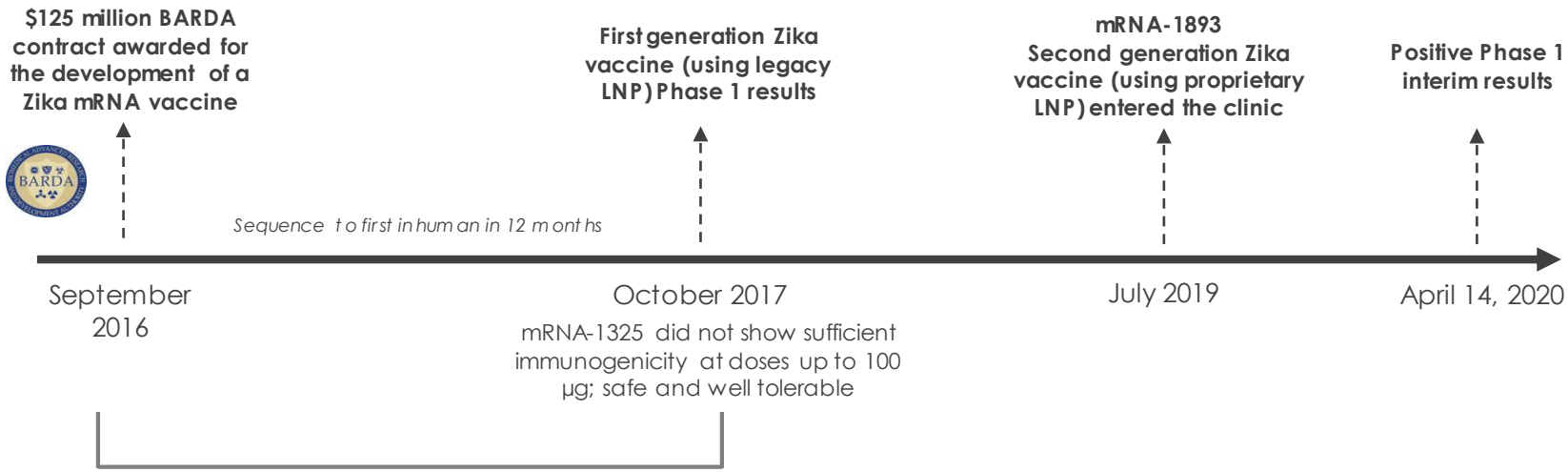
moderna

Zika vaccine (mRNA-1893)

Last program update: May 7, 2020

Modality	ID #	Program	Preclinical development	Phase 1	Phase 2	Phase 3 and commercial	Moderna rights
Prophylactic vaccines	mRNA-1273	Novel coronavirus (SARS-CoV-2) vaccine					Worldwide *BARDA funded*
	mRNA-1647	Cytomegalovirus (CMV) vaccine					Worldwide
	mRNA-1653	hMPV/PIV3 vaccine		Phase 1 (healthy volunteers)	Phase 1b (Age de-escalation) Seropositives		Worldwide
	mRNA-1172/ Merck V172	Respiratory syncytial virus (RSV) vaccine					Merck to pay milestones and royalties
	mRNA-1777	Respiratory syncytial virus (RSV) vaccine					
	mRNA-1893	Zika vaccine					Worldwide *BARDA funded*
	mRNA-1345	Pediatric respiratory syncytial virus (RSV) vaccine *Future respiratory combo*					Worldwide
	mRNA-1189	Epstein-Barr virus (EBV) vaccine					Worldwide
	mRNA-1851	Influenza H7N9 vaccine					Worldwide *Advancing subject to funding*

Zika virus development history



Cell

Vaccine Mediated Protection Against Zika Virus-Induced Congenital Disease

This project has been funded in whole or in part with Federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; Biomedical Advanced Research and Development Authority, under Contract No. HHSO100201600029C.

