ORIGINAL ARTICLE

EDP-938, a Respiratory Syncytial Virus Inhibitor, in a Human Virus Challenge

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ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV) infection causes substantial morbidity and mortality among infants, older adults, and immunocompromised adults. EDP-938, a nonfusion replication inhibitor of RSV, acts by modulating the viral nucleoprotein.

METHODS

In a two-part, phase 2a, randomized, double-blind, placebo-controlled challenge trial, we assigned participants who had been inoculated with RSV-A Memphis 37b to receive EDP-938 or placebo. Different doses of EDP-938 were assessed. Nasal-wash samples were obtained from day 2 until day 12 for assessments. Clinical symptoms were assessed by the participants, and pharmacokinetic profiles were obtained. The primary end point was the area under the curve (AUC) for the RSV viral load, as measured by reverse-transcriptase–quantitative polymerase-chain-reaction assay. The key secondary end point was the AUC for the total symptom score.

RESULTS

In part 1 of the trial, 115 participants were assigned to receive EDP-938 (600 mg once daily [600-mg once-daily group] or 300 mg twice daily after a 500-mg loading dose [300-mg twice-daily group]) or placebo. In part 2, a total of 63 participants were assigned to receive EDP-938 (300 mg once daily after a 600-mg loading dose [300-mg once-daily group] or 200 mg twice daily after a 400-mg loading dose [200-mg twice-daily group]) or placebo. In part 1, the AUC for the mean viral load (hours × $\log_{10}$ copies per milliliter) was 204.0 in the 600-mg once-daily group, 217.7 in the 300-mg twice-daily group, and 790.2 in the placebo group. The AUC for the mean total symptom score (hours × score, with higher values indicating greater severity) was 124.5 in the 600-mg once-daily group, 181.8 in the 300-mg twice-daily group, and 478.8 in the placebo group. The results in part 2 followed a pattern similar to that in part 1: the AUC for the mean viral load was 173.9 in the 300-mg once-daily group, 196.2 in the 200-mg twice-daily group, and 879.0 in the placebo group, and the AUC for the mean total symptom score was 99.3, 89.6, and 432.2, respectively. In both parts, mucus production was more than 70% lower in each EDP-938 group than in the placebo group. The four EDP-938 regimens had a safety profile similar to that of placebo. Across all dosing regimens, the EDP-938 median time to maximum concentration ranged from 4 to 5 hours, and the geometric mean half-life ranged from 13.7 to 14.5 hours.

CONCLUSIONS

All EDP-938 regimens were superior to placebo with regard to lowering of the viral load, total symptom scores, and mucus weight without apparent safety concerns. (ClinicalTrials.gov number, NCT03691623.)

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Respiratory syncytial virus (RSV) infection is a global health challenge that causes substantial morbidity and mortality among infants, older adults, and immunocompromised adults.[1-4] Among U.S. adults, an estimated 177,000 hospitalizations and 14,000 deaths associated with RSV infections occur annually.[4] However, the greatest burden of disease occurs among infants and young children, with over 57,000 hospitalizations and 500,000 emergency department visits among children younger than 5 years of age.[4] In addition to RSV-associated hospitalizations and emergency department visits, outpatient visits for RSV represent approximately 80% of RSV cases across all age groups.[2] Globally, RSV infections in children younger than 5 years of age are estimated to cause 3.2 million hospitalizations and 94,600 to 149,400 deaths, primarily in the developing world.[5]

The only approved therapy for RSV is aerosolized ribavirin. However, approved use is limited to hospitalized infants and young children with severe lower-airway disease caused by RSV, and it is rarely administered owing to its unfavorable safety profile, teratogenic potential, and questionable clinical efficacy.[6,7] Palivizumab, an RSV-specific monoclonal antibody, is approved only for the prevention of serious lower respiratory tract disease caused by RSV in high-risk pediatric patients, such as premature infants and those with particular cardiac and pulmonary conditions.[8] Because of the substantial morbidity and mortality estimates among infants, older adults, and immunocompromised adults, there is a strong need for a safe and effective RSV therapy.

EDP-938 is a nonfusion replication inhibitor of RSV that acts by modulating the viral nucleoprotein (N protein).[9,10] Findings from in vitro time-of-addition studies suggest that EDP-938 would be effective even after the virus has entered a cell, a feature that is distinct from RSV fusion inhibitors.[10] In RSV-infected African green monkeys, an analysis of bronchoalveolar lavage and nasopharyngeal swab samples showed that EDP-938 reduced RSV viral load by more than 4 $\log_{10}$ as compared with vehicle control.[10] Pharmacokinetic data from the first-in-human study showed that EDP-938 was rapidly absorbed, with little accumulation (accumulation ratio, <1.5, calculated by dividing the AUC for the plasma concentration of EDP-938 at steady state by the AUC on day 1), and had a mean half-life ranging from 11 to 18 hours across multiple dosing regimens.[11] Multiple oral doses of EDP-938 of up to 600 mg once daily or 300 mg twice daily were administered for 7 days without evident safety concerns.[11] This RSV challenge trial evaluated the safety and pharmacokinetic and antiviral activity of multiple oral doses of EDP-938 administered to healthy participants who were intranasally inoculated with RSV-A Memphis 37b (M37b).

