mRNA Medicines to Enable Intracellular, Membrane-Bound, and Extracellular Secreted Therapeutics

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Disclosures

- Employee of Moderna
- Stock Ownership - Moderna
Potential mRNA Medicines

Encoded mRNA(s)

Prophylactic vaccines

Cancer vaccines

Intratumoral immunology

Localized regenerative therapeutics

Systemic secreted therapeutics

Ribosome

Flu

H1N8

H7N9

RSV

CMV

hMPV+PIV3

Chikungunya VLP

Zika VLP

PCV neoantigens

Kras

OX40L

IL23

IL12

IL36y

VEGF-A

Fabry

PA

PKU

MMA

GSD1a

Mitocondrion

Protein chain(s)

Mitochondrion

Endoplasmic Reticulum

Nucleus

Cytosol

Systemic intracellular therapeutics
Chikungunya – “that which bends up”

• First described in 1952 following outbreak in Tanzania
• Category C Priority pathogen (NIH)
• No licensed vaccine or therapeutic

**Symptoms**

- Fever, usually lasts about 1 week (90% of patients)
- Myalgia, usually lasts 7–10 days (90% of patients)
- Polyarthralgia, polyarthritis, or both, can last weeks to months (95% of patients)
- Rash, lasts about 1 week (40–50% of patients)

**Infection**

<table>
<thead>
<tr>
<th>2–6 days</th>
<th>Approximately 1 week</th>
<th>Weeks to months</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viremia, usually lasts 5–7 days</td>
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</table>

- IgM detectable 3–8 days after symptom onset, usually persists for 1–3 months
- IgG detectable 4–10 days after symptom onset, persists for years

**Biomarkers**

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Antibody against Chikungunya virus (mRNA-1944)
mRNA-1944 contains two mRNAs that encode for the heavy and light chains of CHKV-24 antibody, which may confer passive immunity

Expected protective level in mice 2
Antibody against Chikungunya virus (mRNA-1944)

Preclinical evidence that mRNA-1944 encodes for functional antibody against Chikungunya virus

mRNA-1944 produces an antibody against Chikungunya virus that is

- Functional
- Protective
- Translates between pre-clinical species
Antibody against Chikungunya virus (mRNA-1944)

**Trial design**

- Randomized, placebo-controlled, single ascending dose study in healthy adults
- All subjects received premedication with antihistamines
- No subjects received corticosteroids (permitted by protocol)

**Key Objectives**

- **Safety**: Evaluate safety and tolerability of escalating doses of mRNA-1944 administered via intravenous infusion
- **Translation of protein**: Evaluate pharmacology of mRNA-1944
- **Activity**: Determine ability of antibody to neutralize viral infection
Antibody against Chikungunya virus (mRNA-1944)

Protective antibody levels of >1µg/mL expected to endure at least 16 weeks at the middle dose of 0.3 mg/kg

Pharmacology

- Administration of mRNA-1944 resulted in dose-related increase in levels of CHKV-24
- Half life (t$_{1/2}$) of antibody was 62 days
- Middle and high dose (0.3 and 0.6 mg/kg) projected to exceed 1 µg/mL target for at least 16 weeks
Antibody against Chikungunya virus (mRNA-1944)
mRNA-1944 driven protein expression results in functional antibody (CHKV-24)

- Neutralizing antibody titers observed at all dose levels, indicating functional antibody production by mRNA-1944
- All placebo subjects below the lower limit of detection
- 100% of subjects administered 0.3 and 0.6 mg/kg had titers >100

Serum neutralization activity 48 hr after mRNA-1944 administration

<table>
<thead>
<tr>
<th>Dose Level (mg/kg)</th>
<th>Percent of Subjects Achieving NT&lt;sub&gt;50&lt;/sub&gt; &gt;100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
</tr>
<tr>
<td>0.1</td>
<td>10</td>
</tr>
<tr>
<td>0.3</td>
<td>100</td>
</tr>
<tr>
<td>0.6</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose Level (mg/kg)</th>
<th>N</th>
<th>GMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6</td>
<td>&lt;10</td>
</tr>
<tr>
<td>0.1</td>
<td>6</td>
<td>113</td>
</tr>
<tr>
<td>0.3</td>
<td>6</td>
<td>718</td>
</tr>
<tr>
<td>0.6</td>
<td>4</td>
<td>538</td>
</tr>
</tbody>
</table>
## Antibody against Chikungunya virus (mRNA-1944)

