Oral COVID-19 Vaccination with QYNDR-RBD is Safe and Immunogenic

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Abstract:

The primary licensed and authorized vaccines available for COVID-19 in the US are mRNA based, while these vaccines were able to be rapidly developed and provide short term protection, next-generation candidates may offer performance advantages in terms of durability/breadth of protection. Other issues that have become apparent as COVID-19 has become endemic and booster doses of mRNA vaccines have been recommended are lack of uptake by the general population and waste of vaccine due to spoilage. Only approximately 20% of the population chose to receive the bivalent booster mRNA vaccine approved for use in 2023. This is well below the needed level of vaccination to achieve herd immunity.

VaxForm and US Specialty Formulations have developed an orally administered COVID vaccine, utilizing the QYNDR platform. (pronounced kinder) This novel vaccination approach brings many advantages over more traditional vaccines, including:

- lower risk for side effects and adverse events which can enhance vaccine uptake
- Allows for self-administration eliminating the need for medical professional administration
- lower production costs as aseptic production is not required
- induction of mucosal response which can reduce virus transmission
- no need for cold chain storage and transport allowing broader, more rapid distribution

QYNDR-RBD vaccine was evaluated in a phase I safety trial conducted in New Zealand. (clinicaltrials.gov # NCT04893512) This was a dose escalation study with 45 subjects split into 3 cohorts. Subjects were monitored for safety and immunogenicity for 1 year following initial dosing. During the trial there were no severe or medically attended adverse events associated with the vaccine. There were also very few solicited symptoms occurring within one week of dose administration. Additionally, there were no serum chemistry or hematological adverse signals observed during the study. The vaccine induced both mucosal IgA and serum IgG antibody responses that lasted for 1 year post vaccination. During the study it was determined that 41 of the 45 subjects were exposed to virus (likely the omicron variant) between 3- and 12-months post vaccination. Of the 40 subjects exposed to COVID-19 eight had a positive PCR test. Subjects having a positive PCR test had a significantly lower level of nasal IgA than subjects remaining PCR negative. This suggests induction of mucosal IgA provided enhanced cross variant protection as trial subjects were vaccinated with RBD from the original Wuhan strain. Vaccination with the QYNDR platform has the potential to enhance vaccine compliance and minimize the impact of potential future COVID pandemics.

