Annual R&D Day

September 8th, 2022
Forward-looking statements and disclaimer

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including statements regarding: Moderna’s vision for mRNA science; the timing of data from Moderna’s trials of its product candidates targeting PCV, MMA, GSD1a and RSV; clinical trends in Moderna’s Phase 1/2 PA trial; Moderna’s launch of COVID-19 vaccine boosters; the initiation of clinical trials for mRNA-1230, targeting SARS-CoV-2, influenza and RSV; Moderna’s pursuit of an accelerated approval pathway for mRNA-1010; expected read out of Moderna’s Phase 3 immunogenicity trial of mRNA-1010; expected initiation of Moderna’s Phase 3 efficacy study of mRNA-1010; enrollment in Moderna’s Phase 3 trial of its CMV vaccine candidate; Moderna’s commercial organization strategic priorities; the timing of potential future product launches; Moderna’s transition to an endemic COVID market; the respiratory vaccines market opportunity, including for COVID-19 vaccines, and the potential to expand the market; the market potential of adult combination vaccines; the market opportunity for vaccines for latent viruses; the market opportunity for therapeutics for rare diseases; and Moderna’s manufacturing capabilities. In some cases, forward-looking statements can be identified by terminology such as “will,” “may,” “should,” “could,” “expects,” “intends,” “plans,” “aims,” “anticipates,” “believes,” “estimates,” “predicts,” “potential,” “continue,” or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. The forward-looking statements in this presentation are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, many of which are beyond Moderna’s control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties, and other factors include, among others, those risks and uncertainties described under the heading “Risk Factors” in Moderna’s Annual Report on Form 10-K for the year ended December 31, 2021 and Quarterly Report on Form 10-Q for the quarter ended March 31, 2022, each filed with the U.S. Securities and Exchange Commission (SEC), and in subsequent filings made by Moderna with the SEC, which are available on the SEC’s website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this presentation in the event of new information, future developments or otherwise. These forward-looking statements are based on Moderna’s current expectations and speak only as of the date of this presentation.
mRNA is the software of life

Binary System

Quaternary System

mRNA is an information molecule
Modernas’s vision for mRNA science

1. mRNA is an information molecule

2. Invest in science to invent novel ways to deliver mRNA into various cell types – each will be a new application, which we call a modality

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Proof-of-concept data from our sentinel programs de-risk our modalities and accelerate our development plans

EXPLORATORY

- Inhaled pulmonary therapeutics
- Localized regenerative therapeutics
- Intratumoral immuno-oncology

EMERGING

- Cancer vaccines
- Systemic secreted & cell surface therapeutics
- Systemic intracellular therapeutics

ESTABLISHED

- Latent virus vaccines
- Respiratory vaccines

Sentinel programs

- CF
- VEGF-A (no LNP)
- Triplet
- Personalized cancer vaccine
- Chikungunya antibody
- PA
- CMV vaccine
- COVID-19 vaccine

- Six programs; four in clinical trials
- Chikungunya antibody data in 2019 de-risked systemic LNP delivery
- Emerging data from PA suggesting clinical benefit
- Personalized cancer vaccine (PCV) Phase 2 data expected in 4Q22
- Respiratory vaccines de-risked
- Latent virus vaccines efficacy readout to come from CMV

Increasing R&D investment
Proof-of-concept data in vaccines were an enabler

- **Proof-of-concept data achieved in vaccines**
  - Enabled Moderna to quickly develop a vaccine against COVID-19
  - Expanded vaccine pipeline with the addition of new vaccine development candidates
    - R&D Day 2019: 7 vaccine programs
    - R&D Day 2022: 32 vaccine programs
Platform advantages and increased investments accelerated vaccine pipeline development

Increased investments and execution accelerated the development of vaccines

- **4 vaccines in late-stage, Phase 3 programs**
  - R&D Day 2019: 0 late-stage programs
  - R&D Day 2022: 4 late-stage programs

- **24 vaccines currently in the clinic**
  - R&D Day 2019: 8 vaccines in clinic
  - R&D Day 2022: 24 vaccines in clinic
Early data from our ongoing PA trial is encouraging and shows potential to have a meaningful clinical impact.

Systemic intracellular modality

**Encouraging interim data from PA Phase 1/2 Paramount study**

- Generally well-tolerated safety profile to date
- Encouraging data shows decrease in the number of metabolic decompensation events (MDEs)
- Initial discussions with regulators supportive of MDE as primary endpoint for a pivotal study
Encouraging signs in a second rare disease

Encouraging interim data from GSD1a Phase 1/2 Balance study

• Early data on safety and pharmacodynamics are consistent and encouraging

• Announcing new rare disease candidate: Ornithine transcarbamylase deficiency (OTC)
  - OTC is a rare genetic condition that causes ammonia to build up in the blood
  - OTC (mRNA-3139) uses the same LNP as GSD1a program
mRNA is a new class of medicines

- COVID vaccines and boosters established mRNA technology for respiratory vaccines
- Respiratory vaccines in Phase 3: seasonal flu, RSV data readouts and launches are next
- We now have encouraging data from our first mRNA therapeutic encoding for an intracellular protein for a rare disease of the liver
- On track to readout PCV Phase 2 data in 4Q22
## Today's agenda

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<tr>
<th>Introduction</th>
<th>Stéphane Bancel, Chief Executive Officer</th>
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<tr>
<td>R&amp;D Day 2022 Overview</td>
<td>Stephen Hoge, M.D., President</td>
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<td>mRNA Therapeutics</td>
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<td>Rare Diseases</td>
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<td>• Organic acidemias overview and real-world burden of disease</td>
<td>Dr. Mark S. Korson, Director of Physician Support Service and Education, VMP Genetics</td>
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<td>• Interim PA Phase 1/2 data</td>
<td>Ruchira Glaser, M.D., SVP, Head, Therapeutics (Rare Disease, Autoimmune &amp; Emerging)</td>
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<td>• Interim GSD1a Phase 1/2 data</td>
<td>Geoffrey Rezvani, M.D., Executive Director, Program Leader (Cardiovascular and Emerging Therapeutics)</td>
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<td>Immune Oncology</td>
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<td>• Personalized Cancer Vaccine (Phase 2 trial overview)</td>
<td>Michelle Brown, M.D., Ph.D., Executive Director, Program Leader, Oncology</td>
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<td>Coffee Break (10 minutes)</td>
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<td>Vaccines: Late-Stage Phase 3 Trials</td>
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<td>COVID Booster/Combination Respiratory Vaccines</td>
<td>Jacqueline Miller, M.D., SVP, Therapeutic Area Head, Infectious Diseases</td>
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<td>Seasonal Influenza Vaccine Phase 3 Trials</td>
<td>Raffael Nachbagauer, M.D., Ph.D., Senior Director, Infectious Disease Development</td>
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<td>Respiratory Syncytial Virus (RSV) Phase 3 Trial</td>
<td>Christine Shaw, Ph.D., VP, Portfolio Head Respiratory Vaccines, Infectious Disease Development</td>
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<td>Commercial Organization Launch Preparation</td>
<td>Arpa Garay, Chief Commercial Officer</td>
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<td>Conclusion</td>
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<td>Stéphane Bancel, Stephen Hoge, Arpa Garay, Ruchira Glaser, Jacqueline Miller, Praveen Aanur</td>
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R&D Day
Introduction

Stephen Hoge, M.D.
President
Modernova has a diverse portfolio of vaccine and therapeutic programs in preclinical and clinical development

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**mRNA therapeutics review**

- **Review of interim PA data** from ongoing Phase 1/2, multiple-dose study
- **Review of early data** from first patients in ongoing GSD1a Phase 1/2, single-dose study
- **Phase 2 personalized cancer vaccine (PCV) trial overview** (data expected in 4Q22)

**Late-stage vaccines**

- **Overview of Phase 3 trials:** Primary endpoints and timing for data readouts
  - COVID boosters & combinations
  - Flu vaccine
  - RSV vaccine
  - CMV vaccine
Proof-of-concept data from our sentinel programs de-risk our modalities and accelerate our development plans

**EXPLORATORY**
- **Modalities**
  - Inhaled pulmonary therapeutics
  - Localized regenerative therapeutics
  - Intratumoral immuno-oncology

**EMERGING**
- **Cancer vaccines**
  - Personalized cancer vaccine
- **Systemic secreted & cell surface therapeutics**
  - Chikungunya antibody
- **Systemic intracellular therapeutics**
  - PA

**ESTABLISHED**
- **Prophylactic vaccines**
  - Latent virus vaccines
  - CMV vaccine
  - COVID-19 vaccine

**Inhaled pulmonary therapeutics**
- CF
- VEGF-A (no LNP)

**Localized regenerative therapeutics**
- Triplet

**Intratumoral immuno-oncology**
- Personalized cancer vaccine
- Chikungunya antibody

**Sentinel programs**
- Six programs; four in clinical trials

- Chikungunya antibody data in 2019 de-risked systemic LNP delivery
- Emerging data from PA suggesting clinical benefit
- Personalized cancer vaccine (PCV) Phase 2 data expected in 4Q22

- Respiratory vaccines de-risked
- Latent virus vaccines efficacy readout to come from CMV

**Increasing R&D investment**
Proof-of-concept data from our sentinel programs de-risk our modalities and accelerate our development plans

**EXPLORATORY**
- Inhaled pulmonary therapeutics
- Localized regenerative therapeutics
- Intratumoral immuno-oncology
- Cancer vaccines
- Systemic secreted & cell surface therapeutics

**EMERGING**
- Systemic intracellular therapeutics
- Personalized cancer vaccine
- Chikungunya antibody
- PA

**ESTABLISHED**
- Latent virus vaccines
- Respiratory vaccines
- Prophylactic vaccines

**Modalities**
- Sentinel programs
  - CF
  - VEGF-A (no LNP)
  - Triplet
  - Personalized cancer vaccine
  - Chikungunya antibody

- PA

**Sentinel programs**
- Six programs; four in clinical trials
- Chikungunya antibody data in 2019 de-risked systemic LNP delivery
- Emerging data from PA suggesting clinical benefit
- Personalized cancer vaccine (PCV) Phase 2 data expected in 4Q22
- Respiratory vaccines de-risked
- Latent virus vaccines efficacy readout to come from CMV

**Increasing R&D investment**
Modern has two distinct LNP delivery systems dosing in rare disease clinical trials

**Rare Diseases in Systemic Intracellular Modality**

- **PA** (Ph 1/2)
- **MMA** (Ph 1/2)

**Organic acidemias use LNP 1**
(same as Chikungunya antibody program)

- **GSD1a** (Ph 1/2)
- **OTC** (Preclinical)

**GSD1a and OTC use LNP 2**
(different LNP with distinct pharmacology)
Encouraging early clinical signs in rare disease modality

PA (mRNA-3927)

- 6 patient-years of experience on drug and all participants eligible have decided to continue on Open Label Extension (OLE) Study
- Generally well-tolerated to date
- Reduction in biomarker (3-HP levels) observed
- Encouraging data shows decrease in the number of metabolic decompensation events (MDEs); Initial discussions with regulators supportive of MDE as primary endpoint for a pivotal study

GSD1a (mRNA-3745)

- Early data on safety and pharmacodynamics are consistent and encouraging
- In two patients, mRNA-3745 was well tolerated to date, and showed extension of fast duration and normalization of glucose during fast
Dr. Korson graduated in medicine from the University of Toronto and completed a pediatric residency at Toronto’s Hospital for Sick Children, followed by a genetics/metabolism fellowship at Boston’s Children’s Hospital. He directed the metabolic clinics at Boston Children’s Hospital until 2000 and across town at Tufts Medical Center until 2014. In 2007, he co-founded and continues to co-direct the SIMD’s North American Metabolic Academy.

