A case study: mRNA-1273-P301

A phase-3 randomized trial of the mRNA-1273 SARS-Cov-2 vaccine in adults 18 years and older

Background
Infection with SARS-COV-2 virus

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV).

An outbreak of the CoV disease (COVID-19) caused by SARS-CoV-2 began in Wuhan, Hubei Province, China in December 2019 and has spread throughout China in 2019.

Global efforts to evaluate novel antivirals and therapeutic strategies to treat severe SARS-CoV-2 infections have intensified, but no proven therapeutic currently exists.

There is an urgent public health need for rapid development of novel interventions to prevent the spread of this disease.

mRNA vaccines*

mRNA vaccines are a new type of vaccine to protect against infectious diseases. mRNA vaccines give instructions to our cells to make a harmless piece of what is called the spike protein found on the surface of the virus that causes COVID-19.

After the protein piece is made, the cell breaks down the instructions and gets rid of them.

Next, the cell displays the protein piece on its surface. Our immune systems recognizes that the protein doesnt belong in our body and begin building an immune response and making antibodies against COVID-19.

At the end of the process, our bodies have learned how to protect against future infection.

*This is from Understanding mRNA COVID-19 Vaccines from the US CDC.

Rationale for the study

The development of the mRNA-1273 vaccine is being accelerated to address the current SARS-CoV-2 outbreak as a result of the uniquely rapid and scalable manufacturing process for mRNA-1273.

The primary goal of this Phase 3 study is to evaluate the vaccine efficacy (VE) of mRNA-1273 to prevent COVID-19, compared to placebo.

The mRNA-1273-P301 trial schema: Events

Moderna Inc. performed this study in order to establish the effectiveness of its mRNA vaccine. The schema of the study (in terms of events) is as follows:

