U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 210854
Supplement #:	S-000
Drug Name:	XOFLUZA™ (baloxavir marboxil, S-033188) 20 mg and 40 mg tablets
Indication(s):	For the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours
Applicant:	Shionogi Inc.
Date(s):	Date Submitted: 04-24-18
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1 EXECUTIVE SUMMARY

Shionogi Inc. submitted this New Drug Application for XOFLUZA™ (baloxavir marboxil, S-033188) 20 mg and 40 mg tablets for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. This review will focus on the applicant's prospective, randomized, double-blind, placebo-controlled, phase 2b and 3 clinical trials to evaluate the safety and efficacy of S-033188 for the proposed indication. The phase 3 trial was conducted in Japan and the United States while the phase 2b trial was conducted in Japan only. Subjects in the phase 3 trial received a single dose of 40 or 80 mg of S-033188, Oseltamivir 75 mg twice daily for five days or placebo. Subjects in the phase 2b trial received 10 mg, 20 mg, 40 mg of S-033188 or placebo.

The primary efficacy endpoint for both trials was the time to alleviation of symptoms (TTAS), defined by the applicant as the time between the initiation of the study treatment and the alleviation of influenza symptoms. The alleviation of symptoms was defined by the applicant as the time (measured in hours) when all of the seven influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) were assessed by the patient as 0 (None) or 1 (Mild) in the patient eDiary, for a duration of approximately one day (at least 21.5 hours).

In the primary efficacy analysis in the phase 3 trial comparing the distribution of TTAS in the S-033188 (n=455) and placebo (n=230) treated subjects who had a confirmed diagnosis of influenza virus infection at Day 1, a statistically significant difference was observed in favor of S-033188 over placebo ($p<0.001$). The median TTAS was 54 hours in S-033188 patients compared to 80 hours in placebo subjects with a median difference in TTAS between the two treatment groups of 21 hours. There was no statistically significant difference observed in the secondary efficacy analysis comparing the TTAS in S-03188 and oseltamivir subjects where the median TTAS in oseltamivir subjects was also 54 hours.

Median TTAS values in the phase 2b trial were similar to those observed in the phase 3 trial. Unlike the phase 3 trial, the statistical significance of the primary efficacy analysis in the phase 2b trial depended on which statistical test was used. There were no statistically significant differences observed between any one of the three S-033188 treatment groups and placebo using the pre-specified Cox proportional hazards model. However, the phase 2b trial was considered to be supportive of the phase 3 trial results by the statistics reviewer because there were statistically significant differences favoring each dose compared to placebo using the Wilcoxon test. The Wilcoxon test is typically used for the primary analysis in influenza trials as it puts more weight on earlier events than the Cox proportional hazards model, which is more powerful when there is proportionality of the hazards. However the proportional hazards assumption does not generally hold for acute uncomplicated influenza because it is an illness of limited duration and survival curves converge after a few days due to spontaneous resolution.

The majority of subjects in the trials were infected with the type A strain of the influenza virus. There were far fewer subjects with the type B strain A highly statistically significant difference

in TTAS was observed between S-033188 and placebo subjects who were infected with Influenza A while there was no statistically significance between the TTAS in S-0331888 and placebo subjects with type B strain. Most importantly, there were also discordant results between the phase 2b and 3 trials for subjects infected with type B influenza where an earlier median TTAS was observed in the placebo subjects than in the S-033188 subjects in the phase 3 trial while the opposite trend was observed in the phase 2b trial.

2 INTRODUCTION

2.1 Overview

Baloxavir marboxil is an anti-influenza virus drug. In the cover letter the applicant states, "Baloxavir marboxil is a prodrug that is converted by hydrolysis to baloxavir, the active form that exerts anti-influenza activity. Baloxavir acts on the cap-dependent endonuclease (CEN), an influenza virus-specific enzyme in the viral RNA polymerase complex and thereby inhibits the transcription of influenza virus genomes resulting in inhibition of influenza virus replication."

There were two pivotal trials that were reviewed in this NDA. Study 1601T0831 (T0831) was a randomized, phase 3, double-blind, multicenter trial in otherwise healthy patients with influenza in Japan and the United States. Subjects aged 20 and 64 in the phase 3 trial were randomized 2:2:1 to receive either a single dose of S-033188 40 or 80 mg, oseltamivir 75 mg BID for five days, or placebo. Subjects aged 12-19 years in the phase 3 trial were randomized 2:1 to weight-based S-033188 40 mg or 80 mg or placebo.

Study 1518T0821 (T0821) was a randomized, phase 2b, double-blind multicenter trial in otherwise healthy patients with influenza in Japan. Subjects in T0821 were randomized 1:1:1:1 to 10 mg, 20 mg, or 40 mg of S-033188 or to placebo.

