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Pharmacokinetics, Safety, and Antiviral Effects of Multiple Doses of the Respiratory Syncytial Virus (RSV) Fusion Protein Inhibitor, JNJ-53718678, in Infants Hospitalized With RSV Infection: A Randomized Phase 1b Study

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Background. This phase 1b study evaluated the pharmacokinetics, safety, and antiviral effects of the respiratory syncytial virus (RSV)–specific fusion inhibitor JNJ-53718678 (JNJ-8678) in hospitalized RSV-infected patients aged >1 to ≤24 months.

Methods. Patients categorized by age (cohort 1: ≥6 to ≤24 months; cohort 2: ≥3 to <6 months; cohort 3: >1 to <3 months) were randomized to oral JNJ-8678 or placebo once daily for 7 days. Dose increases followed data review committee recommendations (cohort 1: 2/6/8/9 mg/kg; cohort 2: 1.5/4.5/6 mg/kg; cohort 3: 1/3/5 mg/kg). Cohort 1 included a 9 mg/kg dose, as target exposures were not reached at lower doses. Sparse pharmacokinetic samples were assessed using population pharmacokinetics modeling. Safety was assessed by adverse events (AEs), laboratory tests, and electrocardiograms. To assess antiviral effects, RSV RNA viral load from nasal swabs was quantified over time using reverse-transcription quantitative polymerase chain reaction.

Results. Patients received JNJ-8678 (n = 37) or placebo (n = 7). Pharmacokinetic parameters were similar at the highest doses for cohorts 1–3 (area under the plasma concentration–time curve from time of administration up to 24 hours postdosing at day 7: 35 840, 34 980, and 39 627 ng × hour/mL, respectively). Two grade 3 AEs were reported (both bronchiolitis; 1 JNJ-8678, 1 placebo), reported as serious AEs; all other AEs were grade 1 or 2. Two additional serious AEs were reported (rhinitis [JNJ-8678]; pneumonia [placebo]). No deaths, grade 4 AEs, or AEs leading to discontinuation were reported. Median RSV viral load change from baseline in JNJ-8678 vs placebo by day 3 was −1.98 vs −0.32 $\log_{10}$ copies/mL.

Conclusions. In RSV-infected infants, JNJ-8678 was well tolerated. Target exposures were reached and antiviral activity was observed.

Clinical Trials Registration. NCT02593851.

Keywords. respiratory syncytial virus; fusion inhibitor; JNJ-53718678; JNJ-8678; infants.

Respiratory syncytial virus (RSV) is the leading cause of serious lower respiratory tract infections (LRTIs) in infants, and is a major cause of hospitalization and mortality worldwide [1, 2]. Globally in 2015, an estimated 3.2 million hospital admissions and 59 600 deaths were due to severe RSV LRTIs in children < 5 years old [1].

Although RSV infection is usually self-limiting, certain populations have a greater risk of severe disease (eg, infants with bronchopulmonary dysplasia or congenital heart disease) [3–5]. While these children are at particular risk of serious RSV infection, studies have shown that most serious episodes occur among otherwise healthy children born close to the RSV season [4], and infection rates peak in infants aged ≤3 months [5].

No direct-acting treatments are approved for RSV-associated bronchiolitis or pneumonia [2, 6, 7]. Options are limited to prophylaxis with palivizumab, a humanized monoclonal antibody with restricted indications, or aerosolized ribavirin, a nonspecific antiviral treatment [8–11]. The American Academy of Pediatrics does not recommend ribavirin to treat children with bronchiolitis [12]. The current standard of care for RSV

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infection is supportive treatment, which may include oxygenation and/or mechanical ventilation [6, 7, 13–15].

JNJ-53718678 (JNJ-8678) is an RSV-specific fusion inhibitor and a potential new treatment for RSV [16]. In vitro, JNJ-8678 showed potent activity against a panel of laboratory-derived and clinically isolated RSV-A and RSV-B strains (50% effective concentration, 0.09–9.50 ng/mL) [16]. In a human challenge study involving healthy volunteers, JNJ-8678 administered as a single dose (25–1000 mg) or multiple doses (250 mg every 24 hours, 500 mg every 24 hours, or 250 mg every 12 hours; fed conditions for 8 days) was well tolerated [17]. When healthy volunteers received 75–500 mg once daily [QD] for 7 days, JNJ-8768 substantially reduced both viral load and clinical disease severity. No clear exposure-response relationship was observed among the active doses [18]. However, as participants start experimental treatment in human challenge studies soon after they are infected with RSV, it remains to be seen how these outcomes translate to natural RSV infection.

This first-in-child phase 1b study evaluated the pharmacokinetics (PK) of multiple oral doses of JNJ-8678 in infants (>1 to ≤24 months of age) hospitalized with RSV infection, as well as safety/tolerability after 7 days of treatment. Since JNJ-8678 was previously generally well tolerated, with PK parameters stable over multiple doses and little accumulation over time in healthy adult volunteers [17], a multiple-dose escalation design was employed. Secondary objectives included the antiviral effects of JNJ-8678 and its impact on the clinical course of RSV infection.