### Summary of related adverse events

<table>
<thead>
<tr>
<th>Cohort (N)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=6)</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>mRNA-1944 0.1 mg/kg (N=6)</td>
<td>Feeling of warmth, transient (1)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>mRNA-1944 0.3 mg/kg (N=6)</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>mRNA-1944 0.6 mg/kg (N=4)</td>
<td>Sinus tachycardia, fever, infusion associated shivering, lightheadedness, hypotension</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Subject 1</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Subject 2</td>
<td>None</td>
<td>Nausea, emesis</td>
<td>None</td>
</tr>
<tr>
<td>Subject 3</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Subject 4</td>
<td>Chills, headache, lightheadedness, gaseousness</td>
<td>EKG abnormal (T wave inversion), emesis, nausea, fever</td>
<td>Sinus tachycardia, elevated WBC</td>
</tr>
</tbody>
</table>

- All AEs were transient and resolved spontaneously without treatment
- No serious AEs in the study
- No meaningful changes in liver or kidney laboratory results
Antibody against Chikungunya virus (mRNA-1944)

Translation from preclinical species to humans

Solid line = Median predicted
Shaded area = 90% prediction interval
Symbols = Individual participant observations
Conclusions: mRNA-1944 achieved the target level of functional protein translation at a well tolerated dose

- Administration of mRNA-1944 resulted in dose-dependent increases in levels of antibody against Chikungunya (CHKV-24)

- Neutralizing antibodies were observed at all dose levels, indicating functional antibody production by mRNA-1944

- None of the participants treated with mRNA-1944 at the low (0.1 mg/kg) or middle (0.3 mg/kg) doses experienced significant adverse events (AEs). Three of the four participants at the high (0.6 mg/kg) dose had infusion related AEs, with the highest grade by subject being Grade 1 (n=1), Grade 2 (n=1) and Grade 3 (n=1)

- mRNA-1944 at 0.3 mg/kg and 0.6 mg/kg provides antibody levels that are expected to be protective against Chikungunya infection (>1 µg/mL) for at least 16 weeks, supporting further development.

- mRNA to protein translation in human was predicted by preclinical data
For the first time, the systemic administration of an mRNA containing LNP has been demonstrated to produce a fully functional complex protein in humans.

Dose dependent pharmacology has been fully predicted from preclinical species with no loss of potency.

Target therapeutic concentrations have been achieved at a well tolerated dose in a healthy volunteer population.

We believe these data strongly support the continued development of our systemic rare disease therapeutic modality that targets both secreted and intracellular proteins.
Progress in the systemic intracellular therapeutics modality to date

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
<th>Systemic intracellular therapeutics</th>
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<tbody>
<tr>
<td>Natural history study initiated</td>
<td>IND Open</td>
<td>MMA mRNA-3704</td>
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<tr>
<td>Successful IND-enabling GLP toxicology studies</td>
<td></td>
<td>PA mRNA-3927</td>
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<tr>
<td>Pre-clinical activity and dose dependent pharmacology in animal models</td>
<td></td>
<td>PKU mRNA-3283</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GSD1a mRNA-3745</td>
</tr>
</tbody>
</table>

Sites open for MMA phase 1/2 trial and actively recruiting patients
MMA (mRNA-3704) utilizes the same LNP formulation as antibody against Chikungunya virus (mRNA-1944)
Thank You!
Chikungunya mAb (mRNA-1944) Team and All Collaborations

Special thanks to the CHIK mAbTeam!

Special thanks to DARPA

and to the PPD Phase 1 Unit, Austin, Texas & Dr. LuAnn Bundrant and Team

and to All of our Study Participants