Supplemental Information

ENROLLMENT AND EXCLUSION CRITERIA

Key enrollment criteria included patients ≥6 months and <18 years of age who were hospitalized with local laboratory-confirmed severe or progressive symptomatic influenza for whom parenteral NA inhibitor therapy was considered by the investigator to be most appropriate (patients who [1] had severe or progressive influenza illness while receiving approved antiviral agents [oral or inhaled] that appeared ineffective; [2] who were considered inappropriate for treatment with approved influenza antivirals because of concerns for achieving effective systemic antiviral exposure from gastrointestinal absorption of nasogastric tube–administered oseltamivir, adverse events and/or inadequate pulmonary exposure with inhaled zanamivir, or inability to actively inhale zanamivir; and [3] who, in the opinion of the investigator, may benefit from IV zanamivir therapy). Prescreening included influenza diagnostic tests using results from local laboratory analyses. Influenza infection was confirmed for initial screening through a locally administered standard-of-care test for influenza A or influenza B (or both) that included the following: an influenza virus antigen test, a virus culture, or reverse transcription PCR. Patients with a negative rapid test result who were suspected of having influenza could have been enrolled after a repeat positive test by reverse transcription PCR, an antigen test, or culture. Only patients with positive influenza tests were considered for inclusion in the study, although it is possible that there may have been a small number of patients with false-positive results. Enrolled patients had to receive their first dose of study medication within 7 days of experiencing influenza-like symptoms. Key exclusion criteria included the following: patients who were unlikely to survive 48 hours; patients who had participated in a study using an investigational influenza medication within 30 days; patients receiving concurrent therapy with another influenza antiviral medication (previous treatment with anti-influenza medications was permitted); elevated alanine aminotransferase ≥3 times the ULN and total bilirubin ≥2 × ULN; alanine aminotransferase >5 × ULN; and unstable cardiac disease or arrhythmia at baseline and history of significant cardiac disease.

TREATMENT

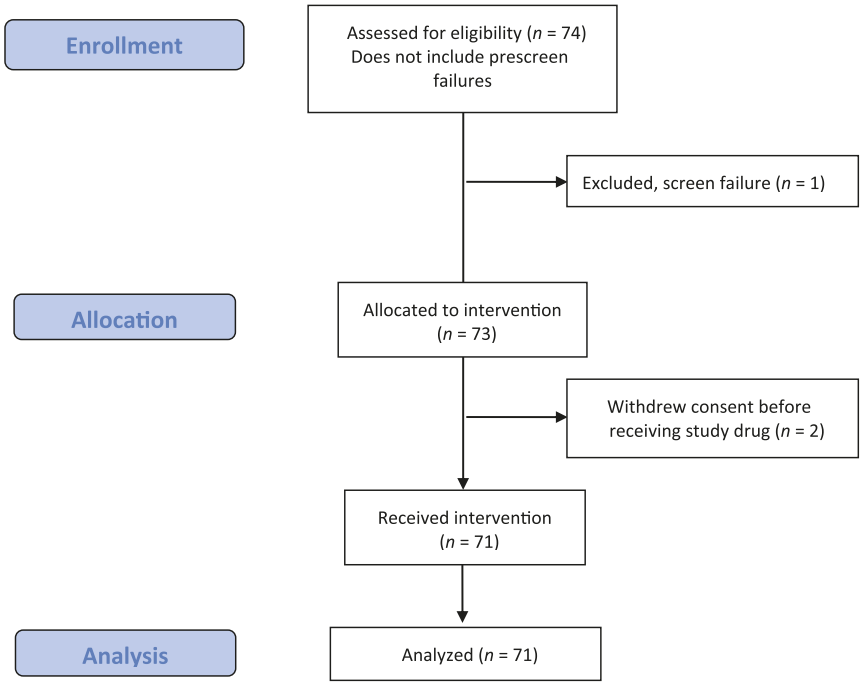
Children from 6 months to <6 years of age with normal renal function received 14 mg/kg twice daily, and patients from 6 to <18 years of age received 12 mg/kg twice daily (maximum dose of 600 mg). Patients with renal impairment received a loading dose similar to patients with normal renal function, followed by an adjusted maintenance dose based on calculated creatinine clearance or creatinine clearance associated with a specific continuous renal replacement therapy (Supplemental Table 4).