METHODS

Patient Selection

Patients were infants born after a normal-term pregnancy (≥ 37 weeks) aged > 1 to ≤24 months, hospitalized ≤ 72 hours prior to randomization with RSV respiratory tract infection diagnosed by polymerase chain reaction (PCR)–based assay. Patients were stratified by age (≥6 to ≤24 months [cohort 1]; 3 to < 6 months [cohort 2]; >1 to < 3 months [cohort 3]). For full selection criteria and PCR-based assay performance characteristics, see the Supplementary Materials.

Study Design

This phase 1b, double-blind, placebo-controlled, randomized, multicenter, multiple ascending-dose study was conducted over 2 parts (Figure 1). Patients were randomized 4:1 on day 1 to oral JNJ-8678 or placebo for 7 days, except for the first dose cohort of each age group in which all patients received JNJ-8678. For full details on administration procedures, see the Supplementary Materials. All patients were evaluated for 28 days postrandomization.

The study was conducted in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulatory requirements. Patients' legally acceptable representatives provided written informed consent for study participation. The study protocol and amendment(s) were reviewed by an independent ethics committee.

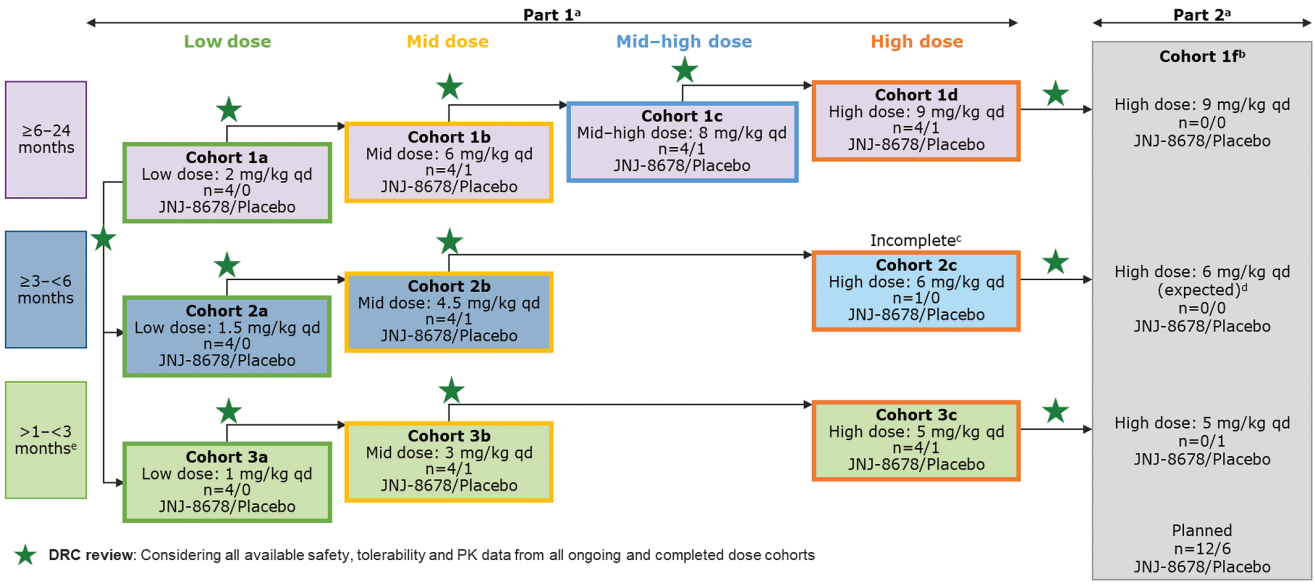

Figure 1. Study design. Patient disposition (parts 1 and 2) at time of the final analysis for each dose cohort. Within each age group (cohorts 1–3) and dose level (cohorts a–d, f), patients were randomized to JNJ-53718678 (JNJ-8678) or placebo (except for cohorts 1a, 2a, and 3a, who all received JNJ-8678). Data were categorized by dose level for analysis: low (cohorts 1a, 2a, and 3a), mid (cohorts 1b, 2b, and 3b), mid-high (cohort 1c), and high (cohorts 1d, 2c, and 3c). [a]Study drug was administered for 7 days. [b]Planned randomization active: placebo was 2:1. [c]Planned randomization active: placebo was 4:1. [d]The target dose regimen for part 2 of cohort f was not yet determined when the study was terminated. [e]This age group had to include overall at least 5 patients >1 month and ≤2 months of age over the first 3 cohorts combined, with a minimum of 1 patient >1 month and ≤2 months of age in each of these cohorts. Abbreviations: DRC, data review committee, PK, pharmacokinetic; QD, once daily.

Study enrollment was interrupted in March 2017 following regulatory authority concerns about the suitability of the JNJ-8678 formulation for a pediatric population, in regards to its excipients and low pH. The study was prematurely terminated in November 2017, with last observation on 21 March 2017, due to the timing of availability of a newly developed formulation and the seasonality of the disease.