Table 1: List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
1601T0831	Phase 3, Randomized, Double-Blind Trial in Japan and USA	One day for S-033188 Five days for oseltamivir	22 days	455 on S-033188 230 on Placebo 375 on Oseltamivir	Otherwise healthy patients 12 years of age and older with influenza who were symptomatic for no more than 48 hours
1518T0821	Phase 2b, Randomized, Double-Blind Trial in Japan	One day for S-033188	22 days	S-033188 100 on 10 mg 100 on 20 mg 100 on 40 mg 100 on Placebo	Otherwise healthy patients 20 years of age and older who were symptomatic for no more than 48 hours

2.2 Data Sources

The application package is located at \\CDSESUB1\evsprod\NDA210854\0000.

Datasets are located in \\CDSESUB1\evsprod\NDA210854\0000\m5\datasets\1601t0831, \\CDSESUB1\evsprod\NDA210854\0000\m5\datasets\1518t0821 and \\CDSESUB1\evsprod\NDA210854\0000\m5\datasets\ise.

Clinical study reports are located in \\CDSESUB1\evsprod\NDA210854\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-\5351-stud-rep-contr while tables and figures for the Integrated Summary of Efficacy (ISE) are located in \\CDSESUB1\evsprod\NDA210854\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-\5353-rep-analys-data-more-one-stud\ise.

The dataset called “adtte” contains data for the time to event endpoints including the primary efficacy endpoint. Other variables for baseline and demographic characteristics are in the adsl datasets for each study and/or the ISE.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted SDTM, listing and analysis datasets along with define.pdf files and SAS programs used to analyze and create analysis datasets. The applicant's submitted data were well-defined along with the summary tables and figures in the clinical study report. There were some discrepancies noticed with respect to consistently defining the censoring variable. The Analysis Data Reviewer's Guides (ADRG) stated that the censored data was indicated as CNSR=0 which was true for the adtte dataset and the SAS program adtte.sas for T0821. However, for T0831 and the ISE, time to event data were censored when CNSR=1. In response to the FDA Information Request dated July 6, 2018 the applicant confirmed this and confirmed that the primary analyses were correct for studies T0821, T0831 and the ISE and did not change based on the updated ADRGs.

The phase 3 protocol and statistical analysis plan (SAP) and relevant analysis decisions were reviewed prior to unblinding of the phase 3 trial. The SAP was finalized in July 2017. In addition, the SAP for the ISE was reviewed in February 2018 prior to unblinding of the phase 3 trial. The protocol and SAP for the phase 2b trial were not reviewed by the FDA as this trial was not conducted in the United States.

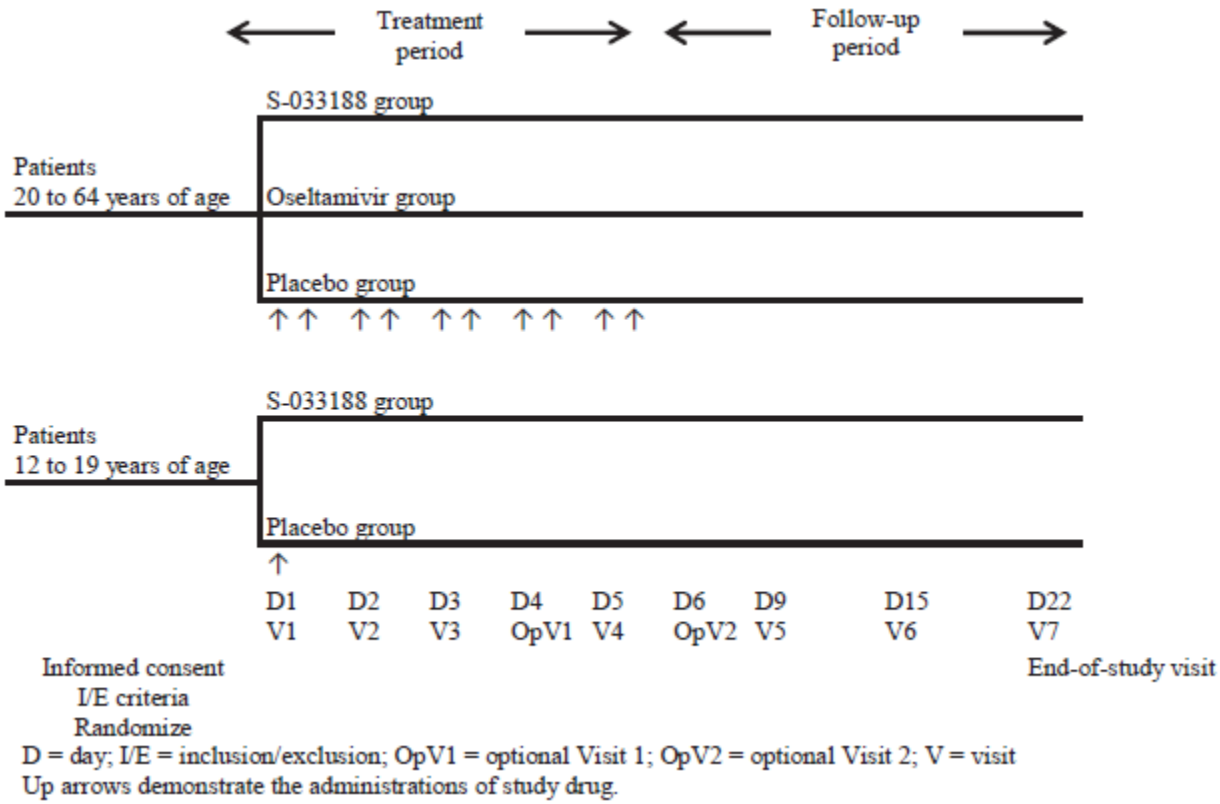
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Note that the summary in Section 3.2.1 is either directly taken from the sponsor's NDA or previous IND submissions, or paraphrased, unless otherwise specified.