In 2017, Dr. Korson joined VMP Genetics as Director of Education and Physician Support Services, providing remote consultative assistance to clinicians at 10 major academic medical centers caring for patients with proven or suspected metabolic disease. He has significant experience in creating innovative educational resources about metabolic diseases for non-genetic clinicians so that they can play more of a role in patient diagnosis and management. Also at VMP Genetics, he directs the Patient-Teacher Registry and Patient-Teacher Video Catalog, with the aim of ensuring that the patient voice plays a bigger role in the education of health professionals. Regionally, Dr. Korson is on the board of the New England Regional Genetics Network, and as a founding board member of Rare New England, hosts the annual Rare Disease Day Speakers Series in New England and their online Medical Genetics Career Fairs.
Therapy for PA + MMA: The need for something better

Mark S. Korson, MD
VMP Genetics
The story of PKU is the story of the specialty of metabolic disease
PROTEIN
PHENYLALANINE

Phenylalanine hydroxylase

TYROSINE
Phenylalanine hydroxylase

Dr. Asbjorn Folling, Norway
Phenylalanine

Phenylalanine hydroxylase

Tyrosine

Phenylpyruvate
Phenyllactate
Phenylacetate
Phenylethylamine

Phenylketones:
Phenylalanine hydroxylase

\[
\text{PHENYLALANINE} \xrightarrow{\text{Phenylalanine hydroxylase}} \text{TYROSINE} \xrightarrow{\text{PhENYLKETONURIA}}
\]
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Intellectual disability</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Psychiatric symptoms</td>
</tr>
<tr>
<td></td>
<td>Lighter pigmentation of skin, hair</td>
</tr>
<tr>
<td></td>
<td>Skin rash</td>
</tr>
</tbody>
</table>
PKU - 
"schneiderzitzen"
PHENYLKETONURIA (PKU)

Pathophysiology

Intellectual disability
Seizures
Psychiatric symptoms
Lighter pigmentation
Skin rash

↑ PHE
↑ PHE
↑ PHE
↓ TYR
↓ TYR
Horst Bickel (1954) proposed a low PHE diet

2 year old girl with PKU:
- PHE dropped
- Phenylketones cleared
- Improved in developmental tasks
Horst Bickel (1954) proposed a low PHE diet

2 year old girl with PKU:
- Reversed when restarted on a high PHE diet
DIETARY THERAPY

SUBSTRATE RESTRICTION - PKU

• Restricting natural protein $\rightarrow$ inadequate protein intake
SUBSTRATE RESTRICTION - PKU

• Restricting natural protein $\rightarrow$ inadequate protein intake

\[ \text{No PHE} + \text{NATURAL PROTEIN} = \text{Diet} \]
SUBSTRATE RESTRICTION - PKU

- Restricting natural protein → inadequate protein intake

\[ \text{Vitamins & minerals} + \text{Natural Protein} = \text{Diet} \]

No PHE
Foods forbidden from amino acid-restricted diets
Permitted - fruit
Permitted - vegetables
Permitted - foods lower in protein content
THE PKU DIET, circa 1980s
A FEW ‘LOW PROTEIN’ FOODS
### RECOMMENDED UNIFORM SCREENING PANEL - 2022

#### Amino acid disorders
- Phenylketonuria
- Homocystinuria
- Maple syrup urine disease
- Tyrosinemia type I
- Citrullinemia type I
- Argininosuccinic aciduria

#### Organic acid disorders
- Propionic acidemia
- Methylmalonic acidemia (MMA, mutase)
- MMA (cobalamin disorders)
- Isovaleric acidemia
- Beta-ketothiolase deficiency
- Holocarboxylase synthetase deficiency
- Glutaric acidemia type I
- 3-MC carboxylase deficiency
- Biotinidase deficiency
- HMG CoA lyase deficiency

#### Fatty acid oxidation defects
- MCAD deficiency
- VLCAD deficiency
- LCHAD deficiency
- Trifunctional protein deficiency
- Carnitine uptake defect

#### Other Metabolic disorders
- Galactosemia
- Pompe disease
- Hurler disease (MPS I)
- X-linked adrenoleukodystrophy

#### Other disorders
- Congenital hypothyroidism
- Congenital adrenal hyperplasia
- Hemoglobinopathies (3)
- Cystic fibrosis
- Severe combined immunodeficiencies
- Critical congenital heart disease
- Hearing loss
- Spinal muscular atrophy
SUCCESS OF PKU SCREENING → MATERNAL PKU

Cognitive/motor disability (92%)
Small head (73%)
In utero growth retardation (40%)
Heart defects (15%)
INADEQUATE PKU MANAGEMENT

Executive function problems
- Inattention
- Cognitive rigidity
- Lack of impulse control

Psychiatric symptoms
- Anxiety
- Depression
- Phobia

Issues with relationships
CHALLENGES TO MANAGEMENT

Adherence difficulty

Neurocog/neuropsych symptoms

Increased PHE levels

Adapted from Brittany Holmes
Survey of 3772 patients with PKU (US):

- % of patients who have elevated PHE levels
  - 18-29 yr = ~ 62%
  - 30 yr and older = ~ 71%
- Adherence to PHE level monitoring
  - 37% of adults 30 + older up test once a year or less

88% of adults with PKU are unable to adhere to a PHE-restricted diet

Jurecki et al, 2017

Hardy et al, 2018
PROBLEM!

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total phenylketonuria patients based on incidence of 1:12,707 (n)</th>
<th>Phenylketonuria patients reported in the clinic (n)</th>
<th>Estimated not in the clinic, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>1,677</td>
<td>1,357</td>
<td>320 (19)</td>
</tr>
<tr>
<td>5–12</td>
<td>2,598</td>
<td>1,924</td>
<td>674 (26)</td>
</tr>
<tr>
<td>13–18</td>
<td>1,977</td>
<td>1,306</td>
<td>671 (34)</td>
</tr>
<tr>
<td>19–24</td>
<td>1,993</td>
<td>1,036</td>
<td>957 (48)</td>
</tr>
<tr>
<td>25–45</td>
<td>6,741</td>
<td>1,557</td>
<td>5,184 (77)</td>
</tr>
<tr>
<td>Total</td>
<td>14,988</td>
<td>7,180</td>
<td>7,808 (52)</td>
</tr>
</tbody>
</table>

Berry et al, 2013
WHAT DO PATIENTS WANT?

Survey by National PKU Alliance (625 patients)
77.7% - most desired lifestyle improvement:
“To be able to increase my protein intake without increasing my symptoms of PKU”

**PKU: from preclinical to marketed products**

### Pre-clinical

- **AGT**
- **HMI-102**
- **SOM-0011**
- **MT**
- **mRNA-3283**
- **UX-501**
- **HMI-103**
- **BMN-307**

### Phase I

- **CDX-6114** (GL-stable PAL variant enzyme)
- **RTX-134** (PAL in red blood cell as cargo)
- **SOM-0011** (Unidentified Activity)
- **AGT**
- **BMN-307**
- **HMI-102**
- **HMI-103**
- **UX-501**
- **mRNA-3283**
- **MT**

### Phase II

- **SYN-200** (Microbiome PAL LAAD)
- **SYN-1618** (Microbiome E coli Nissle PAL LAAD)
- **CNSA-001** (Oral synthetic sepiapterin)

### Phase III / Pre-reg.

- **CDX-6114**
- **CNSA-001**

### Marketed

- **Kuvan**
- **Palynziq**

**Key:**
- microbeime
- Biologic
- Small Molecule
- Gene Therapy
- mRNA

**Note:**
- 20 – 56% response rate
- Associated with severe anaphylaxis

---

**Additional Information:**

- **GI-stable PAL variant enzyme**
- **AAVS-PAH GT**
- **Adult indication, AAV-PAH GT**
- **Ped. indication, AAV-PAH GT**
- **AAV8-PAH GT**
- **PAH mRNA**
- **Small Molecule**

---

**Center for Rare Disease Therapy**

**UPMC | CHILDREN'S HOSPITAL OF PITTSBURGH**
Why am I talking to you about PKU??
CHOLESTEROL SIDE CHAINS
ODD CHAIN FATS
GUT BACTERIAL PROPIONATE

ILE VAL MET THR

PROPIONYL CoA

METHYLMALONYL CoA

METHYLMALONIC ACIDEMIA

SUCCINYL CoA

KREBS CYCLE
CHOLESTEROL

SIDE CHAINS

VAL  MET  THR

ODD CHAIN

FATS

PROPIONYL CoA

METHYLMALONYL CoA

KREBS CYCLE

GUT BACTERIAL PROPIONATE

CHOLESTEROL SIDE CHAINS

ODD CHAIN FATS

DIRECT TOXICITY

ACIDOSIS

ILE

PROPIONYL CoA

METHYLMALONYL CoA

SUCCINYL CoA

KREBS CYCLE
Cholesterol
Side Chains
Odd Chain Fats
Propionyl CoA
Methyllumononyl CoA
Succinyl CoA
Krebs Cycle

ILE VAL MET THR

Gut bacterial Propionate
Direct Toxicity
Acidosis
Suppresses Bone Marrow

Propionate
Odd Chain Fats
CHOLESTEROL SIDE CHAINS

ODD CHAIN FATS

PROPIONYL CoA

METHYLMALONYL CoA

Succinyl CoA

Low Energy

GUT BACTERIAL PROPIONATE

DirecToxicity

AcidoSis

INTOXICATION

Bone Marrow

High Ammonia
**METABOLIC CRISIS** *(aka Metabolic Decompensation Event)*

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Poor feeding, vomiting → dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lethargy, altered consciousness → coma</td>
</tr>
<tr>
<td></td>
<td>Looks “septic”</td>
</tr>
</tbody>
</table>
PROGRESSION OF A METABOLIC CRISIS