METHODS

TRIAL DESIGN AND PROCEDURES

This phase 2a, randomized, double-blind, placebo-controlled, human virus challenge trial was conducted in two parts. In part 1, the trial was powered to assess reductions in both RSV viral load and clinical symptoms; part 2 was planned to be initiated after completion and review of the data from part 1 and was powered for RSV viral load. The participants were 18 to 55 years of age and were assessed as being healthy and serosuitable for the RSV challenge (i.e., they had serum titers of preexisting RSV-A M37b–specific antibodies of ≤810, which represented the lowest 25th percentile of the screened population). After screening, eligible participants were confined to a specialized quarantine unit managed by hVIVO until discharge on day 12. Before inoculation with RSV-A M37b, quarantined participants underwent additional screening to exclude those with respiratory pathogens. On day 0, participants were inoculated intranasally with the RSV-A M37b challenge virus (a 0.8-ml dose containing approximately 4 $\log_{10}$ plaque-forming units).

The decision to start EDP-938 dosing was based on the detection of RSV by qualitative integrated cycler polymerase-chain-reaction (PCR) assay (3M Integrated Cycler, Focus Diagnostics)[12] in nasal-wash samples from day 2 through the morning of day 5. Once RSV infection was identified by qualitative integrated cycler PCR, the participant was randomly assigned to one of three trial groups and received the first dose of EDP-938 or placebo. If RSV infection had not been identified in a participant by the morning of day 5, the participant was randomly assigned to a trial group and received the first dose 12 hours later. The participants in each group received 10 doses of EDP-938 or placebo over a 5-day period. In part 1, the participants were randomly assigned in a 1:1:1 ratio to receive a

once-daily 600-mg dose of EDP-938 followed by placebo at intervals of 11 to 13 hours (the 600-mg once-daily group), a 500-mg loading dose of EDP-938 followed by a 300-mg second dose 11 to 13 hours later and then 300 mg of EDP-938 twice daily (the 300-mg twice-daily group), or placebo twice daily at intervals of 11 to 13 hours. The regimens used in part 2 were selected on the basis of the safety, pharmacokinetic, and efficacy data from part 1. In part 2, the participants were randomly assigned in a 1:1:1 ratio to receive a 600-mg loading dose of EDP-938 followed by placebo 11 to 13 hours later and then a once-daily 300-mg dose of EDP-938 followed by placebo at intervals of 11 to 13 hours (the 300-mg once-daily group), a 400-mg loading dose of EDP-938 followed by a 200-mg second dose 11 to 13 hours later and then 200 mg of EDP-938 twice daily (the 200-mg twice-daily group), or placebo twice daily at intervals of 11 to 13 hours. The participants were discharged on day 12 if they had a negative RSV antigen test and were followed up until day 28. Details regarding the design and conduct of the trial, the eligibility criteria, and the statistical methods are provided in the protocol and the statistical analysis plan, both available with the full text of this article at NEJM.org.

TRIAL OVERSIGHT

The trial was conducted in accordance with the Declaration of Helsinki (1996 version), the International Conference on Harmonisation Good Clinical Practice guidelines, applicable regional and local regulations, and the trial protocol, which was approved by an independent ethics committee (research ethics reference number, 18/YH/0328). All the participants provided written informed consent.

The trial was designed and sponsored by Enanta Pharmaceuticals and managed by hVIVO Services. Data analysis was performed by statisticians at S-Cubed Biometrics in conjunction with the authors. The authors interpreted the data and participated in the preparation of the manuscript, with the support of a medical writing team at Venn Life Sciences (an affiliate of hVIVO Services), and the authors and sponsor made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

ASSESSMENTS

Nasal-wash samples were obtained twice daily from day 2 until the morning of day 12 for qualitative and quantitative RSV assessments. Clinical symptoms were assessed (on a scale of 0 to 3, with a higher score indicating greater severity) by the participants with the use of a 10-item diary card (see the protocol) three times per day beginning immediately before RSV-A M37b inoculation (day 0) and continuing through the morning of day 12. Safety was assessed throughout the trial. Blood samples were collected at prespecified time points for laboratory testing and assessment of EDP-938 plasma concentrations through a validated bioanalytic method. Additional details regarding the assessments are provided in the Supplementary Appendix, available at NEJM.org.

END POINTS

The prespecified primary efficacy end point was the area under the curve (AUC) for the RSV viral load, as measured by reverse-transcriptase–quantitative PCR (RT-qPCR) assay of the nasal-wash samples from the participants inoculated with RSV-A M37b. The key secondary end point was the AUC for the total symptom score obtained from the 10-item diary card. Other secondary end points were the total weight of nasal mucus; the AUC for the RSV viral load, as measured in the nasal-wash samples by cell-based infectivity (plaque) assay; safety; and pharmacokinetic measures. The AUC was calculated by means of the trapezoid rule, which incorporated the actual time of the assessments.[13]

STATISTICAL ANALYSIS

Assuming a 70% reduction in the AUC for the RSV viral load (coefficient of variation, 56%), we calculated that a sample of 12 participants who could be evaluated (i.e., those with confirmed RSV infection) per group would provide part 1 of the trial with 80% power to detect a significant difference between the EDP-938 groups and the placebo group with respect to the primary end point at a two-sided significance level of 0.05. Furthermore, assuming a 70% reduction in the AUC for the total symptom score (coefficient of variation, 79%), we estimated that 21 participants per group would be required to provide 80% power to detect a significant difference between the EDP-938 groups and the placebo group with

respect to clinical symptoms. To account for a 56% rate of infection among inoculated participants and for a dropout rate of less than 1% during the postinoculation period, we planned to recruit 38 participants per group. The results of part 1 showed that a sample of 21 participants per group would be sufficient for part 2.

