program**
- mRNA-1777
- mRNA-1653

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\(^3\) Nat’l Center for Immunizations, Protect Against Respiratory Syncytial Virus, 2017


\(^5\) Henrickson KJ. ClinMicrobiol Rev. 2003 Apr;16(2):242-64.
Human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) overview

- hMPV and PIV3 are RNA viruses that are important causes of respiratory tract infections, particularly in children.
- Increasing rates of diagnosis and association with hospitalization for respiratory illness.
- **Disease burden:** Major cause of hospitalization due to respiratory infection.
  - Symptoms range from mild upper respiratory tract infection to life threatening severe bronchiolitis and pneumonia.
  - Both viruses cause clinically indistinguishable disease.
- **Target population:** infants.
  - Most hMPV or PIV3-associated hospitalizations in children occur under 2 years old.
  - Hospitalization rates in children < 5 years old in the U.S.:
    - hMPV: 1.2 per 1,000
    - PIV3: 0.5 per 1,000
- **Unmet need:** No approved hMPV or PIV3 vaccine.
  - Other companies’ previous attempts focused only on hMPV or PIV alone (no known attempts at a combo vaccine).
hMPV+PIV3 vaccine combines mRNAs encoding antigens from two different viruses

Modern concept: mRNA vaccine, IM-administered, consisting of 2 distinct mRNA sequences, co-formulated, that encode the membrane-bound F proteins of hMPV and PIV3
**hMPV+PIV3 vaccine (mRNA-1653)**

*Pre-clinical data – combo vaccine generates neutralizing titers against each virus*

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**Species:** Mouse

**hMPV neutralizing titers with hMPV+PIV3 mRNA vaccine**

**PIV3 neutralizing titers with hMPV+PIV3 mRNA vaccine**

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*Pre-clinical studies of hMPV and PIV3 combination vaccine demonstrated ability to generate robust neutralizing antibody titers. In separate experiments in NHP (not shown) vaccination conferred protection against hMPV or PIV3 viral challenge.*
**hMPV+PIV3 vaccine (mRNA-1653)**

*Phase 1 design – healthy adults*

**Key Objectives**
- Evaluate safety and immunogenicity through 12 months after the second vaccination
- Select optimal dose and vaccination schedule for further clinical development

**Dosing schedule: Day 1 and Month 1**

**Dose-escalation phase A (N=20)**
- Sequential enrollment
- Randomization 4:1 for mRNA-1653: placebo,
  Five subjects per dose cohort

  - mRNA-1653 25µg or placebo
  - mRNA-1653 75µg or placebo
  - mRNA-1653 150µg or placebo
  - mRNA-1653 300µg or placebo

  *All subjects received 2 doses*

**Dose-selection phase A (N=104)**
- Parallel enrollment
- Randomization of 1:1:1:1,
  26 subjects per dose cohort

  - mRNA-1653 75µg
  - mRNA-1653 150µg
  - mRNA-1653 300µg
  - placebo

  *Within each mRNA-1653 dose level group, subjects randomized 1:1 to receive one or two doses*
hMPV+PIV3 vaccine (mRNA-1653)

Phase 1 in healthy adults
Interim results, through study Month 2 (1 month after second vaccination)

Safety and tolerability

- mRNA-1653 was found to be generally well tolerated
- No serious adverse events (SAEs), adverse events of special interest, or adverse events leading to withdrawal were reported
- Injection site pain was most commonly reported solicited adverse event and grade 3 adverse event

Immunogenicity

- Single vaccination boosted serum neutralization titers against hMPV and PIV3 at all dose levels tested
- Neutralizing antibodies against hMPV and PIV3 present at baseline in all subjects, consistent with prior exposure to both viruses
- 1 month after a single vaccination, hMPV and PIV3 neutralization titers ~6x and ~3x baseline, respectively
- Second vaccination did not further boost antibody titers, suggesting a single vaccination was sufficient to achieve a plateau in neutralizing antibodies in this pre-exposed population

Full data to be presented at future medical meeting
hMPV+PIV3 vaccine (mRNA-1653)

Next step: Phase 1b in pediatric population

- **Phase 1**
  - Healthy adults
  - Safety & immunogenicity

- **Phase 1b**
  - Seropositive pediatric subjects
  - Safety & immunogenicity

- **Phase 2 and 3**
  - Infants
  - Safety, immunogenicity, and vaccine efficacy

*Clinical development plan contingent on regulatory feedback

Pediatric Phase 1b planning in progress
## Moderna’s mosaic of data

**Now 5 positive clinical readouts in prophylactic vaccines**

<table>
<thead>
<tr>
<th>Tolerability</th>
<th>Protein expression</th>
<th>Protein pharmacology</th>
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<tbody>
<tr>
<td>• <strong>945 subjects dosed</strong> across seven vaccine Phase 1 trials, at levels up to 300µg</td>
<td>• <strong>5 positive immunogenicity readouts</strong> from six candidates with Phase 1 data to date</td>
<td>• <strong>hMPV+PIV3</strong> (mRNA-1653) – vaccination boosted serum neutralization titers against hMPV and PIV3 at all dose levels tested</td>
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<td>• <strong>RSV</strong> (mRNA-1777) – Merck initiating planning for Phase 2a based on Phase 1 data</td>
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<td>• <strong>Chikungunya</strong> (mRNA-1388) – 100% seroresponse for subjects at the 100µg dose level</td>
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<td>• <strong>H7 influenza</strong> (mRNA-1851) – 96% of subjects at 25µg achieved HAI titer &gt; 1:40</td>
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<td>• <strong>H10 influenza</strong> (mRNA-1440) – 100% of subjects at 100µg achieved HAI titer &gt; 1:40</td>
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Prophylactic vaccines development pipeline

Encoded mRNA(s)

Ribosome

Encoded mRNA(s)

Protein chain(s)

Nucleus

Endoplasmic Reticulum

Cytosol
Prophylactic vaccines development pipeline

Encoded mRNA(s)

Prophylactic vaccines

Encoded mRNA(s)

Ribosome

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Flu H10N8 H7N9 RSV
Prophylactic vaccines development pipeline

Encoded mRNA(s)

Ribosome

Protein chain(s)

Encoded mRNA(s)

Nucleus

Endoplasmic Reticulum

Cytosol

Flu H10N8

RSV

Chikungunya VLP

Zika VLP

Prophylactic vaccines

VLP

Flu H7N9
Prophylactic vaccines development pipeline

- Encoded mRNA(s)
- Ribosome
- Protein chain(s)
- Cytosol
- Endoplasmic Reticulum
- Nucleus
- Flu H10N8, H7N9, RSV
- hMPV+PIV3
- Chikungunya VLP
- Zika VLP
- Prophylactic vaccines: H10N8, H7N9, RSV, hMPV+PIV3, Chikungunya VLP, Zika VLP

Prophylactic vaccines

- Zika
- VLP
- Chikungunya
- VLP
- RSV
- Flu
- H10N8, H7N9
Prophylactic vaccines development pipeline

- **Encoded mRNA(s)**
- **Ribosome**
- **Protein chain(s)**
- **Nucleus**
- **Endoplasmic Reticulum**
- **Cytosol**

**Prophylactic vaccines**

- Flu
- CMV
- hMPV + PIV3
- Chikungunya VLP
- Zika VLP
- H10N8
- H7N9
- RSV
- Flu
- H10N8
- H7N9
- RSV
- hMPV + PIV3
- Chikungunya VLP
- Zika VLP
- RSV
- H7N9
- H10N8
- Flu