Part 1

Part 1 primarily assessed the PK profile and safety of JNJ-8678. Each age cohort (cohorts 1–3) comprised a minimum of 3 dose cohorts, and could be expanded with 2 additional dose cohorts per age group designed to safely increase dose levels until the target exposures were reached (ie, cohorts a–c, expanded to cohorts d and e if needed).

Dose escalation from cohort 1a to cohorts 1b, 2a, and 3a was dependent on PK and safety/tolerability data evaluation by a Data Review Committee (DRC). All available data were reviewed by the DRC once patients in each dose cohort completed treatment. The target dose to be achieved for each age group was the dose that achieved the targeted mean exposure (ie, similar to the mean exposure observed in adults treated with 500 mg of JNJ-8678 QD represented as an area under the plasma concentration–time curve from time of administration up to 24 hours postdosing [AUC_{24h}] of 31 165 ng · hour/mL).

From day 3 onward, patients could be discharged from hospital after dosing and completion of the required assessments for that day, if considered appropriate by the investigator. For patients discharged before day 7, the parent(s)/caregiver(s) administered the study drug at home until day 7. Following hospital discharge, viral load samples were not collected until the day 7 visit.

Part 2

Part 2 was added by study amendment to increase patient numbers so as to better estimate the antiviral effects of JNJ-8678. A single dose level was selected for evaluation in each age group (that which reached the target exposure in part 1 after review of the PK and safety/tolerability data and recommendation of the DRC). Planned randomization was 2:1 (JNJ-8678:placebo). Due to early study discontinuation, part 2 did not reach completion.

Outcomes

The primary objectives were to evaluate PK, safety, and tolerability of multiple oral JNJ-8678 doses after administration for 7 days in infants hospitalized with RSV infection.

Secondary objectives included the antiviral activity of JNJ-8678 and its impact on the clinical course of RSV infection, as assessed by the clinician. Exploratory objectives included evaluation of JNJ-8678's effect of on the clinical course of RSV infection during and following hospitalization (as assessed by the patient's parent[s]/caregiver[s] and development of viral resistance during JNJ-8678 treatment).

Assessments

PK assessments obtained with the population PK (pop-PK) model, originally developed in adults and subsequently scaled for pediatrics, were based on sparse sampling (heel or finger-prick capillary tube samples); further defined in the Supplementary Materials.

Safety/tolerability evaluations were based on adverse events (AEs), clinical laboratory tests, vital signs, electrocardiograms (ECGs), and physical examination. The Division of Microbiology and Infectious Diseases Pediatric Toxicity Tables (version November 2007) were used to grade AEs and laboratory and ECG abnormalities, as this was the only available toxicity table applicable to the age range studied [19].

Pharmacodynamics (PD) assessments were based on observed antiviral activity and evaluation of the clinical course of RSV infection. RSV viral load was measured from midturbinate nasal swab samples using an RSV quantitative real-time reverse-transcription PCR assay.

Viral resistance analyses were performed based on next-generation sequencing (NGS; Illumina) of the full-length F-gene at baseline and postbaseline in selected samples if RSV viral load was above the limit for NGS. Viral load (including performance characteristics) and resistance assessments are further defined in the Supplementary Materials. The clinical course of RSV infection was assessed based on length of hospital stay and time to clinical stability (maximum of time to end supplemental oxygen, time to end of supplemental feeding, and time to normalization of heart and respiratory rates). To evaluate RSV-related symptoms, 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 device. All questions presented to clinicians and parent(s)/caregiver(s) are provided in Supplementary Table 1.

Sample Size and Statistical Analysis

Cohorts were grouped by dose level: low (cohorts 1a, 2a, and 3a), mid (cohorts 1b, 2b, and 3b), and high (cohorts 1d, 2c, and 3c). Cohort 1c (mid to high) results were presented separately due to the target exposures not being reached, which prevented combining the data with either mid- or high-dose cohorts; however, cohort 1c is included in assessments of all patients receiving JNJ-8678 (Figure 1).

Details of the PK analysis set, safety analysis set, and their parameters are provided in the Supplementary Materials.

In part 1, for each age group, the sample size required to achieve at least 80% power was ≥ 9 patients for linear clearance and ≥ 6 patients for the central volume of distribution. In part 2, the required sample size in the JNJ-8678 groups was

24 patients receiving the selected dose, pooled over all 3 age groups. Further details on sample size calculations are provided in the Supplementary Materials.

The study was not powered to evaluate the impact of JNJ-8678 on the clinical course of RSV infection.

RESULTS

The study was conducted in 10 countries. Of 61 patients screened, 44 were randomized to JNJ-8678 (n = 37) or placebo (n = 7). All treated patients completed the study. At the time of study termination, part 2 had opened for recruitment in cohorts 1 and 3, but only 1 patient in cohort 3 had received study drug (placebo).

Demographics and baseline characteristics were broadly similar across treatment groups, but with imbalances in some categories (Table 1). The median baseline viral load was higher in the JNJ-8678 (combined) group than placebo.

