2. SYNOPSIS

Sponsor: Shionogi & Co., Ltd.	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product: Baloxavir Marboxil	**Volume:**	
Name of Active Ingredient: S-033188	**Page:**	

Study Title: An Open-label Study to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of S-033188 2% Granules after Administration of a Single Dose to Otherwise Healthy Pediatric Patients with Influenza

Investigators and Study Centers: This was a multicenter study conducted at 20 study centers in Japan.

Publication (reference): Not applicable

Study Period:

Between 18 December 2017 (first patient enrolled) and 23 February 2018 (last patient completed)

Phase of Development: 3

Objectives:

- To assess the safety and tolerability of a single dose of S-033188 2% granules in pediatric patients weighing less than 20 kg
- To assess the pharmacokinetics (PK) of S-033188 and its active form (S-033447) after single dose administration of S-033188 2% granules in pediatric patients weighing less than 20 kg
- To assess the efficacy of a single dose of S-033188 2% granules in pediatric patients weighing less than 20 kg

Methodology:

This was an open-label, multi-center, non-controlled study to assess the safety, tolerability, PK, and efficacy of S-033188 2% granules in otherwise healthy pediatric patients whose body weight at Screening was less than 20 kg and aged less than 12 years with influenza virus infection. The patients received a single oral dose of the study drug without regard to meals at the study center on Day 1 (Visit 1). The patients returned to the study center on Days 2, 3 and/or 4, 6, 9, 15, and 22 (Visit 2 to 8).

For efficacy assessment, patient's parent/guardian measured or assessed the following outcome measures from predose on Day 1 through Day 14.

- Body temperature
  Axillary temperature was measured by patient's parent/guardian predose on Day 1, and then 4 times daily (morning, noon, evening and bedtime) until Day 3 and twice daily (morning and evening) from Day 4 to 14.
- Severity of influenza symptoms
  Severity of 2 symptoms (cough, nasal discharge/nasal congestion) was assessed by patient's parent/guardian on a 4-point rating scale (0, Absent; 1, Mild; 2,

Moderate; 3, Severe) predose on Day 1, and then twice daily (morning and evening) until Day 9 and once daily (evening) from Day 10 to 14.

- Ability to perform daily activities
  The ability to perform daily activities was assessed by patient's parent/guardian on a scale of 0 (Unable to perform daily activities at all) to 10 (Able to perform all daily activities as usual) predose on Day 1 and then once daily (evening) until Day 14.

To perform virus typing and subtyping, determination of virus titer and viral RNA load, nasal or throat swabs were collected predose at Visit 1 (Day 1), Visit 2 (Day 2), Visit 3 (Day 3) and/or Visit 4 (Day 4), Visit 5 (Day 6), and Visit 6 (Day 9). When the investigator or subinvestigator determined that influenza symptoms were persisting, specimens were also to be collected at Visit 7 (Day 15) and Visit 8 (Day 22) (or at early termination).

For safety assessment, the following examinations and measurements were performed.

- Physical examination
  Physical examination was performed at every visit including early termination. In addition, symptom-focused physical examination was to be performed at the investigator's discretion if needed.
- Vital sign measurements
  Vital signs were measured at Visit 1 (Day 1), Visit 2 (Day 2), Visit 5 (Day 6), Visit 6 (Day 9), and Visit 7 (Day 15) (or at early termination). Only when the investigator or subinvestigator considered that there were any abnormalities at the visit immediately before Visit 8, necessary measurements were made at Visit 8 (Day 22).
- Clinical laboratory tests
  Clinical laboratory tests were performed at Visit 1 (predose on Day 1) and Visit 5 (Day 6). Only if the investigator or subinvestigator considered that there were any abnormalities at the visit immediately before Visit 7, necessary samples were collected at Visit 7 (Day 15) and Visit 8 (Day 22) (or at early termination).

For PK assessment, blood samples were collected for the measurement of plasma S-033188 and S-033447 concentrations.