T0831 was a randomized, phase 3, double-blind, multicenter trial in otherwise healthy patients with influenza in Japan and the United States. Patients in the 20 to 64-year-old age stratum were randomized in a 2:2:1 ratio to receive a single dose of 40 or 80 mg of S-033188 according to their weight category, 75 mg BID of oseltamivir for 5 days, or placebo. In order to achieve comparable exposure to the drug, patients who weighed < 80 kg at Screening received 40 mg of S-033188, and patients who weighed ≥ 80 kg at Screening received 80 mg of S-033188. According to the applicant, oseltamivir was not used in patients between the ages of 12-19 years due to a caution against use in adolescents in Japan based on possible neuropsychiatric adverse events. Patients in 12 to 19-year-old age stratum were randomized in a 2:1 ratio to receive a single dose of 40 or 80 mg (depending on weight) S-033188 or placebo.

Figure 1: Study T0831 Schematic Diagram



D = day; I/E = inclusion/exclusion; OpV1 = optional Visit 1; OpV2 = optional Visit 2; V = visit
Up arrows demonstrate the administrations of study drug.

Source: Figure 9-1 of the Clinical Study Report for T0831

An interactive response technology (IRT) was used to assign patients to numbers for which treatment has already been randomly assigned. The randomization was stratified by region (Japan, USA), body weight (< 80 kg, ≥ 80 kg) and baseline composite symptom score (≤ 11, ≥ 12).

The study drug was administered orally at the study center on Day 1 (initial dose) within 48 hours of onset of symptoms. Patients 20 to 64 years of age received study drug twice daily for 5 days. For patients aged 12 to 19 years, a single dose of study drug was administered. During the period of the efficacy and safety assessment, i.e., 14 days for efficacy and 22 days for safety, patients returned to the study center at Visit 2 to Visit 7 (Day 2, Day 3, Day 5, Day 9, Day 15, and Day 22) and some patients visited the study center at Optional Visit 1 (Day 4) and/or Optional Visit 2 (Day 6).

The primary objective of T0831 was to evaluate the efficacy of a single oral dose of S-033188 compared with placebo by measuring the TTAS in patients with uncomplicated influenza virus infection. The primary efficacy endpoint was the TTAS (unit: hours), defined by the applicant as the time between the initiation of the study treatment and the alleviation of influenza symptoms. The alleviation of symptoms was defined by the applicant as the time when all of the seven