Pharmacokinetic Results

At the highest doses by cohort of 9, 6, and 5 mg/kg QD (cohorts 1d, 2c, and 3c, respectively), the estimated AUC_{24h} and minimum and maximum plasma concentration (C_{min} and C_{max}) values were similar or slightly higher than the corresponding PK parameters observed for 500 mg JNJ-8678 QD in adults (Table 2). In patients aged ≥6–≤24 months treated with 8 mg/kg QD (cohort 1c), AUC_{24h} was similar to adults; however, the C_{min} and C_{max} target exposures were not reached. Therefore, the DRC recommended a higher dose (9 mg/kg QD) in this age group (cohort 1d). AUC values were similar between cohorts 1c and 1d, with cohort 1d achieving target exposures.

Safety

Most patients had ≥1 AE (76% [28/37] and 86% [6/7] treated with JNJ-8678 and placebo, respectively), most of which were grade 1 or 2 (Table 3). The most frequently reported treatment-emergent AEs are listed in Table 3. Overall, AEs considered by the investigator to be at least possibly related to JNJ-8678 were reported in 30% (11/37) of patients, including anemia (n = 1, cohort 3b, mid-dose; 3 mg/kg QD) and leukocytosis (n = 1, cohort 3c, high-dose; 5 mg/kg QD) (Table 3). Two grade 3 AEs were reported; both were bronchiolitis and reported as serious AEs (SAEs) (Table 3). No deaths, grade 4 AEs, or AEs leading to study discontinuation or permanent discontinuation of study drug were reported.

Four SAEs were reported (JNJ-8678, n = 2; placebo, n = 2; Table 3). In the JNJ-8678 group, SAEs reported were bronchiolitis (8% [1/12], cohort 1b, mid-dose; 6 mg/kg QD) and rhinitis (8% [1/12], cohort 3a, low-dose; 1 mg/kg QD). All 4 were reported as SAEs because of rehospitalization, but not considered related to study drug by the investigator. For patients who received placebo, 1 SAE each of pneumonia and bronchiolitis were reported.

Treatment-emergent nongraded and graded laboratory abnormalities were infrequent across treatment groups (Table 4) and were of low severity (Table 5). No clinically relevant differences in instances of vital sign abnormalities or ECG abnormalities were observed between groups. No dose-level relationship was observed for AEs, laboratory, ECG, or vital sign abnormalities.

Antiviral Effect and Resistance Analyses

The median viral load and median (interquartile range) changes from baseline over time for JNJ-8678 by dose level and placebo are presented in Figure 2*A* and 2*B*, respectively. Across the JNJ-8678 dose levels, no clear dose-response relationship was observed for the antiviral effects of JNJ-8678; therefore, data were combined and compared with placebo; combined results are presented in Figure 2*C* and 2*D*, respectively. By day 3, the median viral load had declined by 1.98 log_{10} copies/mL from baseline in the JNJ-8678 (combined) group and 0.32 log_{10} copies/mL in the placebo group (Figure 2*C*). As patients could be discharged from hospital from day 3, a limited number of patients had viral load results between day 4 and day 6. By the

Table 1. Summary of Baseline Characteristics and Demographics

	JNJ-53718678					Placebo
Characteristic	Low	Mid	Mid-high	High	All Cohorts	All Cohorts
Analysis (safety) set, No.	12	12	4	9	37	7
Female sex, No. (%)	4 (33)	6 (50)	2 (50)	5 (56)	17 (46)	6 (86)
Age at randomization, mo, median (range)	4.4 (2–11)	3.6 (1–11)	8.7 (6–12)	4.8 (1–20)	4.8 (1–20)	3.4 (2–14)
White race, No. (%)	6 (50)	8 (67)	4 (100)	8 (89)	26 (70)	4 (57)
Time between start of respiratory infection and first dosing, d, median (range)	5 (3–7)	5 (4–8)	5 (3–7)	7 (2–9)	5 (2–9)	5 (3–12)
RSV viral load at baseline, log_{10} copies/mL, median (range)	4.89 (2.14–7.96)	4.71 (2.14–8.30)	5.37 (2.88–6.66)	5.73 (5.24–7.12)	5.30 (2.14–8.30)	4.65 (3.69–5.64)
RSV subtype, No. (%)						
A	4 (33)	8 (67)	3 (75)	4 (44)	19 (51)	4 (57)
B	8 (67)	4 (33)	1 (25)	5 (56)	18 (49)	3 (43)

Abbreviation: RSV, respiratory syncytial virus.