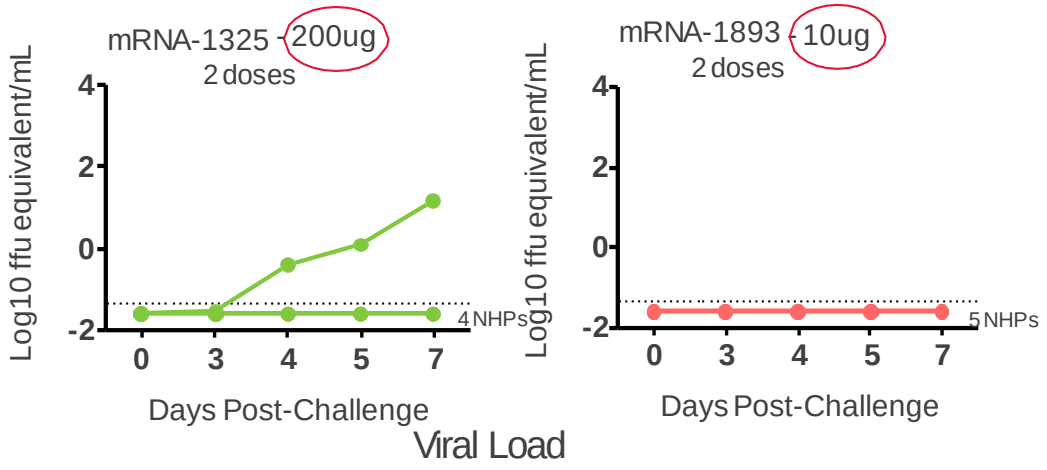
Zika vaccine (mRNA-1893)

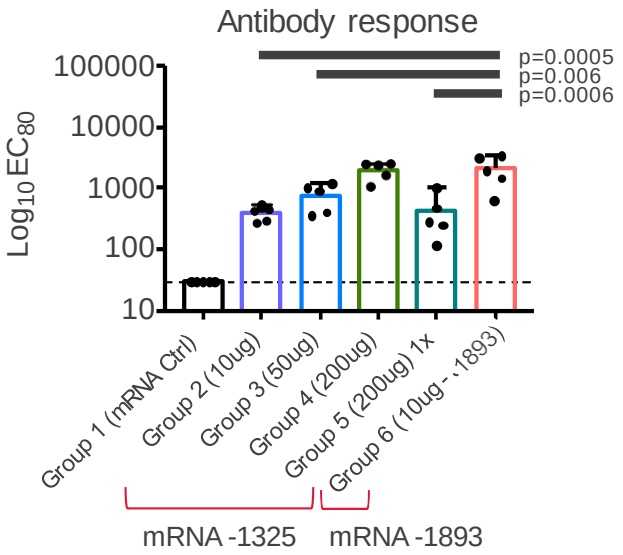
Preclinical data

- In 2016, we progressed mRNA-1325 into Phase 1 studies with BARDA funding, in response to the Zika outbreak. In parallel, we continued research on Zika and identified a backup candidate, mRNA-1893
- At three doses up to 100 µg, mRNA-1325 generated safety data that would permit additional dose escalation, but we did not yet observe desired immune response at those doses
- mRNA-1893, with a different mRNA sequence, shows greater efficacy at 1/20th the dose

Species: **NHP**

mRNA-1893 sequence provided complete protection and robust immune response at 20x lower dose than mRNA-1325