Advanced stage

- Apnea
- Slowing heart rate
- Seizures
- Hypothermia
- Generalized organ dysfunction
- Stroke
- Sudden death
Movements – Infant with an Organic Acidemia

Video from JM Saudubray and Thierry Billette de Vilmeur
<table>
<thead>
<tr>
<th>Neonatal</th>
<th>Coma due to high ammonia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bone marrow suppression → infection</td>
</tr>
<tr>
<td></td>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Infantile spasms</td>
</tr>
</tbody>
</table>

Adapted from C. Venditti, 2020
Infancy/early childhood

“Pure” neurologic syndromes
“Brain dysfunction”
Movement disorder, unsteady gait
Pancreatitis
Infection → crisis + multiorgan failure
Diabetic ketoacidosis
”Stroke”
<table>
<thead>
<tr>
<th>Adolescence</th>
<th>Mental status changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac muscle failure (cardiomyopathy)</td>
</tr>
<tr>
<td></td>
<td>Cardiac arrest</td>
</tr>
</tbody>
</table>

Adapted from C. Venditti, 2020
Movement disorder
Cardiomyopathy
Isolated kidney disease
Optic nerve atrophy → blindness

Adapted from C. Venditti, 2020
HOW PA + MMA PATIENTS ARE MANAGED
CHOLESTEROL SIDE CHAINS

ILE VAL MET THR

GUT BACTERIAL PROPIONATE

CHOLESTEROL

ODD CHAIN FATS

DIRECT TOXICITY

ACIDOSIS

SUPPRESSES BONE MARROW

HIGH AMMONIA

PROPIONYL CoA

METHYLMALONYL CoA

SUCCINYL CoA

KREBS CYCLE
PROTEIN-RESTRICTED DIET

DIRECT TOXICITY
ACIDOSIS
SUPPRESSES BONE MARROW
HIGH AMMONIA

CHOLESTEROL
SIDE CHAINS
ODD CHAIN FATS
GUT BACTERIAL PROPIONATE

ILE VAL MET THR
PROPIONYL CoA

METHYLMALONYL CoA

Succinyl CoA

KREBS CYCLE
DIETARY THERAPY

SUBSTRATE RESTRICTION - PA+MMA

• Restricting natural protein $\rightarrow$ inadequate protein intake

No VAL, ILE, THR, MET

\[ \text{VIMT} + \text{NATURAL PROTEIN} = \text{Diet} \]
CHOLESTEROL SIDE CHAINS

Odd Chain Fats

Acidosis

Ile Val Met Thr

Propionyl CoA

Methyrmalonyl CoA

Succinyl CoA

Krebs Cycle

Direct Toxicity

Suppresses Bone Marrow

High Ammonia

Medications

Gut Bacterial Propionate

Cholesterol Side Chains

Odd Chain Fats
CHOLESTEROL

SIDE CHAINS

VAL  MET  THR

ODD CHAIN FATS

PROPIONYL CoA

METHYLMALONYL CoA

PROPIONATE

ACIDOSIS

DIRECT TOXICITY

SUPPRESSES BONE MARROW

HIGH AMMONIA

GUT BACTERIAL

CHOLESTEROL

SIDE CHAINS

IOD CHAIN FATS

KREBS CYCLE

SUCCINYL CoA

MONITORING/MEDICATIONS
Cholesterol side chains contribute to odd chain fats. Propionyl CoA is affected by gut bacterial propionate, Odd chain fats, and high ammonia. Direct toxicity and acidosis suppress bone marrow. Medications may also play a role in this process. The Krebs cycle is impacted by succinyl CoA.
ACIDOSIS
SUPPRESSES BONE MARROW
HIGH AMMONIA

CHOLESTEROL SIDE CHAINS
ODD CHAIN FATS
GUT BACTERIAL PROPIONATE

IEE VAL MET THR

PROPIONYL CoA

METHYLMALONYL CoA

SUCCINYL CoA

KREBS CYCLE

DIRECT TOXICITY

MEDICATIONS
SO WE HAVE TREATMENTS FOR PA + MMA – YAY!
THIS TREATMENT PLAN IS UNSUSTAINABLE – BOO!
This treatment plan is unsustainable—boo!

- These therapies address the symptoms; they don’t address the underlying problem.
- It’s like playing “medical whack-a-mole.”
- Patients and parents run ICUs at home.
- Think PKU therapy “on steroids.”
We need a therapy that can provide working enzyme...
Propionic Acidemia (PA)

Ruchira Glaser, M.D., M.S.
Senior Vice President, Therapeutic Area Head, Cardiovascular, Rare Diseases & Autoimmune
PA therapy (mRNA-3927) encodes for an intracellular enzyme

Moderna’s mRNA therapy for PA (mRNA-3927) encodes for two proteins that form the deficient enzyme

**PA biology**

- Changes in the **PCCA** and **PCCB** genes cause propionic acidemia
  - These genes provide instructions for making two parts (subunits) of the propionyl-CoA carboxylase enzyme
  - Change in the **PCCA** or **PCCB** genes affect the normal function of the PCC enzyme and prevent the normal breakdown of propionyl-CoA
- As a result, propionyl-CoA and other harmful compounds accumulate causing acute metabolic decompensation events and damage to the brain and other organs, causing the serious health problems associated with propionic acidemia
mRNA-3927 encodes for PCCA and PCCB subunit proteins to form an active PCC enzyme
Ongoing Phase 1/2 Study designed to evaluate safety and pharmacology of mRNA-3927 in participants with PA

First study testing an mRNA therapeutic for intracellular protein replacement

- **Primary endpoints**: Safety and PK/PD
- **Secondary endpoints**: Incidence and severity of adverse events and change in plasma biomarkers (Hydroxypropionic acid (3-HP) and methylcitric acid (2-MC))
- **Exploratory clinical endpoints**: Metabolic decompensations events (MDE), cardiac function, quality of life

**Phase 1/2 Trial Design**

- **Cohort 1** (0.3 mg/kg IV q3wk) N=3
- **Cohort 2** (0.3 mg/kg IV q2wk) N=3
- **Cohort 3** (0.45 mg/kg IV q2wk) N=3
- **Cohort 4** (0.6 mg/kg IV q2wk) N=3
- **Cohort 5+** N=3

Identification of optimal dose triggers dose expansion

**SMC**: Safety monitoring committee

- **Fully enrolled**: N=4-6+

**SMC**: Safety monitoring committee
## mRNA-3927: Summary of demographics and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 0.3 mg/kg q3W (n=4)</th>
<th>Cohort 2 0.3 mg/kg q2W (n=3)</th>
<th>Cohort 3 0.45 mg/kg q2W (n=3)</th>
<th>All (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at enrollment, median (years)</strong></td>
<td>15.42</td>
<td>2.33</td>
<td>3.75</td>
<td>6.71</td>
</tr>
<tr>
<td>Min, Max</td>
<td>5.2, 26.8</td>
<td>1.5, 8.3</td>
<td>1.6, 15.3</td>
<td>1.5, 26.8</td>
</tr>
<tr>
<td><strong>Age at disease onset, median (months)</strong></td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0.1</td>
<td>0.0</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Sex, n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>6</td>
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<tr>
<td><strong>Race, n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Black or African American</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asian</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Other (Black African)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<tr>
<td><strong>Ethnicity, n</strong></td>
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<tr>
<td>Not Hispanic or Latino</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td></td>
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<tr>
<td>Weight at baseline, median (kg)</td>
<td>44.40</td>
<td>15.80</td>
<td>18.00</td>
<td>23.05</td>
</tr>
<tr>
<td>Min, Max</td>
<td>21.6, 66.5</td>
<td>10.6, 24.8</td>
<td>11.2, 42.7</td>
<td>10.6, 66.5</td>
</tr>
<tr>
<td><strong>Genotype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCCA</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>PCCB</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

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Overall Phase 1/2 clinical experience to date

- Ten participants dosed
- Three participants have >1 year of dosing
- 6 patient-years of experience on drug
- Over 120 intravenous doses administered
- Study is ongoing; independent safety monitoring committee approved moving to fourth cohort (0.6 mg/kg)
- All participants eligible have decided to continue on Open Label Extension (OLE) Study
Safety: Overall summary to date

- Generally well-tolerated to date
- No Dose Limiting Toxicities
- No Drug Related Serious Adverse Events
- No Discontinuations due to safety
- Only drug related adverse events were mild to moderate infusion related reactions (<10% of doses)
## Safety: Summary of all adverse events measured

Adverse events (AEs) collected in the trial consist of treatment emergent adverse events (any AE reported after the start of dosing) and drug related AEs.

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.30 mg/kg Q3W (N=4)</td>
<td>0.30 mg/kg Q2W (N=3)</td>
<td>0.45 mg/kg Q2W (N=3)</td>
<td>(N=10)</td>
</tr>
<tr>
<td>Treatment-emergent adverse events¹</td>
<td>3 (75.0)</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>9 (90.0)</td>
</tr>
<tr>
<td>Dose Limiting Toxicity</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs leading to study discontinuation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious adverse events²</td>
<td>2 (50.0)</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td>5 (50.0)</td>
</tr>
<tr>
<td>Drug-related adverse events</td>
<td>2 (50.0)</td>
<td>0</td>
<td>0</td>
<td>2 (20.0)</td>
</tr>
<tr>
<td>Drug-related Serious Adverse Events</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

¹ Treatment-emergent adverse events are defined as AEs reported on or after the date that the intervention began.
² Serious adverse events are defined as AEs including those leading to hospitalization, or disability, or are life-threatening or result in death, or deemed by the investigator as medically important, and include congenital anomaly or birth defect.
# Safety: Summary of serious adverse events

No drug-related SAEs; several SAEs due to underlying disease

<table>
<thead>
<tr>
<th>Safety: Summary of serious adverse events</th>
<th>Cohort 1 0.30 mg/kg Q3W (N=4)</th>
<th>Cohort 2 0.30 mg/kg Q2W (N=3)</th>
<th>Cohort 3 0.45 mg/kg Q2W (N=3)</th>
<th>Total (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Serious Adverse Events</td>
<td>2 (50.0)</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td>5 (50.0)</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>0</td>
<td>1 (33.3)</td>
<td>0</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Gastroenteritis viral</td>
<td>0</td>
<td>1 (33.3)</td>
<td>0</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Mastoiditis</td>
<td>1 (25.0)</td>
<td>0</td>
<td>0</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Parainfluenza virus infection</td>
<td>0</td>
<td>1 (33.3)</td>
<td>0</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Poor venous access</td>
<td>0</td>
<td>0</td>
<td>1 (33.3)</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Staphylococcal sepsis</td>
<td>1 (25.0)</td>
<td>0</td>
<td>0</td>
<td>1 (10.0)</td>
</tr>
</tbody>
</table>