TTCR

Time to resolution of individual vital signs included the following variables: afebrile status, oxygen saturation, return to normal respiratory status, return to normal heart rate, and time to return to normal systolic blood pressure. The resolution of each individual vital sign was defined as follows: afebrile status if axilla temperature ≤36.6°C, oral temperature ≤37.2°C, or rectal, core, or tympanic temperature ≤37.7°C; normal oxygen saturation if oxygen saturation was ≥95%; and respiratory status, heart rate, and systolic blood pressure as per the parameters listed in Supplemental Table 5 for at least 24 hours. If the resolution of individual vital signs was not demonstrated by the time of hospital discharge, the time of hospital discharge was considered as the time of clinical success.

VIROLOGIC ASSESSMENTS

NP swabs were collected for virologic outcome measures and were analyzed by Q^2 (formerly Quest Diagnostics) and Viroclinics Biosciences. NP swabs were flocked and posterior NP samples were obtained according to training manuals and manufacturer's instructions. No independent validation of the adequacy of sample acquisition was undertaken. A limited number of throat swabs and ET samples were also collected for virology analyses. The change in influenza viral load over time was assessed by qRT-PCR. Time to virologic improvement was defined as a 2-log reduction in viral load or as undetectable viral RNA. Subtype PCR assays were performed directly from NP swabs using a reflex