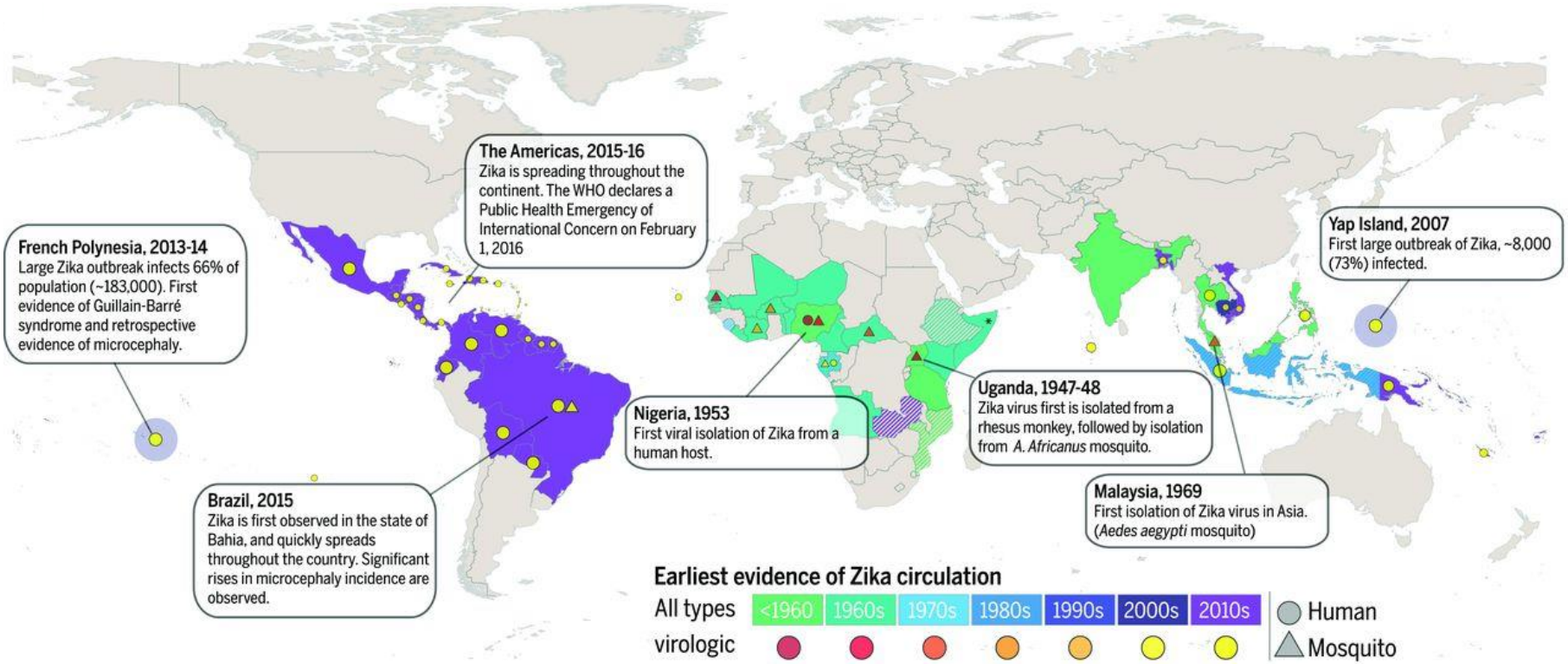


Clinical data and regulatory update

- Phase 1 study with mRNA-1893 fully enrolled
- mRNA-1893 received FDA Fast Track Designation

Last updated: May 7, 2020

Zika is an arbovirus and member of the Flaviviridae family



Assessing the global threat from Zika virus. Science. 12 Aug 2016: Vol. 353, Issue 6300