All participants were first inoculated with RSV-A M37b, regardless of whether they would receive a dose of EDP-938 or placebo; hence, all the participants were included in the safety analysis population. The intention-to-treat (ITT)–infected analysis population included the participants who had been inoculated with RSV-A M37b, had received at least one dose of EDP-938 or placebo, and had confirmed infection, defined as at least two positive viral load RT-qPCR assays specific for the challenge virus reported over two consecutive trial days or a positive viral load RT-qPCR assay specific for the challenge virus and a positive cell-based infectivity assay of the same sample.

The primary and key secondary efficacy end points were prospectively defined and compared across the trial groups in the ITT-infected analysis population by fitting an analysis-of-covariance model, with the trial group as the main effect and the baseline value of the end-point measure as the covariate. The trial focused on safety and pharmacokinetics, and therefore no adjustment for multiplicity was made. Thus, a P value is shown only for the primary end point, and point estimates and 95% confidence intervals are shown for other end points. All P values are two-sided.

In general, data were rarely missing and were not imputed, and summary statistics were reported on the basis of the observed data. The primary and secondary AUC end points were derived with the use of all collected nonmissing data between receipt of the first dose of EDP-938 and day 12. To reduce the potential effect of missing data, participants were included only if they had at least one measurement available on each day from the first dose of EDP-938 to day 12. None of the participants lacked this criterion, and all were included in the analysis of the AUC end points. RT-qPCR values that were not detected or were below the limit of quantification were assigned substitution values, as shown in section 15.1 in the statistical analysis plan. For adverse events with incomplete or missing dates of onset, it was assumed that the event had occurred during the treatment period, unless the stop date for adverse events indicated otherwise. Additional details regarding the statistical analysis are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS

In part 1 of the trial, 115 participants were quarantined, inoculated, and randomly assigned to a trial group. One participant did not receive EDP-938 owing to anxiety after inoculation but remained in quarantine and completed trial assessments to day 12. In part 2, a total of 63 participants were quarantined, inoculated, and randomly assigned to a trial group. An additional participant was quarantined and inoculated but withdrew consent before randomization. The ITT-infected analysis populations included 86 participants in part 1 and 38 participants in part 2. The baseline characteristics of the participants in the safety analysis population were similar across all trial groups in parts 1 and 2 (Table 1). Information on the extent to which the trial participants represented the general population with RSV disease is provided in Table S1 in the Supplementary Appendix. The trial sample was considered to be representative of the general RSV adult population with no underlying medical conditions.

EFFICACY

In part 1, the AUC for the mean RSV viral load, as measured by RT-qPCR assay and expressed as hours × $\log_{10}$ copies per milliliter (the primary end point), was significantly lower in the EDP-938 groups than in the placebo group (204.0 in the 600-mg once-daily group, 217.7 in the 300-mg twice-daily group, and 790.2 in the placebo group) (Table 2). The 95% confidence interval for the least-squares mean difference from placebo was negative in the EDP-938 groups, with P<0.001 for each comparison. The mean RSV viral load decreased faster and earlier in the EDP-938 groups than in the placebo group (Fig. 1). There was little difference between the two EDP-938 groups.

The clinical symptoms of RSV followed a pattern similar to that of the viral load: the AUC for the mean total symptom score, expressed as hours × score (the key secondary end point), was

Table 1. Analysis Populations and Baseline Characteristics of the Participants in Trial Parts 1 and 2.*

Participants	Part 1†				Part 2‡			
	600-mg Once-Daily Group	300-mg Twice-Daily Group	Placebo Group	Total	300-mg Once-Daily Group	200-mg Twice-Daily Group	Placebo Group	Total
Were inoculated — no.	39	38	38	115	21	21	21	63
Underwent randomization — no.	39	38	38	115	21	21	21	63
Were included in the ITT analysis population — no. (%)	38 (97)	38 (100)	38 (100)	114 (99)	21 (100)	21 (100)	21 (100)	63 (100)
Completed trial — no. (%)	39 (100)	38 (100)	38 (100)	115 (100)	21 (100)	21 (100)	21 (100)	63 (100)
Were included in the ITT-infected analysis population — no. (%)	25 (64)	31 (82)	30 (79)	86 (75)	15 (71)	11 (52)	12 (57)	38 (60)
Were included in the PK analysis population — no. (%)	38 (97)	38 (100)	38 (100)	114 (99)	21 (100)	21 (100)	21 (100)	63 (100)
Were included in the safety analysis population — no. (%)	39 (100)	38 (100)	38 (100)	115 (100)	21 (100)	21 (100)	21 (100)	63 (100)
Age — yr	28.5±5.84	27.2±7.50	27.6±7.86	—	23.4±3.22	24.4±5.83	23.1±5.54	—
Sex — no. (%)								
Male	25 (66)	20 (53)	25 (66)	—	11 (52)	10 (48)	12 (57)	—
Female	13 (34)	18 (47)	13 (34)	—	10 (48)	11 (52)	9 (43)	—
Race — no. (%)§								
Asian	1 (3)	1 (3)	2 (5)	—	1 (5)	1 (5)	0	—
Black	0	1 (3)	2 (5)	—	0	1 (5)	0	—
White	33 (87)	32 (84)	31 (82)	—	18 (86)	17 (81)	19 (90)	—
Other	4 (11)	4 (11)	3 (8)	—	2 (10)	2 (10)	2 (10)	—