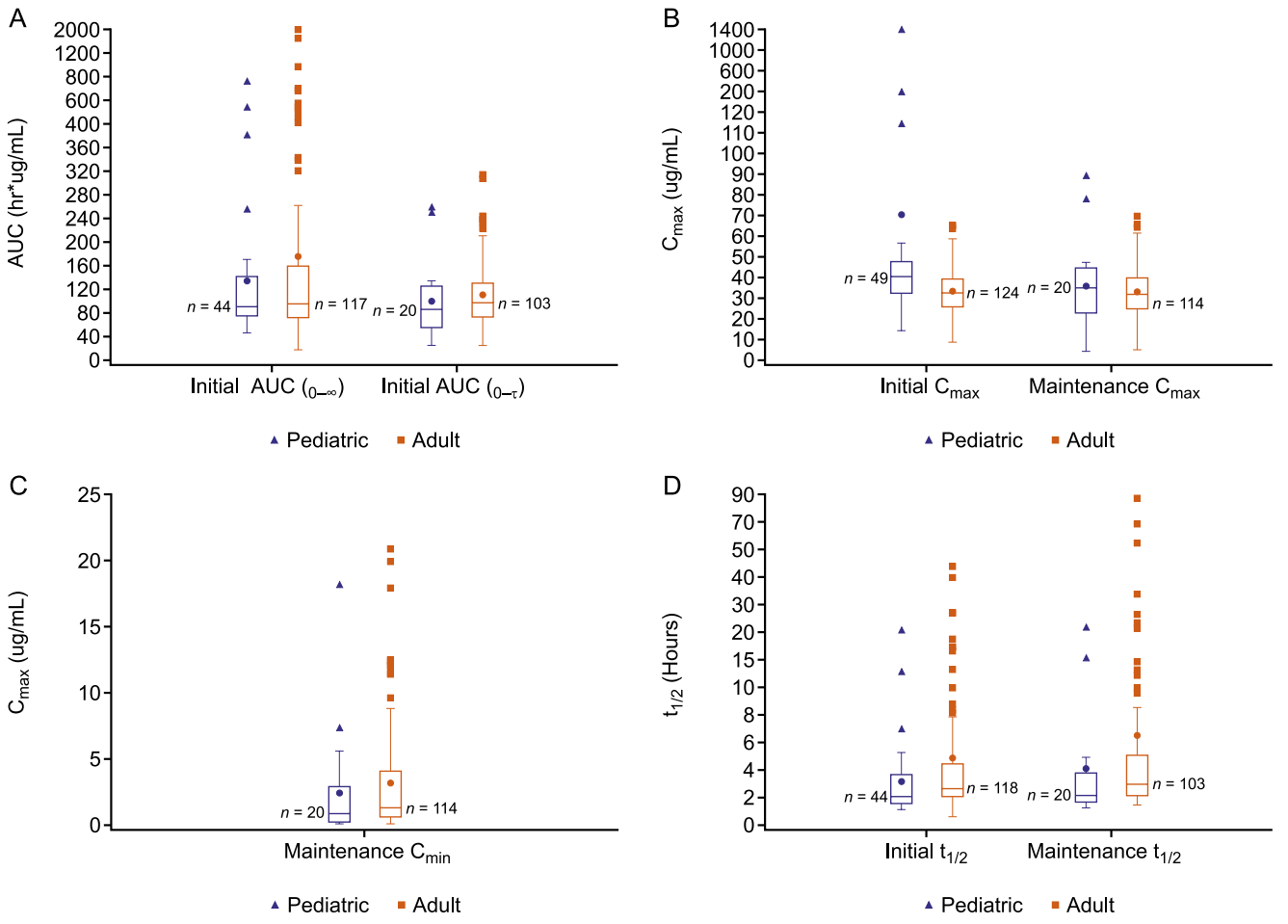


SUPPLEMENTAL FIGURE 3
Patient disposition. WD, withdrawal.

real-time reverse transcription PCR assay. Development of resistance was assessed through genotyping and phenotyping assays. Full-length viral NA and hemagglutinin sequencing was performed on quantitative PCR–positive NP swabs, throat swabs, and ET samples where available. Phenotypic susceptibility to zanamivir was assessed for all positive Madin-Darby Canine Kidney cell cultures by using the NA Star Influenza Neuraminidase Inhibitor Resistance Detection Kit (Applied Biosystems, Foster City, CA).

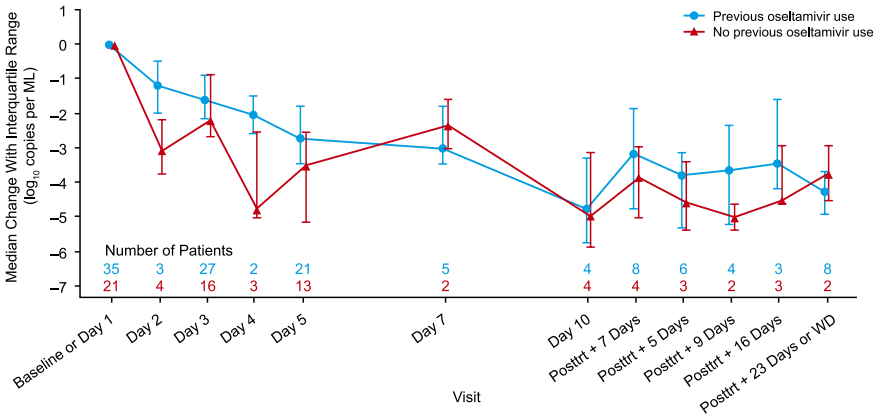
PLANNED SAMPLE SIZE

Target recruitment was initially ~150 adults and adolescents (≥13 years) and 50 children (6 months to <13 years) to collect safety data and adequate PK data to determine appropriate dosing in children. Adult enrollment was much faster than pediatric subjects and was halted at 130, after which the target recruitment for pediatric subjects (6 months to <18 years) was 70.



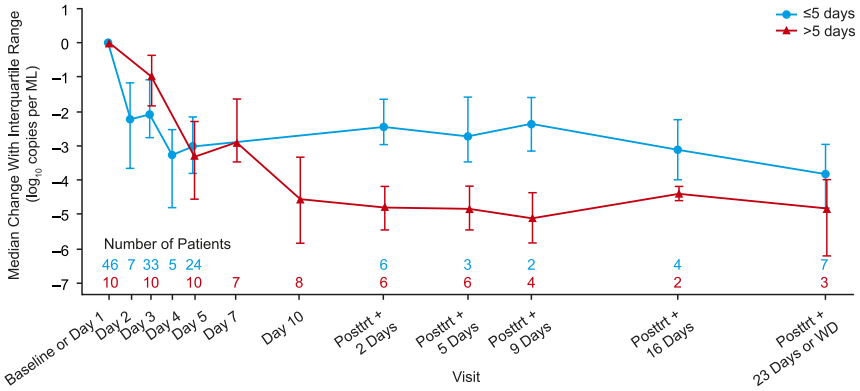
SUPPLEMENTAL FIGURE 4

Comparison of pediatric and adult PK parameters (post hoc analysis). Please note: the upper limits of the y-axes for panels A, B, and D are not linear to enable the visualization of all data points. AUC ($_{0-\infty}$), AUC from time 0 extrapolated to infinity; AUC ($_{0-\tau}$), AUC over a dosing interval of duration; C_{max}, maximum serum concentration; C_{min}, trough serum concentration; $t_{1/2}$, half-life.