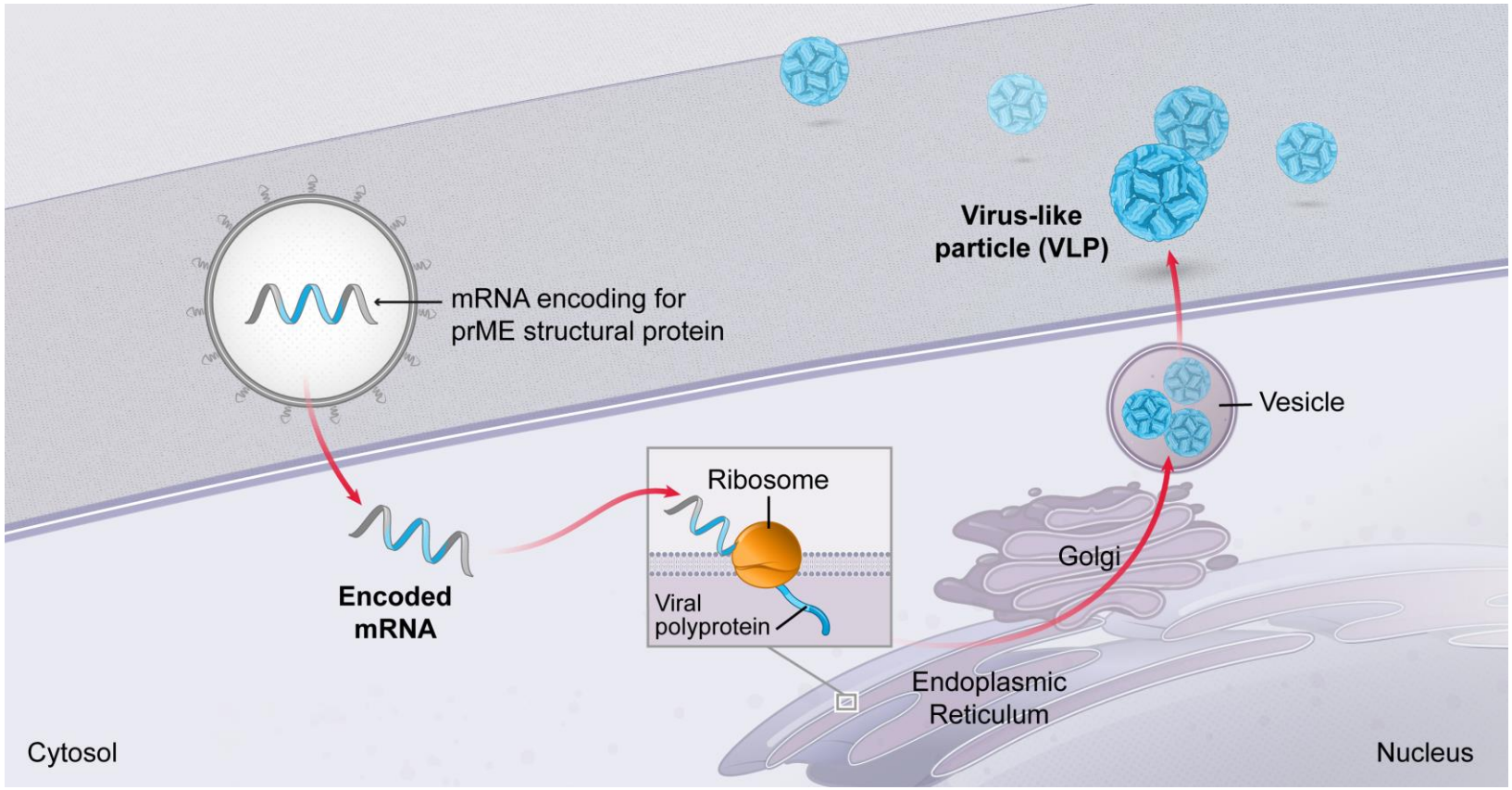
Zika virus overview

- Zika virus (ZIKV): The primary source of ZIKV infection in humans is from bites of infected mosquitoes
  - There have also been cases of sexual, perinatal, and suspected blood-transfusion transmission
- In 2015 and 2016, large outbreaks of Zika virus occurred in the Americas
  - Travel-associated cases in US states, widespread transmission in Puerto Rico and the US Virgin Islands, and limited local transmission in Florida and Texas
- **Disease burden:** Zika can be passed from a pregnant woman to her fetus
  - Increased risk of Guillain-Barré syndrome
  - Microcephaly was the first fetal abnormality to be recognized
  - Increasing evidence that ZIKV may be responsible for other fetal sequelae, such as intracranial calcifications, ventriculomegaly, ocular impairment, brainstem, hypoplasia, intrauterine growth restriction (IUGR), and fetal demise
- **Unmet need:** No approved Zika vaccine

Zika infection sequelae	
Neonatal period	Microcephaly Other severe brain defects
Infancy, childhood, adulthood	Fever Rash Headache Joint pain Red eyes Muscle pain

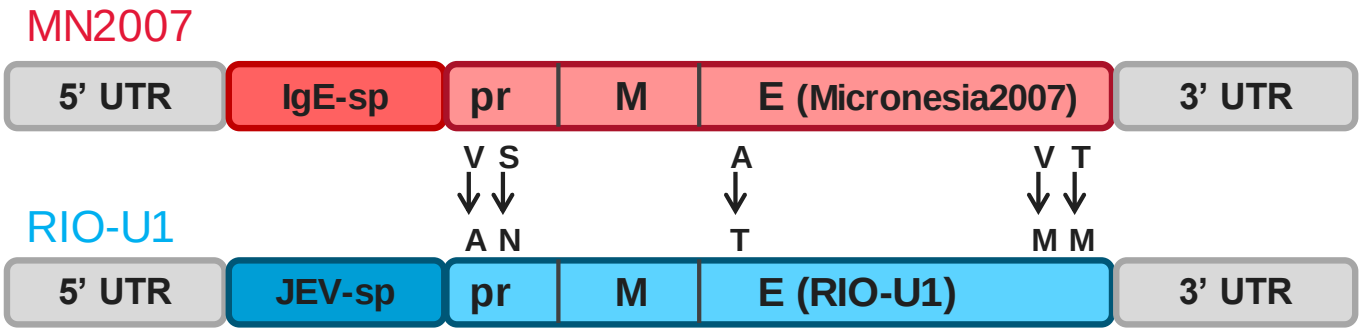
Zika vaccine (mRNA-1893)