* Plus–minus values are means ±SDs. The intention-to-treat (ITT) analysis population included the participants who were inoculated with respiratory syncytial virus A Memphis 37b (RSV-A M37b), underwent randomization, and received at least one dose of EDP-938 or placebo. The ITT-infected analysis population included the participants in the ITT analysis population who had confirmed RSV-A M37b infection. The pharmacokinetic (PK) analysis population included the participants in the ITT analysis population who had at least one available post-dose PK result. The safety analysis population included all the participants who were inoculated with RSV-A M37b, regardless of whether they would receive a dose of EDP-938 or placebo.

† In part 1 of the trial, 115 participants received EDP-938, placebo, or both twice daily over 5 consecutive days for a total of 10 doses. The participants were randomly assigned in a 1:1:1 ratio to receive a once-daily 600-mg dose of EDP-938 followed by placebo at intervals of 11 to 13 hours (the 600-mg once-daily group), a 500-mg loading dose of EDP-938 followed by a 300-mg second dose 11 to 13 hours later and then 300 mg of EDP-938 twice daily (the 300-mg twice-daily group), or placebo twice daily at intervals of 11 to 13 hours.

‡ In part 2 of the trial, 63 participants received EDP-938, placebo, or both twice daily over 5 consecutive days for a total of 10 doses. The participants were randomly assigned in a 1:1:1 ratio to receive a 600-mg loading dose of EDP-938 followed by placebo 11 to 13 hours later and then a once-daily 300-mg dose of EDP-938 followed by placebo at intervals of 11 to 13 hours (the 300-mg once-daily group), a 400-mg loading dose of EDP-938 followed by a 200-mg second dose 11 to 13 hours later and then 200 mg of EDP-938 twice daily (the 200-mg twice-daily group), or placebo twice daily at intervals of 11 to 13 hours.

§ Race was reported by the participants.

Table 2. Efficacy Results in Trial Parts 1 and 2 (ITT–Infected Analysis Population).*

Variable	Part 1			Part 2		
	600-mg Once-Daily Group (N=25)	300-mg Twice-Daily Group (N=31)	Placebo Group (N=30)	300-mg Once-Daily Group (N=15)	200-mg Twice-Daily Group (N=11)	Placebo Group (N=12)
AUC for the mean RSV viral load by RT-qPCR — hr × $\log_{10}$ copies/ml	204.0±173.5	217.7±217.6	790.2±408.8	173.9±194.8	196.2±124.1	879.0±325.7
Standard error	34.7	39.1	74.6	50.3	37.4	94.0
Least-squares mean difference from placebo	−588.1	−564.6	—	−716.1	−736.2	—
95% CI	−719.8 to −456.4	−689.2 to −440.0	—	−879.9 to −552.2	−916.4 to −556.1	—
P value	<0.001	<0.001	—	<0.001	<0.001	—
Least-squares mean difference between EDP-938 groups	−23.5	—	—	20.2	—	—
95% CI	−154.3 to 107.4	—	—	−150.1 to 190.4	—	—
P value	0.70	—	—	0.80	—	—
AUC for the mean total symptom score — hr × score	124.5±115.6	181.8±248.4	478.8±422.3	99.3±180.1	89.6±167.7	432.2±342.5
Standard error	23.1	44.6	77.1	46.5	50.6	98.9
Least-squares mean difference from placebo	−355.9	−326.6	—	−314.0	−312.7	—
95% CI	−506.1 to −205.7	−469.7 to −183.6	—	−494.3 to −133.7	−508.1 to −117.4	—
Least-squares mean difference between EDP-938 groups	−29.3	—	—	−1.3	—	—
95% CI	−179.2 to 120.7	—	—	−185.5 to 183.0	—	—
Mean total weight of nasal mucus — g	13.0±13.0	7.4±11.1	33.4±37.8	3.0±4.4	4.7±6.0	22.4±20.6
Standard error	2.6	2.0	6.9	1.1	1.8	5.9
Least-squares mean difference from placebo	−24.1	−26.0	—	−18.1	−19.3	—
95% CI	−36.6 to −11.6	−37.7 to −14.2	—	−27.2 to −9.1	−29.1 to −9.6	—
Least-squares mean difference between EDP-938 groups	1.9	—	—	1.2	—	—
95% CI	−10.6 to 14.3	—	—	−8.3 to 10.7	—	—

AUC for the mean RSV viral load by CBI assay — hr × $\log_{10}$ PFU/ml	34.1±63.6	35.9±78.0	185.6±161.7	23.7±81.8	26.1±39.1	244.0±138.01
Standard error	12.7	14.0	29.5	21.1	11.8	39.9
Least-squares mean difference from placebo	−153.1	−143.7	—	−207.6	−209.1	—
95% CI	−208.6 to −97.7	−196.2 to −91.1	—	−281.7 to −133.6	−288.0 to −130.1	—
Least-squares mean difference between EDP-938 groups	−9.45	—	—	1.4	—	—
95% CI	−64.7 to 45.7	—	—	−73.2 to 76.1	—	—