SUPPLEMENTAL FIGURE 5

Median change from baseline in viral load, stratified by previous oseltamivir use. Influenza A or B was determined by quantitative PCR (NP samples). Coinfected patients were counted twice in the number of patients. One patient who received oseltamivir during the treatment period (2 days of IV zanamivir plus oseltamivir and 5 additional days of oseltamivir) was included in the viral load reduction analysis and this plot. The patient was included in the previous oseltamivir group and achieved undetectable viral load on day 2 of treatment. Posttrt, treatment; WD, withdrawal.



SUPPLEMENTAL FIGURE 6

Median change from baseline in viral load, stratified by treatment duration (>5 and ≤5 days). One patient who received oseltamivir during the treatment period (2 days IV zanamivir plus oseltamivir and 5 additional days of oseltamivir) was included in the viral load reduction analysis and this plot. The patient was included in the <5 days treatment group and achieved undetectable viral load on day 2 of treatment. Posttrt, treatment; WD, withdrawal.

SUPPLEMENTAL TABLE 4 Initial Dose Amounts and Twice-Daily Maintenance Dose Regimens of IV Zanamivir for Pediatric Patients With Normal and Impaired Renal Function

Age and Weight	Initial Dose	Maintenance Dose (Given q12h)				
		CL_{cr} or CL_{CRRT} (mL/min or mL/min/1.73 m^2)[a]				
		≥80	50–<80	30–<50	15–<30	<15
		Begin Twice-Daily (q12h) Maintenance Dosing 12 h After Initial Dose			Begin Twice-Daily (q12h) Maintenance Dosing 24 h After Initial Dose	Begin Twice-Daily (q12h) Maintenance Dosing 48 h After Initial Dose
Adolescents (13–<18 y)						
≥50 kg body weight	600 mg	600 mg	400 mg	250 mg	150 mg	60 mg
<50 kg body weight	12 mg/kg	12 mg/kg	8 mg/kg	5 mg/kg	3 mg/kg	1.2 mg/kg
Children (6–<13 y)						
≥50 kg body weight	600 mg	600 mg	400 mg	250 mg	150 mg	60 mg
<50 kg body weight	12 mg/kg	12 mg/kg	8 mg/kg	5 mg/kg	3 mg/kg	1.2 mg/kg
Infants and children (6 mo–<6 y)						
≥42.8 kg body weight	600 mg	600 mg	400 mg	250 mg	150 mg	60 mg
<42.8 kg body weight	14 mg/kg	14 mg/kg	9.3 mg/kg	5.8 mg/kg	3.5 mg/kg	1.4 mg/kg

CL_{cr}, creatinine clearance; CL_{CRRT}, creatinine clearance associated with a specific continuous renal replacement therapy; q12h, every 12 hours.

[a] CL_{cr} in mL/min/1.73 m^2 for patients <13 years of age and in milliliters per minute for patients ≥13 years of age.

SUPPLEMENTAL TABLE 5 Parameters for Resolution of Respiratory Status, Heart Rate, and Systolic Blood Pressure

Cohort (Age)	1 (6 mo–<1 y)	2 (1–<2 y)	3 (2–<6 y)	4 (6–<13 y)	5 (13–<18 y)
Normal respiratory status[a] (per min)	≤60	≤40	≤34	≤30	≤24
Normal heart rate (beats per min)	≤160	≤150	≤140	≤120	≤100
Normal systolic blood pressure (mm Hg)	≥70	≥74	≥76	≥80	≥90

[a] Normal respiratory status if there is (1) a return to premorbid oxygen requirement, (2) a return to no supplemental oxygen, or (3) a respiratory rate (without supplemental oxygen).

SUPPLEMENTAL TABLE 6 Summary of TEAEs Occurring in >1 Patient (Safety Population)

