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COVID-19 Vaccine Update and Plans to Generate Evidence Regarding Boosters

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COVID-19, coronavirus disease 2019.

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Final analysis of Phase 3 COVE Study demonstrates vaccine efficacy of 93%

- **COVE Study vaccine efficacy** (95% CI) by primary and secondary endpoints at final analysis[1]:
  - Against **COVID-19: 93.2%** (91.0-94.8)*
  - Against **severe COVID-19: 98.2%** (92.8-99.6)*
  - Against **death caused by COVID-19: 100%** (NE-100.0)

- Sub-group analyses are consistent across different populations

- Safety profile based on extended safety follow up is consistent with Phase 3 COVE study primary results and consistent across population sub-groups

(1) Analysis per protocol set, median follow-up of 5.3 months
* Based on Adjudication Committee assessments

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Phase 3 COVE Study: Vaccine efficacy is durable through six months[1]

First COVID-19 Occurrence[2]	VE (%) (95% CI)[3]
≥14 days after dose 2*	**93.1%** (90.9, 94.9)
≥14 days after dose 2 to <2 months after dose 2*	**91.8%** (86.9, 95.1)
≥ 2 months after dose 2 to <4 months after dose 2*	**94.0%** (91.2, 96.1)
≥4 months after dose 2**	**92.4%** (84.3, 96.8)

(1) Analysis per protocol set, median follow-up of 5.3 months
(2) COVID-19 cases based on adjudication committee assessments; 1 month = 28 days
(3) VE and 95% confidence interval (CI) are based on the exact method conditional on the total number of cases adjusting for person-years using the Poisson distribution for the time period.
* Subjects who were not at risk (cases or censored at prior time period(s)) are excluded from the analysis of this time period
** To earliest of study discontinuation, PDV/unblinding, or data cutoff date of 3/26/2021, longest follow up to 241 days

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Emerging real-world evidence confirms efficacy against variants of concern

- Emerging real-world evidence is consistent with the **effectiveness seen with mRNA-1273 vaccination** (e.g., Canada[1], England[2], and Qatar[3])

- Emerging data also **confirms effectiveness against variants of concern (VOCs),** including Alpha, Beta/Gamma and Delta, even after partial vaccination[1]

1. Effectiveness of COVID-19 vaccines against variants of concern in Ontario, Canada, medRxiv
2. COVID-19 vaccine surveillance report, Public Health England
3. Protection afforded by the BNT162b2 and mRNA-1273 COVID-19 vaccines in fully vaccinated cohorts with and without prior infection, medRxiv

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Updated COVID-19 perspective and strategy for boosters

Our emerging perspective

- We believe that **increased force of infection resulting from Delta**, non-pharmaceutical intervention (NPI) fatigue, and seasonal effects (moving indoors) will lead to an increase of breakthrough infections in vaccinated individuals
- While we see durable Phase 3 efficacy through 6 months, we expect **neutralizing titers will continue to wane** and eventually impact vaccine efficacy
- Given this intersection, we believe **dose 3 booster** will likely be necessary prior to the winter season

Our booster strategy

Advance **a portfolio of booster candidates** in ongoing booster studies at 50 and 100 µg dose levels

I. **Prototype vaccine:** mRNA-1273

II. **Variant-specific booster candidates:** mRNA-1273.351 & mRNA-1273.617 (*new*)

III. **Multi-valent platform:** mRNA-1273.211 & mRNA-1273.213 (*new*)

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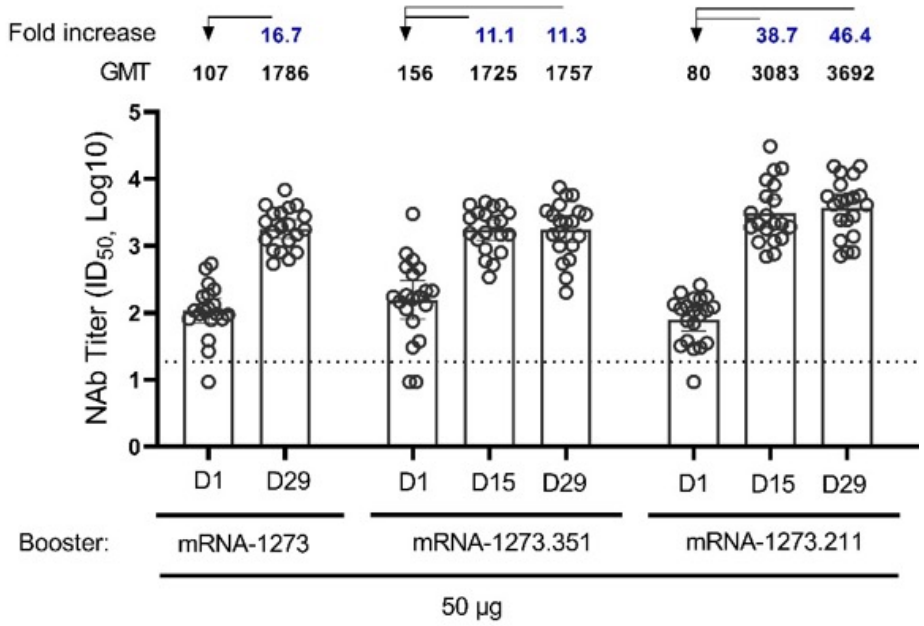
Clinical update: Comparison of booster candidates in P201

