Supplemental Material

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### Table S1. Additional characteristics of the patients at randomization

| Characteristics | JS016 (n = 99) | Control (n = 98) | Total (n = 197) |
|-----------------|----------------|-----------------|-----------------|
| **Vital signs** |                |                 |                 |
| Temperature, °C, median (IQR) | 36.6 (36.1-37.1) | 36.8 (36.4-37.8) | 36.7 (36.3-37.3) |
| SBP, mmHg, mean ± SD | 124 ± 18 | 125 ± 17 | 125 ± 17 |
| DBP, mmHg, mean ± SD | 77 ± 12 | 77 ± 11 | 77 ± 11 |
| Heart rate, bpm, median (IQR) | 76 (70-84) | 82 (74-92) | 80 (70-90) |
| Respiratory rate, /min, median (IQR) | 18 (18-20) | 18 (18-20) | 18 (18-20) |
| SpO2, %, median (IQR) | 97 (96-98) | 97 (97-98) | 97 (96-98) |
| **Laboratory measures** |                |                 |                 |
| pH, median (IQR) | 7.43 ± 0.04 | 7.44 ± 0.05 | 7.43 ± 0.04 |
| PaO2* , mmHg, median (IQR) | 92 (81-125) | 77 (70-93) | 84 (74-99) |
| PaCO2, mmHg, mean ± SD | 37 ± 5 | 36 ± 5 | 37 ± 5 |
| HCO3, mmol/L, mean ± SD | 24 ± 3 | 24 ± 3 | 24 ± 3 |
| White cell count, cells/mm³, median (IQR) | 4800 (3920-5690) | 4705 (3880-5980) | 4770 (3900-5900) |
| Platelet count, 10³ cells/mm³, median (IQR) | 172 (144-228) | 174 (136-216) | 173 (139-221) |
| Total bilirubin, mg/dL, median (IQR) | 0.49 (0.35-0.69) | 0.54 (0.36-0.68) | 0.51 (0.35-0.68) |
| LDH, U/L, median (IQR) | 230 (158-428) | 239 (168-465) | 236 (163-454) |
| ALT, U/L, median (IQR) | 21 (14-38) | 25 (16-36) | 23 (15-37) |
| Creatinine, mg/dL, median (IQR) | 0.70 (0.59-0.81) | 0.67 (0.57-0.80) | 0.68 (0.58-0.81) |

*p<0.05

SBP, systolic blood pressure; DBP, diastolic blood pressure; LDH, lactate dehydrogenase; ALT, alanine aminotransferase.

### Table S2. Treatment and Supportive Care

| Treatment or supportive care | JS016 (n = 99) | Control (n = 98) | Total (n = 197) |
|-----------------------------|----------------|-----------------|-----------------|
| **Medication**              |                |                 |                 |
| Traditional Chinese medicine | 99 (100%) | 98 (100%) | 197 (100%) |
| Glucocorticoid              | 1 (1%) | 2 (2%) | 3 (1.5%) |
| **Supportive care**         |                |                 |                 |
| Supplemental oxygen         | 36 (36%) | 39 (40%) | 75 (38%) |
| Noninvasive ventilation     | 4 (4%) | 0 (1%) | 4 (2%) |
| ECMO                        | 1 (1%) | 1 (1%) | 2 (1%) |
| Vasopressor                 | 1 (1%) | 1 (1%) | 2 (1%) |
| Renal replacement therapy   | 0 (0%) | 1 (1%) | 1 (0.5%) |
Table S3. Six-level ordinal outcomes on day 7, 14 and 21 since randomization

| Outcome | JS016 (n = 99) | Control (n = 98) | Odds ratio (95% CI) | p    |
|---------|----------------|-----------------|----------------------|------|
| Day 7   |                |                 |                      |      |
| 1       | 6 (6%)         | 6 (6%)          | 1.31 (0.70-2.45)     | 0.40 |
| 2       | 67 (68%)       | 56 (57%)        |                      |      |
| 3       | 16 (16%)       | 27 (28%)        |                      |      |
| 4       | 8 (8%)         | 8 (8%)          |                      |      |
| 5       | 1 (1%)         | 1 (1%)          |                      |      |
| 6       | 1 (1%)         | 0 (0%)          |                      |      |
| Day 14  |                |                 | 1.70 (0.93-3.09)     | 0.08 |
| 1       | 70 (71%)       | 56 (57.2%)      |                      |      |
| 2       | 17 (17%)       | 22 (22.4%)      |                      |      |
| 3       | 8 (8%)         | 19 (19.4%)      |                      |      |
| 4       | 1 (1%)         | 0 (0%)          |                      |      |
| 5       | 2 (2%)         | 1 (1%)          |                      |      |
| 6       | 1 (1%)         | 0 (0%)          |                      |      |
| Day 21  |                |                 | 0.85 (0.35-2.06)     | 0.71 |
| 1       | 87 (88%)       | 86 (88%)        |                      |      |
| 2       | 7 (7%)         | 8 (8%)          |                      |      |
| 3       | 2 (2%)         | 3 (3%)          |                      |      |
| 4       | 1 (1%)         | 0 (0%)          |                      |      |
| 5       | 1 (1%)         | 1 (1%)          |                      |      |
| 6       | 1 (1%)         | 0 (0%)          |                      |      |