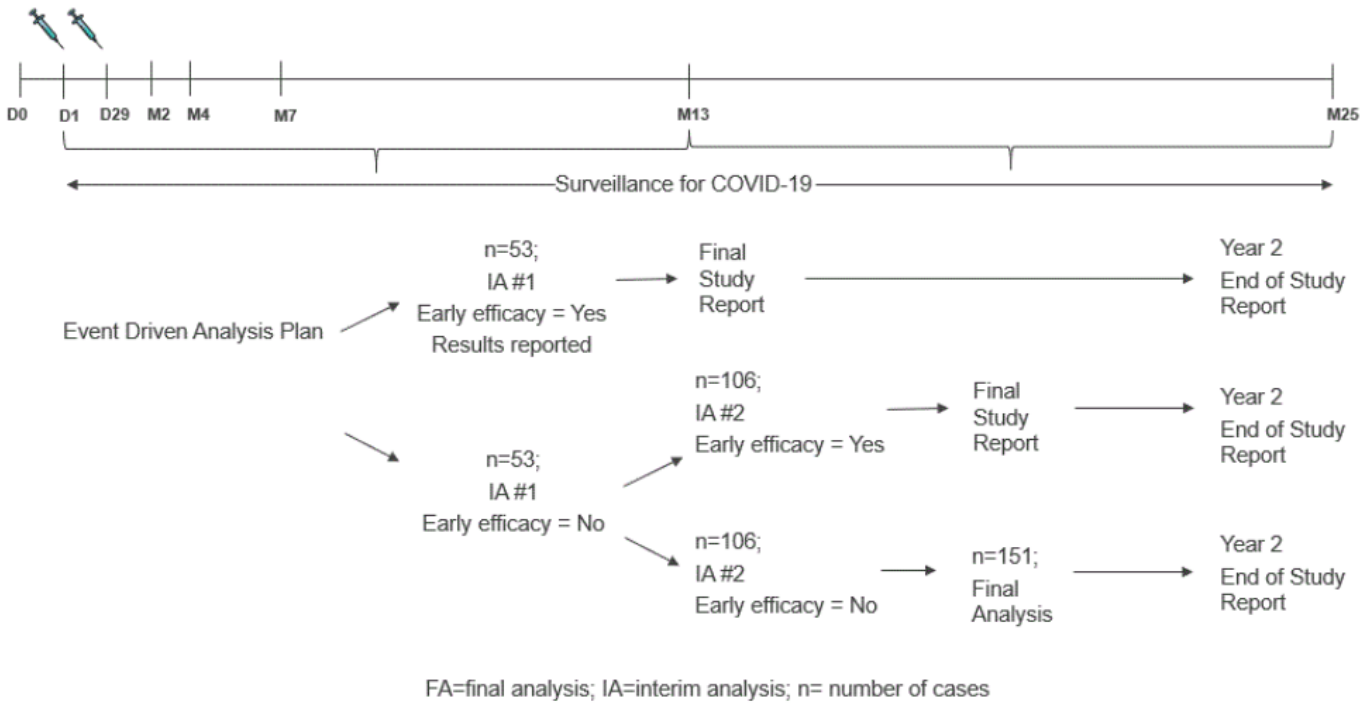

Figure 1: The Moderna study protocol schema in terms of numbers of observed events

The mRNA-1273-P301 trial schema: Patients

In terms of patients, the protocol schema looks as follows:

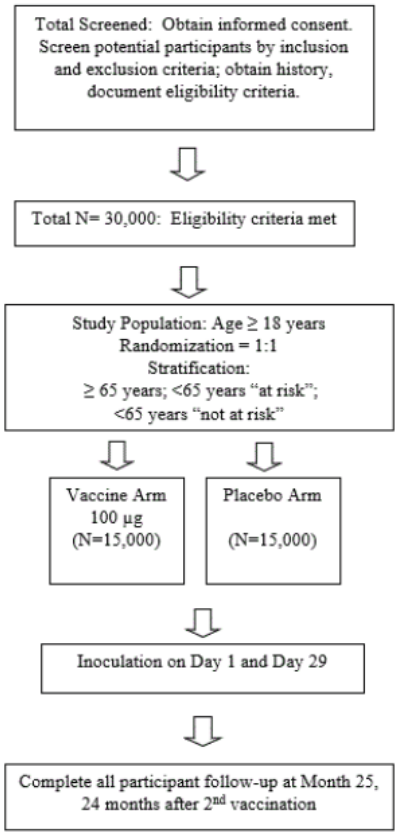

Figure 2: The Moderna study protocol schema in terms of patients enrolled

Primary study objectives

1. The Efficacy primary objective of this study is to assess vaccine efficacy (VE) of mRNA-1273 to prevent the first occurrence of COVID-19 starting 14 days after the second dose of the vaccine. This means
2. The Safety primary objective of this study is to evaluate the safety and reactogenicity* of 2 injections of the mRNA-1273 vaccine given 28 days apart.

*Basically this means any adverse event attributed to the vaccine.

Eligibility criteria

Inclusion criteria are as follows:

1. Adults, $\geq$ 18 years of age at high risk of SARS-CoV-2 infection*
2. Understands and agrees to comply with the study procedures and provides written informed consent.
3. Able to comply with study procedures based on the assessment of the Investigator.

*Adults whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.

Eligibility criteria: Women of childbearing age

Inclusion criteria are as follows:

1. Female participants of nonchildbearing potential may be enrolled in the study.
2. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
   - Has a negative pregnancy test at screening and on the day of the first dose (Day 1).
   - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first dose (Day 1).
   - Has agreed to continue adequate contraception through 3 months following the second dose (Day 29).
   - Is not currently breastfeeding.
   - Adequate female contraception is defined as consistent and correct use of an FDA-approved contraceptive method in accordance with the product label.

Additional eligibility criteria

Additional criteria include:

1. Inclusion criterion regarding male contraception was removed by Amendment 2 of the protocol
2. Healthy adults or adults with pre-existing medical conditions who are in stable condition*.

*A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment.

Exclusion criteria

Participants are excluded from the study if:

1. Is acutely ill or febrile 72 hours prior to or at Screening. Fever is defined as a body temperature $\geq 38.0^{\circ}C/100.4^{\circ}F$.
2. Is pregnant or breastfeeding.
3. Has known history of SARS-CoV-2 infection.
4. Prior investigational coronavirus (SARS-CoV, MERS-CoV) vaccine or simultaneous participation in another interventional study to prevent or treat COVID-19.
5. Demonstrated inability to comply with the study procedures.
6. An immediate family or household member of study personnel.
7. Known or suspected allergy or other significant adverse reaction to the vaccine or its excipients.