Any TEAE by Age Cohort	*n* (%)
Cohort 1: 6 mo–<1 y (*N* = 7)	4 (57)
Cohort 2: 1–<2 y (*N* = 11)	7 (64)
Cohort 3: 2–<6 y (*N* = 12)	8 (67)
Cohort 4: 6–<13 y (*N* = 27)	22 (81)
Cohort 5: 13–<18 y (*N* = 14)	10 (71)
Any TEAE occurring in >1 subject (*N* = 71), all cohorts	51 (72)
Pyrexia	8 (11)
Anemia	4 (6)
Constipation	4 (6)
Neutropenia	4 (6)
Respiratory failure	4 (6)
Vomiting	4 (6)
Drug withdrawal syndrome	3 (4)
Hyperbilirubinemia	3 (4)
Hypertension	3 (4)
Hypoalbuminemia	3 (4)
Hypokalemia	3 (4)
Hypotension	3 (4)
Pneumonia	3 (4)
Skin disorder	3 (4)
Stridor	3 (4)
Adrenal insufficiency	2 (3)
Asthenia	2 (3)
Blood creatine phosphokinase increased	2 (3)
Decubitus ulcer	2 (3)
Deep vein thrombosis	2 (3)
Dermatitis diaper	2 (3)
Diarrhea	2 (3)
Epistaxis	2 (3)
Food intolerance	2 (3)
Fungal skin infection	2 (3)
Generalized edema	2 (3)
Hyperglycemia	2 (3)
Hypernatremia	2 (3)
Hypochloremia	2 (3)
Hypomagnesemia	2 (3)
Lactic acidosis	2 (3)
Mental status changes	2 (3)
Multiorgan failure	2 (3)
Rash	2 (3)
Renal failure	2 (3)
Sepsis	2 (3)
Tachycardia	2 (3)

SUPPLEMENTAL TABLE 7 Summary of PK Parameters by Renal Function Group After Initial Dose of IV Zanamivir

CL_{cr}[a] (mL/min or mL/min/1.73 m^2)	Planned Dose	C_{max} (μg/mL)	$AUC_{(0-\infty)}$ (h per μg/mL)	$t_{1/2}$ (h)	CL (mL/min)	V_{ss} (L)
Cohort 1 (6 mo–<1 y) (*N* = 7)						
≥80	14 mg/kg	36.2 (21) [4]	75.3 (23) [3]	1.84 (19) [3]	27.3 (32) [3]	3.77 (12) [3]
50–<80	14 mg/kg	39.5 (22) [3]	71.8 (33) [3]	1.63 (36) [3]	27.5 (37) [3]	3.40 (42) [3]
Cohort 2 (1–<2 y) (*N* = 6)						
≥80	14 mg/kg	37.8 (24) [5]	72.4 (14) [4]	2.49 (118) [5]	31.0 (12) [4]	3.94 (29) [4]
Cohort 3 (2–<6 y) (*N* = 12)						
≥80	14 mg/kg	41.5 (23) [9]	80.3 (38) [9]	1.60 (34) [9]	42.0 (37) [9]	5.15 (20) [9]
Cohort 4 (6–<13 y) (*N* = 16)						
≥80	600 mg	—	—	—	—	—
≥80	12 mg/kg	44.2 (47) [9]	107 (41) [8]	2.57 (55) [8]	46.7 (47) [8]	9.21 (48) [8]
30–<50	600 mg	40.4 (—) [1]	159 (—) [1]	3.18 (—) [1]	63.0 (—) [1]	16.9 (—) [1]
30–<50	12 mg/kg	1397 (—) [1][b]	761 (—) [1][b]	2.71 (—) [1][b]	6.75 (—) [1][b]	0.53 (—) [1][b]
Cohort 5 (13–<18 y) (*N* = 13)						
≥80	600 mg	34.5 (27) [6]	91.1 (27) [5]	2.06 (47) [5]	110 (27) [5]	18.6 (26) [5]
≥80	12 mg/kg	4.99 (3997) [3][c]	135 (—) [1]	2.16 (—) [1]	53.7 (—) [1]	10.1(—) [1]
50–<80	600 mg	49.1 (20) [2]	312 (29) [2]	6.07 (20) [2]	32.0 (29) [2]	16.5 (48) [2]
Overall (6 mo–<18 y) (*N* = 53)						
≥80	14 mg/kg	39.2 (23) [18]	77.3 (30) [16]	1.87 (61) [17]	35.9 (36) [16]	4.55 (25) [16]
≥80	12 mg/kg	25.6 (327) [12]	110 (40) [9]	2.52 (52) [9]	47.4 (44) [9]	9.31 (45) [9]
≥80	600 mg	34.5 (27) [6]	91.1 (27) [5]	2.06 (47) [5]	110 (27) [5]	18.6 (26) [5]
50–<80	14 mg/kg	39.5 (22) [3]	71.8(33) [3]	1.63 (36) [3]	27.5 (37) [3]	3.40 (42) [3]
50–<80	600 mg	49.1 (20) [2]	312 (29) [2]	6.07 (20) [2]	32.0 (29) [2]	16.5 (48) [2]
30–<50	12 mg/kg	1397 (—) [1][b]	761(—) [1][b]	2.71 (—) [1][b]	6.75 (—) [1][b]	0.53 (—) [1][b]
30–<50	600 mg	40.3 (—) [1]	159(—) [1]	3.18 (—) [1]	63.0 (—) [1]	16.9 (—) [1]