**Serious AEs related to underlying disease**

<table>
<thead>
<tr>
<th>Serious AEs related to underlying disease</th>
<th>Cohort 1 0.30 mg/kg Q3W (N=4)</th>
<th>Cohort 2 0.30 mg/kg Q2W (N=3)</th>
<th>Cohort 3 0.45 mg/kg Q2W (N=3)</th>
<th>Total (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic disorder</td>
<td>1 (25.0)</td>
<td>0</td>
<td>0</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (25.0)</td>
<td>0</td>
<td>1 (33.3)</td>
<td>2 (20.0)</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (25.0)</td>
<td>0</td>
<td>0</td>
<td>1 (10.0)</td>
</tr>
</tbody>
</table>

**Drug-related Serious adverse events**

<table>
<thead>
<tr>
<th>Drug-related Serious adverse events</th>
<th>Cohort 1 0.30 mg/kg Q3W (N=4)</th>
<th>Cohort 2 0.30 mg/kg Q2W (N=3)</th>
<th>Cohort 3 0.45 mg/kg Q2W (N=3)</th>
<th>Total (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Treatment-emergent adverse events are defined as AEs reported on or after the date that the intervention began. All serious adverse events in the study were treatment-emergent adverse events.
Safety: Summary of drug-related adverse events

All drug related AEs were mild to moderate infusion related reactions (IRRs) that occurred in cohort 1 only.

<table>
<thead>
<tr>
<th>Drug-related adverse events</th>
<th>Cohort 1 0.30 mg/kg Q3W (N=4)</th>
<th>Cohort 2 0.30 mg/kg Q2W (N=3)</th>
<th>Cohort 3 0.45 mg/kg Q2W (N=3)</th>
<th>Total (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 (50.0)</td>
<td>0</td>
<td>0</td>
<td>2 (20.0)</td>
</tr>
<tr>
<td>By CTCAE grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (50.0)</td>
<td>0</td>
<td>0</td>
<td>2 (20.0)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (25.0)</td>
<td>0</td>
<td>0</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Grade 3 or above</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total Number of Doses Given</td>
<td>61</td>
<td>49</td>
<td>12</td>
<td>122</td>
</tr>
<tr>
<td>Number of doses with IRRs</td>
<td>11 (18.0)</td>
<td>0</td>
<td>0</td>
<td>11 (9.0)</td>
</tr>
</tbody>
</table>

IRRs: Infusion-related reactions, defined as a drug-related AEs occurring within 24 hours of the start of a dose.
Biomarkers to evaluate PK/PD of mRNA-3927

• While several biomarkers have been described, their pattern in individual patients over time and association with clinical events has not been thoroughly studied.

• No clinically validated biomarkers.

• We explored 3-Hydroxypropionate (3-HP) as a potential biomarker.
Baseline 3-HP biomarker levels highly variable across patients

- Each patient in the trial had four 3-HP values measured from blood draws taken before treatment.
- Pre-treatment 3-HP values are highly variable between patients and within patients.

<table>
<thead>
<tr>
<th>PA genotype</th>
<th>Patient ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCCA</td>
<td>1, 5, 8</td>
</tr>
<tr>
<td>PCCB</td>
<td>2, 3, 4, 6, 7</td>
</tr>
</tbody>
</table>
Adaptive study design to identify optimal dose level and frequency

- Shorten interval from 3 weeks to 2 weeks (Cohort 2)
- Increased dose to 0.45 mg/kg (Cohort 3)
- Increased dose to 0.6 mg/kg (Cohort 4) expected to begin dosing shortly

DLT = dose-limiting toxicity; PD = pharmacodynamic(s); PK = pharmacokinetic(s)
1. The first 2 participants will be ≥ 8 years of age
2. In the dose expansion stage, a minimum of 2 participants with each PA subtype will be enrolled
Significant reduction in 3-HP biomarker observed

- 7/8 patients showed a numerical reduction in 3-HP

Cohort 1
(0.3 mg/kg Q3W)

Cohort 2
(0.3 mg/kg Q2W)

Cohort 3
(0.45 mg/kg Q2W)

Steady-state = 3-HP measurements taken at all visits post 3rd dose
Encouraging trend in 3-HP biomarker

- Patients showed numerically lower 3-HP levels on treatment
- Trend suggestive of potential dose response with a greater decline from baseline at 0.45 mg/kg

Baseline = 3-HP measurements collected from pretreatment visits (N=4 visits/measurements per subject, prior to first dose);
Steady-state = 3-HP measurements taken at all visits post 3rd dose
Metabolic decompensation events are a potential primary endpoint

Protocol definition of MDE

- Exacerbation of symptoms of propionic acidemia: Persistent vomiting, anorexia/failure to feed, lethargy or increased seizure activity and...
  - Requiring emergency medical care (ER or hospitalization admission)

and at least one of:

- Metabolic acidosis (pH < 7.35) with high anion gap, or imminent metabolic acidosis with high anion gap (normal pH with reduced bicarbonate and/or PaCO2)
- Acute Hyperammonemia requiring intervention

Initial discussions with regulators supportive of MDE as primary endpoint for a pivotal study
Summary of metabolic decompensation events (MDEs)

Exposure duration of 3.8 years in participants with ≥1 retrospective MDE

- 48% Relative risk reduction in MDE frequency (p-value = 0.1817)
- No MDEs in two-week dosing interval cohorts
Summary of Phase 1/2 preliminary data; study ongoing to identify optimal dose

- **Expanding clinical experience**: 6 patient-years of experience on drug and all participants eligible have decided to continue drug on the Open Label Extension (OLE) Study

- **Safety**: Generally well-tolerated to date with no drug-related serious adverse events, no discontinuations due to safety and only mild-to-moderate infusion related reactions (<10% of doses)

- **Encouraging early trends in 3-HP biomarkers**: Suggestive of potential dose-dependent pharmacology

- **Clinical endpoints**: Encouraging data shows decrease in the number of metabolic decompensation events (MDEs)

- **Next steps**: Continue to enroll additional cohorts and escalate dose, identify optimal dose for expansion and continue to engage with regulators on registration path
MMA (mRNA-3705) also ongoing in a Phase 1/2 study

Two cohorts are fully enrolled and we will have preliminary data by early 2023

- Evaluating the safety and pharmacology of mRNA-3705 in patients 1 year of age and older with MMA in a multiple ascending dose study
- Secondary endpoints include incidence and severity of adverse events (AEs) and change in plasma biomarkers
- Recruiting patients in United Kingdom, Canada and US
- First two cohorts fully enrolled; study ongoing
  - Recently dosed third patient in 2nd cohort
- Preliminary data expected to be available by early 2023
Glycogen storage disease type 1a (GSD1a)

Geoffrey Rezvani, M.D.
Executive Director, Program Leader
(Cardiovascular and Emerging Therapeutics)
Glycogen storage disease type 1a (GSD1a) overview

GSD1a refers to a rare inherited metabolic disease resulting from a deficiency in the metabolism of glucose.

- **GSD1a biology**
  - GSD1a is caused by mutations within the enzyme glucose 6-phosphatase, G6Pase

- **Clinical manifestations**
  - **Life-threatening** hypoglycemia, long-term liver & kidney damage
  - **Long-term hepatic complications** are observed in 75% of adult patients of which 10% are at risk of malignant transformation into hepatocellular carcinomas (HCC)
Glycogen storage disease type 1a (GSD1a) overview

**Significant unmet medical need**

- No approved therapy for GSD1a
- Current interventions include:
  - **Strict diet control**: frequent consumption of uncooked cornstarch to improve hypoglycemia
  - Feedings by **gastric tube**
  - **Glycosade®** (cornstarch for dietary management)
  - Liver/kidney transplantation
GSD1a therapy (mRNA-3745) encodes for the G6Pase enzyme
Ongoing Phase 1 study of mRNA-3745 in GSD1a

Orphan Drug Designation granted by U.S. FDA

- Evaluate the **safety and pharmacology** of mRNA-3745 in patients 18 years of age and older with GSD1a

- **Single ascending dose study:** Challenging patients twice, on day 3 and day 8
  - **Biomarkers:** blood sugar and lactate
  - **Clinical:** improvement in fasting tolerance 3 days and 8 days after a single dose of mRNA-3745

- **Trial progress:** Enrollment ongoing (first participant dosed in June ’22)
Intravenous infusion of mRNA-3745 with LNP2 without pre-medication was very well tolerated with only mild AEs

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Female, 21 years old</td>
<td>• Female, 18 years old</td>
</tr>
<tr>
<td>• GSD1a diagnosed at 6 months of age, managed with cornstarch</td>
<td>• GSD1a diagnosed at 2 years of age, managed with cornstarch</td>
</tr>
<tr>
<td>• Genotype: c.379_380dup (homo)</td>
<td>• Genotype: c.562G&gt;C c.883C&gt;T (compound het)</td>
</tr>
</tbody>
</table>

**Safety**

• No vital signs changes up to 12 hours post-infusion

• No serious adverse events

• No meaningful changes in safety labs, including hematology and liver function

• Follow up ongoing
Emerging efficacy data in GSD1a

Patient 1 (0.1 mg/kg)

Fast terminated due to confirmed hypoglycemia after clinical symptoms

Evidence of severe metabolic strain with lactate approaching 4 mmol/L

<table>
<thead>
<tr>
<th>Hours</th>
<th>Glucose (mg/dl)</th>
<th>Lactate (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>140</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>120</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Baseline

Fast terminated
Emerging efficacy data in GSD1a

**Patient 1** (0.1 mg/kg)

**Fast duration (hours)**

- Baseline: 4:48h

**Glucose (mg/dL)**

- Baseline
- Fingerstick: 59 mg/dL
- Hypoglycemia (<60 mg/dL)

**Lactate (mmol/L)**

- Baseline
- Severe lactate (>4 mmol/L)
Emerging efficacy data in GSD1a

Patient 1 (0.1 mg/kg)

- Baseline
- Day 3

Fast duration (hours)

Glucose (mg/dl)

Lactate (mmol/L)

Baseline 4:48h +3:12h 8:00h

Maximum permitted

Patient able to complete full fast (limited to 8 hours)

