Monoclonal Antibodies for the Treatment of Patients with COVID-19 & Household Contacts

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Spike protein on the virus binds the ACE2 receptor on human cells. The Virus RNA is released into the cell, where it is translated into proteins that assemble and make-up new virus particles that are then sent back out of the cell.
SARS-CoV-2 comes out of the respiratory tract on:
- small aerosols that stay airborne and are then inhaled
- bigger respiratory droplets that splash into others' nose/mouth/eyes or they land on surfaces and get picked up by touch

The virus is also excreted through human waste
1 Lungs
A cross section shows immune cells crowding an inamed alveolus, or air sac, whose walls break down during attack by the virus, diminishing oxygen uptake. Patients cough, fevers rise, and breathing becomes labored.

2 Liver
Up to half of hospitalized patients have enzyme levels that signal a struggling liver. An immune system in overdrive and drugs given to fight the virus may be causing the damage.

3 Kidneys
Kidney damage is common in severe cases and makes death more likely. The virus may attack the kidneys directly, or kidney failure may be part of whole-body events like plummeting blood pressure.

4 Intestines
Patient reports and biopsy data suggest the virus can infect the lower gastrointestinal tract, which is rich in angiotensin-converting enzyme 2 (ACE2) receptors. Some 20% or more of patients have diarrhea.

5 Brain
Some COVID-19 patients have strokes, seizures, confusion, and brain inflammation. Doctors are trying to understand which are directly caused by the virus.

6 Eyes
Conjunctivitis, inflammation of the membrane that lines the front of the eye and inner eyelid, is more common in the sickest patients.

7 Nose
Some patients lose their sense of smell. Scientists speculate that the virus may move up the nose's nerve endings and damage cells.

8 Heart and blood vessels
The virus (teal) enters cells, likely including those lining blood vessels, by binding to ACE2 receptors on the cell surface. Infection can also promote blood clots, heart attacks, and cardiac inflammation.
Rationale

• Neutralizing antibodies bind to the viral spike protein and block the conformational changes that the spike protein must undergo in order to interact with the cellular receptor angiotensin-converting enzyme 2 (ACE2).

• Antibodies could enhance viral entry into immune cells by binding to the viral spike protein with their Fab portion and to Fc receptors (FcRs) with their Fc domain.
Pharmacological properties of anti-SARS-CoV-2-spike mAb combination for the treatment and prevention of COVID-19

- This combination selected to minimize chances that could result in viral resistance
- Neutralize SARS-CoV-2 virus with an IC50 of 4.5ng/ml (30pM), with cocktail working in an additive fashion
- Has broad neutralization coverage against over 20 circulating RBD sequence variants tested through end of May 2020, as well as both 614D and 614G lineages of the spike protein.
- Preliminary NHP PK data suggests typical half-life of ~21 days
Humanized mice and convalescent patients utilized to generate antibodies against the SARS-CoV-2 spike protein, yielding a large collection of fully-human antibodies that were characterized for binding, neutralization and three dimensional structure.

Based on these criteria, selected pairs of highly-potent individual antibodies that simultaneously bind the receptor-binding domain of the spike protein, providing ideal partners for a therapeutic antibody cocktail that aims to decrease the potential for virus escape mutants that might arise.
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Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies

Alina Baum, Benjamin O. Fuhns, Zzhiera Wuina, Richard Copin, Kristen E. Passad, Vincenzo Russo, Stephanie Giordano, Kathryn Lanza, Nicole Negron, Min Ni, Yiyi Wei, Gurinder S. Atwal, Andrew J. Murphy, Neil Stahl, George D. Yancopoulos, Christos A. Kyriazis

Fig. 1. Escape mutant screening protocol. (A) A schematic is displayed of the VSV-SARS-CoV-2-S virus genome encoding residues 1-1255 of the spike protein in place of the VSV glycoprotein. N, nucleoprotein, P, phosphoprotein, M, matrix, and L, large polymerase. (B) A total of 1.5 × 10^6 pfu of the parental VSV-SARS-CoV-2-S virus was passed in the presence of antibody dilutions for 4 days on Vero E6 cells. Cells were screened for virus replication by monitoring for virally induced cytopathic effect (CPE). Supernatants and cellular RNAs were collected from wells under the greatest antibody selection with detectable viral replication (circled wells: ≥20% CPE). For a second round of selection, 100 μL of the P1 supernatant was expanded for 4 days under increasing antibody selection in fresh Vero E6 cells. RNA was collected from the well with the highest antibody concentration with detectable viral replication. The RNA was deep sequenced from both passages to determine the selection of mutations resulting in antibody escape. (C) The passaging results of the escape study are presented with the qualitative percentage of CPE observed in each dilution (red ≥20% CPE and blue <20% CPE). Black boxes indicate dilutions that were passaged and sequenced in P1 or sequenced in P2. A no antibody control was sequenced from each passage to monitor for tissue culture adaptions.
REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters