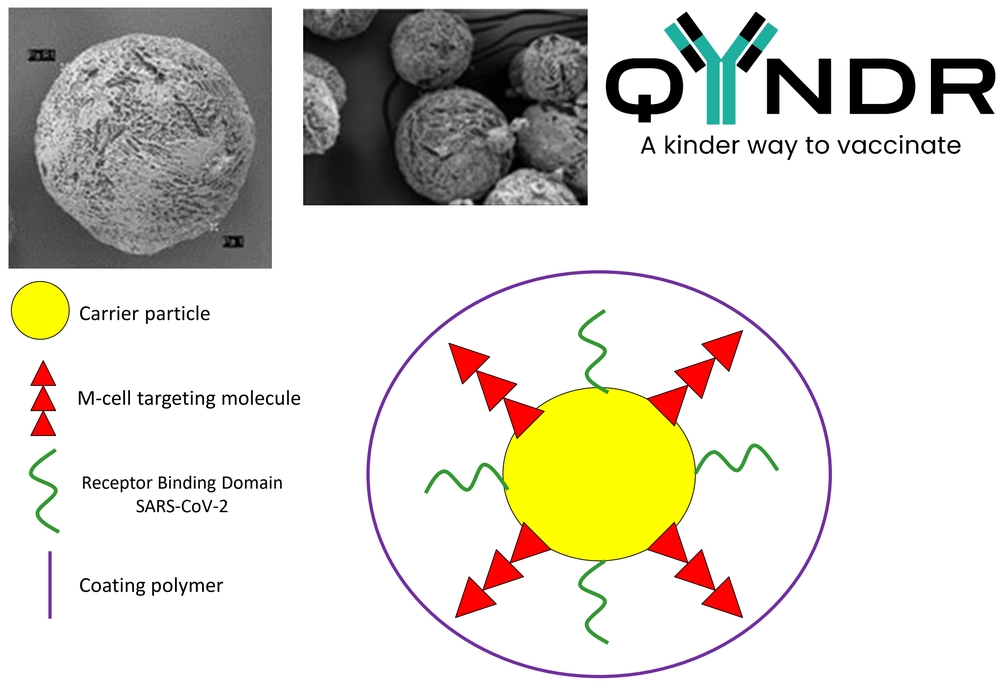


Figure 1. The QYNDR platform (pronounced kinder) was used for oral administration of our COVID-19 vaccine. The platform consists of a delivery particle, antigen, targeting molecule, and enteric microencapsulation. (TOP) SEM of vaccine particles following coacervation for microencapsulation and drying to form a powder.

Phase I Clinical Protocol Summary

- **Safety was primary read out with immunogenicity secondary read out**
- **Dose escalation 50, 100, & 200 μg RBD (original Wuhan Strain)**
  - 15 subjects per cohort (45 total)
    - Cohort 1 (50 μg)
    - Cohort 2 (100 μg)
    - Cohort 3 (200 μg)
  - Doses administered on days 1 & 15
  - 10 mL oral suspension, swish & swallow
- **Safety & Immunogenicity monitored for 1 year**
  - Typical serum safety panels collected
  - Immunology
    - Nasal, Oral, & Serum IgA/IgG
  - COVID Infection Monitoring
    - PCR tests on site visit
    - Adverse event reporting between visits
    - COBAS Elecsys anti-SARS-CoV-2 test (Roche)

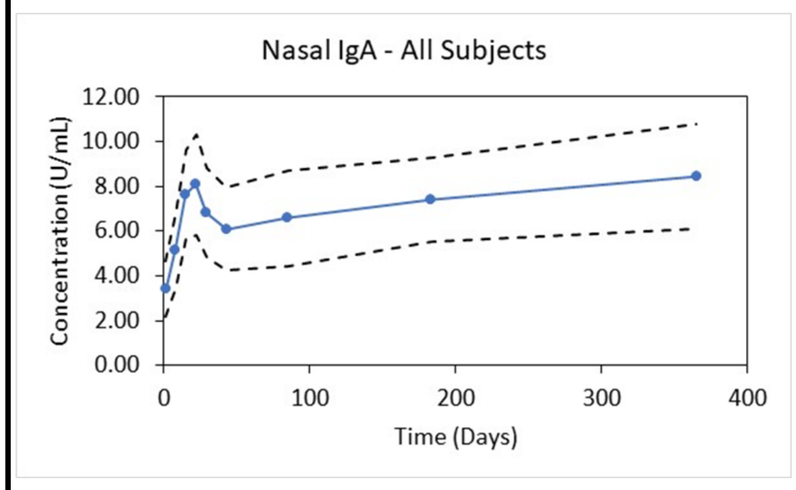
Figure 2. Final container packaging for QYNDR-RBD evaluated in the trial.

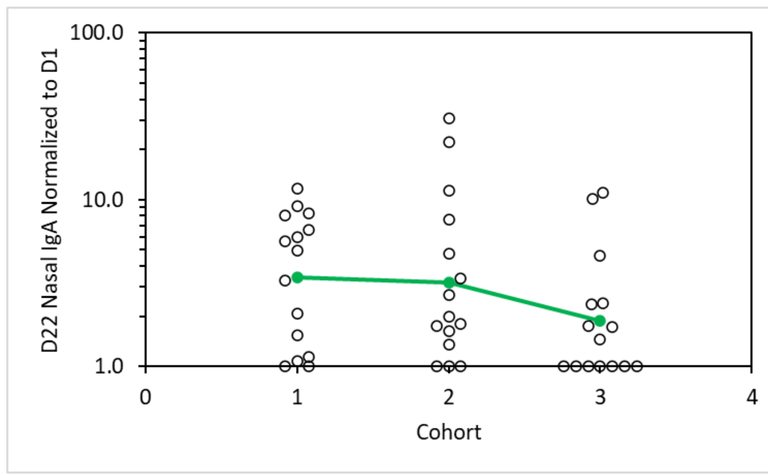
Table 1. Solicited Local and Systemic Reactions During Days 1 to 8 by Maximum Severity - Post Dose 1 and Post Dose 2