Glucose and lactate maintained throughout the fast

Hypoglycemia (<60 mg/dL)

Severe lactate (>4 mmol/L)

Fingerstick: 59 mg/dl

Baseline 59 mg/dl

Baseline

Day 3
Emerging efficacy data in GSD1a

**Patient 1 (0.1 mg/kg)**

- **Baseline**
- **Day 3**: 4:48h + 3:12h
- **Maximum permitted**: 8:00h

**Glucose (mg/dl)**

- Baseline: 120
- Day 3: 100

**Hypoglycemia (<60 mg/dL)**

- Fingerstick: 59 mg/dl

**Lactate (mmol/L)**

- Baseline: 4
- Day 3: 6

**Severe lactate (>4 mmol/L)**

**Patient 2 (0.1 mg/kg)**

- **Baseline**
- **Day 3**: 7:10h
- **Maximum permitted**: 10:15h

**Glucose (mg/dl)**

- Baseline: 125
- Day 3: 100

**Hypoglycemia (<60 mg/dL)**

**Fast terminated**
Emerging efficacy data in GSD1a

**Patient 1 (0.1 mg/kg)**

- **Baseline**
- **Day 3**: 4:48h
- Maximum permitted: +3:12h
- **Day 3**: 8:00h

**Glucose (mg/dl)**

**Patient 2 (0.1 mg/kg)**

- **Baseline**
- **Day 3**: 7:10h
- Maximum permitted*: +3:05h
- **Day 3**: 10:15h

**Glucose (mg/dl)**

**Lactate (mmol/L)**

- Fingerstick: 59 mg/dl
- Hypoglycemia (<60 mg/dL)
- Severe lactate (>4 mmol/L)
Improved fasting tolerance maintained through Day 8

Slight decrease vs. day 3, consistent with G6Pase enzyme half-life

* Maximum Permitted
mRNA-3745 for GSD1a – next steps

• Continue to **evaluate safety** of mRNA-3745 and LNP2
• **Assess fast tolerance** beyond day 8
• **Exploring higher doses** to extend potential repeat dose interval
• **Identify a dose** to move to repeat dose study
Personalized Cancer Vaccine (PCV) Review

Michelle Brown, M.D., Ph.D.

Executive Director, Program Leader, Oncology
Personalized cancer vaccine (mRNA-4157)

Designed to target an individual patient’s unique tumor mutations

- Personalized drug design
- Rapid turnaround times
- Needle-to-needle in just weeks

Personalized Cancer Vaccines

- mRNA encoding up to 34 neoantigens
- Tissue Samples: Tumor (biopsy) and Normal
- Next Generation Sequencing (NGS): Mutations identified in protein neoantigen
- Vaccine Design: Up to 34 neoantigens, Automated algorithm integrated with workflow
- Manufacturing: Manufacturing of mRNA, Aim for one lot per patient
- Administration
PCV vaccine (mRNA-4157) elicits T cells required for curative cancer therapy
Designed to target an individual patient’s unique tumor mutations
Phase 1 study demonstrates PCV induces CD8 T-cell proliferation against selected neoantigens incorporated in vaccine

Previously shared at ASCO 2019

- Greater than 3x increases in neoantigen specific CD8 T-cells were detected post 4th dose vaccination against 10 out of 18 class I targeted neoantigens
- All positive CD8 T-cell responses post vaccination were to neoantigens with high predicted binding affinity of < 500 nm

Flow cytometry plots show increases in % freq. of CD8 cells producing IFNγ 7d post 4th vaccine dose to multiple neoantigens

* Is greater than 3x increased in neoantigen specific CD8 T-cells post vaccination

CD8 T cell responses to individual neoantigens were measured in in vitro stimulated (IVS, expanded) T cells
PCV (mRNA-4157) is ongoing in a Phase 2 trial

Primary endpoint is recurrence free survival compared to pembrolizumab

- Randomized, placebo controlled, PCV + pembrolizumab (KEYTRUDA®) vs. pembrolizumab alone (2:1)
- Resected melanoma patients - high recurrence risk
- Primary endpoint = recurrence free survival (RFS)
- Trial was fully enrolled (~150 participants) in September ’21: Data expected in 4Q22
Previous studies in resected melanoma population: Kaplan-Meier curves for Checkmate-238 and Keynote-054

**Checkmate-238**

1. **12mo RFS:** 70.5% vs. 60.8%

**Keynote-054**

1. **12mo RFS:** 75.4% vs 61.0%


Personalized cancer vaccine (PCV) summary

- **Primary endpoint analysis is RFS;** PCV + pembrolizumab vs. pembrolizumab alone

- Previous PD-1 studies show a **12-month RFS of 70-75%**
- Goal to show an **improved benefit in PCV + pembrolizumab arm compared to pembrolizumab (SOC)**

- **Primary endpoint analysis expected in 4Q 2022**
## Today’s agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction</strong></td>
<td>Stéphane Bancel, Chief Executive Officer</td>
</tr>
<tr>
<td><strong>R&amp;D Day 2022 Overview</strong></td>
<td>Stephen Hoge, M.D., President</td>
</tr>
<tr>
<td><strong>mRNA Therapeutics</strong></td>
<td></td>
</tr>
<tr>
<td>Rare Diseases</td>
<td>Dr. Mark S. Korson, Director of Physician Support Service and Education, VMP</td>
</tr>
<tr>
<td>Rare Diseases</td>
<td>Genetics</td>
</tr>
<tr>
<td>Rare Diseases</td>
<td>Ruchira Glaser, M.D., SVP, Head, Therapeutics (Rare Disease, Autoimmune &amp;</td>
</tr>
<tr>
<td>Rare Diseases</td>
<td>Emerging)</td>
</tr>
<tr>
<td>Rare Diseases</td>
<td>Geoffrey Rezvani, M.D., Executive Director, Program Leader (Cardiovascular</td>
</tr>
<tr>
<td>Rare Diseases</td>
<td>and Emerging Therapeutics)</td>
</tr>
<tr>
<td>Immune Oncology</td>
<td>Michelle Brown, M.D., Ph.D., Executive Director, Program Leader, Oncology</td>
</tr>
<tr>
<td>Coffee Break (10 minutes)</td>
<td></td>
</tr>
<tr>
<td>Vaccines: Late-Stage Phase 3 Trials</td>
<td></td>
</tr>
<tr>
<td>COVID Booster/Combination Respiratory Vaccines</td>
<td>Jacqueline Miller, M.D., SVP, Therapeutic Area Head, Infectious Diseases</td>
</tr>
<tr>
<td>Seasonal Influenza Vaccine Phase 3 Trials</td>
<td>Raffael Nachbagauer, M.D., Ph.D., Senior Director, Infectious Disease Development</td>
</tr>
<tr>
<td>Respiratory Syncytial Virus (RSV) Phase 3 Trial</td>
<td>Christine Shaw, Ph.D., VP, Portfolio Head Respiratory Vaccines, Infectious Disease Development</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV) Vaccine Phase 3 trial</td>
<td>Jacqueline Miller, M.D., SVP, Therapeutic Area Head, Infectious Diseases</td>
</tr>
<tr>
<td>Commercial Organization Launch Preparation</td>
<td>Arpa Garay, Chief Commercial Officer</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Stéphane Bancel, Chief Executive Officer</td>
</tr>
<tr>
<td>Q&amp;A</td>
<td>Stéphane Bancel, Stephen Hoge, Arpa Garay, Ruchira Glaser, Jacqueline</td>
</tr>
<tr>
<td></td>
<td>Miller, Praveen Aanur</td>
</tr>
</tbody>
</table>
COVID Boosters & Respiratory Combination Vaccines

Jacqueline Miller, M.D.

SVP, Therapeutic Area Head, Infectious Diseases
Moderna has launched two vaccine boosters to meet different market needs across the largest markets

**mRNA-1273.214**

(25 µg of mRNA-1273 and 25 µg of Omicron BA.1)

- Induced significantly higher titers than mRNA-1273 against the BA.1 and BA.4/5 sublineages in a clinical trial conducted before the fall booster season
- Authorized in United Kingdom, Switzerland, Australia, Canada and European Union (conditional)

**mRNA-1273.222**

(25 µg of mRNA-1273 and 25 µg of Omicron BA.4/5)

- Based on the BA.4/5 strain and is being developed consistent with recent FDA guidance
- Authorized in United States
Clinical data from Beta/1273 and Omicron BA.1/1273 supports COVID bivalent platform and .222 submission

Local reactogenicity of BA.1 Omicron bivalent (mRNA-1273.214) as 4th dose similar to 2nd dose of primary series and 3rd dose of original (mRNA-1273) in adults

- Pain:
  - Grade 3: 88%
  - Grade 1-2: 84%
  - Grade 3: 77%

- Erythema:
  - Grade 3: 9%
  - Grade 1-2: 5%
  - Grade 3: 7%

- Swelling:
  - Grade 3: 12%
  - Grade 1-2: 5%
  - Grade 3: 7%

- Axillary Swelling or Tenderness:
  - Grade 3: 14%
  - Grade 1-2: 20%
  - Grade 3: 17%

Solicited local adverse reactions within 7 days after injection

No Grade 4 events reported

2nd dose mRNA-1273 (Baden et al, NEJM 2021); 3rd dose mRNA-1273 (Choi et al, Nat Med 2022); 4th dose mRNA-1273.214 (Chalkias et al. medRxiv 2022; in press New Engl J Med)
Clinical data from Beta/1273 and Omicron BA.1/1273 supports COVID bivalent platform and .222 submission

Systemic reactogenicity of BA.1 Omicron bivalent (mRNA-1273.214) as 4th dose generally lower than 2nd dose of primary series and 3rd dose of mRNA-1273 in adults

- Fever
- Headache
- Fatigue
- Myalgia
- Arthralgia
- Nausea / Vomiting
- Chills

Solicited systemic adverse reactions within 7 days after injection

Grade 4 systemic reactions only with 2nd dose of mRNA-1273 (<0.1%)
Clinical data from Beta/1273 and Omicron BA.1/1273 supports COVID bivalent platform and .222 submission

Bivalent Beta vaccine (mRNA-1273.211) as 3rd dose elicited higher neutralizing antibody responses in adults through 6 months compared to mRNA-1273 and monovalent Beta vaccine (mRNA-1273.351)