Number of Patients (Planned and Analyzed):

Planned: 30 patients

Enrolled: 33 patients

Analyzed for efficacy:

- Intention to treat infected (ITTI): 33 patients
- Per protocol set (PPS): 28 patients

Analyzed for safety: 33 patients

Analyzed for PK concentration: 32 patients

Analyzed for PK parameters by intensive sampling: 0 patients

Analyzed for PK/PD: 20 patients

Diagnosis and Main Criteria for Inclusion:

Patients whose body weight at Screening was less than 20 kg and aged less than 12 years with influenza virus infection, who provided written informed assent when feasible and whose parent/legally acceptable representative provided written informed consent prior to initiation of the study and met all of the following inclusion criteria were enrolled: a positive rapid influenza diagnostic test (RIDT) for influenza; fever with an axillary temperature of ≥ 38.0°C; within 48 hours of onset of influenza symptoms at Screening. The onset of influenza symptoms was defined as the time when body temperature first exceeded 37.5ºC. Patients who met any of the following exclusion criteria were not enrolled: severe symptoms of influenza virus infection requiring inpatient treatment; high risk factors; with any disturbance of consciousness; abnormal behavior or convulsions at Screening; with a current condition of encephalitis or encephalopathy; history of encephalitis, encephalopathy, epilepsy, or influenza virus infection associated abnormal behavior within the past 2 years; concurrent infections requiring antimicrobial and/or antiviral therapy at Screening; severe underlying diseases; use of anti-influenza virus drug within 30 days prior to Screening.

Test Product, Dose and Mode of Administration, Lot Number:

Test drug: S-033188 2% granules

Dose and Mode of Administration: On Day 1, a single oral dose of S-033188 2% granules according to the patient's weight (kg) at Screening was administered as presented below.

Study Drug Administered for Each Dose Group

Patient's weight at Screening	Dose of S-033188 (2% granules)
< 10 kg	1 mg/kg (50 mg/kg)
10 to < 20 kg	10 mg (0.5 g [1 packet])

Lot number:

[redacted]

Duration of Treatment: 1 day (single dose administration)

Criteria for Evaluation:

Efficacy Assessment:

Primary Endpoint (Time to alleviation of influenza illness)

Defined as the time from the start of treatment to the time when the criteria (a and b) indicated below were fulfilled, and the clinical condition was sustained for at least 21.5 hours (90% of 24 hours). Patients who did not experience alleviation of influenza illness by the last observation time point were censored at the time point.

a. In the patient diary, cough and nasal discharge/nasal congestion were both rated as 0 (absent) or 1 (mild).
b. Body temperature was < 37.5°C (axillary).

Secondary Endpoints

1. Change from baseline in influenza virus titer and in the amount of virus RNA (reverse transcription polymerase chain reaction [RT-PCR]) at each time point

   Defined as the change from baseline in virus titer and the change from baseline in the amount of virus RNA at each time point, respectively. Baseline was defined as

the last value obtained before administration of the study drug.

2. Proportion of patients positive for influenza virus titer and proportion of patients positive for influenza virus RNA by RT-PCR at each time point
   Defined as the percentage of patients whose virus titer was not less than the lower limit of quantification at each time point to the patients whose virus titer at baseline was not less than the lower limit of quantification, and the percentage of patients with detectable virus RNA at each time point to the patients whose virus RNA at baseline was not less than the lower limit of detection.
3. Area under the curve (AUC) in virus titer and in the amount of virus RNA (RT-PCR)
   Defined as AUC of change from baseline in virus titer and AUC of change from baseline in the amount of virus RNA, respectively. AUC was calculated using the trapezoidal method.
4. Time to cessation of viral shedding by virus titer and by virus RNA
   Defined as the time between study drug treatment and first time when the virus titer was less than the lower limit of quantification, and the time between the initiation of the study treatment and first time when virus RNA by RT-PCR was less than the lower limit of detection, respectively. Patients whose virus titer and the amount of virus RNA had not reached cessation by the last observation time point were treated as censored patients at the last observation time point in each assessment.
5. Time to resolution of fever
   The time to resolution of fever was defined as the time between study drug treatment and the resolution of fever. The resolution of fever was defined to be achieved when the patient's self-measured axillary temperature became less than 37.5ºC and was maintained at less than 37.5ºC for at least 12 hours. Patients who did not experience resolution of fever by the last observation time point were censored at the last observation time point.
6. Proportion of patients reporting normal temperature at each time point
   Defined as the percentage of patients whose axillary temperature dropped to less than 37.5ºC in the analysis population at each time point.
7. Time to alleviation of individual symptoms
   The time to alleviation of individual symptoms was defined as the time between study drug treatment and the alleviation of individual symptom. The alleviation of a symptom was defined to be achieved when the symptom was assessed as 0 (Absent) or 1 (Mild) for at least 21.5 hours (90% of 24 hours). Patients who did not experience alleviation of each influenza symptom by the last observation time point were censored at the last observation time point.
8. Time to resumption of normal activity
   Defined as the time between the initiation of the study treatment and the time when the patient's parent/guardian assessed the patient's daily activities as 10. Patients who did not experience resumption of normal activity by the last observation time point were censored at the last observation time point.
9. Incidence of influenza-related complications (death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, otitis media)
   Defined as the percentage of patients who experienced each influenza-related complication (death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, otitis media) after the initiation of the study treatment.