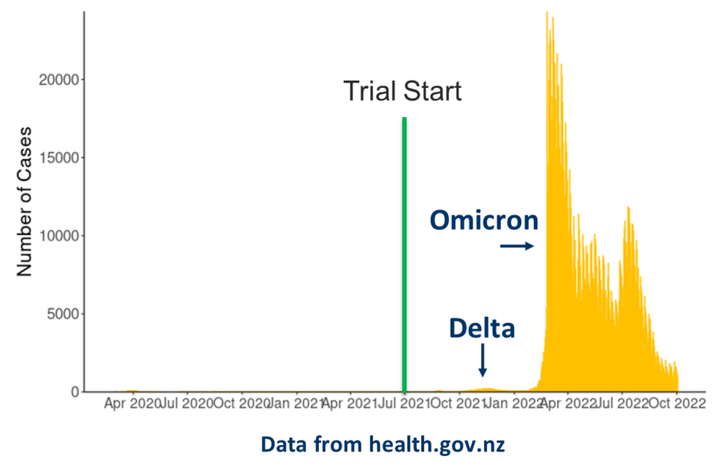
	CoV2-OGEN1			
	50 μg (N=15) n (%)	100 μg (N=15) n (%)	200 μg (N=15) n (%)	Overall (N=45) n (%)
Subjects with at Least One Solicited Local or Systemic Reaction				
No Symptom	5 (33.3)	6 (40.0)	4 (26.7)	15 (33.3)
Grade 1	9 (60.0)	7 (46.7)	5 (33.3)	21 (46.7)
Grade 2	1 (6.7)	1 (6.7)	5 (33.3)	7 (15.6)
Grade 3	0	1 (6.7)	1 (6.7)	2 (4.4)
Subjects with at Least One Solicited Local Reaction				
No Symptom	10 (66.7)	10 (66.7)	7 (46.7)	27 (60.0)
Grade 1	4 (26.7)	4 (26.7)	6 (40.0)	14 (31.1)
Grade 2	1 (6.7)	0	1 (6.7)	2 (4.4)
Grade 3	0	1 (6.7)	1 (6.7)	2 (4.4)
Subjects with at Least One Solicited Systemic Reaction				
No Symptom	8 (53.3)	8 (53.3)	5 (33.3)	21 (46.7)
Grade 1	6 (40.0)	5 (33.3)	4 (26.7)	15 (33.3)
Grade 2	1 (6.7)	2 (13.3)	6 (40.0)	9 (20.0)
Grade 3	0	0	0	0

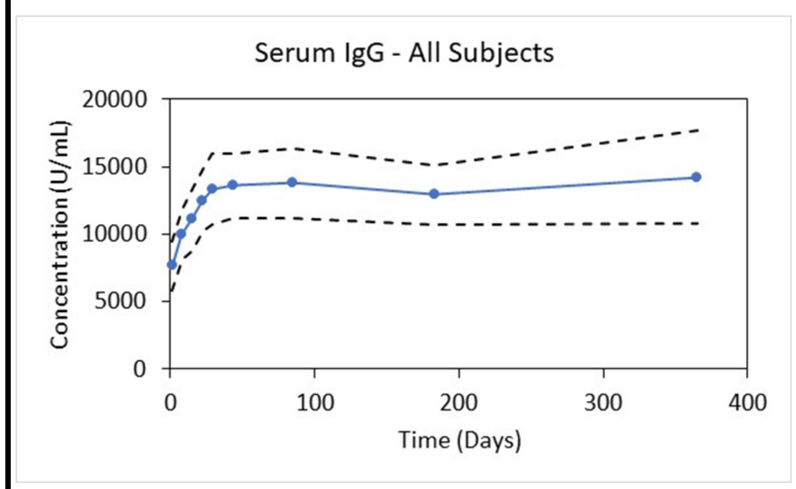
N= number of subjects in the population; n (%) = number and percent of subjects with TEAEs; E= event; TEAE= tr eatment-emergent adverse event. Note: Subjects are counted once if the same reaction occurred more than one time.