Expression of prME can give rise to non-infectious, virus-like particles



Signal peptide and amino acid difference in the pRME ORF

Between the mRNA-1325 (MN2007) and mRNA-1893 (RIO-U1) mRNA constructs



- Rio strain sequence was not available at the time of initial sequence selection
- Once additional sequences became available, the RIO-U1 strain was used for **RIO-U1** mRNA as it reflected the most current circulating strain
- Five amino acid differences in the pr and E sequences between **MN2007** and **RIO-U1**
- JEV-sp was selected for **RIO-U1** based upon the potential for improved processing of flavivirus VLPs[1]

1. Zhang *et al. Nature* 2016. A CRISPR screen defines a signal peptide processing pathway required by flaviviruses.

Zika vaccine (mRNA-1893)

Phase 1 trial design – 4 dose levels tested: 10, 30, 100 and 250 µg

Key objective:

- To assess safety, reactogenicity, and immunogenicity of several dose levels of mRNA-1893 given with a 2-dose regimen at 28-day interval

Primary endpoint: Safety

Secondary endpoints:

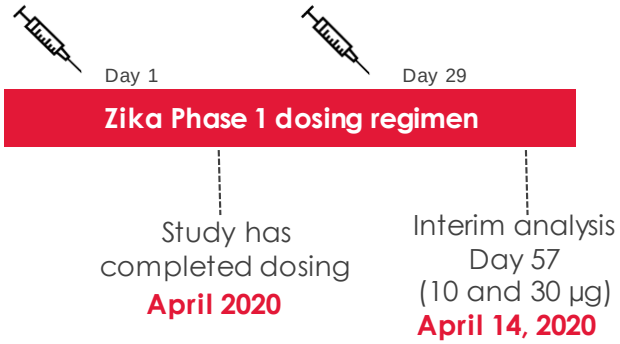
- ZIKV-specific neutralizing antibodies as measured by Plaque Reduction Neutralization Test (PRNT50) at D29, D57, 7 months and 13 months post-last vaccine administration

Exploratory endpoints:

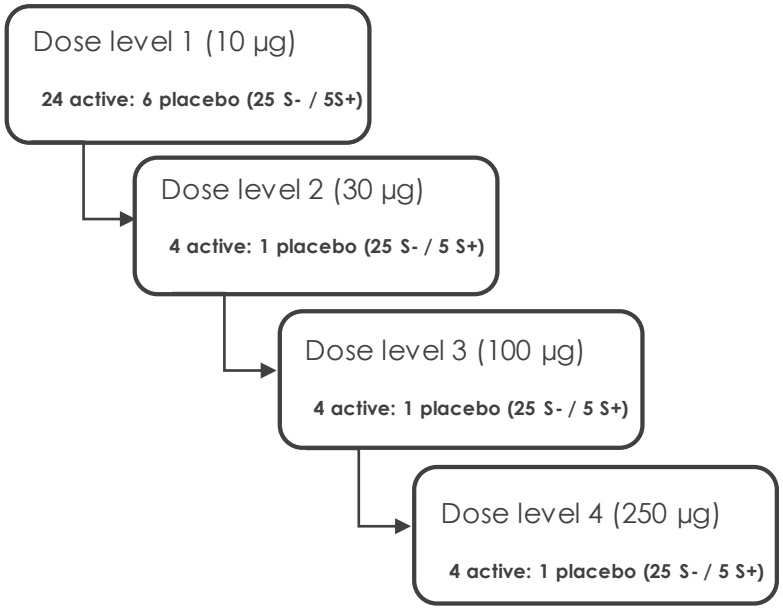
- ZIKV-specific neutralizing antibodies as measured by Microneutralization (MN), Reporter Virus Particle neutralization (RVP) at D29, D57, 7 Months and 13 Months

Trial progress:

- Study has completed dosing
- **Interim analysis Day 57 10µg and 30µg – April 14th, 2020**



mRNA-1893-P101 Study Design



Zika vaccine (mRNA-1893) Phase 1 interim analysis

Safety profile (10 and 30 µg cohorts)