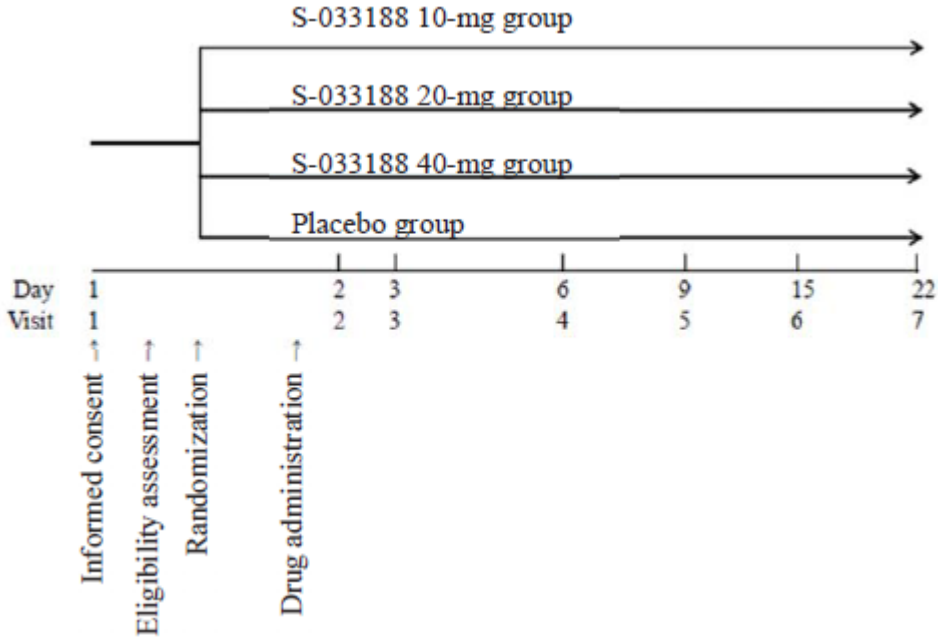
influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) were assessed by the patient as 0 (None) or 1 (Mild) in the patient eDiary, for a duration of at least 21.5 hours (24 – 10% × 24 hours).

Secondary objectives of T0831 were

- to evaluate the efficacy of a single, oral dose of S-033188 compared with oseltamivir 75 mg daily (BID) for 5 days by measuring the TTAS in patients with uncomplicated influenza virus infection.
- to evaluate the efficacy of a single, oral dose of S-033188 compared with placebo by measuring the secondary endpoints in patients with uncomplicated influenza virus infection.
- to evaluate the efficacy of a single, oral dose of S-033188 compared with oseltamivir 75 mg BID for 5 days by measuring the secondary endpoints in patients with uncomplicated influenza virus infection.

T0821 was a randomized, phase 2b, double-blind trial with subjects randomized 1:1:1:1 to 10 mg, 20 mg, 40 mg of S-033188 or placebo. T0821 was conducted in Japan only. The randomization used the stochastic minimization method for balancing the following 2 factors: the composite symptom score (a total of 7 influenza symptom scores) at baseline (q11 or ≥12) and the current smoking status (smoking or nonsmoking).

Figure 2: Study T0821 Schematic Diagram



Source: Figure 9-1 of the Clinical Study Report for T0821

Patients in T0821 received a single oral dose of the assigned 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, 6, 9, 15, and 22 (Visit 2 to 7; Patients visited the study center at Visit 3 [on Day 3] if circumstances permitted) for the assessment of efficacy during the 14 days between Visits 1 and 6 and safety during the 22 days between Visits 1 and 7.

The primary objective of T0821 was to evaluate the efficacy of S-033188 (10, 20 and 40 mg) versus placebo as measured by the TTAS in patients with influenza virus infection. The primary efficacy endpoint was the TTAS as defined above for T0831. The secondary efficacy objective of the study was to assess the efficacy of S-033188 (10, 20 and 40 mg) versus placebo as measured by the secondary endpoints in patients with influenza virus infection.

An important secondary efficacy endpoint in influenza trials was the time to resolution of fever which was defined in both trials as the time when the patient's self-measured axillary temperature became less than 37ºC for a duration of at least 12 hours.

3.2.2 Statistical Methodologies

The Intent-to-Treat-Infected (ITTI) population was the primary analysis population that consisted of the patients who received the study drug with a confirmed diagnosis of influenza. Confirmation of influenza was based on the results of the reverse transcription polymerase chain reaction (RT-PCR) test on Day 1 in T0831 and for a positive rapid antigen test (RAT) for influenza at enrollment for T0821. The population was analyzed according to the treatment to which the patients were randomized.

Kaplan-Meier curves, median survival time and 95% CIs were obtained without stratification with the treatment group indicator variable in the strata statement. Patients who did not experience alleviation of symptoms were censored at the last observation time point. If at least one of the 7 influenza symptom scores were missing at the time of assessment, the missing assessment of influenza symptoms were to be treated conservatively as having moderate or severe symptoms (as failures) at the corresponding date and time of assessment.

For the phase 2b trial, the applicant used the Cox proportional hazards model for the primary analysis adjusting for stratification variables of composite symptom scores (q11 vs. ≥12) and smoking status (yes, no). The applicant used the Hommel method in the phase 2b trial to adjust for multiplicity as the primary analysis compared the distribution of the TTAS for the three doses of S-033188 against the distribution of the TTAS in the placebo arm. In the phase 2b trial, the applicant used the stratified Gehan generalized Wilcoxon test as a secondary efficacy analysis (stratified by the same stratification factors as the primary efficacy analysis). The statistics reviewer used the Gehan Wilcoxon test to compare each dose of S-033188 against placebo, using the Hochberg procedure to control for multiplicity.