Exclusion criteria (cont'd)

8. Bleeding disorder considered a contraindication to intramuscular injection or phlebotomy.
9. Has received or plans to receive a non-study vaccine within 28 days prior to or after any dose of the vaccine
10. Has participated in an interventional clinical study within 28 days prior to the day of enrollment.
11. Immunosuppressive or immunodeficient state, asplenia, recurrent severe infections (HIV-positive participants with CD4 count $geq350$ cells/mm^3 and on stable antiretroviral therapy are permitted]).
12. Has received systemic immunosuppressants or immune-modifying drugs for >14 days within 6 months
13. Has received systemic immunoglobulins or blood products within 3 months prior to screening.
14. Has donated $\geq$ 450 mL of blood products within 28 days prior to screening.

Study treatment

Treatment groups	Investigational product	Age (years)	Total number of participants*
mRNA-1273	mRNA-1273 100 μg	≥ 18	15,000
Placebo	Placebo	≥ 18	15,000
Total			30,000

Table 1: Study treatment and cohorts involved

*See below.

Delay or discontinuation of study treatment

Criteria for delay of study treatment include the following:

1. Acute moderate or severe infection with or without fever at the time of dosing
2. Fever, defined as body temperature $\geq 38.0^{\circ}C (100.4^{\circ}F)$ at the time of dosing

   Participants with a minor illness without fever, as assessed by the investigator, can be administered vaccine.

Discontinuation of study treatment

The investigator, in consultation with the Sponsors medical monitor, may withhold a participant from further dosing if the participant experiences any of the following:

1. Becomes pregnant
2. Develops symptoms or conditions listed in the exclusion criteria
3. Experiences an AE (other than reactogenicity) after dosing that is considered by the investigator to be related to IP (Section 8.3.4) and is of Grade-3 (severe) or greater intensity
4. Experiences an AE or SAE that, requires study medication withdrawal
5. Experiences a clinically abnormal vital sign measurement or finding on physical examination that, in the judgment of the investigator, requires medication withdrawal

Participant withdrawal

Participants who withdraw from the study will not be replaced.

A withdrawal from the study refers to a situation wherein a participant does not return for the final visit planned in the protocol.

Participants will be considered lost to follow-up (LTFU) if they repeatedly fail to return for scheduled visits without stating an intention to withdraw consent and they cannot be contacted by the study site.

The statistical management of participant withdrawals is discussed in the Statistical Section.

Statistical considerations
Cohort definition

The following cohorts are defined for the study*:

- Randomization Set: All participants who are randomized
- Full Analysis Set (FAS): All randomized participants who received at least one dose.
- Modified Intent–to-Treat (mITT) Set: FAS participants with no immunologic or virologic evidence of prior COVID-19
- Per-protocol (PP) Set: All mITT participants who received planned doses per schedule and have no major protocol deviations
- Immunogenicity subset: All FAS participants with a valid immunogenicity test result prior to the first dose

We focus on the PP set.

*Here we gloss over design considerations which stratify the study by age and underlying risk factors.

Statistical considerations: *Sample size*

The study makes the following considerations, which affect the final sample size:

1. COVID-19 incidence is assumed to be 0.75% in six months in the placebo group
2. The null hypothesis of the study is that the vaccine has HR=0.7 (i.e., $H_0 : HR \geq 0.7^*$). The alternative hypothesis is that $H_a : HR \leq 0.3$
3. Alpha level is one-side 0.025 and power is 90%
4. It is further assumed that patients will enter uniformly over a 3-month period with a one year hazard of LTFU at 2%. It is also assumed that up to 15% will be unevaluable for the PP set.

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* Note that this is much different (and much more conservative) than the usual null hypothesis $H_0 : HR = 1$!

Sample size of the fixed study

We can estimate the number of events required for such a study as follows:

```
> nSurv(lambdaC = -log(1-.0075)/6, hr = 0.4, hr0 = 0.7, eta = -log(1-.02)/12, R=3, gamma = 25000/3, T = 10

Fixed design, two-arm trial with time-to-event
outcome (Lachin and Foulkes, 1986).
Solving for:  Follow-up duration
Hazard ratio                    H1/H0=0.4/0.7
Study duration:                     T=8.3208
Accrual duration:                          3
Min. end-of-study follow-up: minfup=5.3208
Expected events (total, H1):          148.3641

                                Some output excluded
```

Thus, $D = 149$ events are required patients will be enrolled in each group.