a A score of 1 indicated not hospitalized; 2, hospitalized without supplemental oxygen; 3, supplemental oxygen; 4, noninvasive ventilation or high flow nasal cannula; 5, invasive ventilation or ECMO; and 6, death. ALT, alanine transaminase. AST, aspartate transaminase.
| Outcome | JS016 (n = 99) | Control (n = 98) | Odds ratio (95% CI) | p    |
|---------|----------------|-----------------|--------------------|------|
|         |                |                 |                    |      |
| Negative conversion rate of SARS-CoV-2 nucleic acid on day 7 a | 19% (18/97) | 10% (10/97) | 2.29 (0.93-5.65) | 0.07 |
| ORF gene | 20% (19/97) | 24% (23/97) | 0.73 (0.33-1.62) | 0.43 |
| N gene | 19% (18/97) | 10% (10/97) | 2.29 (0.93-5.65) | 0.07 |
| Negative conversion rate of SARS-CoV-2 nucleic acid on day 14 a | 82% (80/97) | 78% (76/97) | 1.35 (0.65-2.83) | 0.43 |
| ORF gene | 82% (80/97) | 79% (77/97) | 1.27 (0.60-2.68) | 0.53 |
| N gene | 82% (80/97) | 78% (76/97) | 1.35 (0.65-2.83) | 0.43 |
| Negative conversion rate of SARS-CoV-2 nucleic acid on day 21 a | 99% (96/97) | 94% (91/97) | 5.93 (0.69-50.77) | 0.10 |
| ORF gene | 99% (96/97) | 96% (93/97) | 4.13 (0.44-38.51) | 0.21 |
| N gene | 99% (96/97) | 94% (91/97) | 5.93 (0.69-50.77) | 0.10 |

a SARS-CoV-2 nucleic acid was defined as negative if both ORF and N gene turned negative.
Figure S1. Probability of negative conversion of SARS-CoV-2 nucleic acid, ORF gene, and N gene. Hazard ratios (HR) were estimated using log-rank test of Cox proportional-hazards model, adjusted for age, site, and six-level ordinal scale of clinical status at randomization.
Table S5. Serum SARS-CoV-2 Specific Antibody from Randomization to Day 21