Table 2. Summary of JNJ-53718678 Pharmacokinetic Parameters, by Dose Cohort

			Mean AUC_{24h}, ng × h/mL (CV%)		Mean C_{min}, ng/mL (CV%)		Mean C_{max}, ng/mL (CV%)	
Cohort	Dose, mg/kg	No.	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
1a	2	4	6047.2 (17.5)	7738.8 (27.4)	81.4 (58.8)	114.0 (77.7)	546.8 (35.7)	721.3 (31.2)
1b	6	4	18 067.6 (59.7)	26 482.4 (15.1)	155.5 (89.3)	225.7 (66.5)	1960.5 (58.1)	3304.2 (12.3)
1c	8	4	28 655.3 (23.6)	33 528.7 (32.2)	244.1 (90.4)	323.9 (95.7)	3346.9 (13.0)	4298.8 (11.2)
1d	9	4	24 971.7 (43.8)	35 840.1 (22.6)	333.2 (62.3)	615.9 (75.2)	2371.8 (70.8)	3389.4 (52.9)
2a	1.5	4	6658.4 (25.6)	8620.9 (17.3)	88.3 (39.2)	124.0 (49.1)	727.5 (68.7)	938.0 (53.3)
2b	4.5	4	26 345.5 (11.8)	28 904.2 (32.3)	319.8 (16.9)	363.0 (18.9)	2533.2 (25.0)	3021.8 (41.2)
2c	6	1	30 484.8 (…)	34 980.3 (…)	428.6 (…)	517.3 (…)	2556.8 (…)	3131.0 (…)
3a	1	4	4495.6 (4.8)	5827.0 (12.3)	72.6 (41.1)	100.9 (46.3)	374.2 (18.5)	498.0 (13.2)
3b	3	4	14 741.1 (13.9)	26 135.3 (14.1)	342.9 (14.3)	650.2 (15.5)	958.2 (15.2)	1671.2 (14.6)
3c	5	4	22 800.2 (6.8)	39 627.7 (26.4)	458.7 (54.9)	929.0 (62.1)	1866.6 (51.7)	3001.8 (25.1)

In adults, mean AUC_{24h} was 31 165 ng × hour/mL (CV%, 40.7); mean C_{min} was 460 ng/mL (CV%, 82.4); and mean C_{max} was 2655 ng/mL (CV%, 22.3).
Abbreviations: AUC_{24h}, area under the plasma concentration–time curve from time of administration up to 24 hours postdosing; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CV%, coefficient of variation; PK, pharmacokinetics.

day 7 follow-up visit, viral load in most samples (around 80% of patients, Supplementary Figure 1) had become negative (target not detected) or could not be quantified (target detected).

The least squares differences in change from baseline of JNJ-8678 by dose level and combined groups compared with placebo are summarized in Supplementary Tables 2 and 3, respectively, and Supplementary Figure 2. No marked differences in viral load kinetics between RSV-A and RSV-B were observed (Supplementary Figure 3).

Baseline F-gene sequencing data were available for 30 of 44 patients (25/37 receiving JNJ-8678 and 5/7 placebo). Paired baseline and postbaseline sequencing data were available for 16 of 44 patients (14/37 receiving JNJ-8678 and 2/7 placebo). None of these patients had baseline polymorphisms or emerging genetic variations during or after treatment, when considering the 8 F-protein positions of specific interest for JNJ-8678 or the 20 F-protein positions of interest for the RSV-fusion inhibitor class, except 1 placebo patient who had a baseline V144I polymorphism (further described in the Supplementary Materials).

Clinical Course and Severity of Infection

Median length of hospital stay was similar between JNJ-8678 (combined) (77.7 hours) and placebo (77.5 hours); the maximum length of hospital stay observed was 150.4 hours and 144.5 hours, respectively (Figure 3A). No difference was observed between JNJ-8678 (combined) and placebo in median time to clinical stability following the start of study treatment (47.4 and 56.7 hours, respectively); all patients were clinically stable after 123.5 hours and 121.1 hours, respectively (Figure 3B).

No differences in evaluation of RSV symptoms were observed between JNJ-8678 (combined) and placebo, as assessed by the clinician and parent(s)/caregiver(s) through PRESORS.

DISCUSSION

In this first report of any direct-acting RSV antiviral treatment in a pediatric population, target JNJ-8678 exposures were reached in the dose cohorts evaluating the highest doses in each age group, providing potentially effective dose regimens

Table 3. Summary Table of Adverse Events

	JNJ-53718678					Placebo
Adverse Event	Low	Mid	Mid-High	High	All Cohorts	All Cohorts
Analysis (safety) set, No.	12	12	4	9	37	7
Any AE	9 (75)	10 (83)	2 (50)	7 (78)	28 (76)	6 (86)
Any worst grade 1 or 2 AE	9 (75)	10 (83)	2 (50)	7 (78)	28 (76)	5 (71)
Any worst grade 3 or 4 AE	0	1 (8)	0	0	1 (3)	1 (14)
Serious AE[a]	1 (8)	1 (8)	0	0	2 (5)	2 (29)
Any AE possibly related to placebo/JNJ-53718678	3 (25)	4 (33)	2 (50)	2 (22)	11 (30)	0
Any AE probably related to placebo/JNJ-53718678	0	1 (8)	0	0	1 (3)	0
Most frequent AEs (>5%)						
Vomiting	0	3 (25)	1 (25)	4 (44)	8 (22)	4 (57)
URTI	1 (8)	4 (33)	0	3 (33)	8 (22)	0
Soft feces	2 (17)	3 (25)	2 (50)	0	7 (19)	0

Data are presented as no. (%).
Abbreviations: AE, adverse event; URTI, upper respiratory tract infection.
[a]Serious due to rehospitalization in the follow-up phase and considered not related to study drug by the investigator.