The study will last 8.5 months, which means 10 months after the first patient is randomized (it takes 29 days for the second dose and 14 days for patients to be considered *at risk* for COVID-19).

Introducing interim analyses

The study team also introduced a number of additional design considerations:

1. Interim analyses
   Two interim analyses (IAs) and one final analyses would be performed, at the $t = 0.35, 0.70$ and 1.0 study fraction
2. An O'Brien-Fleming one-sided bound was considered

Estimation of study parameters

The assumption of 0.75% six-month incidence in the placebo group is translated to λ_C, the *hazard* in the placebo group as follows:

$$0.075 = \int_0^6 \lambda_C e^{-\lambda_C t} dt \Rightarrow 0.075 = -e^{-\lambda_C t} \Big|_0^6 \Rightarrow 0.075 = 1 - e^{-6\lambda_C}$$

Solving, we get $\lambda_C = -\log(1 - 0.075)/6$. Similarly, the hazard for the vaccine group is $-\log(1 - 0.003)/6$.

Note that the hazard ratio is $HR = 0.4$ (since 0.3% is 60% lower than 0.75%).

By similar arguments, the hazard corresponding to a one-year LTFU rate of 2% is $\eta_C = \eta = -\log(1 - 0.02)/12$ (where the unit is month, so one year is 12 months).

Final study design

The study design is as follows:

```
> x<-gsSurv(k = 3, test.type = 1, timing = c(.35, .7, 1), sfu = sfLDOF,
            lambdaC = -log(1-.0075)/6, hr = 0.4, hr0 = 0.7,
            eta = -log(1-.02)/12, R=3, gamma = 25500/3)
> x

Time to event group sequential design with HR= 0.4
Non-inferiority design with null HR= 0.7
Equal randomization:          ratio=1
One-sided group sequential design with
90 % power and 2.5 % Type I Error.

  Analysis  N   Z   Nominal p  Spend
         1  53 3.61    0.0002 0.0002
         2 106 2.44    0.0073 0.0072
         3 151 2.00    0.0227 0.0176
     Total                   0.0250

++ alpha spending:
 Lan-DeMets O'Brien-Fleming approximation spending function with none = 1.

Boundary crossing probabilities and expected sample size
assume any cross stops the trial
```

More output

```
Upper boundary (power or Type I Error)
          Analysis
   Theta      1      2      3 Total  E{N}
  0.0000 0.0002 0.0072 0.0176 0.025 150.1
  0.2661 0.0463 0.5683 0.2854 0.900 120.3
             T     n    Events HR efficacy
IA 1  3.859605 25500  52.65496       0.259
IA 2  6.233435 25500 105.30997       0.435
Final 8.280428 25500 150.44279       0.505
Accrual rates:
    Stratum 1
0-3      8500
Control event rates (H1):
      Stratum 1
0-Inf         0
Censoring rates:
      Stratum 1
0-Inf         0
```

As written in the protocol, three interim analyses will occur after 53, 106 and 151 cases have occurred.

These are expected to occur 3.5, 6.5 and 8.5 months after 14 days following the second dose or after 5, 8 and 10 months from the first randomized patient.