* Plus–minus values are means ±SD. The least-squares mean differences in the treatment effect and the 95% confidence intervals (CIs) were obtained from fitting an analysis-of-covariance model to the end point with the trial group as a main effect and the baseline value of the end-point measure as a covariate. The data were normally distributed, and arithmetic means are presented. The least-squares mean difference between EDP-938 groups was calculated as the value in the once-daily EDP-938 group minus the value in the twice-daily EDP-938 group. AUC denotes area under the curve, CBI cell-based infectivity, PFU plaque-forming unit, and RT-qPCR reverse-transcriptase–quantitative polymerase chain reaction.

124.5 in the 600-mg once-daily group, 181.8 in the 300-mg twice-daily group, and 478.8 in the placebo group (Table 2). The mean total symptom score decreased more quickly in the EDP-938 groups than in the placebo group (Fig. 1). The 95% confidence intervals for the difference from placebo were negative, indicating that the AUC values for the total symptom score in the placebo group were higher.

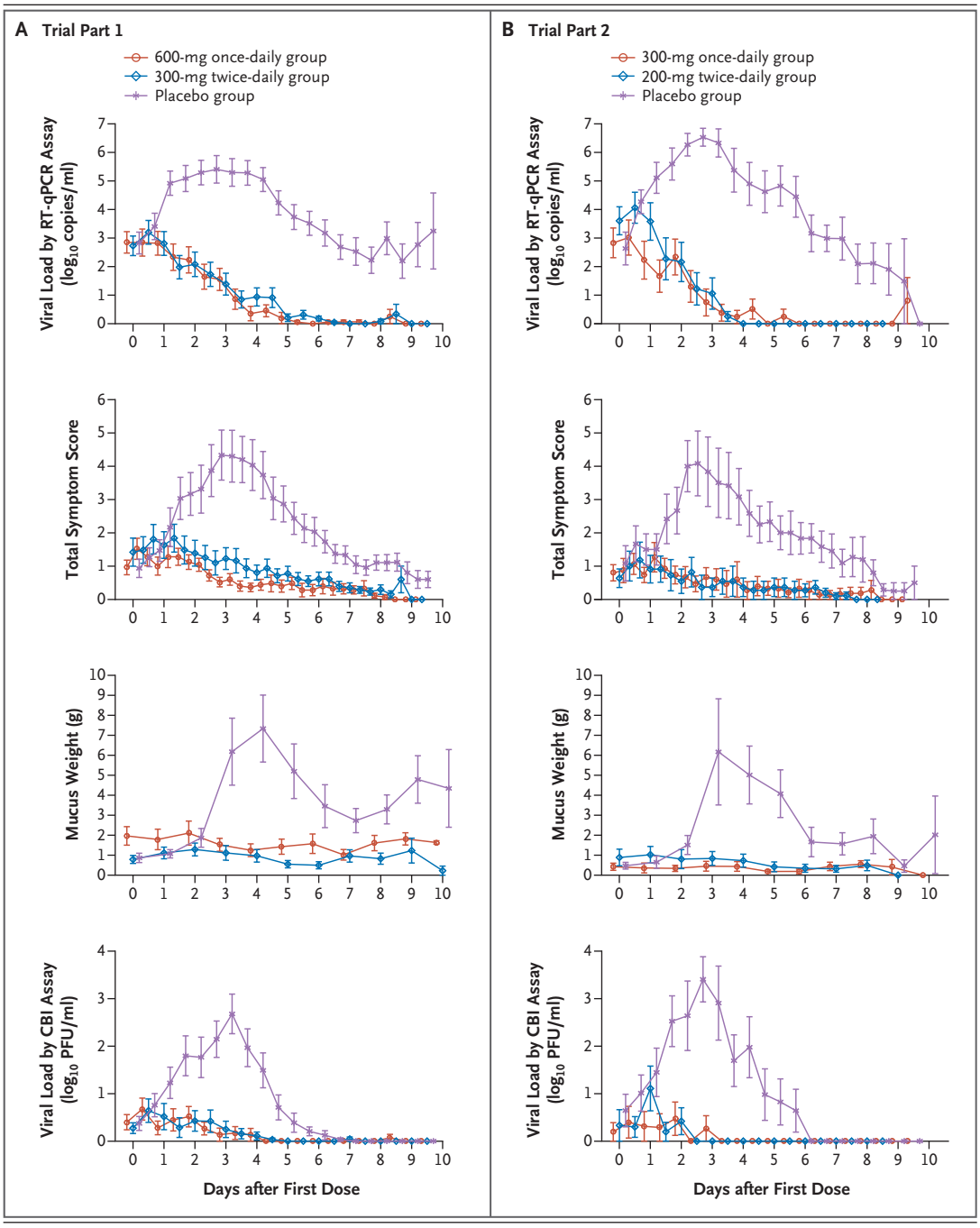
In part 2, the results regarding the AUC for the mean RSV viral load followed a pattern similar to that in part 1, with lower values in the EDP-938 groups than in the placebo group (173.9 in the 300-mg once-daily group, 196.2 in the 200-mg twice-daily group, and 879.0 in the placebo group) (Table 2 and Fig. 1). Marked attenuation of clinical symptoms was also observed; the AUC for the mean total symptom score was 99.3 in the 300-mg once-daily group, 89.6 in the 200-mg twice-daily group, and 432.2 in the placebo group (Table 2 and Fig. 1).