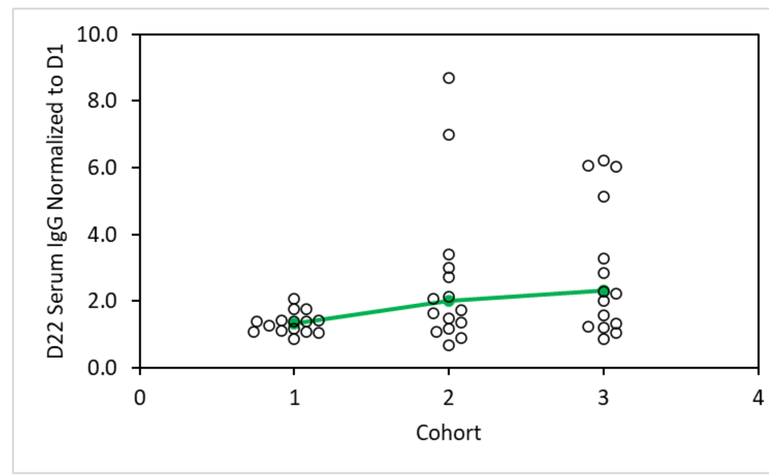
Overall, the safety profile of QYNDR-RBD was generally safe and tolerated following administration of two oral doses at dose levels of 50, 100 or 200 μg.
During days 1 to 8 of post dose 1 and 2, 21 (46.7 %) subjects reported Grade 1, 7 (15.6 %) subjects reported Grade 2 and 2 (4.4 %) subject reported Grade 3 solicited local or systemic reaction; 18 subjects experienced local reaction and 24 subjects experienced at least one systemic reaction. The most frequently reported solicited local reaction was malaise/general discomfort (11 subjects) followed by diarrhoea (9 subjects). The most frequently reported solicited systemic reaction was fatigue (17 subjects) followed by headache (14 subjects) and chills (7 subjects). The Grade 3 or severe local reactions reported were malaise and nausea.











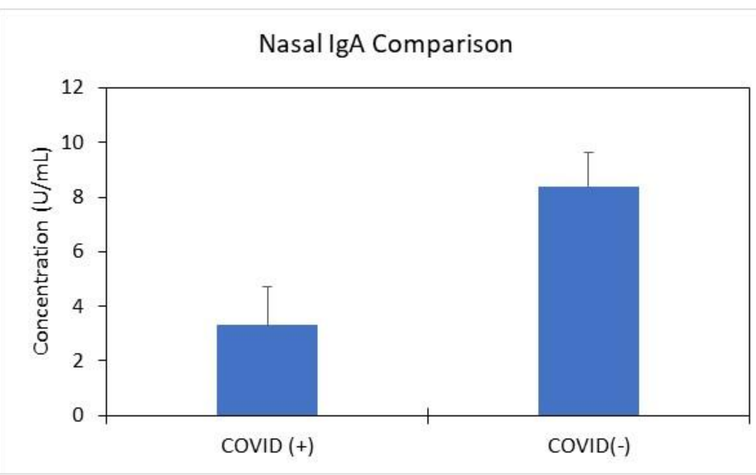


Figure 3. RBD specific antibody production was monitored for 1 year. For the study as a whole, both nasal IgA (Top) and serum IgG (Bottom) remained elevated through 1 year post administration. (Solid line is the geometric mean, Dashed lines are the 95% CI) Subjects were dosed on days 1 and 15 of the study. This demonstrates the durability of the immune response following oral vaccination.

Figure 4. Individual immune responses on day 22, which was one week post dose 2. Nasal IgA response was inversely proportional to the dose received (Top) while serum IgG response was directly proportional to dose (Bottom). All subjects in the study had an immune response to vaccination by day 22 of the study. RBD specific IgA & IgG antibody responses were determined by ELISA.