O-B Bounds

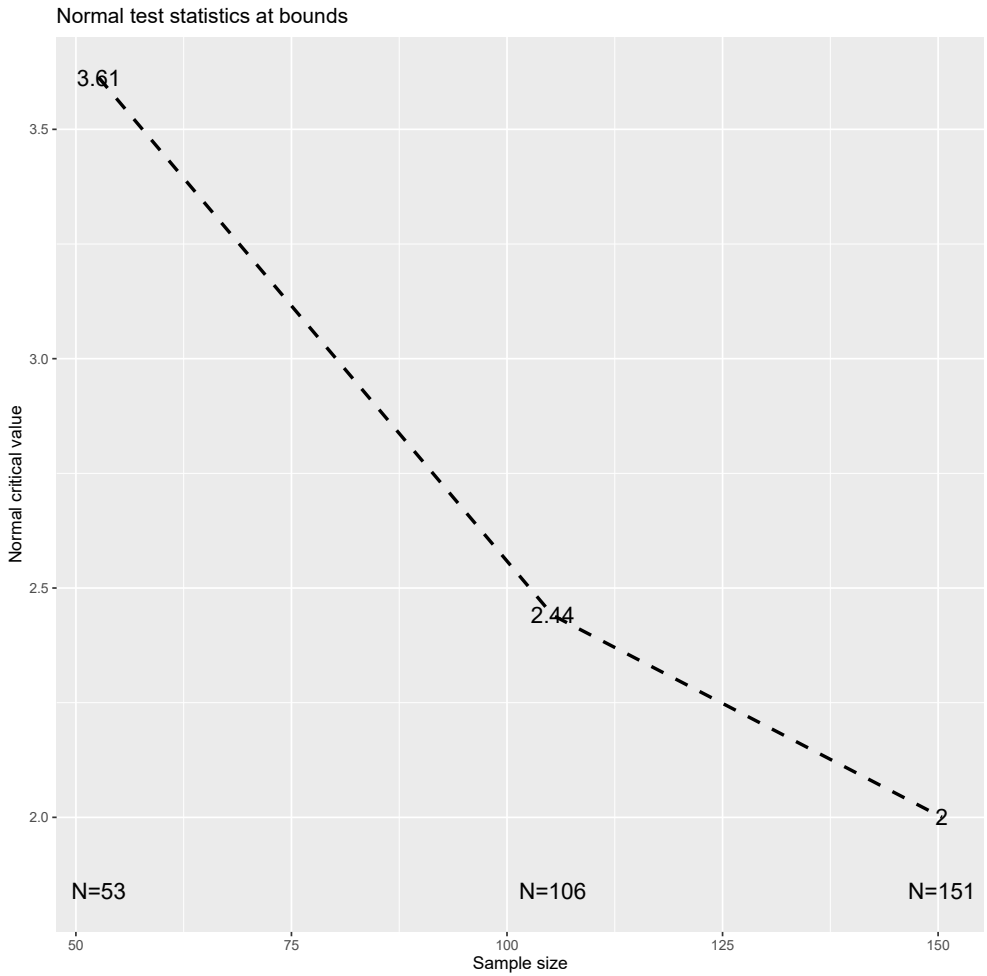

Figure 3: O'Brien-Fleming bounds in the Moderna study

Results: *CONSORT statement*

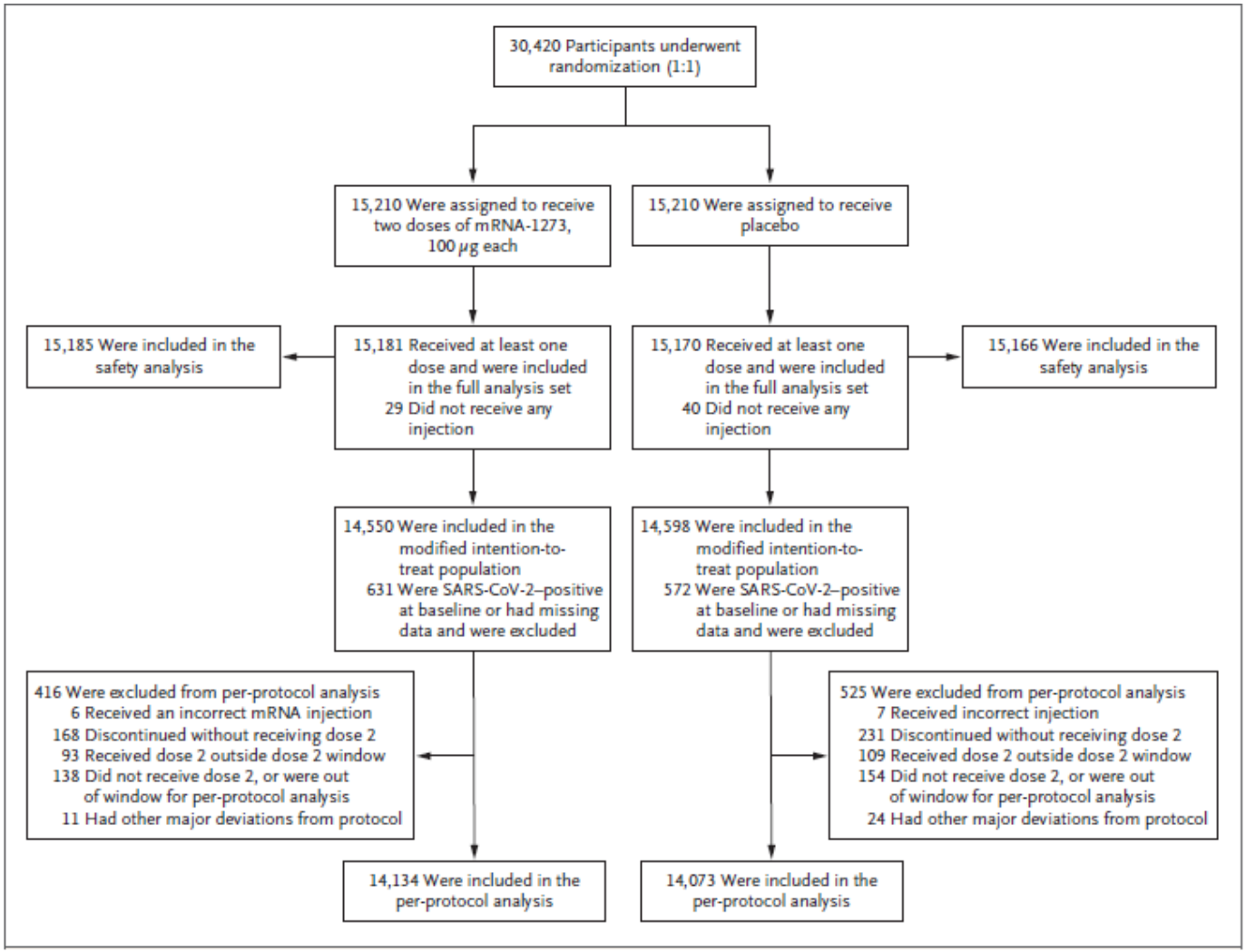

Figure 4: Moderna trial CONSORT statement

Study history

Between July 27, 2020, and October 23, 2020, a total of 30,420 participants underwent randomization at 99 centers, and 15,210 participants in each group were assigned to receive two doses of either placebo or mRNA-1273 (100 μg)

The first interim analysis was conducted on data up to November 25, 2020. By that time, participants had a median follow-up duration of 63 days (range, 0 to 97) after the second dose.

Efficacy

The first interim analyis (IA1) was based on a total of 95 cases (62.9% information of the target total number of 151 events).

The Lan-DeMets OBrien-Fleming approximation for the O'Brien-Fleming bound is

$$f(t;\alpha) = 2 - 2\Phi(Z_{1-\alpha/2}/\sqrt{t})$$

```
> sfLDOF(0.025, 95/151)$spend
[1] 0.004715777
```

This means that the p-value boundary at IA1 was $p = 0.0047$.

Results from IA1

At IA1 there were 90 cases in the placebo group and 5 cases in the vaccine group

$$VE = \frac{R_u}{R_u + R_v} = \frac{90}{95} = 0.947$$

indicating $VE = 94.7\%$ efficacy.

The one-sided p-value was $p < 0.0001 < 0.0047$. Therefore, the pre-specified statistical criterion for study success was demonstrated at IA1.

Findings were similar across key secondary analyses.

Per protocol analysis

The following figure shows the PP analysis results, based on 196 cases, of which 11 were in the vaccine group (VE=94.1%).