In both parts of the trial, mucus production was more than 70% lower in each EDP-938 group than in the placebo group (Table 2 and Fig. 1). In addition, in both trial parts, the RSV viral load measured by cell-based infectivity assay was also lower in the EDP-938 groups than in the placebo group (Table 2 and Fig. 1), a result consistent with the findings for RSV viral load measured by RT-qPCR assay.

SAFETY

In part 1 of the trial, 29 adverse events occurred among 20 participants in the 600-mg once-daily group, 30 occurred among 21 participants in the 300-mg twice-daily group, and 41 occurred among 21 participants in the placebo group. Adverse events that were more common in one or both EDP-938 groups than in the placebo group included headache (in 4 participants in the 600-mg once-daily group, 1 in the 300-mg twice-daily group, and 3 in the placebo group), dizziness (in 4, 0, and 1, respectively), and diarrhea (in 3, 3, and 0, respectively). All adverse events that occurred in the EDP-938 groups were mild except for a single event of moderate dyspepsia. Adverse events possibly related to EDP-938, as determined by the principal investigator, occurred in 4 participants in the 600-mg once-daily group and 10 participants in the 300-mg twice-daily group (Table 3).

In part 2 of the trial, 17 adverse events oc-



curred among 8 participants in the 300-mg once-daily group, 19 occurred among 10 participants in the 200-mg twice-daily group, and 14 among 11 participants in the placebo group. Nausea, dizziness, and upper respiratory tract infection occurred in at least 3 participants across the trial groups and were more common in one or both EDP-938 groups than in the placebo group (nausea occurred in 1 participant in the 300-mg once-daily group, 3 in the 200-mg twice-daily group, and 0 in the placebo group; dizziness in 0, 2, and 1, respectively; and upper respiratory tract infection in 1, 2, and 1, respectively). All adverse events that occurred in the EDP-938 groups were mild except for a single event of moderate paresthesia at the venipuncture site. Adverse events possibly related to EDP-938 occurred in 3 participants in the 300-mg

Figure 1 (facing page). Viral Load, Clinical Symptoms, and Mucus Weight in Trial Parts 1 and 2.

Shown are the mean (±SE) respiratory syncytial virus loads, total symptom scores, and mucus weight from the time immediately before administration of the first dose until 10 days afterward in the intention-to-treat–infected analysis population, which included the participants who had been inoculated with the respiratory syncytial virus A Memphis 37b strain, had received at least one dose of EDP-938 or placebo, and had confirmed infection. In part 1 of the trial, 115 participants received EDP-938, placebo, or both twice daily over 5 consecutive days for a total of 10 doses. The participants were randomly assigned in a 1:1:1 ratio to receive a once-daily 600-mg dose of EDP-938 followed by placebo at intervals of 11 to 13 hours (the 600-mg once-daily group), a 500-mg loading dose of EDP-938 followed by a 300-mg second dose 11 to 13 hours later and then 300 mg of EDP-938 twice daily (the 300-mg twice-daily group), or placebo twice daily at intervals of 11 to 13 hours. In part 2 of the trial, 63 participants received EDP-938, placebo, or both twice daily over 5 consecutive days for a total of 10 doses. The participants were randomly assigned in a 1:1:1 ratio to receive a 600-mg loading dose of EDP-938 followed by placebo 11 to 13 hours later and then a once-daily 300-mg dose of EDP-938 followed by placebo at intervals of 11 to 13 hours (the 300-mg once-daily group), a 400-mg loading dose of EDP-938 followed by a 200-mg second dose 11 to 13 hours later and then 200 mg of EDP-938 twice daily (the 200-mg twice-daily group), or placebo twice daily at intervals of 11 to 13 hours. The total symptom score is the sum of the scores for all 10 symptoms that were listed in the diary card and assessed by the participants 3 times daily. The score for each symptom ranged from 0 to 3, with higher scores indicating greater severity (additional details are provided in Section 10.7.2.1 of the statistical analysis plan, available with the protocol at NEJM.org). CBI denotes cell-based infectivity, PFU plaque-forming unit, and RT-qPCR reverse-transcriptase–quantitative polymerase chain reaction.

once-daily group and in 2 in the 200-mg twice-daily group (Table 3).

In both trial parts, all events resolved during follow-up except for an event of hematoma at a venipuncture site in part 1. No serious adverse events that led to discontinuation of the trial regimen occurred, and no participant was withdrawn from the trial as a result of an adverse event (Table 3).

PHARMACOKINETICS

The data regarding the plasma pharmacokinetic measures after the last dose of EDP-938 on day 5 are shown in Table 4. EDP-938 was rapidly absorbed; the median EDP-938 T_{max} (time to reach the maximum plasma concentration) ranged from 4 to 5 hours across all regimens. Similarly, the geometric mean half-life ranged from 13.7 to 14.5 hours across all regimens and appeared to be independent of dose and frequency of administration. A steady state was reached with the third dose of EDP-938. The geometric mean $CL_{ss/F}$ (apparent systemic clearance) and $V_{ss/F}$ (volume of distribution at steady state) were also generally similar across all regimens and appeared to be independent of dose and frequency of administration.

