**Supplementary Material**

**Methods**

**Selection criteria**

RSV-related illness excluded, patients had to be in otherwise good health based on physical examination, medical history, vital signs, electrocardiogram (ECG) and laboratory tests performed at screening. Infants were excluded from study enrollment if the initial hospitalization was in the intensive care unit and/or if they were in need for invasive endotracheal mechanical ventilation, had major congenital anomalies and/or known or suspected immunodeficiency.

**Study design**

Study drug administration was to be started as soon as possible after confirmation of eligibility, and ≤8 hours after randomization. Study drug was to be administered q.d. on Days 1 through 7, with dosing recommended to be administered under fed conditions at approximately the same time each day.

**Assessments**

PK assessments were based on sparse sampling over 7 days, whereby each patient had 2 blood samples taken to determine JNJ-8678 concentrations. Bio-analyses were performed using liquid chromatography-tandem mass spectrometry.

RSV viral load was measured from mid-turbinate nasal swab samples using a quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR, performance characteristics below) assay for RSV RNA.

Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS) questionnaires were completed separately by the clinician and the parent(s)/caregiver(s) on an electronic instrument provided at the study site. Clinician PRESORS questionnaires were completed on an electronic device twice daily by the Investigator for the duration of hospitalization (recall period 12 hours) and once
on Day 7, Day 14, and Day 28 upon discharge of the patient (recall period 24 hours). Parent(s)/caregiver(s) PRESORS questionnaires were completed 3 times daily from Day 1 through Day 14 and q.d. Day 15 through Day 28. Analysis of PRESORS completed by clinician and parent(s)/caregiver(s) were summarized descriptively and presented graphically (data not shown). No difference was observed between JNJ-8678 (combined) treatment group and placebo. Viral load data were determined using an RSV-A/B qRT-PCR assay (DDL Diagnostic Laboratory, Rijswijk, The Netherlands) with a lower limit of quantification (LLOQ) of \(3.00 \log_{10} \text{copies/mL}\) for RSV-A and \(2.40 \log_{10} \text{copies/mL}\) for RSV-B and a limit of detection (LOD) of \(2.75 \log_{10} \text{copies/mL}\) for RSV-A and \(1.89 \log_{10} \text{copies/mL}\) for RSV-B. Viral load results that were positive but non-quantifiable (target detected) were imputed with the midpoint between LLOQ and LOD on the log scale (i.e., \(2.87 \log_{10} \text{copies/mL}\) for RSV-A and \(2.14 \log_{10} \text{copies/mL}\) for RSV-B). Undetectable viral load results (target not detected) were imputed as 0. Viral resistance was analyzed using NGS (Illumina, San Diego, CA, USA) of the full-length RSV F-gene, with a 1% read frequency cut-off (DDL Diagnostic Laboratory, The Netherlands). NGS was performed at baseline (screening or Day 1), at the last evaluable on-treatment time point, and during follow-up in selected samples from active and placebo patients, where the RSV viral load was sufficiently high to permit successful amplification and sequencing of the sample. The resistance analyses for JNJ-8678 considered lists of F-protein amino acid positions of specific interest (list of 8 positions: 141, 143, 394, 398, 400, 486, 488, and 489, based on in-vitro selection experiments with JNJ-8678 and/or in-vitro reduced susceptibility to JNJ-8678). The resistance analyses for the class of RSV fusion inhibitors considered a list of 20 positions: 127, 138, 140, 141, 143, 144, 323, 338, 392, 394, 398, 399, 400, 401, 474, 486, 487, 488, 489, and 517, based on in-vitro selection experiments, clinical observations, and/or in-vitro reduced susceptibility to RSV fusion inhibitors [1–3].

Genetic variations were defined as changes from reference sequence RSV-A Long (GenBank Accession number AY911262) for RSV-A samples and RSV-B strain 9320 (GenBank Accession number
AY353550) for RSV-B samples. Genetic variations were analyzed with an NGS-read frequency of ≥3%.

Baseline polymorphisms were defined as genetic variations detected at baseline with an NGS-read frequency of ≥15%. Emerging genetic variations were defined as genetic variations detected post-baseline with an NGS-read frequency of ≥15% but not present at baseline (read frequency <3%).

**Statistical Analysis Methods and Sample Size**

The PK analysis set comprised all patients treated with any dose of JNJ-8678 for whom PK samples were collected. PK parameters were derived using pop-PK modeling. The AUC\textsubscript{24h}, minimum plasma concentration (C\textsubscript{min}), and maximum plasma concentration (C\textsubscript{max}) were estimated for Days 1, 3, and 7.

The safety analysis set comprised all patients who received any dose of study drug (JNJ-8678 or placebo).

The efficacy set (RSV viral load and PD [including exploratory]) endpoints were analyzed in patients who had been confirmed as RSV positive by central testing and who had received at least 1 dose of study drug (the ‘as-treated-infected’ population). Data were analyzed graphically and descriptively.