10. Incidence of influenza-related complications particularly seen in pediatric patients (influenza-associated encephalitis or encephalopathy, febrile seizures, myositis)
    Defined as the percentage of patients who experienced influenza-related complications seen particularly in pediatric patients (influenza-associated encephalitis or encephalopathy, febrile seizures, myositis) after the initiation of the study treatment.

Other Assessment:

Serum antibody titer, polymorphic and treatment-emergent amino acid substitutions in the polymerase acidic protein (PA) gene, drug susceptibility in patients with evaluable virus, and intrahousehold infection rate

Safety Assessment:

Adverse events (AEs), treatment-related AEs, serious AEs (SAEs), vital signs, and clinical laboratory test results

Pharmacokinetics Assessment:

Plasma concentrations of S-033188 and S-033447

Statistical Methods:

Efficacy:

(1) Analysis Populations

The ITTI population consisted of all patients who received the study drug with a confirmed diagnosis of influenza virus infection and with GCP compliance. Confirmation of influenza virus infection was based on the results of RT-PCR. The PPS population consisted of all patients who were in the ITTI population and did not meet any of the following conditions:

- Patients with any protocol inclusion or exclusion violations
- Patients with study procedure violations
- Patients with inadequate follow-up

The primary efficacy analysis population was the ITTI population. The PPS population was used for the sensitivity analysis of the primary efficacy endpoint.

(2) Primary Endpoint (Time to Alleviation of Influenza Illness)

For the ITTI population, a survival curve of time to alleviation of influenza illness ("cough", "nasal discharge/nasal congestion", and "elevated temperature") (duration of influenza illness) was estimated by using the Kaplan-Meier method, and the median time to alleviation of influenza illness and its 95% confidence interval (CI) were calculated. Furthermore, for the PPS population, the same analysis was performed as a sensitivity analysis to check the consistency of these results.

(3) Secondary Endpoints

1. Change from baseline in influenza virus titer and in the amount of virus RNA (RT-PCR) at each time point
   Only patients in the ITTI population whose virus titer at baseline were greater than or equal to the lower limit of quantification were included in the analyses. Summary statistics for the change from baseline in virus titer were calculated for each time point. For only patients in the ITTI population whose virus RNA at baseline were greater than or equal to the lower limit of detection, a similar

analysis was conducted for the change from baseline in the amount of virus RNA.

2. Proportion of patients positive for influenza virus titer and proportion of patients positive for influenza virus RNA by RT-PCR at each time point
   Only patients in the ITTI population whose virus titer at baseline were greater than or equal to the lower limit of quantification were included in the analyses. The number of patients positive for influenza virus titer was counted and the percentage of those patients in the group of patients positive for virus titer at baseline and its 95% CI were calculated for each time point. For only patients in the ITTI population whose virus RNA at baseline were greater than or equal to the lower limit of detection, a similar analysis was conducted for proportion of patients positive for influenza virus RNA by RT-PCR.
3. AUC in virus titer and in the amount of virus RNA
   Only patients in the ITTI population whose virus titer at baseline were greater than or equal to the lower limit of quantification and who has an observed value for virus titer on Day 9 were included in the analyses. Summary statistics for AUC of virus titer were calculated. For only patients in the ITTI population whose virus RNA at baseline were greater than or equal to the lower limit of detection and who has an observed value for virus RNA on Day 9, a similar analysis was conducted for AUC of the amount of virus RNA.
4. Time to cessation of viral shedding by virus titer and by virus RNA
   Only patients in the ITTI population whose virus titer/RT-PCR at baseline were greater than or equal to the lower limit of quantification were included in the analyses. A survival curve of time to cessation of viral shedding by virus titer was estimated by using the Kaplan-Meier method, and the median time to cessation of viral shedding by virus titer and its 95% CI were calculated. For only patients in the ITTI population whose virus RNA at baseline were greater than or equal to the lower limit of detection, a similar analysis was conducted for time to cessation of viral shedding by virus RNA.
5. Time to resolution of fever
   For the ITTI population, a survival curve of time to resolution of fever was estimated by using the Kaplan-Meier method, and the median time to resolution of fever and its 95% CI were calculated.
6. Proportion of patients reporting normal temperature at each time point
   For the ITTI population, the number of patients whose body temperature had been less than 37.5ºC were counted and the percentage of those patients in the analysis population and its 95% CI were calculated for each time point.
7. Time to alleviation of individual symptoms
   For only patients in the ITTI population whose evaluated influenza symptom score is “2: moderate” or “3: severe” at baseline, a survival curve of time to alleviation of each symptom of influenza (two symptoms: “cough” and “nasal discharge/nasal congestion”) was estimated by using the Kaplan-Meier method, and the median time to alleviation of each symptom and its 95% CI were calculated.
8. Time to resumption of normal activity
   For only patients in the ITTI population whose score for normal activities of daily life is not “10” at baseline, a survival curve of time to return to capability of activities of daily living (ADL) was estimated by using the Kaplan-Meier method,