Alina Baum1, Dharani Ajjhodla1, Richard Copin1, Anbo Zhou1, Kathryn Lanza1, Nicole Negron1, Min Ni1, Yi Wei1, Kasha Mohammadi1, Bret Musser1, Garinder S. Atwal1, Adelekan Oyejide1, Yenny Goez-Gazi1, John Dutton1, Elizabeth Clemmons3, Hilary M. Staples1, Carmen Bartley1, Benjamin Klaiffe2, Kendra Alfonso1, Michal Gazi1, Olga Gonzalez2, Edward Dick Jr.2, Ricardo Carrion Jr.2, Laurent Pessaint3, Maciel Porte3, Anthony Cook3, Renita Brown4, Vanessa Ali5, Jack Greenhouse6, Tammy Taylor6, Hanne Andersen7, Mark G. Lewis7, Neil Stahl7, Andrew J. Murphy8, George D. Yancopoulos8, Christos A. Kyrtsonis*8

1Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591, USA. 2Southwest National Primate Research Center, Texas Biomedical Research Institute, San Antonio, TX 78245, USA. 3BIORX, Rockville, MD 20850, USA.

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An urgent global quest for effective therapies to prevent and treat COVID-19 disease is ongoing. We previously described REGN-COV2, a cocktail of two potent neutralizing antibodies (REGN10987+REGN10933) targeting non-overlapping epitopes on the SARS-CoV-2 spike protein. In this report, we evaluate the in vivo efficacy of this antibody cocktail in both rhesus macaques, which may model mild disease, and golden hamsters, which may model more severe disease. We demonstrate that REGN-COV2 can greatly reduce virus load in lower and upper airways and decrease virus induced pathological sequelae when administered prophylactically or therapeutically in rhesus macaques. Similarly, administration in hamsters limits weight loss and decreases lung titers and evidence of pneumonia in the lungs. Our results provide evidence of the therapeutic potential of this antibody cocktail.
REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters


REGN-COV2 (Bamlanivimab) is a neutralizing antibody against the SARS-CoV-2 spike protein. This antibody was shown to prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters.

An urgent global quest for effective therapies to prevent and treat COVID-19 disease is ongoing. We previously described REGN-COV2, a cocktail of two potent neutralizing antibodies, REGN0123 and REGN0123, targeting non-overlapping epitopes on the SARS-CoV-2 spike protein. In this report, we evaluate the in vivo efficacy of this antibody cocktail in both rhesus macaques, which may model milder disease, and golden hamsters, which may model more severe disease. We demonstrate that REGN-COV2 can greatly reduce virus load in lower and upper airways and decrease viral-induced pathologic sequelae when administered prophylactically or therapeutically in rhesus macaques. Similarly, administration in hamsters limits weight loss and decreases lung filers and evidence of pneumonia in the lungs. Our results provide evidence of the therapeutic potential of this antibody cocktail.
## SITE & ENROLLMENT UPDATE
(AS OF 22Sept20)

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<tr>
<td><strong>R10933-10987-COV-2066</strong></td>
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<td><strong>SITES ACTIVE</strong></td>
<td><strong>84</strong></td>
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</table>
| **PATIENTS ENROLLED**  | **Phase 1 = 57**  
                        | **Phase 2 = 229**  |
Hospitalized patients ≤ 72 hours, with COVID-19 symptoms ≤ 10 days

Screening: confirmation of eligibility (inclusion/exclusion criteria)

Randomization

Co-administered REGN10933+REGN10987 2.4 g IV

Co-administered REGN10933+REGN10987 8.0 g IV

Placebo IV

In-person follow up until D29 and phone follow up until D57
### Inclusion Criteria