Change from baseline viral load was explored using a general linear model at a specific day, with JNJ-8678 dose level and baseline viral load as covariates.

In Part 1, sample size for each age group was calculated to achieve a 95% confidence interval (CI) within 60–140% of the geometric mean estimates for the PK parameters. This was ≥9 patients for linear clearance and ≥6 patients for the central volume of distribution. In Part 2, sample size was calculated (24 receiving the selected dose, pooled over all age groups) to obtain estimates of the mean viral load AUC (from Day 1 to 7; secondary endpoint) to fall within ± 50 log\textsubscript{10} 144 hours.copies/mL of the true value with 95% confidence. With an assumed standard deviation (SD) of 120 log\textsubscript{10} 144 hours.copies/mL, 24 patients receiving the selected dose, pooled over all 3 age groups, were required. The expected total number of placebo patients (N=13) across both parts of the study would allow the estimation of the mean viral load AUC in the control group to fall within
±75 $\log_{10}$ 144 hours.copies/mL of the true value with 95% confidence (95% CI half-width) with an expected SD of 120 $\log_{10}$ 144 hours.copies/mL.

**Supplementary Material References**

1. Roymans D, Alnajjar SS, Battles MB, et al. Therapeutic efficacy of a respiratory syncytial virus fusion inhibitor. Nat Commun 2017; 8:167.

2. Marty FM, Chemaly RF, Mullane KM, et al. A phase 2b, randomized, double-blind, placebo-controlled multicenter study evaluating antiviral effects, pharmacokinetics, safety, and tolerability of presatovir in hematopoietic cell transplant recipients with respiratory syncytial virus (RSV) infection of the lower respiratory tract [published online ahead of print, 2019 Dec 3]. Clin Infect Dis 2019; ciz1167. doi:10.1093/cid/ciz1167. Accessed 22 January 2020.

3. Chemaly RF, Dadwal SS, Bergeron A, et al. A phase 2, randomized, double-blind, placebo-controlled trial of presatovir for the treatment of respiratory syncytial virus upper respiratory tract infection in hematopoietic-cell transplant recipients [published online ahead of print, 2019 Dec 3]. Clin Infect Dis. 2019;ciz1166. doi:10.1093/cid/ciz1166. Accessed 22 January 2020.
Supplementary Table S1. PRESORS Questionnaires Completed Separately by Clinician and Parent(s)/Caregiver(s)

**Clinician PRESORS**

| Question | Description |
|----------|-------------|
| 1        | Worst score per day for the assessment of the patient’s activity level |
| 2        | Worst score per day for the assessment of the patient’s quality of sleep |
| 3        | Worst score per day for the assessment of the patient’s work of breathing |
| 3.1      | Worst score per day for the assessment of the presence of intercostal retractions |
| 3.2      | Worst score per day for the assessment of the presence of tracheosternal retractions |
| 3.3a     | Worst score per day for the assessment of the presence of nasal flaring |
| 3.3b     | Worst score per day for the assessment of the presence of head bobbing |
| 3.3c     | Worst score per day for the assessment of the presence of grunting |
| 3.3d     | Worst score per day for the assessment of the presence of central cyanosis |
| 4        | Worst score per day for the assessment of episodes of apnea |
| 5        | Worst score per day for the assessment of the frequency of the patient’s cough |
| 6        | Worst score per day for the assessment of the amount of the patient’s nasal secretions |
| 7        | Worst score per day for the assessment of the patient’s wheezing |
| 8        | Worst score per day for the assessment of the patient’s way of feeding |
| 8.1      | Worst score per day for the assessment of the patient’s amount of feeding |
| 9        | Worst score per day for the assessment of the patient’s overall health status |

**Parent(s)/caregiver(s) PRESORS**

| Question | Description |
|----------|-------------|
| 1        | Worst score per day for the assessment of the patient’s activity level |
| 2        | Worst score per day for the assessment of the patient’s quality of sleep |
| 3        | Worst score per day for the assessment of the patient’s amount of sleep |
| 4        | Worst score per day for the assessment of the patient’s crying/fussiness |
| 5        | Worst score per day for the assessment of the patient’s breathing sounds |
| 5.1      | Worst score per day for the assessment of the timing of occurrence of breathing sounds in the breathing cycle |
| 6        | Worst score per day for the assessment of the patient’s work of breathing |
| 6.1a     | Worst score per day for the assessment of the presence of breathing problems due to a stuffy or runny nose |
| Question       | Description                                                                                           |
|----------------|-------------------------------------------------------------------------------------------------------|
| 6.1b           | Worst score per day for the assessment of the presence of gasping or breathing pauses                   |
| 7              | Worst score per day for the assessment of the presence of signs of cyanosis                           |
| 8              | Worst score per day for the assessment of the frequency of the patient’s cough                        |
| 9              | Worst score per day for the assessment of frequency of vomiting or spitting-up by the patient          |
| 9.1            | Worst score per day for the assessment of vomiting or spitting-up during coughing                      |
| 10             | Worst score per day for the assessment of the patient’s amount of feeding                              |
| 11             | Worst score per day for the assessment of the patient’s amount of fluid intake                         |
| 12             | Worst score per day for the assessment of patient’s urination                                         |
| 16             | Worst score per day for the assessment of the patient’s overall health status                          |
## Supplementary Table S2. Viral Load Least Square Means of Change from Baseline JNJ-8678 by Dose Level versus Placebo in All Age Groups