	Solicited ARs post-Dose 1 (solicited safety set)			Solicited ARs post-Dose 2 (solicited safety set)			
	Placebo N=12 N(%)	10µg N=24 N(%)	30µg N=24 N(%)		Placebo N=12 N(%)	10µg N=23 N(%)	30µg N=23 N(%)
Local reactions							
Pain	1/12 (8.3%) –	12/24 (50%) –	12/23 (52.2%) –	**Pain**	1 /12 (8.3%) –	8/23 (34.8%) –	11/22 (50%) –
Redness	–	–	–	**Redness**	–	–	1/20 (5) –
Swelling	–	–	–	**Swelling**	–	–	2/20 (10) –
Systemic reactions							
Fever	–	1/24 (4.2) –	–	**Fever**	–	1/23 (4.3) –	3/22 (13.6) –
Headache	3/12 (25) –	7/24 (29.2) –	5/23 (21.7) –	**Headache**	3/12 (25) –	5/23 (21.7) –	8/22 (36.4) –
Fatigue	2/12 (16.7) –	8/24 (33.3) –	5/23 (21.7) –	**Fatigue**	1/12 (8.3) –	6/23 (26.1) –	10/22 (45.5) –
Myalgia	1/12 (8.3) –	5/24 (20.8) –	3/23 (13) –	**Myalgia**	1/12 (8.3) –	7/23 (30.4) –	4/22 (18.2) –
Arthalgia	–	2/24 (8.3) –	2/23 (8.7) –	**Arthalgia**	2/12 (16.7) –	4/23 (17.4) –	4/22 (18.2) –
Nausea	–	4/24 (16.7) –	2/23 (8.7) –	**Nausea**	1/12 (8.3) –	2/23 (8.7) –	1/22 (4.5) –
Chills	–	1/24 (4.2) –	–	**Chills**	2/12 (16.7) –	1/23 (4.3) –	5/22 (22.7) –
Rash	–	1/24 (4.2) –	–	**Rash**	–	–	–

- Both 10 and 30 µg dose levels were generally well tolerated
- No grade 3 adverse reactions (ARs) were reported
- No serious adverse events (SAEs) related to mRNA-1893 were reported at either dose levels

N: number of participants in solicited safety set. The denominator of the rate is the number of participants who submitted any data for the respective event

One subject experienced a situational anxiety and depression event, and was hospitalized in a mental health center. This was reported as 2 SAEs and was unrelated to the vaccine administration. One participant experienced a Grade 4 Prothrombin Test increase at Day 29 with no clinical manifestations, this was considered not related to mRNA-1893 administration

Last updated: May 7, 2020

Zika vaccine (mRNA-1893) Phase 1 interim analysis

Immunogenicity in flavivirus baseline seronegative participants

Immunogenicity in Flavivirus Baseline Seronegative Participants (Per-Protocol Set)			
	$PRNT_{50}$		
	Placebo	10µg	30µg
Baseline	8.0	9.5	8.0
GMT post-dose 1	8.0	8.5	14.0
GMT post-dose 2	8.0	195.6	303.4
Seroconversion rate Post-dose 1; Post-dose 2	0%; 0%	5%; 94.4%	40%; 100%
	MN		
	Placebo	10µg	30µg
Baseline	14.0	14.0	14.0
GMT post-dose 1	14.0	58.9	129.7
GMT post-dose 2	14.0	1,195.3	1,478.0
Seroconversion rate Post-dose 1; Post-dose 2	0%; 0%	75%; 100%	85%; 100%

Reporter Virus Particle neutralization (RVP) data are pending
Seroconversion is defined as a change in $PRNT_{50}$ from below the lower limit of quantification to a $PRNT_{50}$ equal to or above LLOQ, or a multiplication by at least 4 in subjects with pre-existing $PRNT_{50}$ titers; Seroconversion is defined as a change in MN from below the lower limit of quantification to a MN equal to or above LLOQ, or a multiplication by at least 4 in subjects with pre-existing MN titers.

Zika vaccine (mRNA-1893) Phase 1 interim analysis

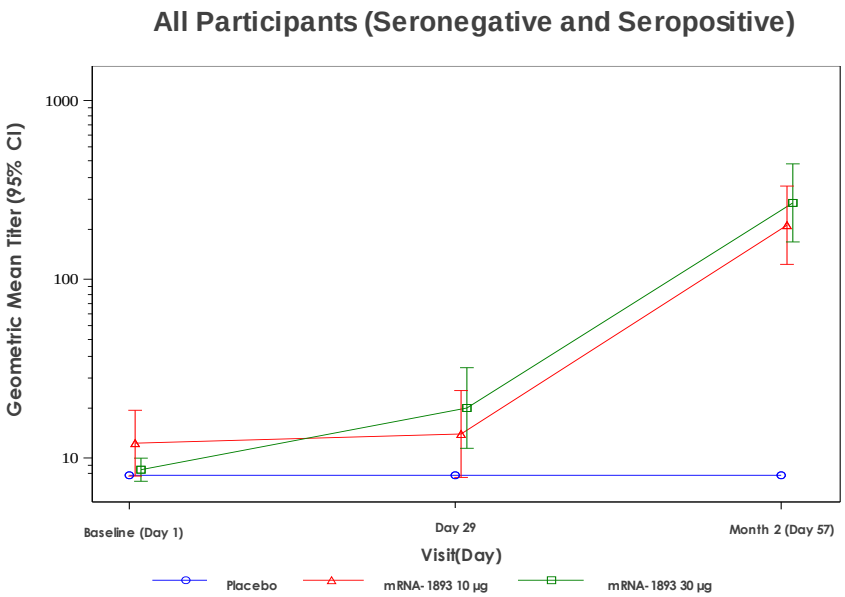
Immunogenicity in flavivirus baseline seropositive participants