Table 4. Laboratory Safety: Tabulation of Treatment-emergent Nongraded Abnormalities Observed in at Least 5% of the Patients Receiving JNJ-53718678

	JNJ-53718678					Placebo
Laboratory Test	Low	Mid	Mid-high	High	All	All Cohorts
Analysis (safety) set, No.	12	12	4	9	37	7
Chemistry						
Alkaline phosphatase						
No.	12	12	4	9	37	7
Below	0	2 (17)	1 (25)	0	3 (8)	1 (14)
Above	1 (8)	1 (8)	0	0	2 (5)	0
Bicarbonate						
No.	11	12	4	8	35	6
Below	0	2 (17)	1 (25)	3 (38)	6 (17)	3 (50)
Above	1 (9)	2 (17)	0	0	3 (9)	0
Chloride						
No.	12	12	4	9	37	7
Below	0	1 (8)	0	0	1 (3)	1 (14)
Above	1 (8)	2 (17)	2 (50)	0	5 (14)	1 (14)
Urea						
No.	9	12	3	9	33	7
Below	1 (11)	4 (33)	0	0	5 (15)	1 (14)
Above	1 (11)	0	0	0	1 (3)	0
Hematology						
Activated partial prothrombin time						
No.	12	11	4	9	36	7
Above	3 (25)	0	1 (25)	1 (11)	5 (14)	0
Eosinophils						
No.	12	11	4	8	35	7
Below	0	0	0	0	0	1 (14)
Above	4 (33)	2 (18)	1 (25)	0	7 (20)	1 (14)
Eosinophils/leukocytes						
No.	9	9	4	4	26	5
Below	0	0	1 (25)	0	1 (4)	1 (20)
Above	2 (22)	3 (33)	1 (25)	1 (25)	7 (27)	1 (20)
Erythrocyte mean corpuscular hemoglobin						
No.	12	12	4	9	37	7
Below	2 (17)	1 (8)	1 (25)	0	4 (11)	0
Above	0	1 (8)	0	0	1 (3)	0
Erythrocytes						
No.	12	12	4	9	37	7
Below	0	2 (17)	0	1 (11)	3 (8)	0
Above	1 (8)	1 (8)	2 (50)	0	4 (11)	1 (14)
Leukocytes						
No.	12	12	4	9	37	7
Above	1 (8)	2 (17)	0	3 (33)	6 (16)	1 (14)
Lymphocytes						
No.	12	11	4	9	36	7
Below	0	0	0	0	0	1 (14)
Above	2 (17)	2 (18)	1 (25)	1 (11)	6 (17)	1 (14)
Lymphocytes/leukocytes						
No.	9	9	4	4	26	5
Below	0	1 (11)	0	0	1 (4)	1 (20)
Above	2 (22)	3 (33)	0	1 (25)	6 (23)	1 (20)
Monocytes/leukocytes						
No.	9	9	4	4	26	5
Below	2 (22)	1 (11)	0	0	3 (12)	0
Above	2 (22)	3 (33)	0	0	5 (19)	0
Neutrophils/leukocytes						
No.	9	9	4	4	26	5
Below	3 (33)	3 (33)	0	0	6 (23)	1 (20)
Above	0	1 (11)	0	0	1 (4)	1 (20)

Data are presented as no. (%).

Table 5. Laboratory Safety: Tabulation of Treatment-emergent Worst Toxicity Grades Observed in at Least 5% of the Patients Receiving JNJ-53718678

	JNJ-53718678					Placebo
Laboratory Test	Low	Mid	Mid-High	High	All Cohorts	All Cohorts
Hyperkalemia						
No.	12	12	4	9	37	6
Grade 1	4 (33)	3 (25)	2 (50)	1 (11)	10 (27)	4 (67)
Grade 2	0	1 (8.3)	0	1 (11)	2 (5)	0
Hypoglycemia						
No.	12	12	4	9	37	7
Grade 1	0	0	0	3 (33)	3 (8)	1 (14)
Hyponatremia						
No.	12	12	4	9	37	7
Grade 2	1 (8)	0	1 (25)	1 (11)	3 (8)	0
Hemoglobin						
No.	12	12	4	9	37	7
Grade 1	1 (8)	1 (8)	0	0	2 (5)	1 (14)
Grade 2	0	1 (8)	0	0	1 (3)	0

Data are presented as no. (%). Emergent abnormalities that occurred during both treatment phase and follow-up period are included.

for future studies. Our study design allowed target exposures to be readily identified: Patients were categorized by age (≥6 to ≤24 months; ≥3 to <6 months; >1 to <3 months), and each age group started at a low dose (weight-based for each group), before a DRC reviewed PK and safety/tolerability data upon completion of treatment, to decide upon the initiation and dose