1. Singed informed consent
2. Adult ≥18 years of age
3. SARS-CoV-2-positive antigen or molecular diagnostic test ≤72 hours from randomization
4. COVID-19 symptom onset ≤10 days from randomization
5. Hospitalized for COVID-19 illness for ≤72 hours with at least 1 of the following at randomization:
   - **Cohort 1A**: with symptoms of COVID-19, but do not require oxygen supplementation
   - **Cohort 1**: O2 saturation >93% on low-flow oxygen via nasal cannula, simple face mask, or other similar device
   - **Cohort 2**: High intensity oxygen therapy but not on mechanical ventilation
     - Non-rebreather mask (SpO2 ≤96% while receiving an oxygen flow rate of at least 10 L/min)
     - High-flow device (eg, AIRVO™ or Optiflow™) with at least 50% FiO2
     - Non-invasive ventilator, including continuous positive airway pressure (CPAP), to treat hypoxemia (excluding isolated use for sleep-disordered breathing)
   - **Cohort 3**: On mechanical ventilation

### Exclusion Criteria

1. (Only for phase 1)
2. Not expected to survive >48 hours from screening
3. Receiving extracorporeal membrane oxygenation (ECMO)
4. Has new-onset stroke or seizure disorder during hospitalization
5. Initiated on renal replacement therapy due to COVID-19
6. Has circulatory shock requiring vasopressors at randomization
7. Received convalescent plasma or IVIG in the past 5 months or plan to receive during the study
8. Participation in a clinical research study, including any double-blind study, evaluating an investigational product within 30 days and less than 5 half-lives of the investigational product prior to the screening visit lives of the investigational product prior to the screening visit
   - Note: The use of remdesivir, hydroxychloroquine, or other treatments [except for COVID COVID-19 convalescent plasma or IVIG] used for COVID COVID-19 treatments as local SOC, an open open-label study or compassionate use protocol is permitted.
9. Any physical examination findings, history of illness, and/or concomitant medications that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study
10. Known allergy or hypersensitivity to components of study drug
11. Pregnant or breastfeeding women
12. Continued sexual activity in women of childbearing potential (WOCBP)* or sexually active men who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose
**Study Design**
**R10933-10987-COV-2067**

Non-hospitalized patients with COVID-19 and symptoms ≤ 7 days

Screening: confirmation of eligibility (inclusion/exclusion criteria)

Randomization

Co-administered REGN10933+REGN10987 2.4 g IV

Co-administered REGN10933+REGN10987 8.0 g IV

Placebo IV

In-person follow up every other day until D15 and twice weekly until D29
### Inclusion Criteria

1. **Adult** ≥18 years of age

2. SARS-CoV-2-positive antigen or molecular diagnostic test ≤72 hours from randomization

3. [Criterion removed]

4. Meets 1 of the following 2 criteria:
   a. **Symptomatic Cohort** (All Phases): Has symptoms consistent with COVID-19 as determined by the investigator with onset ≤7 days before randomization
   b. **Asymptomatic Cohort** (Phase 2): Meets all of the following:
      - Has had no symptoms consistent with COVID-19 (as determined by the investigator) occurring at any time <2 months prior to randomization
      - Has had no positive SARS-CoV-2 test results from a sample collected >7 days prior to randomization
      - Has had no known contact (of any duration) with an individual who has confirmed COVID-19 or confirmed positive SARS-CoV-2 test result >14 days prior to randomization.

5. Maintains O2 saturation ≥93% on room air

6. Singed informed consent

7. Is willing and able to comply with study procedures, including providing samples for viral shedding testing

### Exclusion Criteria

1. Hospital addition prior to randomization, due to COVID-19

2. Participation in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, or intravenous immunoglobulin (IVIG) within 3 months or less than 5 half-lives of the investigational product prior to the screening visit

3. Prior, current, or planned future use of any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2, IVIG (any indication), systemic corticosteroids (any indication), or COVID-19 EUA approved treatments, where prior use is defined as the past 30 days or less than 5 half-lives of the investigational product from screening

4. [Criterion consolidated with criterion #3]

5. [Criterion removed]