|                | JS016       | Control | P     |
|----------------|-------------|---------|-------|
|                | (n = 99)    | (n = 98)|       |
| At randomization |             |         |       |
| IgG            | 0.26 (0.08-5.20) | 0.23 (0.06-2.90) | 0.14  |
|                | (n = 85)    | (n = 86) |       |
| IgM            | 0.50 (0.10-4.30) | 0.38 (0.10-2.96) | 0.11  |
|                | (n = 85)    | (n = 86) |       |
| Day 2          |             |         | < 0.001|
| IgG            | 388.20 (376.65-398.34) | 6.92 (1.62-26.26) |         |
|                | (n = 87)    | (n = 77) |       |
| IgM            | 5.83 (1.29-14.31) | 4.28 (0.77-10.74) | 0.09   |
|                | (n = 86)    | (n = 77) |       |
| Day 7          |             |         |       |
| IgG            | 390.97 (377.43-399.64) | 32.34 (11.90-141.51) | 0.01   |
|                | (n = 93)    | (n = 90) |       |
| IgM            | 10.78 (3.85-25.36) | 11.96 (5.31-31.08) | 0.26   |
|                | (n = 93)    | (n = 90) |       |
| Day 14         |             |         |       |
| IgG            | 403.35 (398.09-417.15) | 102.45 (33.11-255.63) | 0.04   |
|                | (n = 38)    | (n = 53) |       |
| IgM            | 13.69 (4.46-30.39) | 17.64 (7.42-34.88) | 0.98   |
|                | (n = 39)    | (n = 53) |       |
| Day 21         |             |         |       |
| IgG            | 398.53 (395.41-402.06) | 172.72 (59.33-266.49) | 0.05   |
|                | (n = 9)     | (n = 13) |       |
| IgM            | 12.70 (1.96-23.45) | 22.07 (11.70-27.65) | 0.16   |
|                | (n = 9)     | (n = 13) |       |
Figure S2. Serum SARS-CoV-2 Specific Immunoglobulin. Serum SARS-CoV-2 specific IgG and IgM was compared between the JS016 group and the control group using general linear models for repeated measures, adjusted for age, site, and six-level ordinal scale of clinical status at randomization. * p < 0.05.
| Outcome                  | JS016     | Control    | Comparison (95% CI) | p   |
|--------------------------|-----------|------------|---------------------|-----|
| **Moderate disease**     |           |            |                     |     |
| Number of patients, n/N  | 86/99     | 84/98      |                     | 0.99|
| Primary outcome a        |           |            |                     |     |
| 1                        | 83 (97%)  | 84 (100%)  |                     |     |
| 2                        | 0 (0%)    | 0 (0%)     |                     |     |
| 3                        | 1 (1%)    | 0 (0%)     |                     |     |
| 4                        | 0 (0%)    | 0 (0%)     |                     |     |
| 5                        | 1 (1%)    | 0 (0%)     |                     |     |
| 6                        | 1 (1%)    | 0 (0%)     |                     |     |
| Secondary outcomes       |           |            |                     |     |
| 28-day mortality         | 1 (1%)    | 0 (0%)     |                     | 0.99|
| Ventilator-free days     | 28 (28-28)| 28 (28-28)| 0.74 (0.35-1.57)    | 0.44|
| Length of hospital stay  | 13 (11-16)| 12 (10-14)| 0.45 (0.10-2.08)    | 0.31|
| Negative conversion rate | 85% (72/85)| 79% (66/84)| 1.50 (0.66-3.38)    | 0.33|
| of SARS-CoV-2            |           |            |                     |     |
| ORF gene                 | 85% (72/85)| 80% (67/84)| 1.38 (0.60-3.16)    | 0.45|
| N gene                   | 85% (72/85)| 79% (66/84)| 1.50 (0.66-3.38)    | 0.33|
| Adverse events           | 3 (3%)    | 0 (0%)     |                     | 0.99|
| **Severe disease**       |           |            |                     |     |
| Number of patients, n/N  | 13/99     | 14/98      |                     | 1.82|
| Primary outcome a        |           |            | (0.07-49.05)        | 0.72|
| 1                        | 12 (92%)  | 13 (93%)   |                     |     |
| 2                        | 0 (0%)    | 0 (0%)     |                     |     |
| 3                        | 0 (0%)    | 0 (0%)     |                     |     |
| 4                        | 0 (0%)    | 1 (7%)     |                     |     |
| 5                        | 1 (8%)    | 0 (0%)     |                     |     |
| 6                        | 0 (0%)    | 0 (0%)     |                     |     |
| Secondary outcomes       |           |            |                     |     |
| 28-day mortality         | 0 (0%)    | 0 (0%)     |                     |     |
| Ventilator-free days     | 28 (28-28)| 28 (28-28)| 0.25 (0.01-5.16)    | 0.37|
| Length of hospital stay  | 14 (13-21)| 16 (14-19)| 1.13 (0.04-35.36)   | 0.94|
| Negative conversion rate | 67% (8/12)| 77% (10/13)| 1.40 (0.15-12.92)   | 0.77|
| of SARS-CoV-2            |           |            |                     |     |
| ORF gene                 | 67% (8/12)| 77% (10/13)| 1.40 (0.15-12.92)   | 0.77|
| N gene                   | 67% (8/12)| 77% (10/13)| 1.40 (0.15-12.92)   | 0.77|
| Adverse events           | 0 (0%)    | 1 (7%)     |                     | 0.99|
| Outcome | JS016 | Control | Comparison (95% CI) | p  |
|---------|-------|---------|---------------------|----|
|         |       |         |                     |    |
| No supplemental oxygen requirement at randomization |       |         |                     |    |
| Number of patients, n/N | 63/99 | 60/98 |                     |    |
| Primary outcome * |       |         |                     |    |
| 1 | 62 (98%) | 60 (100%) |                     | 0.99 |