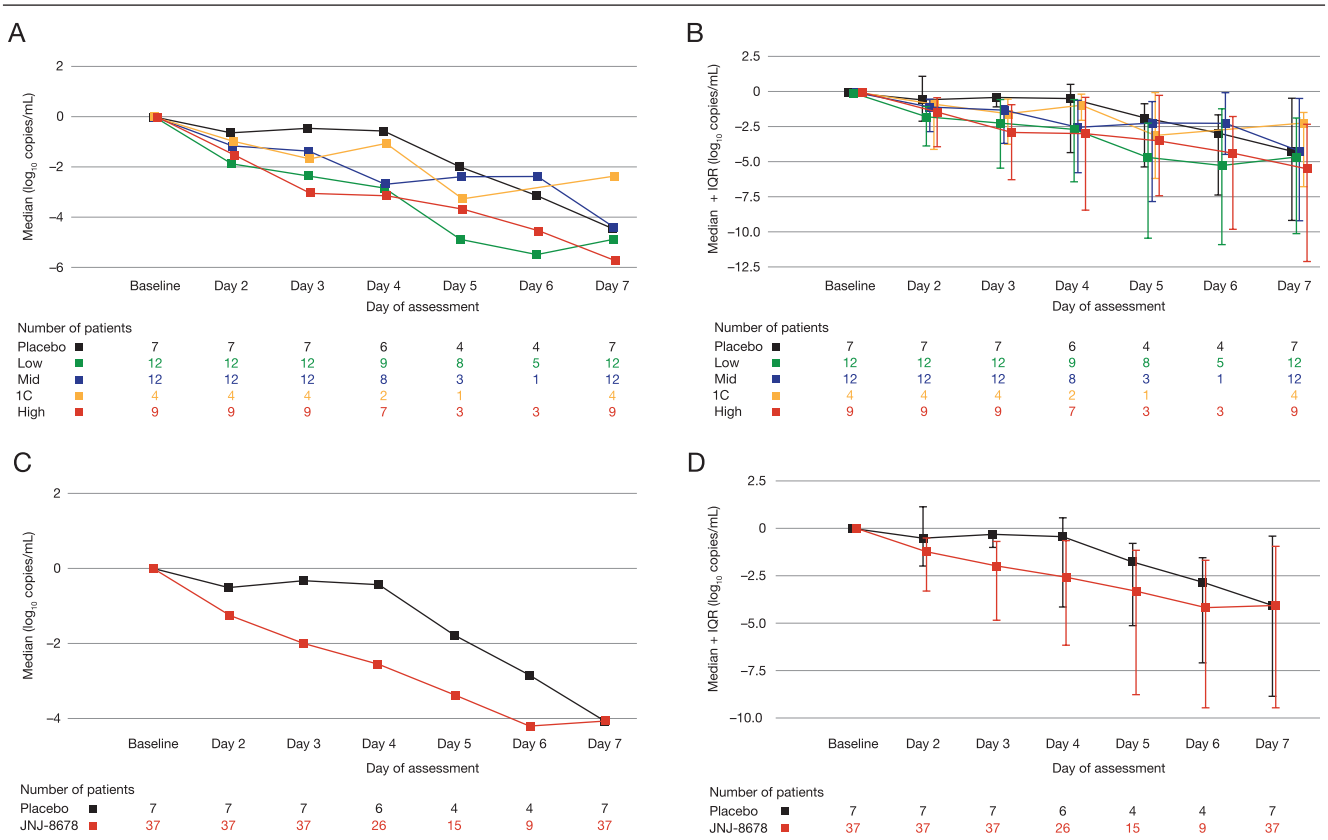

Figure 2. *A*, Median viral load over time to day 7 by treatment group and placebo. *B*, Median (and IQR) viral load changes from baseline over time by dose level and placebo. *C*, JNJ-53718678 (JNJ-8678) median viral load over time to day 7 viral load changes from baseline over time in all doses combined. *D*, JNJ-8678 median (and IQR) viral load over time to day 7 viral load changes from baseline over time in all doses combined. For respiratory syncytial virus (RSV) A, the limit of detection (LOD) was 2.75 $\log_{10}$ copies/mL and the lower limit of quantification (LLOQ) was 3.00 $\log_{10}$ copies/mL; for RSV-B, the LOD was 1.89 $\log_{10}$ copies/mL and the LLOQ was 2.40 $\log_{10}$ copies/mL. Abbreviation: IQR, interquartile range.