Because the proportional hazards assumption is violated, the Wilcoxon tests were more powerful than the Cox proportional hazards or logrank tests. Therefore, the applicant decided to use the Peto-Prentice version of the generalized Wilcoxon test as the primary analysis for the phase 3

trial while the reviewer used the Gehan generalized Wilcoxon test. The Peto and modified Peto approaches are variations of the Wilcoxon test and typically produce similar results. The reviewer chose to use the more common Gehan version of the Wilcoxon test in part because the applicant used this version in their phase 2b trial and because it has been more commonly used than the other versions. In contrast, the log rank test can yield quite different results from the Wilcoxon tests when hazards are not proportional. The reviewer performed sensitivity analyses using the log rank, Peto and modified Peto versions of the Wilcoxon test. For the phase 3 trial the reviewer and the applicant adjusted for stratification variables at randomization that included composite symptom scores (q11 vs. ≥12) and geographic region (Japan, USA).

The reviewer obtained median treatment differences using the Hodges-Lehman estimator setting censored values equal to the maximum follow-up time for efficacy of 14 days. The applicant used differences between the median TTAS that was obtained separately for each treatment group (this will be discussed later in Section 5.1, the Statistical Issues section of the review).

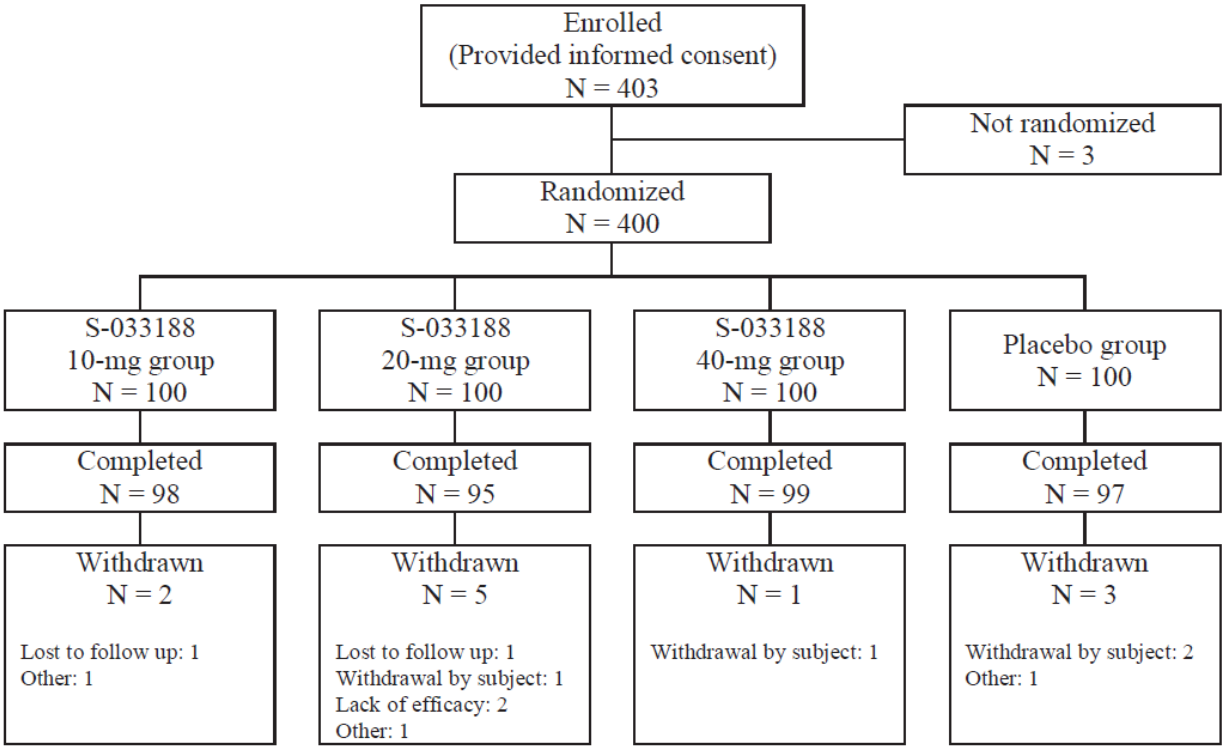
The Greenwood method was used by the applicant in the calculation of the CIs for medians in each treatment group, and the 95% CI of difference of median times was obtained using the bootstrap percentile method in T0831 only.