Validated clinical assays (NIH VRC)

Wild-type (D614G) Neutralization



The geometric mean neutralizing antibody titers with 95% confidence intervals are denoted. The titers for individual participants are shown by the circles. The fold increase versus titers measured at Days 15 and 29 versus titers measured before the boost are shown. The horizonal dotted lines indicate the lower limit of quantification. N=20 participants per booster cohort.
D, day, GMT, geometric mean titer; ID_{50}, 50% inhibitory dilution; NAb, neutralizing antibody.

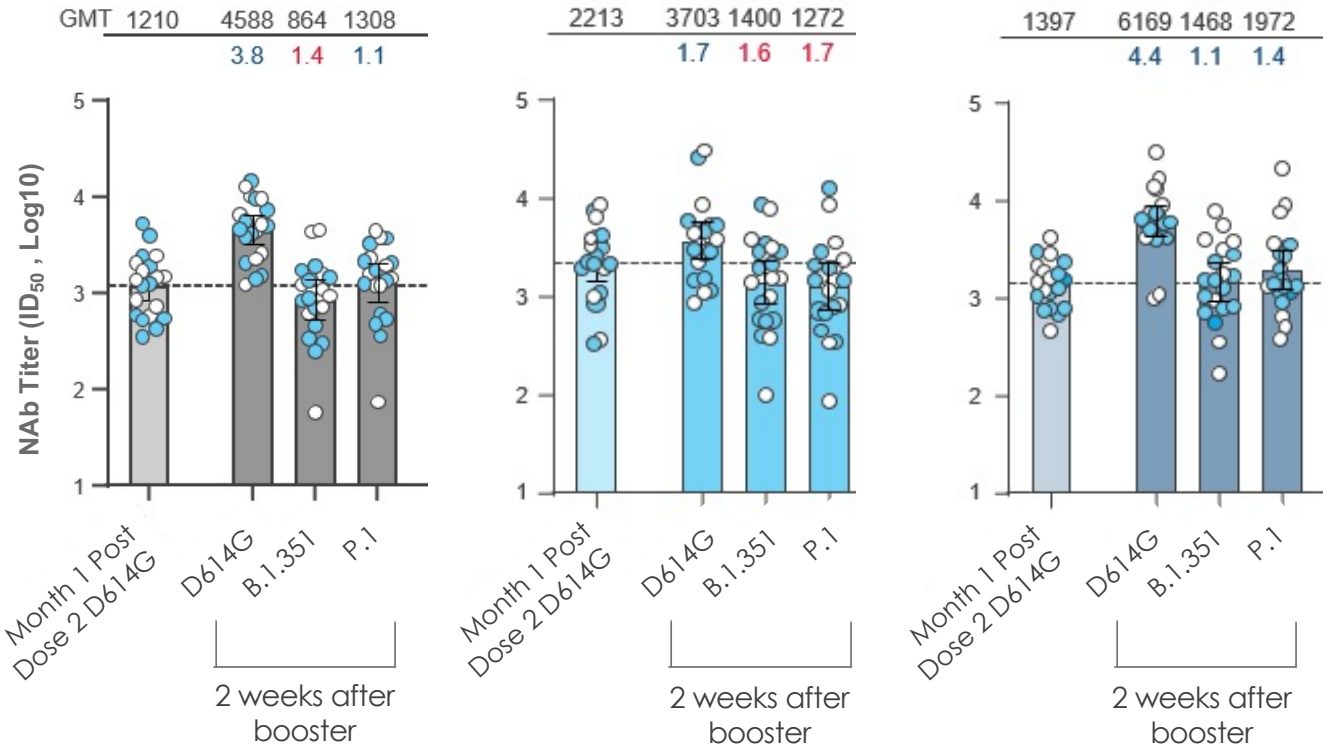
Choi et al, in press

Exploratory analysis using research assays

mRNA-1273 booster
50µg, N=20

mRNA-1273.351 booster
50µg, N=20

mRNA-1273.211 booster
50µg, N=20



The geometric mean neutralizing antibody titers with 95% confidence intervals are denoted. The titers for individual participants are shown by the circles. The horizonal dotted line indicates the lower limit of quantification. The wild-type D614G GMT 1 month after the primary vaccination series is indicated by the gray line. The fold increase versus The GMT titers against the wild-type D614G and variants measured in participants before the booster or 2 weeks after the booster were evaluated versus peak titers measured against the wild-type D614G 1 month after the primary vaccination series; the fold changes for each virus are shown.