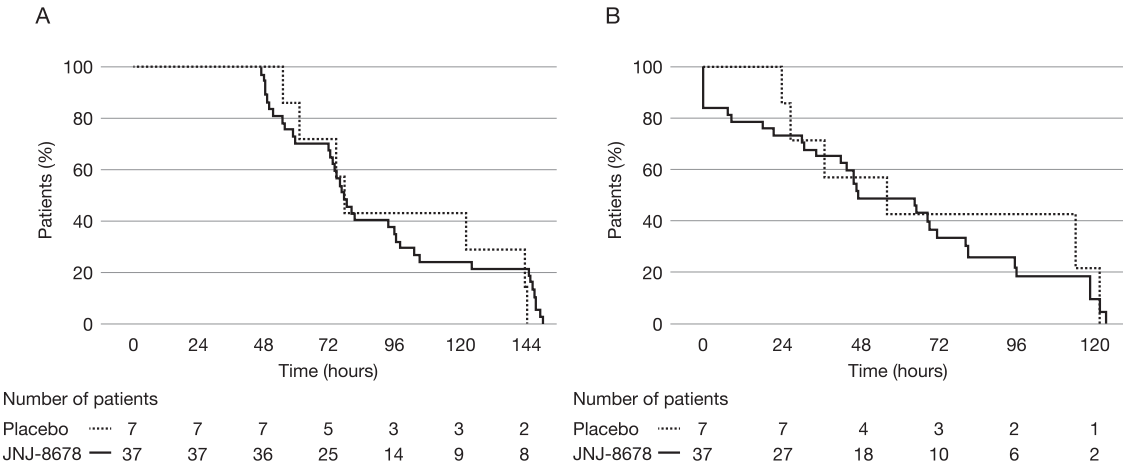

Figure 3. Kaplan-Meier graphs of length of hospital stay (*A*) and time to clinical stability (*B*), all JNJ-53718678 (JNJ-8678) doses combined vs all placebo doses. Clinical stability was defined as maximum of time to end supplemental oxygen, time to end of supplemental feeding, time to normalized heart rate, and time to normalized respiratory rate.

of the next cohort. Treatment with JNJ-8678 administered for 7 days was well tolerated and, importantly, there were no new safety signals in this pediatric population compared with previous studies in healthy adults. Reported AEs were symptoms not uncommon in infants and typical of those which present during RSV infection [20].

There was a greater reduction in viral load with JNJ-8678 than placebo, suggesting a rationale to clinically evaluate JNJ-8678 for the treatment of RSV infection. However, the sample size was small, particularly for patients receiving placebo. Therefore, larger studies are needed to confirm viral load course; such studies should be powered to assess effects in clinical outcomes, to ascertain the clinical relevance of the JNJ-8678 antiviral effects. In addition, the small sample size did not allow detailed statistical analysis to model the PK/PD relationship, as recommended in the US Food and Drug Administration guidelines; however, this will be assessed in phase 2 (NCT03656510) and phase 3 trials. In a previous challenge study in adults, no clear dose-response relationship was observed across JNJ-8678 dose levels [18]. However, longitudinal RSV dynamics in RSV-infected infants are very different from those in adults, with higher peak viral loads and longer duration of shedding exhibited in children, due to factors favoring prolonged RSV replication [21, 22]. Hence, future PK/PD studies in infants are crucial.

No JNJ-8678 treated patients with F-gene sequencing data available had baseline polymorphisms or emerging genetic variations associated with reduced in vitro susceptibility to JNJ-8678 during or after treatment. Further studies are needed to fully investigate the clinical resistance profile of JNJ-8678.

Study enrollment was halted following concerns raised by regulatory authorities regarding the suitability of the JNJ-8678 formulation used in this study for a pediatric population. However, these concerns were related to the pH and excipients of the formulation and not the active compound of JNJ-8678. Given the timing of availability of a newly developed oral formulation compliant with regulatory authority requirements, and given the seasonal nature of RSV disease, the sponsor took the decision to terminate the study prematurely in November 2017. Despite the premature study termination, the sample size was reached for the PK and safety analyses (part 1), and as such we consider our conclusions to be valid.

It is widely recognized that RSV is the leading cause of severe LRTIs in infants worldwide for which treatment options are limited [13, 14, 23, 24]. Ribavirin remains the only licensed antiviral agent against RSV infection; however, it is currently only approved in some countries and its use remains controversial [12, 25]. Given that there are doubts over ribavirin's efficacy and concerns over its safety profile, there is a clear need for alternative options for the treatment of RSV infection [13, 14]. Ribavirin is also associated with challenges when administered intravenously or by aerosol; therefore, oral solutions such as JNJ-8678 offer practical benefits in a clinical setting [25]. In addition to JNJ-8678, a number of other direct-acting RSV antivirals have been identified [26–34]. While several, like JNJ-8678, continue development, the future of presatovir and BTA-C585 remains in doubt due to failure to meet viral load endpoints [33, 34]. Current treatments for RSV infection remain largely supportive [13, 14], highlighting the need for new therapies, particularly for pediatric populations where the incidence of RSV-related hospitalization is high.

The current study has also demonstrated that JNJ-8678 has an acceptable safety profile within the pediatric population. As such, a phase 2 study is ongoing to further evaluate the safety, antiviral activity, and clinical course of a newly formulated JNJ-8678 oral suspension in a pediatric population [35].

In conclusion, during this first-in-child study of JNJ-8678, target exposures were reached and treatment was well tolerated. These findings support further clinical development of JNJ-8678 as a potential new treatment for RSV infection.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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