Due to similar primary efficacy results in the phase 2b and 3 trials, the statistics reviewer combined data from the phase 2b and 3 trials to obtain greater power for subgroup analyses. Subgroup analyses were also performed only for subjects in the phase 3 trial for subgroups that were not included in the phase 2b trial (e.g., Whites, U.S. subjects, adolescents). As discordant results were observed in the phase 2b and 3 trials for subjects infected with the type B strain of the influenza virus, influenza B results were also analyzed separately for each trial. The applicant also performed other selected subgroup analyses.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

In T0821, only 3 out of 403 enrolled subjects were not randomized; while the remaining 400 subjects were randomized with exactly 100 subjects randomized to each treatment group. Only 11 subjects withdrew from the trial.

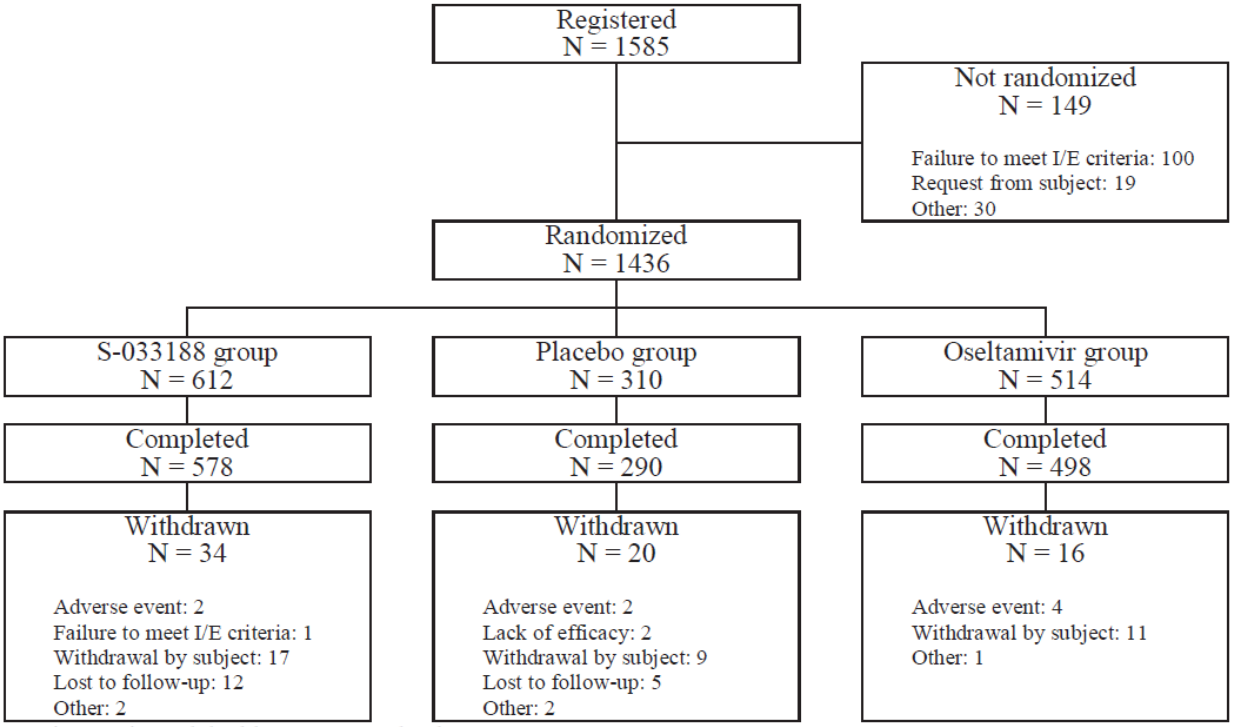
Figure 3: Patient Disposition for Study T0821



Source: Table 10-1 of the Clinical Study Report for T0821

In T0831, there were 1585 subjects who consented to participate in the study and were registered; 149 were not randomized mostly due to the 100 subjects who failed to meet the inclusion/exclusion criteria. The remaining 1436 subjects were randomized with 612 subjects randomized to the S-033188 treatment group, 310 randomized to the placebo treatment group and 514 randomized to the oseltamivir treatment group. A total of 34, 20 and 16 subjects respectively in the S-033188, placebo and oseltamivir treatment groups withdrew from the study prior to completion. Withdrawal by the subject was the most prevalent reason for study discontinuation, followed by loss to follow-up, adverse events, and other reasons (e.g., problems related to the eDiary).

Figure 4: Patient Disposition for Study T0831



Patient registered doubly was counted only once.

Source: Figure 10-1 of the Clinical Study Report for T0831

In the phase 2b trial, age and BMI appeared to be similar in the four treatment groups while the percentage of females appeared to be slightly lower in the S-033188 10 mg arm compared to other treatment groups. All but one subject in the trial was Asian and all but three subjects were outpatients. One third of the subjects were smokers in each treatment arm. There appeared to be similar composite symptom scores and body temperatures at baseline in each treatment arm. The majority of subjects in each treatment arm had influenza for >12 to 24 hours with the exception of the S-033188 40 mg arm where the majority of subjects had influenza for >24 to 36 hours. The majority of subjects (75-79%) were diagnosed as having the influenza A strain of the virus while the remaining 21-25% had influenza B. The majority of influenza A subjects had the H1N1 subtype followed by the H3NX subtype. The percentage of subjects who received influenza vaccination ranged from 20% for the S-033188 20 mg treatment group to 37% for the S-033188 40 mg treatment group.