| 2 | 0 (0%) | 0 (0%) |                     |    |
| 3 | 1 (2%) | 0 (0%) |                     |    |
| 4 | 0 (0%) | 0 (0%) |                     |    |
| 5 | 0 (8%) | 0 (0%) |                     |    |
| 6 | 0 (0%) | 0 (0%) |                     |    |
| Secondary outcomes |       |         |                     |    |
| 28-day mortality | 0 (0%) | 0 (0%) |                     |    |
| Ventilator-free days within 28 days, median (IQR) | 28 (28-28) | 28 (28-28) |                     | 1.0 |
| Length of hospital stay, days, median (IQR) | 12 (10-14) | 14 (11-17) | 0.19 (0.04-1.07) | 0.06 |
| Negative conversion rate of SARS-CoV-2 nucleic acid on day 14 b | 90% (57/63) | 77% (46/60) | 2.90 (1.03-8.16) | 0.04 |
| ORF gene | 90% (57/63) | 78% (47/60) | 2.64 (0.93-7.52) | 0.07 |
| N gene | 90% (57/63) | 77% (46/60) | 2.90 (1.03-8.16) | 0.04 |
| Adverse events | 1 (2%) | 0 (0%) |                     | 0.96 |
| Supplemental oxygen requirement at randomization |       |         |                     |    |
| Number of patients, n/N | 36/99 | 38/98 |                     |    |
| Primary outcome * |       |         |                     | 0.72 (0.04-12.07) | 0.82 |
| 1 | 33 (92%) | 37 (97%) |                     |    |
| 2 | 0 (0%) | 0 (0%) |                     |    |
| 3 | 0 (0%) | 0 (0%) |                     |    |
| 4 | 0 (0%) | 1 (3%) |                     |    |
| 5 | 2 (5%) | 0 (0%) |                     |    |
| 6 | 1 (3%) | 0 (0%) |                     |    |
| Secondary outcomes |       |         |                     |    |
| 28-day mortality | 1 (3%) | 0 (0%) |                     | 0.99 |
| Ventilator-free days within 28 days, median (IQR) | 28 (28-28) | 28 (28-28) | 0.21 (0.03-1.59) | 0.13 |
| Length of hospital stay, days, median (IQR) | 14 (12-21) | 14 (11-17) | 3.15 (0.31-32.25) | 0.34 |
| Negative conversion rate of SARS-CoV-2 nucleic acid on day 14 b | 68% (23/34) | 81% (30/37) | 0.49 (0.15-1.62) | 0.24 |
| ORF gene | 68% (23/34) | 81% (30/37) | 0.49 (0.15-1.62) | 0.24 |
| N gene | 68% (23/34) | 81% (30/37) | 0.49 (0.15-1.62) | 0.24 |
| Adverse events | 2 (5%) | 1 (3%) | 2.51 (0.16-39.13) | 0.51 |
| Outcome                  | JS016          | Control        | Comparison (95% CI) | p    |
|--------------------------|----------------|----------------|---------------------|------|
|                          | Number of patients, n/N |                |                     |      |
|                          | 13/99          | 19/98          |                     |      |
| ≤ 4 days since symptom onset |                |                |                     |      |
| Primary outcome a         | 13 (100%)      | 18 (95%)       |                     | 1.0  |
| 1                        | 0 (0%)         | 0 (0%)         |                     |      |
| 2                        | 0 (0%)         | 0 (0%)         |                     |      |
| 3                        | 0 (0%)         | 0 (0%)         |                     |      |
| 4                        | 0 (0%)         | 1 (5%)         |                     |      |
| 5                        | 0 (0%)         | 0 (0%)         |                     |      |
| 6                        | 0 (0%)         | 0 (0%)         |                     |      |
| Secondary outcomes       |                |                |                     |      |
| 28-day mortality         | 0 (0%)         | 0 (0%)         |                     |      |
| Ventilator-free days within 28 days, median (IQR) | 28 (28-28) | 28 (28-28) | 1.0 |
| Length of hospital stay, days, median (IQR) | 13 (11-14) | 18 (14-22) | 0.01 (0-0.17) | 0.003 |
| Negative conversion rate of SARS-CoV-2 nucleic acid on day 14 b | 92% (12/13) | 61% (11/18) | 22.58 (1.03-493.31) | 0.048 |
| ORF gene                 | 92% (12/13) | 61% (11/18) | 22.58 (1.03-493.31) | 0.048 |
| N gene                   | 92% (12/13) | 61% (11/18) | 22.58 (1.03-493.31) | 0.048 |
| Adverse events           | 0 (0%)         | 0 (0%)         |                     |      |
| > 4 days since symptom onset |                |                |                     |      |
| Primary outcome a         | 55 (93%)       | 52 (100%)      |                     | 0.99 |
| 1                        | 0 (0%)         | 0 (0%)         |                     |      |
| 2                        | 1 (2%)         | 0 (0%)         |                     |      |
| 3                        | 0 (0%)         | 0 (0%)         |                     |      |
| 4                        | 2 (3%)         | 0 (0%)         |                     |      |
| 5                        | 1 (2%)         | 0 (0%)         |                     |      |
| 6                        | 0 (0%)         | 0 (0%)         |                     |      |
| Secondary outcomes       |                |                |                     |      |
| 28-day mortality         | 1 (2%)         | 0 (0%)         |                     | 0.99 |
| Ventilator-free days within 28 days, median (IQR) | 28 (28-28) | 28 (28-28) | 0.34 (0.09-1.33) | 0.12 |
| Length of hospital stay, days, median (IQR) | 13 (11-14) | 18 (14-22) | 2.16 (0.33-14.26) | 0.42 |
| Negative conversion rate of SARS-CoV-2 nucleic acid on day 14 b | 81% (46/57) | 85% (44/52) | 0.69 (0.23-2.06) | 0.51 |
| ORF gene                 | 81% (46/57) | 87% (45/52) | 0.56 (0.18-1.76) | 0.32 |
| N gene                   | 81% (46/57) | 85% (44/52) | 0.69 (0.23-2.06) | 0.51 |
| Adverse events           | 2 (3%)         | 1 (2%)         | 2.36 (0.18-31.77) | 0.52 |