Values denote geometric mean (%CVb) [*n*]. Because of missed samples, not all parameters could be estimated for all patients. $AUC_{(0-\infty)}$, AUC from time 0 to infinity; CL, clearance; CLcr, creatinine clearance; C_{max}, maximum serum concentration; $t_{1/2}$, elimination half-life; V_{ss}, volume of distribution at steady state; %CVb, percent coefficient of variation between patients; —, not applicable.

[a] CL_{cr} in mL/min/1.73 m^2 for patients <13 y of age and in milliliters per minute for patients ≥13 y of age.

[b] High serum concentrations for a single patient.

[c] Geometric mean of C_{max} impacted by low serum concentrations for patient 2462.

SUPPLEMENTAL TABLE 8 Summary of Maintenance Dose PK Parameters by Renal Function Group

CL_{cr}[a] (mL/min or mL/min/1.73 m^2)	Planned Dose	C_{max} (μg/mL)	$AUC_{(0–12)}$ (h per μg/mL)	$t_{1/2}$ (h)	CL (mL/min)	V_{ss} (L)	C_{min} (μg/mL)
Cohort 1, 6 mo–<1 y (*N* = 7)							
—	—	—	—	—	—	—	—
Cohort 2, 1–<2 y (*N* = 6)							
≥80	14 mg/kg	38.0 (—) [1]	68.2 (—) [1]	1.68 (—) [1]	31.8 (—) [1]	3.77 (—) [1]	0.30 (—) [1]
Cohort 3, 2–<6 y (*N* = 12)							
≥80	14 mg/kg	43.2 (9) [4]	81 (28) [4]	1.76 (20 [4]	40.4 (35) [4]	5.23 (32) [4]	0.28 (107) [4]
Cohort 4, 6 to <13 y (*N* = 15)							
≥80	12 mg/kg	45.2 (48) [4]	90.3 (45) [4]	1.81 (41) [4]	68.6 (34) [4]	9.82 (8) [4]	0.56 (248) [4]
30–<50	5 mg/kg	25.7 (—) [1]	99.9 (—) [1]	2.39 (—) [1]	21.4 (—) [1]	4.68 (—) [1]	1.40 (—) [1]
Cohort 5, 13–<18 y (*N* = 13)							
≥80	400 mg[b]	20.2 (—) [1][b]	45.9 (—) [1][b]	1.67 (—) [1][b]	145 (—) [1][b]	21.0 (—) [1][b]	0.19 (—) [1][b]
≥80	600 mg	25.7 (52) [2]	64.5 (30) [2]	1.73 (21) [2]	155 (30) [2]	23.2 (25) [2]	0.21 (132) [2]
50–<80	400 mg	89.4 (—) 1]	250 (—) [1]	4.74 (—) [1]	26.7 [1]	9.88 [1]	7.36 (—) [1]
15–<30	150 mg	25.3 (—) [1]	259 (—) [1]	21.8 (—) [1]	—	—	18.2 (—) [1]
Overall, 6 mo–<18 y (*N* = 53)							
≥80	14 mg/kg	42.1 (10) [5]	78.3 (25) [5]	1.74 (17) [5]	38.5 (32) [5]	4.90 (32) [5]	0.28 (88) [5]
≥80	12 mg/kg	45.2 (48) [4]	90.3 (45) [4]	1.81 (41) [4]	68.6 (34) [4]	9.82 (8) [4]	0.56 (248) [4]
≥80[b]	400 mg[b]	20.2 (—) [1][b]	45.9 (—) [1][b]	1.67 (—) [1][b]	145 (—) [1][b]	21.0 (—) [1][b]	0.19 (—) [1][b]
≥80	600 mg	25.7 (52) [2]	64.5 (30) [2]	1.73 (21) [2]	155 (30) [2]	23.2 (25) [2]	0.21 (132) [2]
50–<80	400 mg	89.4 (—) 1]	250 (—) [1]	4.74 (—) [1]	26.7 (—) [1]	9.88 (—) [1]	7.36 (—) [1]
30–<50	5 mg/kg	25.7 (—) [1]	99.9 (—) [1]	2.39 (—) [1]	21.4 (—) [1]	4.68 (—) [1]	1.40 (—) [1]
15–<30	150 mg	25.3 (—) [1]	259 (—) [1]	21.8 (—) [1]	—	—	18.2 (—) [1]