and the median time to return to capability of ADL and its 95% CI were calculated.

9. Incidence of influenza-related complications
   For the ITTI population, the number of patients who had experienced influenza-related complications (death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, otitis media) was counted, and the percentage of those patients in the analysis population and its 95% CI were calculated.
10. Incidence of influenza-related complications seen particularly in pediatric patients
    For the ITTI population, the number of patients who had experienced each influenza-related complication reported particularly in pediatric patients (influenza-associated encephalitis or encephalopathy, febrile seizures, myositis) was counted, and the percentage of those patients in the analysis population and its 95% CI were calculated.

Safety:

The safety population consisted of patients who received at least one dose of the study drug with GCP compliance. The number of patients who had experienced at least 1 AE, deaths, other SAEs, and AEs leading to early termination of study were counted. The number of those AEs, which were counted by case reported, was also presented. Treatment-related AEs were summarized in the same way as AEs for overall summary.

The number of patients who had experienced the AEs was counted and the incidences and their 95% CIs were calculated using Medical Dictionary for Regulatory Activities (MedDRA) system organ classes and preferred terms. Severity and outcome were also summarized by system organ class and preferred term.

Summary statistics for vital signs and laboratory test data were presented for each scheduled time point and for the change from baseline to each time point. Qualitative laboratory test data at baseline and at scheduled time point were classified according to test category, and the frequency of each pair was presented in a two-dimensional contingency table.

Other Endpoints:

Statistical methods for the other endpoints were as follows:

- Serum antibody titer
  For the ITTI population, serum antibody titers measured on Day 1 and Day 15 (or early termination) were summarized using the frequency of each category and the corresponding percentage. The ratio of Day 15 value relative to Day 1 value was categorized, and the frequency of each category and the corresponding percentage were tabulated. For Day 15/Day 1 ratio, the geometric mean value was also calculated. Furthermore, the categorized serum antibody titers on Day 1 and Day 15 were cross-tabulated. These analyses were performed by influenza virus subtype based on RT-PCR (A/H1N1pdm, A/H3, and B). The categories for serum antibody titer (Day 1 and Day 15) and for the Day 15/Day 1 ratio were pre-specified in the statistical analysis plan.
- Polymorphic and treatment-emergent amino acid substitutions in the PA gene
  The patients in the ITTI population who had sequencing performed at baseline and last RT-PCR positive time point were included in the analysis. Amino acid substitutions data on Day 1 and at the last RT-PCR positive time point were cross-

tabulated for each amino acid position in PA region and influenza virus subtype of sequence sample (A/H1N1pdm, A/H3, and B). Furthermore, for the patients who had treatment-emergent amino acid substitutions in the PA region, their amino acid positions were listed. For the patients who had polymorphic amino acid substitutions in the PA region at Screening, a similar listing was presented.