a A score of 1 indicated not hospitalized; 2, hospitalized without supplemental oxygen; 3, supplemental oxygen; 4, noninvasive ventilation or high flow nasal cannula; 5, invasive ventilation or ECMO; and 6, death.

b SARS-CoV-2 nucleic acid was defined as negative if both ORF and N gene turned negative.
Table S7. Imputation of Missing Data for SARS-CoV-2 Nucleic Acid Tests

| SARS-CoV-2 Nucleic acid tests | Original data missing | Data imputation a | Data missing in final analysis |
|-------------------------------|-----------------------|-------------------|-------------------------------|
| Day 7                         |                       |                   |                               |
| ORF gene                      | 55% (109/197)         | 54% (106/197)     | 1.5% (3/197)                  |
| N gene                        | 46% (91/197)          | 45% (88/197)      | 1.5% (3/197)                  |
| Day 14                        |                       |                   |                               |
| ORF gene                      | 84% (165/197)         | 82% (162/197)     | 1.5% (3/197)                  |
| N gene                        | 84% (165/197)         | 82% (162/197)     | 1.5% (3/197)                  |
| Day 21                        |                       |                   |                               |
| ORF gene                      | 95% (188/197)         | 94% (185/197)     | 1.5% (3/197)                  |
| N gene                        | 94% (185/197)         | 92% (182/197)     | 1.5% (3/197)                  |

a Since one of the requisites for discharge was two consecutive negative tests of SARS-CoV-2 nucleic acid, nucleic acid tests were imputed to be negative if the patient had already been discharged.
Protocol

Efficacy and Safety of a Recombinant Neutralizing Human Anti-SARS-CoV-2 Monoclonal Antibody (JS016) in Hospitalized Chinese Patients with SARS-CoV-2 Infection (COVID-19)

Short title: Efficacy and Safety of JS016 in COVID-19 Patients

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1. Protocol Summary

1.1 Rationale
Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a global pandemic including millions of critical cases and deaths. There is an urgent need for effective and safe therapies. JS016 is a recombinant neutralizing human SARS-CoV-2 monoclonal antibody binding to SARS-CoV-2 S protein, and thus provides potential therapeutic effects by blocking the attachment and entry of the virus into human cells. This study aims to evaluate the efficacy and safety of JS016 in patients hospitalized with COVID-19. The data from this study will inform decisions of the clinical use of JS016.

1.2 Design
This is a multicenter, randomized, open-label, controlled trial to evaluate the efficacy and safety of JS016 in patients hospitalized with COVID-19. Patients hospitalized to participating hospitals with moderate to severe COVID-19 will be randomized to receive standard care or standard care plus a single intravenous dose of JS016, and followed up for 28 days after randomization. The primary outcome, for clinical efficacy evaluation, is a six-level ordinal scale of clinical status on day 28 since randomization. Secondary outcomes include safety outcomes and other endpoints reflecting clinical efficacy. We plan to enroll a sample size of 200 participants. There will be a Data and Safety Monitoring Board.

2. Background and Study Rationale
Since the first reports of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the illness is still far from optimal control. The World Health Organization (WHO) declared COVID-19 outbreak a global pandemic on March 11, 2020. Globally, as of Jan 2021, there have been more than 100 million confirmed cases, including more than 2.5 million deaths, reported to WHO. 5-32% of patients required ICU admission, and mortality rates varies between 1.4-33%\(^1\)-9. However, except dexamethasone which has been shown to decrease mortality\(^{10}\), there is a lack of additional effective and safe therapies.

The SARS-CoV-2 enters host cells through binding of the spike (S) protein to the cell surface receptor angiotensin-converting enzyme 2 (ACE2)\(^{11}\). As the crucial component of viral surface, the S protein can be further separated into S1 and S2 subdomains, with S1 binding to the host receptor and S2 mediating membrane fusion. The receptor-binding domain (RBD) at the S1 C-terminal domain engages cell surface ACE2 receptor. Once in the cell, the virus completes genome replication, protein translation, assembly, and shedding.

Recombinant neutralizing human SARS-CoV-2 monoclonal antibody JS016, obtained from a B lymphocyte of a COVID-19 survivor, binds with high affinity to the RBD within the S1 subdomain of the SARS-CoV-2 S protein, thus blocks the binding between the virus and the cell surface receptor ACE2. The blocking of viral entry into cells is expected to relieve symptoms, mitigate the severity of disease, and improve clinical outcomes in patients infected with COVID-19. In vitro study and animal models showed potent neutralizing and therapeutic effects of JS016 on SARS-CoV-2 infection\(^{12}\). Two phase I trials among healthy volunteers has demonstrated a tolerable and safe drug profile of JS016.
This study aims to evaluate the efficacy and safety of JS016 in patients hospitalized with COVID-19. The data from this study will inform decisions of the clinical use of JS016.

3. Study Design
This is a phase 2/3, multicenter, randomized, open-label, controlled trial to evaluate the efficacy and safety of JS016 in patients hospitalized with moderate or severe COVID-19 illness.

3.1 Participating Hospitals
The First Affiliated Hospital of Harbin Medical University, Heilongjiang, China
The First Hospital of Suihua, Heilongjiang, China
Shijiazhuang People’s Hospital, Hebei, China

3.2 Study Population
3.2.1 Inclusion Criteria
Participants are eligible to be included in the study only if all of the following criteria apply:
1. Between 18 to 85 years of age at the time of randomization
2. With confirmed moderate or severe SARS-CoV-2 infection (COVID-19) according to Eighth Edition of Clinical Practice of COVID-19 issued by China National Health Commission
3. Within 7 days since symptom onset or 4 days since the development of severe illness