Values denote geometric mean (%CVb) [*n*]. Because of missed samples, not all parameters could be estimated for all patients. $AUC_{(0–12)}$, AUC over the dosing interval (τ) of 12 hours; CL, clearance; CLcr, creatinine clearance; C_{max}, maximum serum concentration; $t_{1/2}$, elimination half-life; V_{ss}, volume of distribution at steady state; %CVb, percent coefficient of variation between patients; —, not applicable.

[a] CL_{cr} in mL/min/1.73 m^2 for patients <13 y of age and in milliliters per minute for patients ≥13 y of age.

[b] Patient received less than the planned maintenance dose of 12 mg/kg.

SUPPLEMENTAL TABLE 9 Research Facilities, Hospitals, and Institutions That Enrolled Pediatric Patients for This Study

Research Facility, Hospital, or Institution
CHR d'Orléans – Hôpital de la Source, Service de Réanimation Médicale Polyvalente, 14, Avenue de l'Hôpital, Orléans Cedex 2, 45067 France
CHU-Hôpital Dupuytren, Service de Réanimation polyvalente, 2 Avenue Martin Luther King, Limoges Cedex 87042, France
Yamanashi Prefectural Central Hospital, 1-1-1, Fujimi, Kofu, Yamanashi 400-8506, Japan
Shonan Kamakura General Hospital, 1370-1, Okamoto, Kamakura, Kanagawa 247-8533, Japan
Red Cross Children's Hospital, Fifth Floor, ICH Building, Klipfontein Rd, Rondebosch 7700, South Africa
Hospital Gregorio Marañón, C/Dr Esquerdo, 46, Madrid 28007, Spain
Primary Children's Medical Center, 100 North Mario Capecchi Drive, Salt Lake City, Utah 84113-1100
Nationwide Children's Hospital Research Institute, Pediatric Infectious Disease, ED 153, 700 Children's Way, Columbus, Ohio 43205
LeBonheur Children's Hospital, 848 Adams St, Patient Care Floors, Memphis, Tennessee 38103
University of Toledo College, Pediatric Pharmacology Research Center, Suite 980, 2142 North Cove Blvd, Toledo, Ohio 43606
Rady Children's Hospital San Diego, Center for Pediatric Clinical Research, MC 5105, 3020 Children's Way, San Diego, California 92123
Tampa General Hospital, 1 Tampa General Circle, Tampa, Florida 33606
Children's National Medical Center, 111 Michigan Ave NW, Washington, District of Columbia 20010
St Jude Children's Research Hospital, Translational Trials Unit, Mail Stop 600, 262 Danny Thomas Place, Memphis, Tennessee 38105-3678
Children's Hospital of Wisconsin, MS 681, 9000 West Wisconsin Ave, Milwaukee, Wisconsin 53226
Oregon Health & Science University, Research Pharmacy Services, CR 9-4, CR-9-4, 3181 SW Sam Jackson Park Rd, Portland, Oregon 97239
Children's Mercy Hospitals and Clinics, Pediatric Clinical Pharmacology and Medical Toxicology, 2401 Gillham Rd, Kansas City, Missouri 64108
The Children's Hospital of Alabama, Central Pharmacy, 1600 7th Ave South, Birmingham, Alabama 35233
Children's Hospital of Pittsburgh of UPMC, Infectious Disease, Third Floor AOB, 4401 Penn Ave, Pittsburgh, Pennsylvania 15224
Baylor College of Medicine, Texas Children's Hospital, Suite 221-D, BCM-280, 1 Baylor Plaza, Houston, Texas 77030
Children's Hospitals and Clinics of Minnesota, 345 North Smith Ave, St Paul, Minnesota 55102
Riley Hospital for Children, 705 Riley Hospital Drive, ROC 4270, Indianapolis, Indiana 46202
Arkansas Children's Hospital, 1 Children's Way, Little Rock, Arkansas 72202
The Emory Children's Center, 2015 Uppergate Dr NE, Atlanta, Georgia 30322
The Children's Place, St Louis, Missouri 63110