| Analysis set: as treated-infected, n | JNJ-8678 | Placebo |
|--------------------------------------|----------|----------|
|                                      | Low 12   | Mid 12   | Mid-high 4 | High 9 | All Cohorts 7 |
| **Day 2**                            |          |          |            |
| LS mean (90% CI)                     | -1.66 (-2.32; -0.99) | -1.15 (-1.81; -0.49) | -1.71 (-2.85; -0.56) | -1.42 (-2.21; -0.63) | -0.12 (-1; 0.75) |
| LS difference versus placebo (90% CI) | -1.53 (-2.62; -0.44) | -1.02 (-2.12; 0.08) | -1.58 (-3.02; -0.14) | -1.3 (-2.51; -0.09) | - |
| **Day 3**                            |          |          |            |
| LS mean Estimate 90% CI              | -2.56 (-3.17; -1.95) | -1.24 (-1.85; -0.64) | -1.56 (-2.62; -0.51) | -2.24 (-2.97; -1.51) | -0.33 (-1.14; 0.48) |
| LS difference versus placebo Estimate 90% CI | -2.23 (-3.23; -1.22) | -0.91 (-1.93; 0.1) | -1.23 (-2.56; 0.1) | -1.91 (-3.02; -0.79) | - |
| **Day 4**                            |          |          |            |
| LS mean Estimate 90% CI              | -2.76 (-3.83; -1.7) | -2.39 (-3.52; -1.26) | -0.58 (-2.85; 1.7) | -3.4 (-4.63; -2.17) | -1.26 (-2.6; 0.08) |
| LS difference versus placebo Estimate 90% CI | -1.5 (-3.2; 0.19) | -1.13 (-2.89; 0.64) | 0.69 (-1.99; 3.36) | -2.14 (-4; -0.28) | - |
| **Day 5**                            |          |          |            |
| LS mean Estimate 90% CI              | -4.27 (-5.42; -3.12) | -3.02 (-4.9; -1.14) | -2.32 (-5.67; 1.03) | -3.06 (-4.99; -1.13) | -2.72 (-4.49; -0.96) |
| LS difference versus placebo Estimate 90% CI | -1.55 (-3.68; 0.58) | -0.3 (-2.88; 2.28) | 0.4 (-3.53; 4.33) | -0.34 (-3.07; 2.4) | - |
| **Day 6**                            |          |          |            |
| LS mean Estimate                     | -3.82   | -5.8     | -         | -2.76   | -4.02     |
|                | Low                  | 90% CI               | Mid                  | 90% CI               | Mid-high             | 90% CI               | High                  | 90% CI               | Placebo   | All Cohorts |
|----------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|-----------------------|----------------------|-----------|-------------|
| **90% CI**     |                      |                      |                      |                      |                      |                      |                       |                      |           |             |
| LS difference  |                      | (-5.47; -2.17)       |                      |                      | (-10.29; -1.3)       |                      |                      | (-4.87; -0.64)       | (-5.93; -2.1) |
| (versus placebo) | Estimate             | 0.2                  | -1.78                |                      | -                    | 1.26                 |                       | (-1.99; 4.51)        |           |             |
| **90% CI**     |                      | (-2.68; 3.08)        |                      |                      | (-5.88; 2.32)        |                      |                       |                      |           |             |
| **Day 7**      |                      |                      |                      |                      |                      |                      |                       |                      |           |             |
| LS mean        |                      |                      |                      |                      |                      |                      |                       |                      |           |             |
| Estimate       | -4.11                | (-5.16; -3.66)       | -4.14                | (-4.89; -3.4)        | -2.6                 | (-3.89; -1.31)       | -3.96                 | (-4.85; -3.06)       | -4.3      | (-5.29; -3.31) |
| **90% CI**     |                      | (-1.34; 1.12)        | (-1.09; 1.4)         |                      | (0.07; 3.32)         | (-1.02; 1.71)        |                       |                      |           |             |
| **Day 14**     |                      |                      |                      |                      |                      |                      |                       |                      |           |             |
| LS mean        |                      |                      |                      |                      |                      |                      |                       |                      |           |             |
| Estimate       | -3.96                | (-4.83; -3.09)       | -4.25                | (-5.11; -3.39)       | -4.15                | (-5.64; -2.66)       | -5.4                  | (-6.43; -4.37)       | -3.61     | (-4.76; -2.47) |
| **90% CI**     |                      | (-1.77; 1.07)        | (-2.08; 0.8)         | (-2.42; 1.34)        | (-3.37; -0.22)       |                       |                      |                      |           |             |
| **Day 28**     |                      |                      |                      |                      |                      |                      |                       |                      |           |             |
| LS mean        |                      |                      |                      |                      |                      |                      |                       |                      |           |             |
| Estimate       | -5.1                 | (-5.39; -4.81)       | -5.1                 | (-5.39; -4.81)       | -4.38                | (-4.88; -3.88)       | -4.77                 | (-5.11; -4.42)       | -5.1      | (-5.49; -4.72) |
| **90% CI**     |                      | (-0.48; 0.48)        | (-0.48; 0.49)        | (0.09; 1.36)         | 0.72                 | (0.09; 1.36)         | 0.34                  | (-0.19; 0.87)        |           |             |
### Supplementary Table S3. Viral load Least Square Means of Change from Baseline JNJ-8678 (Combined) versus Placebo in All Age Groups