3.2.2 Exclusion Criteria
Participants are excluded from the study if any of the following criteria apply:
1. Critical COVID-19 illness
2. Tested positive of SARS-CoV-2 specific antibodies, including immunoglobulin G (IgG) and immunoglobulin M (IgM) before enrollment
3. Class III or IV heart failure, or left ventricular ejection fraction lower than 30 percent
4. Confirmed or suspected active tuberculosis
5. Chronic renal failure requiring renal replacement therapy
6. Malignancy, including solid and hematologic malignancy
7. Pregnant or breastfeeding

3.2.3 Definitions
Suspected case of SARS-CoV-2 infection is defined as a person who meets:
One or more epidemiological criteria and two or more clinical criteria
OR
Two or more clinical criteria and a positive test of SARS-CoV-2 specific immunoglobulin M (IgM)
OR
All of the three clinical criteria, in the absence of epidemiological history

Epidemiological Criteria:
Residing or travel to a community with COVID-19 case any time within the 14 days prior to symptom onset
Contact of SARS-CoV-2 infected patients any time within the 14 days prior to symptom onset
Contact of patients with fever or respiratory tract symptoms from a community with COVID-19 case any time within the 14 days prior to symptom onset
Cluster onset, i.e., two or more cases with fever and/or respiratory tract symptoms in settings like family, office, or class, within 14 days

Clinical Criteria:
Fever and/or COVID-19 related symptoms
Typical chest imaging findings suggestive of COVID-19
Normal or decreased white blood cell and lymphocyte count

Confirmed case of SARS-CoV-2 infection is defined as a suspected case with a positive pathogenic or serologic test, including:
A positive RT-PCR test of SARS-CoV-2 nucleic acid
Viral genetic sequence highly homologous to the known sequence of SARS-CoV-2
A positive test of SARS-CoV-2 specific antibodies, including IgM and IgG
Positive conversion of SARS-CoV-2 specific IgG, an increase of IgG titer by four times or more

Disease Severity:
Moderate illness is defined as fever or respiratory tract symptoms with pulmonary infiltration.
Severe illness is diagnosed if a patient presents with any of the following conditions:
1. Dyspnea or respiratory rate ≥ 30 per minute
2. Arterial oxygen saturation ≤ 93% on room air at sea level
3. A ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) ≤ 300mmHg
4. Progressive worsening of symptoms, and pulmonary infiltration progressing by more than 50 percent within 24 to 48 hours.

Critical illness is diagnosed if a patient develops respiratory failure requiring mechanical ventilation, shock, and/or multiple organ dysfunction requiring ICU admission.

3.3 Intervention
Participants are randomly assigned in a 1:1 ratio to receive standard care (control group) or standard care plus a single intravenous infusion of JS016, stratified by sites and disease severity at randomization (i.e., moderate or severe illness). A dose of 50mg/kg is based on tolerability, safety, and pharmacokinetic data. The standard care, based on the Eighth Edition of Clinical Practice of COVID-19 issued by China National Health Commission, includes monitoring, supplemental oxygen, respiratory support, and other supportive therapies. Other medications are allowed except for those providing exogenous antibodies against SARS-CoV-2.

3.4 Objectives and outcomes

| Objectives                  | Outcomes                                                                 |
|-----------------------------|--------------------------------------------------------------------------|
| Primary                     | Six-level ordinal scale of clinical status on 28 days since randomization¹⁴-¹⁶ (eTable 1) |
| Efficacy of JS016 on clinical status |                                                                           |
| Secondary                   |                                                                           |
Efficacy of JS016 on clinical outcomes
- Mortality rate within 28 days since randomization
- Ventilator free days within 28 days since randomization
- Length of hospital stay

Efficacy of JS016 on viral clearance
- Negative conversion rate of SARS-CoV-2 nucleic acid on day 14 since randomization.
- Negative conversion rate of SARS-CoV-2 nucleic acid on day 7 and 21 will also be recorded. SARS-CoV-2 nucleic acid was defined as negative if both ORF and N gene turned negative.

Safety assessment
- Adverse events (AEs) including allergic reaction, secondary infection, elevated alanine or aspartate transaminase (ALT or AST), acute kidney injury, acute myocardial infarction, septic shock, and gastrointestinal bleeding

### Table 1. The primary outcome: six-level ordinal scale of clinical status

| Score | Clinical status                                                      |
|-------|---------------------------------------------------------------------|
| 1     | Not hospitalized and without supplemental oxygen                   |
| 2     | Hospitalized without supplemental oxygen                            |
| 3     | Hospitalized with supplemental oxygen                               |
| 4     | Hospitalized with noninvasive ventilation or high flow nasal cannula|
| 5     | Hospitalized with invasive ventilation or ECMO                       |
| 6     | Death                                                                |

### 3.5 Data Collection
Data are collected on randomization and day 7, 14, 21, and 28 since randomization. Case report form is attached in the Appendix.