Immunogenicity in Flavivirus Baseline Seropositive Participants (Per-Protocol set)			
	$PRNT_{50}$		
	Placebo	10µg	30µg
Baseline	8.0	41.5	12.3
GMT post-dose 1	8.0	147.9	88.1
GMT post-dose 2	8.0	224.1	150.9
Seroconversion rate Post-dose 1; Post-dose 2	0%; 0%	50%; 50%	75%; 75%
	MN		
	Placebo	10µg	30µg
Baseline	14.0	54.0	39.4
GMT post-dose 1	14.0	375.0	226.7
GMT post-dose 2	14.0	645.9	578.5
Seroconversion rate Post-dose 1; Post-dose 2	0%; 0%	100%; 75%	75%; 75%

Seroconversion is defined as a change in $PRNT_{50}$ from below the lower limit of quantification to a $PRNT_{50}$ equal to or above LLOQ, or a multiplication by at least 4 in subjects with pre-existing $PRNT_{50}$ titers; Seroconversion is defined as a change in MN from below the lower limit of quantification to a MN equal to or above LLOQ, or a multiplication by at least 4 in subjects with pre-existing MN titers.

Zika vaccine (mRNA-1893) Phase 1 interim analysis

Immunogenicity ($PRNT_{50}$) at Day 57 – all participants (per-protocol set)

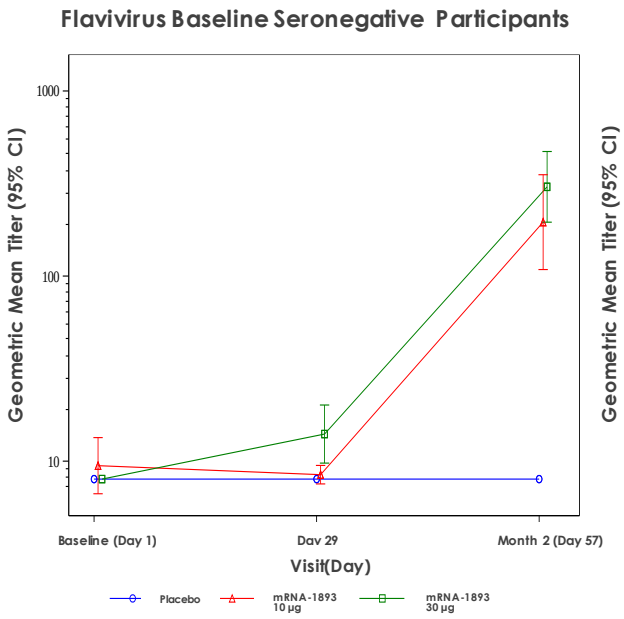


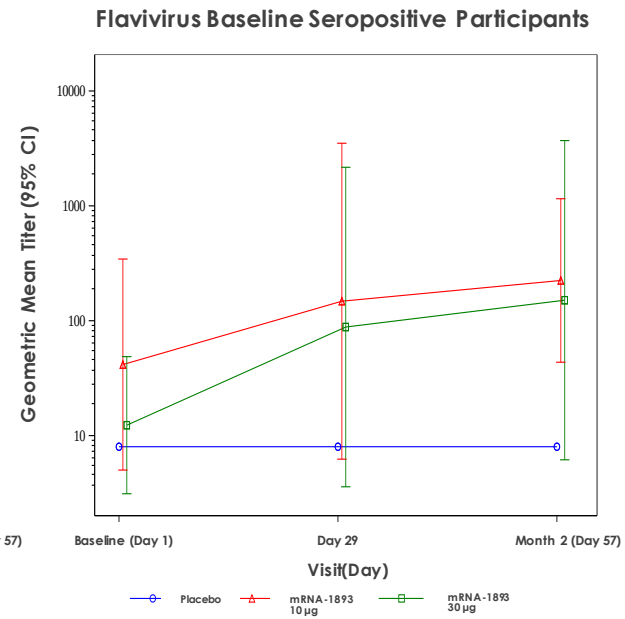
- Both 10 µg and 30 µg dose levels induce a strong ZIKV-specific neutralizing antibody response
- There is a clear benefit of a two-dose series given at 28-day interval