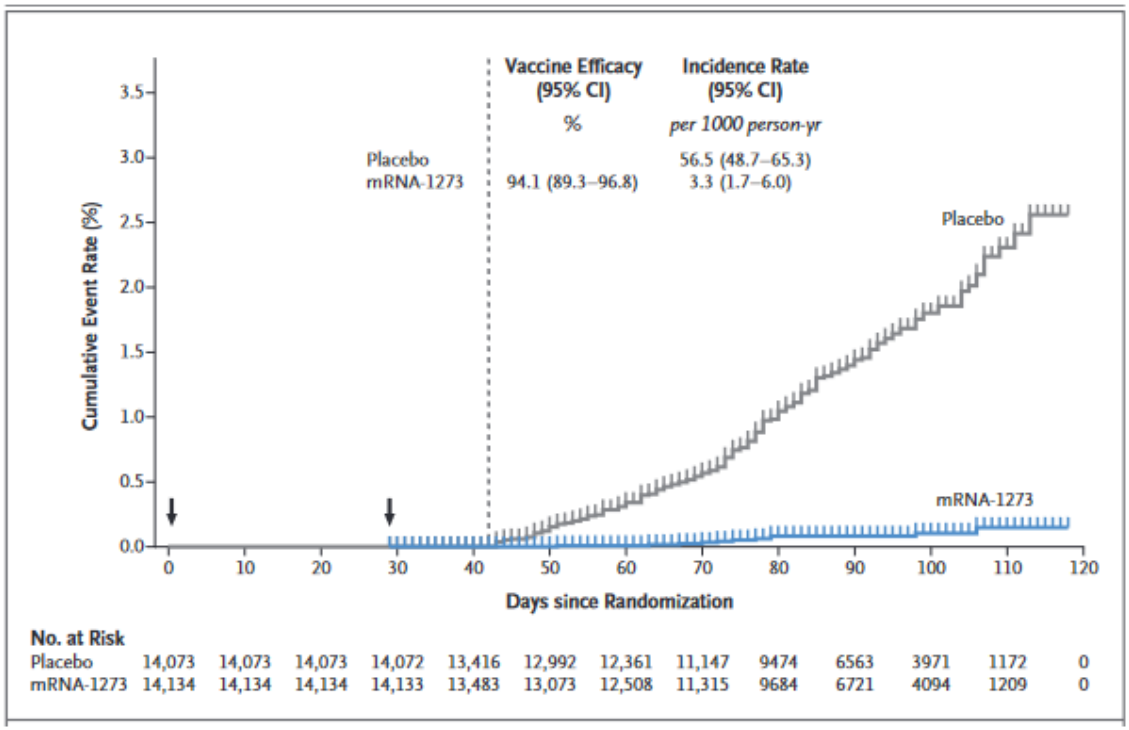

Figure 5: Per protocol analysis results (Fig. 3A in Baden et al., 2021)

Modified ITT analysis

The following figure shows the mITT analysis results, based on 269 cases, of which 19 were in the vaccine group (VE=92.9%).