On day 5, after completion of the assigned regimen, the geometric mean plasma concentration at 24 hours was 287 ng per milliliter in the 300-mg once-daily group and 491 ng per milliliter in the 600-mg once-daily group, whereas the geometric mean plasma concentration at 12 hours was 525 ng per milliliter in the 200-mg twice-daily group and 822 ng per milliliter in the 300-mg twice-daily group. These concentrations at 12 and 24 hours are approximately 14.5 to 40 times as high as the in vitro EC_{90} (the effective concentration at which there is a 90% decrease in viral replication) for EDP-938 against RSV-A M37b.

DISCUSSION

This trial was designed in two parts. Part 1 was powered for both viral load and total symptom score and represented the main proof-of-concept portion of the trial. Part 2 was conducted after the data analysis in part 1 and was powered for viral load. The main purpose of part 2 was to evaluate lower doses in an attempt to identify a minimally effective dose in the human virus challenge model.

The results of parts 1 and 2 show that EDP-938 administered orally for 5 days reduced both the RSV viral load and clinical symptoms in healthy participants challenged with a clinical RSV strain. The adverse events were generally mild and resolved. A minimally effective dose was not identified, and there was no apparent dose–response relationship regarding efficacy measures across EDP-938 regimens.

The results of the plasma pharmacokinetic measures of EDP-938 were generally similar to those observed in the first-in-human study.[11] EDP-938 was rapidly absorbed and had a half-life that supports once- or twice-daily dosing. After 5 days of dosing, the trough plasma concentra-

Table 3. Adverse Events in Trial Parts 1 and 2 (Safety Analysis Population).*

Adverse Event	Part 1			Part 2		
	600-mg Once-Daily Group (N=38)	300-mg Twice-Daily Group (N=38)	Placebo Group (N=38)	300-mg Once-Daily Group (N=21)	200-mg Twice-Daily Group (N=21)	Placebo Group (N=21)
Adverse events — no.	29	30	41	17	19	14
Participants with adverse events — no. (%)†	20 (53)	21 (55)	21 (55)	8 (38)	10 (48)	11 (52)
Participants with grade 1 adverse events	20 (53)	20 (53)	18 (47)	7 (33)	10 (48)	9 (43)
Participants with grade 2 adverse events	0	1 (3)	3 (8)	1 (5)	0	2 (10)
Participants with ≥1 adverse event possibly related to trial regimen — no. (%)‡	4 (11)	10 (26)	10 (26)	3 (14)	2 (10)	3 (14)
Participants with ≥1 adverse event possibly related to RSV-A M37b — no. (%)‡	11 (29)	13 (34)	13 (34)	2 (10)	7 (33)	7 (33)
Participants with the most common adverse events reported — no. (%)§						
Abdominal pain	0	2 (5)	1 (3)	0	0	1 (5)
Increase in alanine aminotransferase level	0	2 (5)	2 (5)	0	0	0
Catheter site–related reaction	1 (3)	1 (3)	2 (5)	0	0	0
Decrease in appetite	1 (3)	0	2 (5)	0	0	0
Diarrhea	3 (8)	3 (8)	0	1 (5)	1 (5)	0
Dizziness	4 (11)	0	1 (3)	0	2 (10)	1 (5)
Dyspepsia	1 (3)	2 (5)	0	0	0	0
Ear pain	0	1 (3)	2 (5)	0	1 (5)	0
Decrease in forced expiratory volume	2 (5)	1 (3)	0	0	0	1 (5)
Headache	4 (11)	1 (3)	3 (8)	0	1 (5)	2 (10)
Musculoskeletal chest pain	1 (3)	0	0	0	2 (10)	0
Nausea	1 (3)	1 (3)	3 (8)	1 (5)	3 (14)	0
Rash	0	0	2 (5)	0	0	1 (5)
Skin irritation	0	0	2 (5)	0	0	0
Upper respiratory tract infection	2 (5)	2 (5)	4 (11)	1 (5)	2 (10)	1 (5)
Viral upper respiratory tract infection	1 (3)	0	1 (3)	0	2 (10)	0
Vomiting	0	1 (3)	1 (3)	1 (5)	0	0

* The safety analysis population included 115 participants in part 1 and 63 participants in part 2. An adverse event was listed if it occurred after the start of the trial regimen (the first oral dose of EDP-938 was administered 12 hours after confirmation of a positive nasal-wash sample by RT-qPCR assay) in 2 or more participants receiving EDP-938 or placebo or both across parts 1 and 2. Safety was assessed throughout the duration of the trial up to follow-up day 31.

† Grade 1 adverse events were considered to be those that led to a mild level of discomfort and did not interfere with the performance of regular activities; grade 2 adverse events, those that led to a moderate level of discomfort and considerably interfered with the performance of regular activities; and grade 3 adverse events, those that led to a severe level of discomfort and prevented the performance of regular activities. Grade 2 adverse events that occurred in part 1 included dyspepsia in 1 participant in the 300-mg twice-daily group and hypoacusis (in 1 participant) and headache (in 2 participants) in the placebo group. Grade 2 adverse events that occurred in part 2 included paresthesia at the venipuncture site in 1 participant in the 300-mg once-daily group and increased aspartate aminotransferase level (in 1 participant) and headache (in 1 participant) in the placebo group. There were no adverse events of worse severity than moderate.