Figure 5. There was almost no COVID in New Zealand for the first 6 months of the clinical study. (Top) By January 2022 nearly 80% of the population had been vaccinated so the country opened back up which resulted in a large spike in COVID infections. Based on infection rates it would be expected to have 18 PCR(+) cases in our clinical study. However, we only had 8 PCR(+) infections in the study suggesting a reduction of infection risk compared to mRNA injection. Subjects that remained COVID (-) had a significantly higher level of nasal IgA than those that were PCR(+) for COVID. This suggests mucosal IgA is a critical component for prevention of infection.

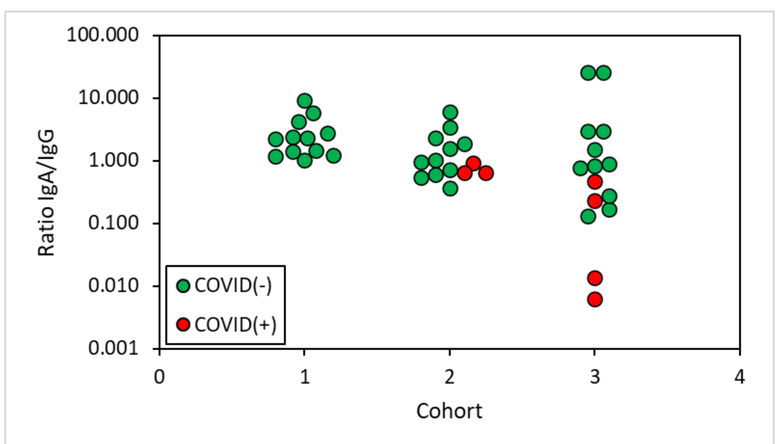


Figure 6. Subjects that had a ratio of nasal IgA (normalized to D1) to serum IgG (normalized to D1) greater than 1 remained COVID(-). All 8 subjects that were PCR(+) for COVID had pre-exposure ratios of nasal IgA to serum IgG less than 1. This suggests the importance of mucosal immunity in prevention of COVID infection.

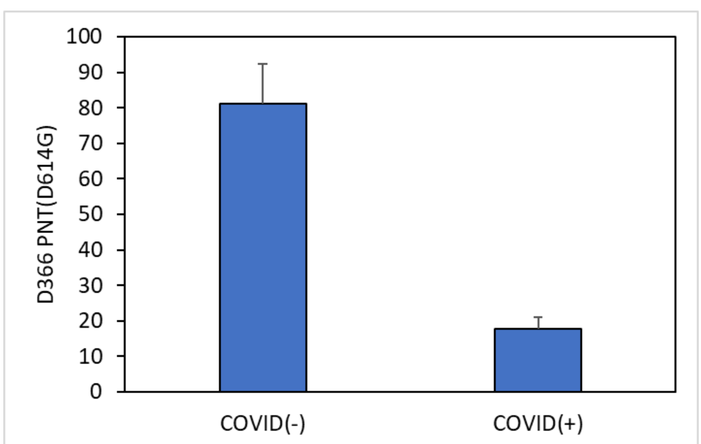


Figure 7. Subjects that had remained PCR(-) for COVID infection had a significantly greater post exposure increase in serum pseudovirus neutralization titer (PNT) on day 366 than subjects that became PCR(+). This suggests subjects which had mucosal responses to vaccination were better primed to respond to virus exposure.

Conclusion

QYNDR-RBD was found to be generally safe and well tolerated following 2 doses of 50, 100 or 200 μg administered orally. Mucosal and systemic immune responses peaked between day 22 and 29 of the trial. Nasal IgA and serum IgG remained elevated through the 1 year of the clinical study. This demonstrates good durability of the immune response to oral vaccination.
There was a reduction in risk of infection compared to the general population over the course of the study. Subjects that remained PCR negative had significantly higher levels of nasal IgA than subjects that were PCR(+). Those subjects also had significantly higher post exposure neutralizing antibody titer. This demonstrates the critical nature of mucosal immunity in prevention of COVID infection.
Vaccination with the QYNDR platform has the potential to enhance vaccine compliance and minimize the impact of potential future COVID pandemics. Future studies will evaluate the effectiveness of the QYNDR platform in boosting pre-existing immunity whether from vaccination or prior infection.

Acknowledgments
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