### 3.6 Schedule of Activities

| Study day               | Screen | Randomization | Day 2 | Day 7 | Day 14 | Day 21 | Day 28 |
|-------------------------|--------|---------------|-------|-------|--------|--------|--------|
| Informed consent        | X      |               |       |       |        |        |        |
| Inclusion and exclusion | X      |               |       |       |        |        |        |
| criteria review          |        |               |       |       |        |        |        |
| Demographics            |        |               |       |       |        |        |        |
| Coexisting conditions   |        |               |       |       |        |        |        |
| Onset date and symptoms |        |               |       |       |        |        |        |
| Height                  |        |               |       |       |        |        |        |
| **Weight**                                      |   |   |   |   |
|------------------------------------------------|---|---|---|---|
| Vital signs and peripheral oxygen saturation (SpO₂) | X | X | X | X |
| Respiratory support and parameters               | X | X | X | X |
| Vasopressors and dosage                          | X | X | X | X |
| Complete blood count                             | X | X | X | X |
| C-reactive protein (CRP) or high-sensitivity CRP | X | X | X | X |
| Chemistry panel                                  | X | X | X | X |
| Bilirubin                                       | X | X | X | X |
| Alanine transaminase (ALT)                       | X | X | X | X |
| Aspartate transaminase (AST)                     | X | X | X | X |
| Creatinine                                      | X | X | X | X |
| Lactate dehydrogenase                            | X | X | X | X |
| Arterial blood gas                               | X | X | X | X |
| SARS-CoV-2 specific antibody test                | X | X | X | X |
| SARS-CoV-2 nucleic acid test                     |   | X | X | X |
| Adverse events                                   | X | X | X | X | X |
| Clinical status                                  |   |   |   | X |
| Administer study intervention (IV infusion)      | X |   |   |   |
| Other medications                                | X | X | X | X | X |

### 4. Sample Size Estimates

According to the distribution across the six-level ordinal outcome of another study among similar patients, we calculated that the initial enrollment of 200 patients would have 80% power to detect an odds ratio of 1.50 for a better outcome category with a one-sided type I error of 0.3. The rationale of choosing a high type I error rate is to prevent enrolling too many patients to an investigational drug that is unlikely to be effective.

### 5. Statistical Analyses

The efficacy will be analyzed among all randomized participants who received study intervention and provided at least one post-randomization measurement of outcomes. Participants will be analyzed according to the intervention to which they were randomized. (Intention to treat). Safety profile will be analyzed according to the intervention they actually received.

The primary outcome will be analyzed by mixed ordinal logistic regression. Binary outcomes will be compared with the use of mixed logistic-regression model. 28-day mortality and negative
conversion rates of SARS-CoV-2 nucleic acid will be analyzed by Cox proportional-hazards model. Continuous outcomes will be assessed with the use of generalized linear models or general linear models for repeated measures. All models will be adjusted for age, site, and clinical ordinal scale at randomization. P value less than 0.05 will be considered statistically significant. Statistical analyses will be performed by SPSS 22.0.

6. Data and Safety Monitoring Plan
6.1 Benefit/Risk Assessment
Since JS016 is a neutralizing antibody originated from human, off-target binding and tissue cross-reactivity is considered unlikely. Furthermore, the introduction of amino acid substitutions in the fragment crystallizable (Fc) region of JS016 lowered the risk of antibody-dependent enhancement effect and Fc-mediated acute lung injury in animal models. Potential risks of allergic reaction are also considered low based on good tolerability and safety profile of JS016 among healthy volunteers. Given the potent neutralizing activity of JS016 and the lack of effective therapy for COVID-19, the overall assessment of benefit and risk is favorable.

6.2 Protection against Study Risks
All participants will be acknowledged of the aim, process, and potential risks and benefits of the study. Informed consent will be obtained. Due to strict respiratory isolation regulations in participating hospitals, verbal consent will be allowed if approved by ethics committees. The confidentiality of all study participants will be protected. A participant may withdraw from the study at any time at the request of his/her own or representative, but data collected before the withdrawal can be used for analyses.

6.3 Management of Allergic Reactions
Infusions of the study drug will be administered at a controlled rate, and participants will be closely monitored during infusion. Infusing rate will be adjusted or stopped if indicated. Allergic reactions occur during or within six hours after infusion, and include symptoms and signs of, but do not limit to, fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus, myalgia, and dizziness. The severity of allergic reactions will be evaluated using the Division of Allergy and Infectious Diseases (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events and managed by investigators based on standard clinical practice. If the infusion is definitively discontinued, the participant will remain in the study for follow-up and further evaluations shown in the SoA.

6.4 Adverse Events (AEs) and Serious Adverse Events (SAEs)
An AE is any untoward or unfavorable medical occurrence in a participant, including any abnormal sign, symptom, or disease, temporally associated with their participation in study, whether or not considered related to the study. If a diagnosis is clinically evident (or subsequently determined), the diagnosis, rather than the individual signs and symptoms or lab abnormalities, will be recorded as the AE. Adverse events are serious if they lead to one of the following outcomes:
- Death
- Life-threatening (i.e., an immediate threat to life)
• Hospitalization or prolongation of hospitalization
• Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
• Congenital abnormalities/birth defects
• Other important medical events that may jeopardize the participant and/or may require intervention to prevent one of the outcomes listed above

Severity of AEs will be evaluated according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events\textsuperscript{18}. AEs will be reported by participants, caregivers, or investigators, the last of whom are responsible for documenting, recording, and following up AEs. All AEs and SAEs will be collected from randomization to day 28, and followed up until resolution, stabilization, or loss of follow-up. The DSMB may request to stop enrollment for safety reasons, inform ethics committees, and determine whether it is safe to resume the study.