Neutralizing antibody responses against Beta in adults through 6 months

- Prototype mRNA-1273 (N = 149) - 6.8-fold decrease from Day 29 to Day 181
- Monovalent Beta mRNA-1273.351 (N = 20) - 8.2-fold decrease from Day 29 to Day 181
- Bivalent Beta mRNA-1273.211 (N = 295) - 3.2-fold decrease from Day 29 to Day 181
Clinical data from Beta/1273 and Omicron BA.1/1273 supports COVID bivalent platform and .222 submission

Bivalent Beta vaccine (mRNA-1273.211) as 3rd dose elicited higher neutralizing antibody responses in adults through 6 months compared to mRNA-1273

Neutralizing antibody responses in adults through 6 months

Ancestral with D614G

<table>
<thead>
<tr>
<th></th>
<th>Day 29</th>
<th>Day 181</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancestral</td>
<td>1.28</td>
<td>1.68</td>
</tr>
<tr>
<td>Beta</td>
<td>1.33</td>
<td>2.74</td>
</tr>
<tr>
<td>Omicron</td>
<td>2.17</td>
<td>2.32</td>
</tr>
<tr>
<td>Delta</td>
<td>1.77</td>
<td>1.23</td>
</tr>
</tbody>
</table>

Chalkias et al. Research Square 2022, doi: 10.21203/rs.3.rs-1555201/v1—in press Nature Medicine
Clinical data from Beta/1273 and Omicron BA.1/1273 supports COVID bivalent platform and .222 submission

4th dose (2nd booster) with BA.1 Omicron bivalent booster (mRNA-1273.214) resulted in higher neutralizing antibody titers against Omicron BA.4/BA.5 across age groups, including ≥65-year-olds, than mRNA-1273

Neutralizing antibody responses in adults through 1 month

![Graph showing neutralizing antibody titers](image-url)
BA.4/5 Omicron-targeting bivalent booster (mRNA-1273.222) ongoing in a clinical study

- mRNA-1273.222 arm fully enrolled on August 25th
- Primary objectives
  - Safety, reactogenicity
  - Immunogenicity: neutralizing antibody response comparison of .222 50 µg vs. mRNA-1273 50 µg (historical comparator) against BA.4/5 when administered as 4th doses based on GMR and SRR-difference

P205 mRNA-1273.222 study

<table>
<thead>
<tr>
<th>mRNA-1272.222 (50 µg)</th>
<th>mRNA-1273 (50 µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=512</td>
<td>N=377</td>
</tr>
</tbody>
</table>

mRNA-1273.222 & mRNA-1273 administered as a 4th dose
Participants previously received mRNA-1273 primary series (100 µg) and mRNA-1273 (50 µg) booster dose at least 3 months prior with no known SARS-CoV-2 infection within 3 months prior to enrollment

GMR: Geometric mean ratio
SRR: Seroconversion response ratio
Advantages of mRNA platform accelerates authorization of up-to-date boosters

We can simultaneously move COVID variant boosters into the clinic and prepare for launches because we can leverage:

**Clinical data generated from bivalent platform:** Advanced multiple variant booster vaccines (Beta, Delta, Omicron and bivalents)

**Chemistry, manufacture and control data:** Manufacturing process and inputs are the same across vaccines

**Preclinical data:** Models in mice have translated effectively to clinical data
mRNA platform allows for rapid development and manufacturing timelines

1H22
Two variant vaccines into clinic
• Omicron (BA.1)-specific (.529)
• Omicron (BA.1)/1273 bivalent (.214)

2H22
Scale manufacturing for .214/.222

9.1.2022
EU & Canada authorize mRNA-1273.214

8.15.2022
UK authorizes mRNA-1273.214

2H22

8.31.2022
FDA authorizes mRNA-1273.222

8.30.2022
Australia authorizes mRNA-1273.214

8.29.2022
Switzerland authorize mRNA-1273.214

6.28.2022
FDA VRBPAC meeting
• FDA announcement two days later that they prefer Omicron vaccine against BA.4/5

2021
Four variant vaccines into clinic
• Beta-specific (.351)
• Beta/1273 bivalent (.211)
• Delta-specific (.617)
• Beta/Delta bivalent (.213)
Rapid licensure of vaccines against COVID sets the stage for respiratory vaccines and combinations

**COVID (mRNA-1273)**
- Omicron (BA.1) variant + wild-type, Omicron (BA.4/5) variant + wild-type

**Seasonal Flu (mRNA-1010)**
- HA glycoproteins (A/H1N1, A/H3N2 and influenza B/Yamagata and B/Victoria lineages)

**RSV (mRNA-1345)**
- RSV Prefusion F protein

- Bivalent vaccine
- 50 µg booster dose level in adults
- Observed higher effectiveness in real-world evidence (RWE)

- Quadrivalent vaccine
- 50 µg dose level in adults
- 18+ immunogenicity Ph 3 study ongoing
- 50+ efficacy Ph 3 study planned for fall 2022

- Monovalent vaccine
- 50 µg dose level in adults
- 60+ efficacy Ph 2/3 study ongoing
- 50+ immunogenicity Ph 3 study ongoing
Combination vaccines in pipeline to leverage efficacy of standalone vaccines

Current combination pipeline

Older adults
- COVID + flu (mRNA-1073) fully enrolled in Phase 1/2
- COVID + flu + RSV (mRNA-1230) in preclinical

Pediatrics
- hMPV + PIV3 (mRNA-1653) in Phase 1
- RSV + hMPV (mRNA-1365) in preclinical
Running co-administration studies to help prepare for launches

Phase 3 randomized, observer-blind study

Evaluating safety, tolerability and immunogenicity of mRNA-1345, an mRNA vaccine targeting respiratory syncytial virus (RSV), when given alone or co-administered with a seasonal influenza vaccine or SARS-CoV-2 vaccine in adults ≥ 50 years of age.

Co-administration arms:
- RSV vaccine (mRNA-1345)
- Seasonal influenza vaccine (Afluria® quadrivalent)
- RSV vaccine (mRNA-1345)
- COVID booster (mRNA-1237.214)

NIH U.S. National Library of Medicine
ClinicalTrials.gov
NCT05330975

Seasonal Flu Vaccine Program

Raffael Nachbagauer, M.D., Ph.D.
Senior Director, Infectious Disease Development
Seasonal influenza (flu) overview

Influenza (influenza A and influenza B) occurs seasonally and varies in severity each year, causing respiratory illnesses and placing a substantial burden on healthcare systems.

Disease burden:

- Worldwide, there are 3-5M severe cases of influenza and 290-650K influenza-related respiratory deaths annually.\(^1\)
- About 8% of the US population experiences symptoms from influenza each year, with 140-710K hospitalizations and 12-52K deaths per year.\(^2\)
- Peak influenza activity is seen in temperate climates during fall to winter and is reflected in increased outpatient visits, urgent care visits, and hospitalizations.

### Influenza symptoms & complications

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Pneumonia (viral and/or bacterial)</td>
</tr>
<tr>
<td>Cough</td>
<td>Ear infections</td>
</tr>
<tr>
<td>Sore throat</td>
<td>Sinus infections</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>Exacerbation of chronic conditions (e.g. asthma,</td>
</tr>
<tr>
<td>Fatigue</td>
<td>heart failure)</td>
</tr>
<tr>
<td>Vomiting/diarrhea</td>
<td></td>
</tr>
</tbody>
</table>

mRNA-1010 is our influenza vaccine candidate furthest advanced in clinical development

1:1:1:1 ratio for mRNA sequences encoding HAs of 4 strains (A/H1N1, A/H3N2, B/Victoria and B/Yamagata)
## Two Phase 3 studies will support licensure of mRNA-1010

Immunogenicity trial in Southern Hemisphere ongoing; efficacy trial in Northern Hemisphere expected to start in the fall

### Immunogenicity trial

- Study ongoing in Southern Hemisphere
- Targeted enrollment of 6,000 participants
  - Fully enrolled study in August
- Study intended to support initial licensure based on demonstrated safety and immunogenicity; received favorable feedback from FDA and EMA

### Efficacy trial

- Will be conducted in Northern Hemisphere
- Study start planned for this fall
- Expected to enroll approximately 23,000 participants
- Intended to fulfill post-licensure requirement to demonstrate efficacy after initial approval based on immunogenicity
mRNA-1010 Phase 3 immunogenicity study in adults 18+ is fully enrolled

- **Number of participants:** ~6,000
  - ~30% of participants ≥ 50 to < 65 years old
  - ~20% of participants ≥ 65 years old
- **Primary endpoints**
  - Safety
  - Non-inferior immunogenicity (GMT and seroconversion rate)
- **Secondary endpoints**
  - Superior immunogenicity
- **Site locations**
  - Australia, Argentina, Colombia, Panama and Philippines
mRNA-1010 Phase 3 efficacy study in adults 50+

Expected to start in fall 2022

- **Number of participants:** 23,000
  - Approximately 50% will be 65+ and ~10% will be 75+
- **Primary endpoints**
  - Non-inferior (NI) relative vaccine efficacy (rVE) in preventing first episode of RT-PCR-confirmed protocol-defined influenza-like illness (ILI) caused by any strain of influenza A or B
  - Safety
- **Secondary endpoints**
  - Superior rVE in preventing first episode of RT-PCR-confirmed protocol-defined ILI caused by any strain of influenza A or B
  - rVE based on additional definitions
  - rVE to prevent hospitalization associated with influenza illness
- **Study duration**
  - Approximately one year of follow up
  - Efficacy studies can span multiple years
Flu vaccine program accelerating towards pivotal results

Phase 3 immunogenicity trial expected to read out in 1H23
Trial is expected to support initial licensure

Phase 3 efficacy trial in Northern Hemisphere expected to start fall 2022
Will fulfill regulatory requirement to demonstrate efficacy post-licensure

mRNA-1010 is our influenza candidate vaccine furthest in development
Additional candidates that encode for additional antigens (NA) already in the clinic (mRNA-1020/-30); candidates encoding for additional HA s for enhanced breadth planned for 2023 (mRNA-1011/-12)
Older Adults RSV Vaccine Program

Christine Shaw, Ph.D.
VP, Portfolio Head, Respiratory Vaccines, Infectious Disease Development
Respiratory syncytial virus (RSV) is a large burden in older adults

RSV is a common seasonal respiratory virus

• There are ~177,000 hospitalizations in adults 65+ due to RSV in the U.S. each year, and ~14,000 deaths\(^1\)

• Globally it is estimated that there are more than 1.5 million episodes of acute respiratory tract infection and ~336,000 hospitalizations related to RSV each year\(^2\)

• RSV burden in older adults is underestimated due to a lack of routine testing\(^3\)

• Annual cost of RSV hospitalizations in US adults aged ≥50 years is estimated to be >$1 billion USD\(^4\)