Last updated: May 7, 2020

Zika vaccine (mRNA-1893) Phase 1 interim analysis

Immunogenicity ($PRNT_{50}$) at Day 57 by baseline flavivirus serostatus (per-protocol set)



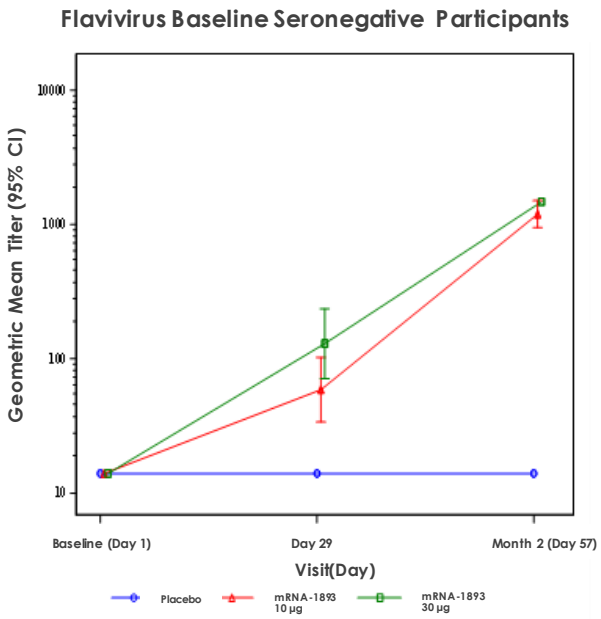


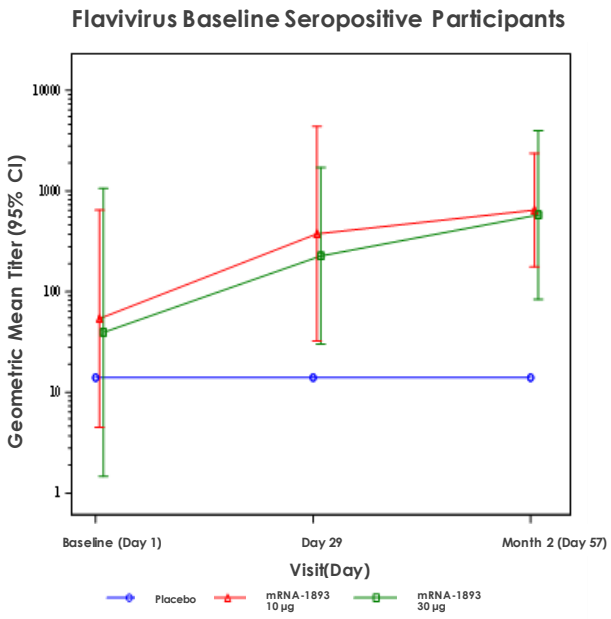
- In seronegative participants, there was a clear advantage of a second vaccine administration in terms of ZIKV-specific neutralizing antibody response
- In seronegative participants, a dose response observed after first vaccine administration
- In seropositive participants, mRNA-1893 was able to mount a ZIKV-specific neutralizing antibody response; compatible with a specific booster response

Last updated: May 7, 2020

Zika vaccine (mRNA-1893) Phase 1 interim analysis

Immunogenicity (MN) at Day 57 by baseline flavivirus serostatus (per-protocol set)





- MN data are consistent with the $PRNT_{50}$ data
- MN titers are higher compared to those reported by $PRNT_{50}$; consistent with the known differences between the assays

Last updated: May 7, 2020

Zika vaccine (mRNA-1893) Phase 1 interim analysis

Immunogenicity at Day 57 – conclusions

- The 10 µg and 30 µg dose levels induce a strong neutralizing ZIKV-specific antibody response in both flavivirus infection naive participants and in participants with pre-existing flavivirus antibodies as shown by the GMTs and the seroconversion rates
- Notably, the 30 µg dose level is sufficient to seroconvert baseline flavivirus seronegative subjects following only a single vaccine administration
- Both MN and $PRNT_{50}$ assays provide equivalent guidance for data interpretation in terms of ZIKV-specific neutralizing immune response

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