6. Known allergy or hypersensitivity to components of study drug

7. Discharged/planned discharged, to a quarantine center

8. Pregnant or breastfeeding women

9. Continued sexual activity in women of childbearing potential (WOCBP)* or sexually active men who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose
• Serological status highly correlated with baseline viral load (p<0.0001)
• Significantly reduced viral load.
• REGN-COV2 rapidly reduced viral load through Day 7 in seronegative patients (key virologic endpoint)
• Virologic effects were most pronounced in patients who had high viral loads and/or were SARS-CoV-2 sero-antibody negative at baseline.
• Sero-antibody negativity, high viral load, and pre-existing risk factors correlate with higher risk for medically-attended visit.
• Analysis (n=799): 57% reduction in the proportion of patients with medically-attended visits for COVID-19 (2.8% combined treatment arms vs 6.5% placebo, p=0.024).
• Similar treatment effects were observed in the two dose levels tested (2.4 g low dose; 8.0 g high dose)
• Serious adverse events were numerically more frequent with placebo than REGN-COV2 treatment (0.8% high dose, 1.6% low dose; 2.3% placebo).
• Infusion reactions: 1.5% high dose; 0% low dose; 0.4% placebo).
SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Peter Chen, M.D., Ajay Nirula, M.D., Ph.D., Barry Heller, M.D., Robert L. Gottlieb, M.D., Ph.D., Joseph Boscia, M.D., Jason Morris, M.D., Gregory Huhn, M.D., M.P.H.T.M.; Jose Cardona, M.D., Bharat Moharla, M.D., Valentina Stosor, M.D., Imad Shawa, M.D., Andrew C. Adams, Ph.D., Jacob Van Naarden, B.S., Kenneth L. Custer, Ph.D., Lei Shen, Ph.D., Michael Durante, M.S., Gerard Oakley, M.D., Andrew E. Schade, M.D., Ph.D., Janelle Sabo, Pharm.D., Dipak R. Patel, M.D., Ph.D., Paul Kleckota, M.D., Ph.D., and Daniel M. Skovronske, M.D., Ph.D., for the BLAZE-1 Investigators

![Interim Analysis Table]

- 101 Patients were enrolled and assigned to 700 mg of LY-CoV555 monotherapy
- 107 Patients were enrolled and assigned to 2800 mg of LY-CoV555 monotherapy
- 101 Patients were enrolled and assigned to 7000 mg of LY-CoV555 monotherapy
- 143 Patients were enrolled and assigned to placebo

**Figure 1. Enrollment and Trial Design.**
Table 3. Hospitalization.

<table>
<thead>
<tr>
<th>Key Secondary Outcome</th>
<th>LY-CoV555</th>
<th>Placebo</th>
<th>Incidence</th>
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<tbody>
<tr>
<td></td>
<td>no. of patients/total no.</td>
<td>%</td>
<td></td>
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<tr>
<td>Hospitalization</td>
<td>9/143</td>
<td>6.3</td>
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<tr>
<td>700 mg, 1/101</td>
<td>1.0</td>
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<tr>
<td>2800 mg, 2/107</td>
<td>1.9</td>
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<tr>
<td>7000 mg, 2/101</td>
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<td>Pooled doses, 5/309</td>
<td>1.6</td>
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* Data for patients who presented to the emergency department are included in this category.

Figure 2. SARS-CoV-2 Viral Load in All Patients and According to Trial Group on Day 7.

Panel A shows the SARS-CoV-2 viral load (as measured by the cycle threshold on reverse-transcriptase–polymerase-chain-reaction assay) for all the patients who received either LY-CoV555 or placebo and for whom viral-load data were available at the time of the interim analysis. The box plots indicate the patients who were not hospitalized, and the red squares indicate those who were hospitalized. Such hospital contact was found to be associated with a high viral load on day 7. The boxes represent interquartile ranges, with the horizontal line in each box representing the median and the whiskers showing the minimum and maximum values (excluding outliers that were more than 1.5 times the values represented at each end of the box). Panel B shows the cumulative probability that patients in each trial group would have the indicated cycle threshold of viral load on day 7.

Figure 3. Symptom Scores from Day 2 to Day 11.

Shown is the difference in the change from baseline (delta value) in symptom scores between the LY-CoV555 group and the placebo group from day 2 to day 11. The symptom scores ranged from 0 to 24 and included eight domains, each of which was graded on a scale of 0 (no symptoms) to 3 (severe symptoms). The 1 bars represent 95% confidence intervals. Details about the symptom-scoring methods are provided in the Supplementary Appendix.
COVID-19: SWISS CHEESE MODEL
Layers of protection against COVID-19