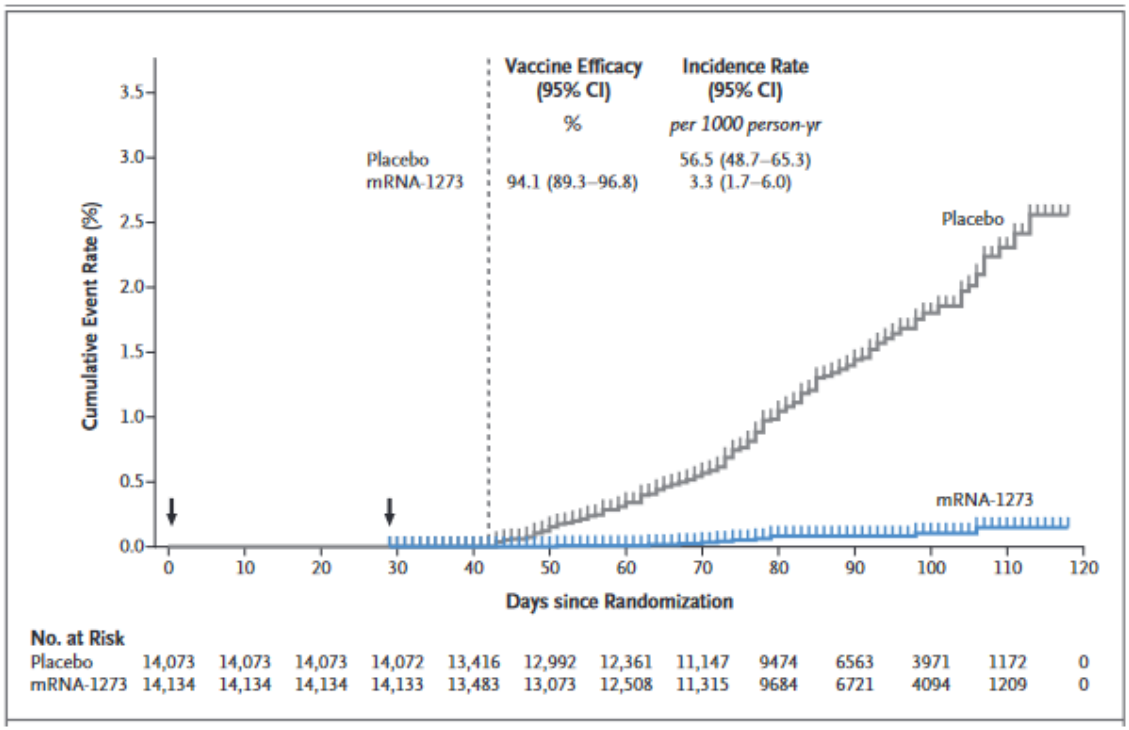

Figure 6: Per modified ITT analysis results (Fig. 3B in Baden et al., 2021)

Safety

The following figure shows safety summaries in the study.

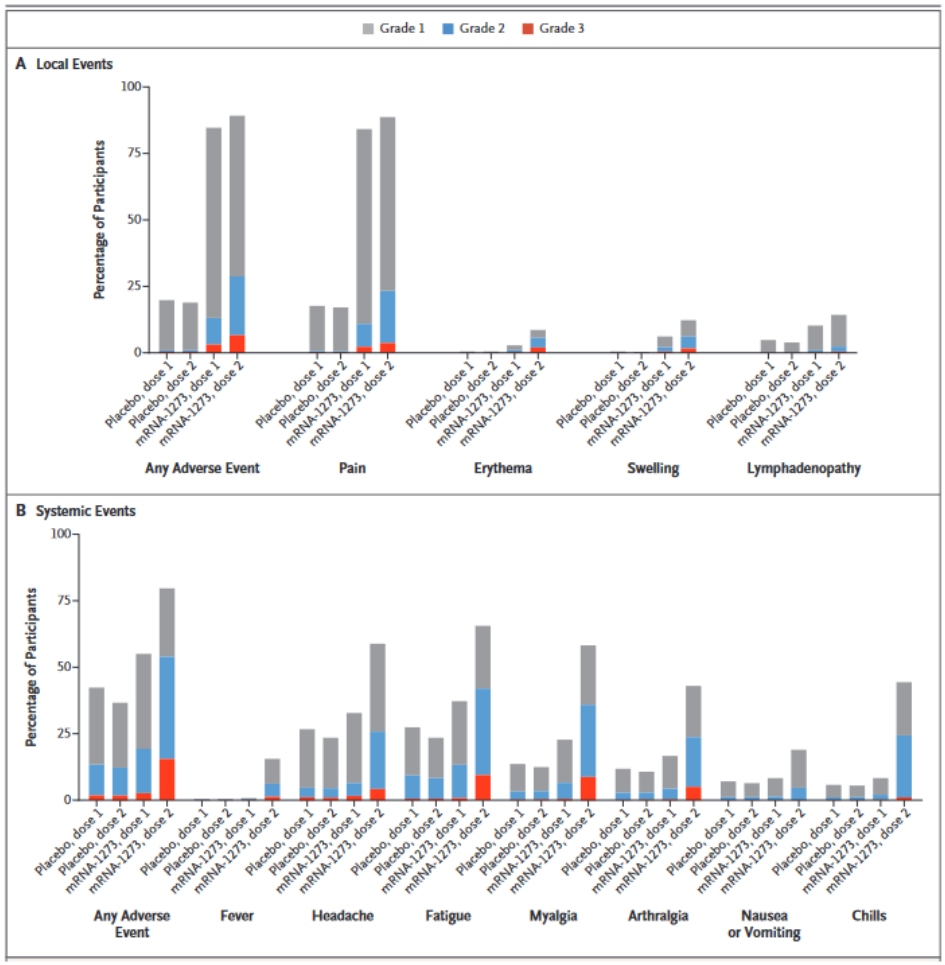

Figure 7: Safety of the mRNA-1273 vaccine (Fig. 2 in Baden et al., 2021)

Conclusions

The mRNA-1273 vaccine showed 94.1% efficacy at preventing Covid-19 illness, including severe disease.

Aside from transient local and systemic reactions, no safety concerns were identified.