7. Data and Safety Monitoring
Study supervisors will be responsible for ensuring participants’ safety and for reporting AEs to the Ethics Committees and Data and Safety Monitor Board (DSMB). There will be an independent DSMB who are responsible to evaluate the progress of the study and the quality of data collection, management, and analyses. Another goal of the DSMB is to review interim data and use pre-specified rules to determine the continuing safety and efficacy of the investigational drug. Only masked data will be presented to the DSMB. All data are confidential. Participant identities will be kept confidential unless safety concerns necessitate unmasking some or all data.
**Appendix**

**Case Report Form**

### Site

- □ The First Affiliated Hospital of Harbin Medical University
- □ The First Hospital of Suihua
- □ Shijiazhuang People’s Hospital

### Demographics and Coexisting Conditions

| Initial of name | Gender | □ Male | □ Female |
|-----------------|--------|--------|----------|
| Age             | Date of admission |
| Height          | cm      | Weight | kg       |
| Coexisting conditions | □ Diabetes | □ Coronary heart disease | □ Malignancy |
|                 | □ Hypertension | □ Chronic lung disease | □ Chronic kidney disease |

### Disease Onset

| Date of symptom onset |
|-----------------------|
| Symptoms of onset | □ Fever | □ Dyspnea | □ Cough | □ Others |

### Randomization

| Date of randomization | Disease severity at randomization | □ Moderate | □ Severe |
|-----------------------|----------------------------------|------------|---------|
| Assignment            | □ JS016 | □ Control |

### Clinical and Laboratory Parameters

| Drug | Dosage | Respiratory rate (/min) | SpO₂ (%) | Respiratory support | Randomization | Day 2 | Day 7 | Day 14 | Day 21 |
|------|--------|-------------------------|----------|---------------------|---------------|-------|-------|--------|--------|
|      |        |                         |          | □ Nasal cannula     |               |       |       |        |        |
|      |        |                         |          | Oxygen flow (L/min) |               |       |       |        |        |
|      |        |                         |          | □ HFNC              |               |       |       |        |        |
|      |        |                         |          | Oxygen flow (L/min) |               |       |       |        |        |
|      |        |                         |          | FiO₂ (%)            |               |       |       |        |        |
|      |        |                         |          | □ NIV               |               |       |       |        |        |
|      |        |                         |          | FiO₂ (%)            |               |       |       |        |        |
|      |        |                         |          | EPAP (cmH₂O)        |               |       |       |        |        |
| Respiratory support | Randomization | Day 2 | Day 7 | Day 14 | Day 21 |
|--------------------|---------------|-------|-------|--------|--------|
| □ IMV              |               |       |       |        |        |
| FiO₂ (%)           |               |       |       |        |        |
| PEEP (cmH₂O)       |               |       |       |        |        |
| □ ECMO             |               |       |       |        |        |
| pH                 |               |       |       |        |        |
| PaO₂ (mmHg)        |               |       |       |        |        |
| PaCO₂ (mmHg)       |               |       |       |        |        |
| HCO₃ (mmol/L)      |               |       |       |        |        |
| White cell count (/μL) |           |       |       |        |        |
| Lymphocyte count (/μL) |            |       |       |        |        |
| Platelet count (/μL) |             |       |       |        |        |
| CRP or hsCRP (mg/L) |               |       |       |        |        |
| Total bilirubin (μmol/L) |           |       |       |        |        |
| LDH (U/L)          |               |       |       |        |        |
| ALT (U/L)          |               |       |       |        |        |
| Creatinine (μmol/L) |               |       |       |        |        |
| SARS-CoV-2 IgG     |               |       |       |        |        |
| SARS-CoV-2 IgM     |               |       |       |        |        |
| SARS-CoV-2 CT value|               |       |       |        |        |
| N gene             |               |       |       |        |        |
| ORF gene           |               |       |       |        |        |

**Adverse Events (from randomization to day 28)**

- □ Allergic reaction
- □ Acute kidney injury
- □ Elevated ALT or AST
- □ Secondary infection
- □ Septic shock
- □ Gastrointestinal bleeding
- □ Others:

**Medications (from randomization to day 28)**

- □ Antiviral medication:
- Traditional Chinese Medicine □ Y □ N
- Glucocorticoids □ Y □ N
- □ Others:

**Supportive Therapies (from randomization to day 28)**

|               | □ NIV | □ IMV | □ Vasopressor | □ CRRT | □ ECMO |
|---------------|-------|-------|--------------|--------|--------|
| Initiation date |       |       |              |        |        |
| Termination date |     |       |              |        |        |

**Clinical outcomes (day 28 since randomization)**

- □ Death Date of death
- □ Discharge Date of discharge
- □ Hospitalized □ Nasal cannula □ HFNC □ NIV □ IMV □ ECMO
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