- **Awareness** of risk and how to prevent infection at the individual level
- **Vaccine**
  Under development but only estimated for large scale roll-out middle to end of 2021
- **Social Distancing**
  - At least 2 meters apart
  - Avoid any gatherings
  - Government lockdowns
- **Hand Hygiene & Masks & Cleaning**
- **COVID-19 Case**
- **Clinical management**
- **Testing & Contact tracing & Quarantine & Isolation**
- **Emergency Response**
- **Fatality**

**Primary prevention**

**Secondary prevention**

**Tertiary prevention**

**Plan**
- Quality Management System
- Do
- Check

**Act**
In advanced disease, SARS-CoV-2 can cause immune system dysregulation.
Project Title: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY ASSESSING THE EFFICACY AND SAFETY OF ANTI-SPIKE SARS-COV-2 MONOCLONAL ANTIBODIES IN PREVENTING SARS-COV-2 INFECTION IN HOUSEHOLD CONTACTS OF INDIVIDUALS INFECTED WITH SARS-COV-2

Protocol Number: R10933-10987-COV-2069
Study Design
R10933-10987-COV-2069

Asymptomatic subjects with Household Contacts of Individuals Infected with SARS-CoV-2

Screening: confirmation of eligibility (inclusion/exclusion criteria)

Randomization

REGN10933 and REGN10987, 1200 mg (one dose of 4 SC injections)

Placebo

In-person follow up every week for the first month and every 4 weeks for 7 months
<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>1. Adult ≥18 years of age</td>
<td>1. Subject-reported history of prior positive SARS-CoV-2 RT-PCR test or positive SARS-CoV-2 serology test at any time before the screening</td>
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<tr>
<td>2. Asymptomatic household contact with exposure to an individual with a diagnosis of SARS-CoV-2 infection (index case). To be included in the study, subjects must be randomized within 96 hours of collection of the index cases’ positive SARS-CoV-2 diagnostic test sample</td>
<td>2. Lived with individuals who have had previous SARS-CoV-2 infection</td>
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<td>3. Subject anticipates living in the same household with the index case until study day 29</td>
<td>3. Active respiratory or non-respiratory symptoms consistent with COVID-19</td>
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<td>4. Judged to be in good health based on medical history and physical examination at screening/baseline, including subjects who are healthy or have a chronic, stable medical condition</td>
<td>4. History of respiratory illness with sign/symptoms of SARS-CoV-2 infection, in the opinion of the investigator within the prior month to screening</td>
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<td>5. Willing and able to comply with study visits and study-related procedures/assessments</td>
<td>5. Nursing home resident</td>
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<td>6. Provide informed consent signed by study subject or legally acceptable representative</td>
<td>6. Any physical examination findings, and/or history of any illness, concomitant medications or recent live vaccines that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the subject by their participation in the study</td>
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<td>7. Current hospitalization or was hospitalized (ie, &gt;24 hours) for any reason within 30 days of the screening visit</td>
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<td>8. History of significant multiple and/or severe allergies (eg, latex gloves), or anaphylactic reaction to prescription or non-prescription drugs or food</td>
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<td>9. Treatment with another investigational agent in the last 30 days or within 5 half-lives of the investigational drug, whichever is longer, prior to the screening visit</td>
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<td>10. Received an investigational or approved SARS-CoV-2 vaccine</td>
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<td>11. Received investigational or approved passive antibodies for SARS-CoV-2 infection prophylaxis (eg, convalescent plasma or sera, monoclonal antibodies, hyperimmune globulin)</td>
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<td>12. Use of hydroxychloroquine/chloroquine or anti-SARS-viral agents, eg, remdesivir, within 60 days of screening</td>
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<td>13. Member of the clinical site study team and/or immediate family</td>
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<td>14. Sexually active men who are unwilling to use the following forms of medically acceptable birth control during the study drug follow-up period and for 8 months after single dose of study drug</td>
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<td></td>
<td>15. Pregnant or breastfeeding women</td>
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<tr>
<td></td>
<td>16. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 8 months after the last dose</td>
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New York nurse dies from coronavirus, family and co-workers say

NEW YORK CITY — A healthy nurse worker at one of the New York City hospitals under siege by the coronavirus has died, according to co-workers and his sister.

Kelsen Kelly, an assistant nurse manager at the Mount Sinai West hospital in Manhattan, died Tuesday from the virus after he got sick two weeks ago, multiple friends and ex-social media coworkers said.

This is Dr Shirin Rouhani-Rad, an Iranian medic who has died of COVID-19
IT'S OKAY
WE GOT THIS!