- Drug susceptibility testing for test substances
  The patients infected with multiple virus types were excluded from this analysis. The summary statistic for 50% effective concentration (EC_{50}) at baseline and the ratio of EC_{50} for baseline sample relative to that for the reference strain were presented by influenza virus subtype based on RT-PCR (A/H1N1pdm, A/H3, and B). A/Victoria/361/2011 was used as the reference strain for the virus subtype with A/H1N1pdm and A/H3, and B/Wisconsin/1/2010 for the virus subtype with B.
- Intrahousehold infection rate
  The intrahousehold infection rate and its 95% CI were calculated for each time period under the assumption that the number of household members with influenza infection was distributed according to Poisson distribution. Statistical model was pre-specified in the statistical analysis plan.

Pharmacokinetics:

(1) Plasma Concentrations

The PK concentration population consisted of all patients who received at least one dose of the study drug and had at least one evaluable PK assay result. The PK parameter population consisted of all patients with at least one PK parameter estimated.

For patients with blood samples collected over time, plasma S-033188 and S-033447 concentrations were listed and summarized by dose and scheduled sampling time with the number of non-missing observations (N), arithmetic mean (Mean), standard deviation (SD) and coefficient of variation (CV%, calculated by SD/Mean × 100), geometric mean (Geometric Mean) and coefficient of variation for Geometric Mean (CV% Geometric Mean, calculated by $[\exp(sd^2)-1]^{1/2} \times 100$, where sd was the standard deviation for natural log [ln]-transformed data), median, minimum and maximum values. The plasma concentration profiles were plotted against the actual sampling time to determine the PK of S-033188 and S-033447.

The C_{24} was listed and summarized by dose with N, Mean, SD, CV%, Geometric Mean, CV% Geometric Mean, median, minimum and maximum values.

The following PK parameters by intensive sampling were calculated for each patient based on the plasma concentration data of S-033188 and S-033447 by using a model-independent approach: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration after dosing ($AUC_{0\text{-last}}$).

Actual sampling time was used for PK analyses.

(2) Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis

The PK/PD analysis population consisted of all subjects who had PD data with C_{24}. The relationships between the following efficacy endpoints and C_{24} were assessed.

- Time to alleviation of influenza illness
- Change from baseline in influenza virus titer and in the amount of virus RNA (RT-

PCR) at each time point
- AUC in virus titer and in the amount of virus RNA (RT-PCR)
- Time to cessation of viral shedding by virus titer and by virus RNA
- Time to resolution of fever (axillary temperature < 37.5°C)
- Time to alleviation of individual symptoms
- Time to resumption of normal activity

Summary of Results

Study Population:

All of the 33 patients who enrolled in the study completed the study. The safety analysis population and the ITTI population were comprised of all of the 33 patients. The PPS population consisted of 28 patients. In the ITTI population, the most common influenza virus strain was B subtype (36.4%), followed by A/H1N1pdm subtype (33.3%), A/H3 subtype (27.3%), and others (3.0%).

Efficacy:

Time to Alleviation of Influenza Illness (Primary Endpoint)

The median time to alleviation of influenza illness (95% CI) was 45.3 (28.5, 64.1) hours for the ITTI population. The analysis for the PPS population, performed for sensitivity analysis, showed comparable results to those for the ITTI population.

Change from Baseline in the Influenza Virus Titer

More than 4-log reduction in the mean virus titer was observed on the next day of the treatment with S-033188 (−4.62 $\log_{10}$ [50% tissue culture infective dose ($TCID_{50}$)/mL] on Day 2) in the ITTI population. Although temporary increase of the mean virus titer was observed after Day 2 in patients infected with type A/H3 virus and type B virus, all subtypes showed more than 5-log reduction in the mean of influenza virus titer on Day 9.

Change from Baseline in Virus RNA (RT-PCR)

The mean change from baseline in the amount of virus RNA was −1.61 $\log_{10}$ (virus particles/mL) on Day 2 and −3.53 $\log_{10}$ (virus particles/mL) on Day 9 in the ITTI population.

Proportion of Patients Positive for Influenza Virus Titer

The proportion of patients positive for influenza virus titer was 59.4% on Day 2 in the ITTI population. Although the proportion of patients positive for influenza virus titer was 70.0% on Day 4 and 65.6% on Day 6, it reduced to 6.3% on Day 9.

Proportion of Patients Positive for Influenza Virus RNA by RT-PCR

The proportion of patients positive for influenza virus RNA reduced from 100.0% on Day 2 to 75.8% on Day 9 in the ITTI population.