|                        | JNJ-8678 All Cohorts | Placebo All Cohorts |
|------------------------|----------------------|---------------------|
| Analysis set: as treated-infected, n | 37                   | 7                   |

#### Day 2

|                      | Estimate    | 90% CI          | LS difference (with placebo) | Estimate    | 90% CI          |
|----------------------|-------------|-----------------|------------------------------|-------------|-----------------|
| LS mean              | -1.44       | -1.81; -1.07    | -1.13                        | -2.26       | -0.39           |
|                      |             |                 |                              |             |                 |

#### Day 3

|                      | Estimate    | 90% CI          | LS difference (with placebo) | Estimate    | 90% CI          |
|----------------------|-------------|-----------------|------------------------------|-------------|-----------------|
| LS mean              | -1.95       | -2.31; -1.58    | -1.18                        | -0.74       | -0.06           |
|                      |             |                 |                              |             |                 |

#### Day 4

|                      | Estimate    | 90% CI          | LS difference (with placebo) | Estimate    | 90% CI          |
|----------------------|-------------|-----------------|------------------------------|-------------|-----------------|
| LS mean              | -2.65       | -3.29; -2.02    | -2.61                        | -0.54       | -0.15           |
|                      |             |                 |                              |             |                 |

#### Day 5

|                      | Estimate    | 90% CI          | LS difference (with placebo) | Estimate    | 90% CI          |
|----------------------|-------------|-----------------|------------------------------|-------------|-----------------|
| LS mean              | -3.67       | -4.49; -2.85    | -4.31                        | -1.86       | -1.33           |
|                      |             |                 |                              |             |                 |

#### Day 6

|                      | Estimate    | 90% CI          | LS difference (with placebo) | Estimate    | 90% CI          |
|----------------------|-------------|-----------------|------------------------------|-------------|-----------------|
| LS mean              | -3.86       | -4.89; -2.84    | -5.23                        | -2.26       | -1.76           |
|                      |             |                 |                              |             |                 |

#### Day 7

|                      | Estimate    | 90% CI          | LS difference (with placebo) | Estimate    | 90% CI          |
|----------------------|-------------|-----------------|------------------------------|-------------|-----------------|
| LS mean              | -4.02       | -4.45; -3.59    | -5.29                        | -2.25       | 1.76            |
|                      |             |                 |                              |             |                 |

#### Day 14

|                      | Estimate    | 90% CI          | LS difference (with placebo) | Estimate    | 90% CI          |
|----------------------|-------------|-----------------|------------------------------|-------------|-----------------|
| LS mean              | -4.42       | -4.91; -3.92    | -4.82                        | -2.02       | -2.52           |
|                      |             |                 |                              |             |                 |

#### Day 28

|                      | Estimate    | 90% CI          | LS difference (with placebo) | Estimate    | 90% CI          |
|----------------------|-------------|-----------------|------------------------------|-------------|-----------------|
| LS mean              | -4.94       | -5.11; -4.77    | -5.49                        | -0.74       | -0.51           |
|                      |             |                 |                              |             |                 |
Supplementary Figure S1. Viral load: proportion of patients with undetectable and <LLOQ values over time by dose level in all age groups
Supplementary Figure S2. Viral load: LS difference in change from baseline (JNJ-8678 combined versus placebo): LS difference + 90% CI (adjusted for baseline) in the as treated-infected population
Supplementary Figure S3. Change from baseline viral load versus time between start of respiratory infection and first dosing for RSV-A and RSV-B by dose cohort