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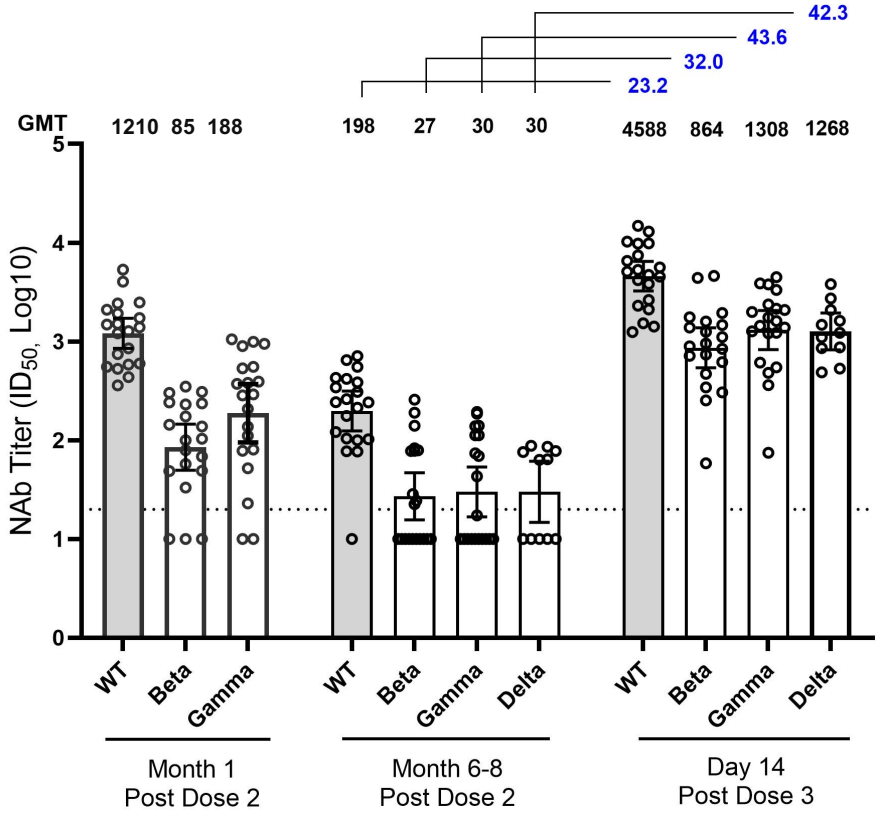
Performance of mRNA-1273 booster (>6 months) against VOC

Dose 3 booster of 50 µg of mRNA-1273

Pseudovirus neutralization titers



The geometric mean neutralizing antibody titers with 95% confidence intervals are denoted. The titers for individual participants are shown by the circles. The geometric mean fold increase versus titers measured 6-8 months post dose 2 are shown for each variant. The horizonal dotted lines indicate the lower limit of quantification. N=20 participants per booster cohort; GMT, geometric mean titer; ID50, 50% inhibitory dilution; NAb, neutralizing antibody

Choi et al, in press

Six months post second dose, neutralizing antibodies against wild-type (D614G) strain remained detectable

Neutralizing antibodies against **VOC started lower, and waned substantially** by six months after the second dose

Dose 3 (50 µg) booster of **mRNA-1273 significantly increased GMT for all VOC** Beta (B.1.351) by 32-fold, Gamma (P.1) by 43.6-fold and Delta (B.1.617.2) by 42.3-fold

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Clinical update: Phase 2 results from prototype booster

Earlier this year, our Phase 2 study of mRNA-1273 was amended to offer a 3rd dose of mRNA-1273 (50 µg) to all interested participants >6 months after dose 2 (n=344)

Top-line results: *(manuscript in preparation)*

- Neutralizing antibody **titers had waned significantly** prior to boosting at ~6 months
- A third dose (50 µg) of mRNA-1273 boosted neutralizing titers **above the Phase 3 benchmark**
- After third dose, **similar level of neutralizing titers were achieved across age groups**, notably in older adults (age ≥65)
- Safety profile following dose 3 was **similar to that observed** previously for dose 2 of mRNA-1273

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Key takeaways on COVID booster (dose 3)

- We believe a booster (dose 3) is likely to be necessary this fall, particularly in the face of Delta
- Clinical data appears to support 50 µg of mRNA-1273 for booster; no obvious advantage for Beta containing candidates
- We will wait for 100 µg data (coming weeks) to confirm selection of 50 µg as booster dose before filing

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