‡ Whether an adverse event was possibly related to a trial regimen or to RSV-A M37b was determined by the principal investigator.

§ The most common adverse events were considered to be those that occurred in 3 or more participants.

Table 4. Plasma Pharmacokinetic Measures of EDP-938 after Administration of the Last Dose in Trial Parts 1 and 2 (PK Analysis Population).*

Measure	Part 1†		Part 2	
	600-mg Once-Daily Group (N=38)	300-mg Twice-Daily Group (N=35)	300-mg Once-Daily Group (N=21)	200-mg Twice-Daily Group (N=20)
C_{max}				
Geometric mean — ng/ml	1740	1480	1010	901
%GCV	52.8	33.4	15.9	27.9
Median T_{max} — hr				
Median	4.52	4.10	4.98	4.04
Min–max	1.9–17.0	0.0–10.1	1.0–15.9	0.0–10.0
Half-life				
Geometric mean — hr	14.5	13.8	14.5	13.7
%GCV	25.4	27.4	31.3	23.5
$CL_{ss/F}$				
Geometric mean — liters/hr	26.9	24.1	21.3	25.0
%GCV	44.8	28.4	17.6	23.9
$V_{ss/F}$				
Geometric mean — liters	560	476	442	491
%GCV	42.8	23.1	24.1	28.8
C_{12}				
Geometric mean — ng/ml	NA	822	NA	525
%GCV	NA	35.2	NA	30.0
C_{24}				
Geometric mean — ng/ml	491	NA	287	NA
%GCV	46.9	NA	31.6	NA
AUC_{0-last}				
Geometric mean — hr×ng/ml	32,000	27,300	20,500	17,800
%GCV	52.9	40.8	32.1	29.0
T_{last}				
Geometric mean — hr	76.9	66.1	76.6	65.0
%GCV	11.0	11.3	13.7	12.1
AUC_{0-12}				
Geometric mean — hr×ng/ml	NA	12,600	NA	8030
%GCV	NA	29.2	NA	24.9
AUC_{0-24}				
Geometric mean — hr×ng/ml	22,700	NA	14,100	NA
%GCV	45.7	NA	18.4	NA

* Values are presented as the geometric mean, with the percentage of geometric coefficient of variation (%GCV), for all measures except T_{max}, for which the values are presented as the median, with the minimum–maximum (min–max) range. The %GCV was calculated as the square root of the back-transformed standard deviation of plasma concentration of EDP-938 and is expressed as percentage. AUC_{0-12} denotes area under the plasma concentration–time curve (time 0 to 12 hours), AUC_{0-24} area under the plasma concentration–time curve (time 0 to 24 hours), AUC_{0-last} area under the plasma concentration–time curve (time 0 to last quantifiable concentration), C_{12} plasma concentration at 12 hours, C_{24} plasma concentration at 24 hours, C_{max} maximum observed plasma concentration, $CL_{ss/F}$ apparent systemic clearance, NA not applicable, T_{last} time to the first measurable nonzero concentration, T_{max} time to reach the maximum plasma concentration, and $V_{ss/F}$ volume of distribution at steady state.

† In part 1, the plasma concentrations were below the limit of quantification in 1 participant in the 300-mg twice-daily group.

tion was approximately 14.5 to 40 times as high as the in vitro EC_{90} of RSV-A M37b across dosing groups in parts 1 and 2.

The healthy human virus challenge model provided an interrogation of the clinical safety and efficacy of EDP-938 before the conduct of studies in at-risk populations. A potential limitation of the challenge model is that RSV infection can be diagnosed and treated early. By comparison, in the clinic, RSV infection may manifest later in the disease course with more severe, advanced infection (i.e., lower-airway disease). It has been suggested that in persons at risk, such later manifestations could attenuate the clinical efficacy of a new treatment, particularly that of agents that block viral entry, such as RSV fusion inhibitors.[14] In addition, it has been suggested that for an intervention against RSV, a therapeutic window for symptom duration may exist, analogous to the window observed in approved treatments of influenza.[15-17] Because EDP-938 functions through a different mechanism of action (i.e., inhibition of the viral N protein, which is effective at the stages of entry into human cells and after entry), it is possible that the window for an intervention with EDP-938 may be longer. Intervention with EDP-938 after only a short symptom window of up to 48 hours in adults with upper respiratory tract infection is currently being evaluated in an ongoing clinical study (ClinicalTrials.gov number, NCT04196101).

In this human virus challenge trial, all EDP-938 regimens were shown to be superior to placebo with regard to the lowering of viral load, total symptom scores, and mucus weight. The safety profiles of the four EDP-938 regimens studied were similar to the profile of placebo, with no apparent dose–response relationship regarding efficacy measures. The EDP-938 trough plasma concentrations were approximately 14.5 to 40 times as high as the in vitro EC_{90} of RSV-A M37b across dosing groups. These findings support the exploration of EDP-938 activity in populations with RSV infection, including those most at risk for severe RSV infection.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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