---

Long-term RSV infection sequelae

- Severe acute respiratory infection and lower respiratory tract infections
- Exacerbation of chronic obstructive pulmonary disease
- Higher 1 year mortality after severe illness

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1. RSV in Older Adults and Adults with Chronic Medical Conditions, CDC. [https://www.cdc.gov/rsv/high-risk/older-adults.html](https://www.cdc.gov/rsv/high-risk/older-adults.html)
RSV vaccine (mRNA-1345) encodes a stabilized prefusion F glycoprotein
Pivotal Phase 3 trial in older adults has enrolled more than 24,000 participants

- **Pivotal Phase 3 efficacy study**
  - Adults ≥ 60 years of age
  - Placebo-controlled, case-driven design
- **Expect to enroll ~34,000 participants in multiple countries:** locations influenced by RSV epidemiology
  - Phase 2 portion enrolled ~2,000 participants
  - Phase 3 portion started in February 2022 after DSMB review of Phase 2 portion
- Primary endpoints are **safety and vaccine efficacy**
- Primary efficacy analysis will be **triggered based on accrual of RSV cases**
Enrollment is accelerating going into northern hemisphere fall/winter

Currently enrolled >24,000 subjects and enrollment is expected to complete this year

- Enrolling in 20 different countries
- Using global surveillance networks to follow RSV seasonality, which has been disrupted by the pandemic
- Sites set up in northern hemisphere ahead of expected fall/winter surge

Phase 3: Approximate enrollment per month

<table>
<thead>
<tr>
<th>Month</th>
<th>Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb</td>
<td>~200</td>
</tr>
<tr>
<td>Mar</td>
<td>~1400</td>
</tr>
<tr>
<td>Apr</td>
<td>~1500</td>
</tr>
<tr>
<td>May</td>
<td>~2400</td>
</tr>
<tr>
<td>Jun</td>
<td>~3300</td>
</tr>
<tr>
<td>Jul</td>
<td>~5200</td>
</tr>
<tr>
<td>Aug</td>
<td>~7000</td>
</tr>
</tbody>
</table>

Total enrolled includes Phase 2 subjects that count to Phase 3 endpoint
ConquerRSV trial is on track to meet D&I targets

Currently enrolling in >200 sites in 20 countries

US Enrollment Based on Demographic Composition

<table>
<thead>
<tr>
<th>Demographic Composition</th>
<th>Current %</th>
</tr>
</thead>
<tbody>
<tr>
<td>White, non-Hispanic</td>
<td>~ 65%</td>
</tr>
<tr>
<td>Hispanic/LatinX</td>
<td>~ 14%</td>
</tr>
<tr>
<td>Black or African American</td>
<td>~18%</td>
</tr>
<tr>
<td>Asian</td>
<td>~ 2%</td>
</tr>
<tr>
<td>Others</td>
<td>~ 1%</td>
</tr>
</tbody>
</table>

Persons of Color: Current ~ 35%
Target 31%
We will be evaluating endpoints across the spectrum of RSV clinical disease

- Throughout the trial, we will be measuring multiple endpoints across the spectrum of RSV clinical disease, including:
  - RSV lower respiratory tract disease (LRTD) with 2 or more signs/symptoms
  - RSV LRTD with 3 or more signs/symptoms
  - RSV-associated hospitalizations
  - RSV acute respiratory disease (ARD)

- Case accrual begins 14 days after vaccination

- Study is designed and powered to accrue sufficient cases in one season (fall/winter 2022-2023)

- In November, we will have enough safety data to submit applications (6 months safety for ~6,000 participants)
### Overview of primary efficacy endpoint

Expect to reach enough cases for the first interim analysis this winter season (already accruing RSV cases in study)

<table>
<thead>
<tr>
<th>Approximate # of cases* (% of total cases)</th>
<th>VE: Efficacy bound</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interim analysis #1</strong></td>
<td>~0.76</td>
</tr>
<tr>
<td>43 (40%)</td>
<td></td>
</tr>
<tr>
<td><strong>Interim analysis #2</strong></td>
<td>~0.61</td>
</tr>
<tr>
<td>75 (70%)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary analysis</strong></td>
<td>~0.53</td>
</tr>
<tr>
<td>106 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

* RSV LRTD with 2+ signs/symptoms

---

Interim Boundaries Using O’Brien-Fleming Spending Function

LRTD: Lower-respiratory tract disease
Overview of primary efficacy endpoint

Expect to reach enough cases for the first interim analysis this winter season (already accruing RSV cases in study)

Interim Boundaries Using O’Brien-Fleming Spending Function

<table>
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<tr>
<th>Approximate # of cases* (% of total cases)</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Interim analysis #1</strong></td>
<td></td>
</tr>
<tr>
<td>43 (40%)</td>
<td>~0.76</td>
</tr>
<tr>
<td><strong>Interim analysis #2</strong></td>
<td></td>
</tr>
<tr>
<td>75 (70%)</td>
<td>~0.61</td>
</tr>
<tr>
<td><strong>Primary analysis</strong></td>
<td></td>
</tr>
<tr>
<td>106 (100%)</td>
<td>~0.53</td>
</tr>
</tbody>
</table>

* RSV LRTD with 2+ signs/symptoms

If 65% efficacy

~90% probability at primary analysis

~60% probability at IA #2

~10% probability at IA #1
Overview of primary efficacy endpoint

Expect to reach enough cases for the first interim analysis this winter season (already accruing RSV cases in study)

Interim Boundaries Using O’Brien-Fleming Spending Function

<table>
<thead>
<tr>
<th>Approximate # of cases* (% of total cases)</th>
<th>VE: Efficacy bound</th>
<th>Interim analysis #1</th>
<th>Interim analysis #2</th>
<th>Primary analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>43 (40%)</td>
<td>~0.76</td>
<td>~99% probability at primary analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 (70%)</td>
<td>~0.61</td>
<td>~90% probability at IA #2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>106 (100%)</td>
<td>~0.53</td>
<td>~40% probability at IA #1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* RSV LRTD with 2+ signs/symptoms

If 75% efficacy

~40% probability at IA #1
~90% probability at IA #2
~99% probability at primary analysis
RSV vaccine (mRNA-1345) summary and next steps

- **Continuing to enroll more patients and open additional sites;** ready for expected northern hemisphere RSV surge

- **Phase 3 efficacy trial could readout this winter,** depending on number of cases accrued in the study and vaccine effectiveness; target safety follow up will be reached by November

- **mRNA-1345 is also ongoing in a Phase 1 trial in pediatric populations;** RSV is also a large burden in the pediatric population
CMV Vaccine Program

Jacqueline Miller, M.D.
SVP, Therapeutic Area Head, Infectious Diseases
Cytomegalovirus (CMV) Overview

Sequelae include:

• At birth: microcephaly, chorioretinitis, seizures, sensorineural hearing loss
• Long term: cognitive impairment, cerebral palsy, seizure disorder, sensorineural hearing loss

1 in 200 babies in the U.S. are born with a congenital CMV infection (CMV infection is present at birth)

1 in 5 will have severe, life-altering health problems

Most common infectious cause of congenital sensorineural hearing loss worldwide

>$1B in annual healthcare costs

CMV vaccine comprises six mRNAs encoding the CMV pentamer complex and gB antigens together.
CMV vaccine (mRNA-1647) Phase 3 trial is >40% enrolled

- Randomized, observer-blind, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of mRNA-1647 to evaluate prevention of primary infection

- Enrollment is ongoing in the U.S. and internationally
  - Expected to enroll up to 6,900 women of childbearing age
  - Approximately 150 sites globally

- Participants must be at a higher risk of contracting CMV
  - Participants aged ≥20 years must anticipate having direct exposure (home, socially or occupationally) to at least 1 child ≤5 years of age

- Goal to enroll a diverse group of U.S. participants into the study

- Primary efficacy analysis will be triggered based on accrual of seroconversion cases; meeting the primary objective will be the basis for filing
CMV vaccine (mRNA-1647) Phase 3 trial ongoing worldwide

Enrolling in ~150 sites in 12 countries

### US Enrollment Targets Based on Demographic Composition

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Target</th>
<th>Current %</th>
</tr>
</thead>
<tbody>
<tr>
<td>White, non-Hispanic</td>
<td>58%</td>
<td>52%</td>
</tr>
<tr>
<td>Hispanic/LatinX</td>
<td>23%</td>
<td>33%</td>
</tr>
<tr>
<td>Black or African American</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Asian</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Others</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>58%</td>
<td>52%</td>
</tr>
<tr>
<td><strong>Persons of color</strong></td>
<td>42%</td>
<td>48%</td>
</tr>
</tbody>
</table>
### Overview of primary efficacy endpoint

#### Efficacy Boundaries with Alpha-allocation between 2 Planned Analyses

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Approximate # of Cases</th>
<th>One-sided Alpha</th>
<th>VE: Efficacy Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Analysis</td>
<td>81</td>
<td>0.5%</td>
<td>~ 57.7%</td>
</tr>
<tr>
<td>End of Study (EOS) Analysis</td>
<td>112</td>
<td>2.0%</td>
<td>~ 49.1%</td>
</tr>
</tbody>
</table>

![Graph showing vaccine efficacy over different vaccine efficacy percentages](#)
CMV infection is a frequent complication after transplantation

Infection occurs due to transmission from the transplanted organ, reactivation of latent infection, or after a primary infection in seronegative patients

- The harmful effects of CMV in transplant recipients result from:
  - The direct effect of the virus on various organs and systems
    - Mainly causing pneumonia, gastrointestinal tract disease, hepatitis, encephalitis, and retinitis
  - The indirect immunomodulatory effects of the virus
    - Predisposing patients to graft rejection and other opportunistic infections

- In solid organ transplantation (SOT), the greatest risk factor for CMV disease is a serological mismatch between the donor and the recipient (the recipient is CMV seronegative and the donor is seropositive)

<table>
<thead>
<tr>
<th>Incidence of CMV disease risk³</th>
<th>Donor+/recipient –</th>
<th>Recipient +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>0-50%</td>
<td>2-15%</td>
</tr>
<tr>
<td>Liver</td>
<td>8-40%</td>
<td>0-4%</td>
</tr>
<tr>
<td>Lung</td>
<td>10-33%</td>
<td>7-19%</td>
</tr>
<tr>
<td>Heart</td>
<td>0-25%</td>
<td>0-14%</td>
</tr>
</tbody>
</table>

Donor+/recipient – Recipient +

Allogeneic HSCT⁴

⁴.