Table 2: Demographics and Baseline Characteristics for Study T0821

		S-033188 10 mg N=100 n (%)	S-033188 20 mg N=100 n (%)	S-033188 40 mg N=100 n (%)	Placebo N=100 n (%)	P-value [a]
Age (years)	n	100	100	100	100	Pa=0.9820
	Mean	37.7	37.9	37.3	37.4	
	SD	11.3	10.8	10.6	10.6	
	Min	20	20	20	20	
	Median	36.0	36.5	38.0	37.0	
	Max	62	60	63	64	
	20<= to <=29	26 (26.0)	26 (26.0)	27 (27.0)	28 (28.0)	
	30<= to <=39	32 (32.0)	33 (33.0)	30 (30.0)	28 (28.0)	
	40<= to <=49	24 (24.0)	24 (24.0)	28 (28.0)	32 (32.0)	
	50<= to <=59	13 (13.0)	16 (16.0)	11 (11.0)	9 (9.0)	
	60<= to <=64	5 (5.0)	1 (1.0)	4 (4.0)	3 (3.0)	
BMI	n	100	100	100	100	Pa=0.7408
	Mean	23.10	22.71	22.64	22.60	
	SD	3.94	3.83	3.49	2.99	
	Min	17.4	16.7	17.3	16.5	
	Median	22.45	22.00	22.25	22.50	
	Max	34.7	36.6	34.9	32.4	
Sex	Male	68 (68.0)	58 (58.0)	60 (60.0)	61 (61.0)	Pe=0.4924
	Female	32 (32.0)	42 (42.0)	40 (40.0)	39 (39.0)	

a Pa, one-way ANOVA; Pk, Kruskal-Wallis test; Pe, Fisher's exact test; Pc, Chi-squared test.
b Duration of influenza is defined as (Date of first study treatment) - (Onset date of symptoms).

		S-033188 10 mg N=100 n (%)	S-033188 20 mg N=100 n (%)	S-033188 40 mg N=100 n (%)	Placebo N=100 n (%)	P-value [a]
Race	American Indian or Alaska Native	0	0	0	0	Pe=1.0000
	Asian	100 (100.0)	99 (99.0)	100 (100.0)	100 (100.0)	
	Black or African American	0	0	0	0	
	Native Hawaiian or Other Pacific Islander	0	0	0	0	
	White	0	0	0	0	
	Other	0	1 (1.0)	0	0	
Inpatient/outpatient	Inpatient	1 (1.0)	0	1 (1.0)	1 (1.0)	Pe=1.0000
	Outpatient	99 (99.0)	100 (100.0)	99 (99.0)	99 (99.0)	
Smoking habits	Yes	33 (33.0)	32 (32.0)	31 (31.0)	33 (33.0)	Pe=0.9952
	No	67 (67.0)	68 (68.0)	69 (69.0)	67 (67.0)	
Composite symptom scores at baseline	n	100	100	100	100	Pa=0.6672
	Mean	12.7	12.4	12.2	12.3	
	SD	3.2	3.0	2.8	2.7	
	Min	5	5	6	5	
	Median	13.0	12.0	12.0	13.0	
	Max	20	19	19	18	
	<=11	36 (36.0)	36 (36.0)	36 (36.0)	36 (36.0)	
	>=12	64 (64.0)	64 (64.0)	64 (64.0)	64 (64.0)	
Body temperature (°C) at baseline	n	100	100	100	100	Pa=0.6612
	Mean	38.45	38.52	38.50	38.46	
	SD	0.44	0.46	0.45	0.45	
	Min	38.0	38.0	38.0	38.0	
	Median	38.30	38.50	38.40	38.40	
	Max	39.8	40.3	40.1	40.1	
Duration of influenza (hrs) [b]	0<= to <= 12	7 (7.0)	15 (15.0)	12 (12.0)	11 (11.0)	Pk=0.5146
	12< to <=24	38 (38.0)	40 (40.0)	28 (28.0)	42 (42.0)	
	24< to <=36	30 (30.0)	18 (18.0)	36 (36.0)	22 (22.0)	
	36< to <=48	25 (25.0)	27 (27.0)	24 (24.0)	25 (25.0)	
Result of rapid antigen test	A	79 (79.0)	75 (75.0)	76 (76.0)	76 (76.0)	Pe=0.9208
	B	21 (21.0)	25 (25.0)	24 (24.0)	24 (24.0)	
	A and B	0	0	0	0	
	Not Defined	0	0	0	0	
Virus subtyping	A (Unknown)	0	0	0	0	Pc=0.2632
	A/H1N1pdm	66 (66.0)	71 (71.0)	61 (61.0)	69 (69.0)	
	A/H1N1	0	0	0	0	
	A/H3NX	13 (13.0)	5 (5.0)	12 (12.0)	6 (6.0)	
	A/H5NX	0	0	0	0	
	A/H7NX	0	0	0	0	
	B	21 (21.0)	23 (23.0)	24 (24.0)	23 (23.0)	
	Mixed infection	0	1 (1.0)	1 (1.0)	2 (2.0)	
	Unknown	0	0	2 (2.0)	0	
Influenza vaccination	Yes	34 (34.0)	20 (20.0)	37 (37.0)	31 (31.0)	Pe=0.0450
	No	66 (66.0)	80 (80.0)	63 (63.0)	69 (69.0)	