AUC Adjusted by Baseline in Virus Titer and Virus RNA

The mean AUC for the change from baseline in the influenza virus titer was

−832.2 log_{10} ($TCID_{50}$/mL)·hours in the ITTI population, and the mean AUC for the change from baseline in the amount of virus RNA was −434.0 log_{10} (virus particles/mL)·hours in the ITTI population.

Time to Cessation of Viral Shedding by Virus Titer and Virus RNA

The median time to cessation of viral shedding evaluated by virus titer (95% CI) was 48.0 (24.0, 144.0) hours, and the median time to cessation of viral shedding evaluated by virus RNA (95% CI) was 240.0 (240.0, not calculable) hours in the ITTI population.

Time to Resolution of Fever (Axillary Temperature < 37.5°C)

The median time to resolution of fever (95% CI) was 34.0 (25.0, 43.1) hours in the ITTI population.

Proportion of Patients Reporting Normal Temperature (Axillary Temperature < 37.5°C)

The proportion of patients reporting normal temperature was 21.2%, 42.4%, and 93.9% at 12, 24 and 48 hours after the treatment, respectively, in the ITTI population.

Time to Alleviation of Individual Symptoms

The median time to alleviation of cough symptom (95% CI) in the ITTI population was 20.6 (1.0, 130.8) hours. The median time to alleviation of nasal discharge/nasal congestion symptom (95% CI) in the ITTI population was 52.7 (16.3, 92.4) hours.

Time to Resumption of Normal Activity

The median time to resumption of normal activity (95% CI) was 80.3 (51.5, 131.4) hours in the ITTI population.

Incidence of Influenza-related Complications

Two post-treatment cases of otitis media and 1 post-treatment case of bronchitis were reported as influenza-related complications in the ITTI population. No influenza-related complication other than otitis media and bronchitis was reported.

Incidence of Influenza-related Complications Seen Particularly in Pediatric Patients

No influenza-related complication seen particularly in pediatric patients was reported in the ITTI population.

Treatment-emergent Amino Acid Substitutions in the PA Gene

Major treatment-emergent changes in amino acid sequence were as follows: I38T (3 cases of I38T/I mixture detected in 2 patients infected with type A/H3 virus and 1 patient infected with type A/H1N1pdm virus) and I38M (2 cases detected in 2 patients infected with type A/H3 virus).

Safety:

- No deaths, SAEs, or AEs leading to study discontinuation were reported. AEs were reported in 18 of 33 patients (54.5%, 24 events).
- Treatment-related AE was reported in 1 of 33 patients (3.0%, 1 event): 1 case of platelet count increased, which was classified as Grade 1 and was resolving.
- The most common AE was vomiting (18.2%, 6 cases in 6 patients). All cases of vomiting were classified as Grade 1 and considered not related to the study drug.
- All AEs were classified as Grade 1 or 2 in severity and no severe AEs classified as Grade 3, 4 or 5, were reported. All the AEs classified as Grade 2 were considered not related to the study drug. All AEs resolved or were resolving.
- No patients experienced AEs related to liver function.
- For clinical laboratory tests, no clinically meaningful findings or trends were found in the changes from baseline. No clinically meaningful findings or trends were noted in vital signs.

Pharmacokinetics:

Plasma S-033188 concentrations were measured for 12 patients aged < 2 years. Of the 12 patients, plasma S-033188 concentrations for 7 patients were above lower limit of quantification (0.100 ng/mL) and for 5 patients were BLQ (< 0.100 ng/mL) at 0.5 to 2 hours postdose. The highest concentration was 0.986 ng/mL. All plasma S-033188 concentrations at other sampling points were BLQ for the 12 patients.

The geometric means (CV% geometric mean) of C_{24} were 46.8 (53.1%) and 69.4 (35.6%) ng/mL in the 10-mg and 1-mg/kg dose groups, respectively. The C_{24} values were comparable with those in adult Phase 3 study (geometric mean [CV% geometric mean]; 47.4 [68.8%] ng/mL) and previous pediatric study (geometric mean [CV% geometric mean]; 80.2 [43.2%], 54.9 [41.6%], and 40.4 [50.6%] ng/mL in the 40-, 20-, and 10-mg dose groups, respectively).

The C_{24} values among dietary conditions were similar.

No clear relationship was found between C_{24} and each efficacy endpoint.

Conclusions

Single oral dose of S-033188 2% granules investigated in the study is considered to be well tolerated and effective in pediatric patients with influenza virus infection.

Report Date: 3 July 2018