1. Azevedo, Luiz et al., *Clinics (Sao Paulo)* (2015), https://doi.org/10.6061/clinics/2015(07)09
Investigation of mRNA-1647 in the transplant population

Anticipating trial start-up in late 2022

- **Objective**: Design a proof-of-concept trial or trials to evaluate the safety, efficacy and immunogenicity of mRNA-1647 in allogeneic hematopoietic stem cell transplant recipients and solid organ transplant recipients

- **Design**: Utilize mRNA-1647 as an adjunct to standard of care for the prevention of CMV

- **Considerations**: Evaluation of mRNA-1647 in a unique immunocompromised population, assessing:
  - Safety
  - Ability of mRNA-1647 to elicit an immune response
  - Durability of the immune response
  - Ability of mRNA-1647 to prevent either CMV reactivation or reinfection
  - Impact of mRNA-1647 on transplant-related and CMV-related outcomes
CMV vaccine (mRNA-1647) is advancing in a pivotal Phase 3 study

CMV is a large unmet need in women of child-bearing age; CMV is also a large healthcare burden in the transplant population and we plan to start a study evaluating plan to start a study in transplant population.

CMVictory trial is >40% enrolled and we are on track to meet D&I targets.

Timing of readout depends on number of CMV cases accrued in study.
Commercial Preparedness

Arpa Garay
Chief Commercial Officer
Commercial organization strategic priorities

1. Compete in 2023 endemic market
2. Create/expand respiratory vaccine markets (RSV, flu, combos)
3. Educate HCPs and the public about CMV in advance of CMV vaccine launch
4. Gear up for potential launch of therapeutics
Late-stage vaccines and potential launch timing

<table>
<thead>
<tr>
<th>Respiratory Infectious Diseases</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Licensed</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA-1273 SARS-CoV-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRNA-1010 Seasonal Flu (HA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRNA-1345 RSV (older adults)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Earliest 2023</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Latent and Public Health Infectious Diseases</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Licensed</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA-1647 CMV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Potential 2026</td>
</tr>
</tbody>
</table>

- **COVID boosters**: Launching Omicron-targeting bivalent candidates
- **Flu**: Immunogenicity readout expected in 2023
- **RSV**: Depending on RSV case accrual, efficacy could readout in 2023
- **CMV**: Depending on enrollment and CMV infection accrual, earliest efficacy could readout in 2024-2025
Transitioning to an endemic COVID market

### Pandemic context

- Nationalized country vaccine procurement, including a single point of contact for all EU sales
- Accelerated regulatory review (product approvals, labeling, packaging, CMO site qualification …)

### Endemic market

- More **fragmented commercial model; in U.S.:**
  - USG buys for Medicare, Medicaid
  - Private insurance health plans (UNH, Cigna, Blue Cross)
  - Private commercial market: Development of commercial market to large employers

- **EU countries procuring individually**
  - A variety of commercial models in EU countries (tender, national procurement, regional procurement) requiring different capabilities

- **Flu market could be a proxy for seasonality of sales:** Commercial process for fall season usually starts in December of the preceding year
  - Orders are typically completed by end of Q1, but additional orders can be made throughout year
  - Manufacturing timelines, competition and previous seasons are factors for sales timing
Endemic market dynamics: global sales infrastructure

- Moderna has direct presence in almost all major markets where respiratory vaccines have high utilization/sales
  - 91% of the flu market
  - 87% of the pneumococcal vaccine market

AMC-92 countries are supplied under the Gavi Agreement, with UNICEF / PAHO support
The respiratory vaccines market is substantial, and could be even larger with new, improved solutions

<table>
<thead>
<tr>
<th>How does COVID change the respiratory vaccines market?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recognition of vaccines as the gold standard in preventing disease burden and medical costs</td>
</tr>
<tr>
<td>• Increased awareness of mRNA vaccine efficacy</td>
</tr>
<tr>
<td>• Economic and social disruption from pandemic</td>
</tr>
<tr>
<td>• Recommendations for broader age groups¹</td>
</tr>
</tbody>
</table>

## Endemic COVID market: Opportunity to expand from high-risk population

### COVID market

- Recent pandemic COVID vaccines market >$100 billion\(^1\)
- In high-income countries, the eligible high-risk population is ~340 million
  - High-risk population due to age 65+ and adults 50-65 with at least one risk factor\(^2\)

### Potential U.S. COVID market (high-risk population only and all adults)

<table>
<thead>
<tr>
<th>COVID vaccine price assumptions</th>
<th>$64</th>
<th>$82</th>
<th>$100</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk population in U.S. (~82M) only</td>
<td>$5.2B</td>
<td>$6.7B</td>
<td>$8.2B</td>
</tr>
<tr>
<td>All adults (18+ yrs) population in U.S. (~258M) @ 50% coverage rate</td>
<td>$8.3B</td>
<td>$10.6B</td>
<td>$12.9B</td>
</tr>
</tbody>
</table>

- **U.S. flu vaccine coverage ratio in all adults (18+ yrs) is ~50%\(^3\); generally lower in other high-income countries**
- **Recent Centers for Medicare & Medicaid Services (CMS) price for CY22/23 was $64\(^4\)**

---

\(^1\) Reported and expected vaccine sales
\(^3\) CDC, [https://www.cdc.gov/flu/fluvaxview/coverage-2021estimates.htm](https://www.cdc.gov/flu/fluvaxview/coverage-2021estimates.htm)
Flu market: Opportunity to expand the market with premium vaccines

**Flu market**

**Market dynamics**

**Current influenza market** $5-6+ billion

**Market could grow even larger with better, more effective vaccines**

**Addressable population**
- Aim for recommendation in older adults (>65 years old)
- Adults 18+ eligible
- Explore pediatric indications

**Enhanced vaccines**
- Premium vaccines with improved vaccine efficacy get a higher price (> $50/dose) and are growing at a faster rate²

### Reported Global Influenza Vaccine Sales¹

USD, billions

<table>
<thead>
<tr>
<th>Year</th>
<th>Enhanced</th>
<th>Standard-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>$2.8B</td>
<td>$2.8B</td>
</tr>
<tr>
<td>2016</td>
<td>$3.2B</td>
<td>$3.2B</td>
</tr>
<tr>
<td>2020</td>
<td>$5.8B</td>
<td>$5.8B</td>
</tr>
</tbody>
</table>

**Enhanced CAGR (2016-2020): +15%**

**Standard-dose CAGR (2016-2020): +5%**

Note: Source: EvaluatePharma, IQVIA MIDAS, Sanofi Vaccine Day (2021); High-dose products include Fluzone HD, Flublok, Fluad; total sales estimated

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1. EvaluatePharma, IQVIA MIDAS, Sanofi Vaccine Day (2021); High-dose products include Fluzone HD, Flublok, Fluad; total sales estimated
2. [https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/VaccinesPricing](https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/VaccinesPricing)
## Older adults RSV market is a >$10 billion market

<table>
<thead>
<tr>
<th>RSV market</th>
<th>Market dynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV market has the potential to be &gt;$10 billion market¹</td>
<td></td>
</tr>
</tbody>
</table>

### Addressable population
- Older adults (>65 years old)
- Pediatric trials ongoing

### Market share
- Depends on efficacy readout compared to other late-stage competitors

### Price
- Innovative, best-in-class vaccines have pricing power

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¹ Analyst reports, FiercePharma
Adult combination vaccines have the potential to transform the vaccine market

Benefits of combination vaccines

- Higher compliance
- Better uptake
- Larger benefit to healthcare system
  - Administration cost for a vaccine can be $40 per shot\(^1\)
- Consumer convenience

Vaccines for latent viruses have different market dynamics when compared to respiratory vaccines

- **Latent viruses** (such as herpes viruses and HIV) do not follow seasonal patterns
- Demand is more constant over time, and market increases by expanding eligible populations (such as going down in age)
- **Innovative vaccines can grow to multi-billion businesses**
  - Gardasil: >$5B revenue in 2021; price is $250 per course\(^1\)
  - Shingrix: >$2B revenue in 2021; price is $340 per course\(^2\)

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**CMV market**

**CMV is a $2-5 billion opportunity**

- Build and expand the CMV market
  - Older adolescents/women of child-bearing age (4 million births a year in the U.S.)
  - Toddlers
- **New indications**
  - CMV transplant population

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1. Revenue: Evaluate Pharma estimates; Price
2. Revenue: Evaluate Pharma estimates; Price
## Rare disease marketing dynamics

### Unique regulatory benefits:
High unmet need allows for accelerated timelines with regulators

### KOLs:
Limited exposure to patients with rare disease require more education to diagnose and treat; concentrated base of patients through patient advocacy group

### Increased awareness drives diagnosis:
Epidemiology estimates often understated for rare diseases without treatment options

### Other unique factors of rare disease:
Additional benefits from Orphan Drug Designation (ODD)

<table>
<thead>
<tr>
<th>Rare Diseases</th>
<th>mRNA-3927</th>
<th>mRNA-3705</th>
<th>mRNA-3745</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<tbody>
<tr>
<td>PA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Earliest 2024</td>
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<tr>
<td>MMA</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Earliest 2024</td>
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<tr>
<td>GSD1a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TBD</td>
</tr>
</tbody>
</table>
Commercial preparedness summary

We have the **global scale** to compete in the COVID endemic market

Preparing for **multiple vaccine** launches between 2023-2026

Respiratory vaccines markets are **large, multi-billion-dollar opportunities** and combination vaccines provide **competitive advantages**

Latent virus vaccines have different market dynamics and **CMV offers a >$2 billion market opportunity**

**mRNA therapeutics in rare diseases can move quickly** given regulatory pathway and motivated population
Conclusion

Stéphane Bancel
CEO
### Never been as optimistic

**Last 10 years**

- We believed mRNA might work
- Capital constrained

**2022**

- We know mRNA can work safely
- Unique balance sheet for a 10-year-old biotech (~$18B)
The next 2-3 quarters are going to be really interesting

Select catalysts

- **PA & GSD1a** showing encouraging data
  - Could see a pivotal study in PA start in 2023 (MDEs)
  - De-risks our rare liver disease programs

- **PCV** Phase 2 data in 4Q22

- **Flu** Phase 3 data in 1Q23

- **RSV** Phase 3 data could readout this winter
Moderna has been built to create a lot of optionality

- Flu Phase 3
- RSV Phase 3
- PCV Phase 2
- PA enabling the rare disease portfolio
- CF (can we deliver mRNA into the lung)
- More vaccines (coming from the Moderna Infectious Disease lab)
- Gene editing
- Expansion of the Moderna mRNA platform to enable new families of drugs
Thank you Collaborators, investigators and patients and their families...!
Our mission
To deliver on the promise of mRNA science to create a new generation of transformative medicines for patients.