a Pa, one-way ANOVA; Pk, Kruskal-Wallis test; Pe, Fisher's exact test; Pc, Chi-squared test.
b Duration of influenza is defined as (Date of first study treatment) - (Onset date of symptoms).

Source: Table 11-2 of the Clinical Study Report for T0821

Note that the applicant included p-values for testing to compare treatment differences for each demographic or baseline characteristics which is not recommended. The randomization should balance the distribution of each subgroup across treatment groups and even if there are differences, they are likely due to chance. Senn (Statistics in Medicine, 1994; Statistical Issues in Drug Development, 1997) advises against performing inferential statistical tests of baseline characteristics as these tests are misleading. Subgroups with statistically significant treatment by baseline interactions can potentially have little if any impact on treatment effects and do not need to be adjusted for in the analysis. Conversely subgroups that have baseline tests that are not statistically significant can potentially have a significant impact on treatment effects and should be adjusted for in the analysis (See Senn's references for further details).

Age, height, weight and BMI appeared to be similar in the three treatment groups in the phase 3 trial while the percentage of females appeared to be slightly lower in the oseltamivir active control arm compared to other treatment groups. The majority of subjects (75-80%) in each treatment group were Japanese while the remaining 15-20% of the subjects in each treatment group were from the U.S. The majority of subjects in the study were Asian (77-81%) while 16-19% were White, followed by 2-5% of the subjects who were Black or African American. Only 5-7% of the subjects in each treatment arm were Hispanic or Latino.

The percentage of smokers ranged from 21% in the S-033188 arm to 27% in the oseltamivir arm. There appeared to be similar composite symptom scores and body temperatures at baseline in each treatment arm. The majority of subjects in each treatment arm had influenza for >12 to 24 hours followed by subjects with influenza >24 to 36 hours. The majority of subjects (79-84%) were diagnosed as having the influenza A strain of the virus, while only 8-9% of the subjects in each treatment group had influenza B. The majority of subjects in each arm (85-88%) had the influenza A H3 subtype. The percentage of subjects who received influenza vaccination ranged from 24% for the S-033188 and placebo arms to 26% in the oseltamivir treatment group.

Table 3: Demographics and Baseline Characteristics for Study T0831

		S-033188 N=456 n (%)	Placebo N=231 n (%)	Oseltamivir N=377 n (%)
Age (years)	n	456	231	377
	Mean	33.5	33.9	36.0
	SD	13.5	13.7	11.8
	Min	12	12	20
	Median	32.0	33.0	35.0
	Max	64	64	64
	≥12 to ≤19	80 (17.5)	38 (16.5)	0
	≥20 to ≤29	121 (26.5)	61 (26.4)	134 (35.5)
	≥30 to ≤39	92 (20.2)	47 (20.3)	104 (27.6)
	≥40 to ≤49	97 (21.3)	48 (20.8)	77 (20.4)
	≥50 to ≤59	52 (11.4)	30 (13.0)	51 (13.5)
	≥60 to ≤64	14 (3.1)	7 (3.0)	11 (2.9)
Height (cm)	n	456	231	377
	Mean	166.09	166.80	167.19
	SD	9.27	8.65	8.84
	Min	141.5	143.1	144.1
	Median	165.45	166.40	167.30
	Max	190.5	190.5	195.5
Weight (kg)	n	456	231	377
	Mean	65.39	67.88	68.46
	SD	15.12	15.57	16.29
	Min	40.1	40.6	42.0
	Median	62.70	66.20	65.50
	Max	111.1	136.9	137.5
	<80	377 (82.7)	190 (82.3)	306 (81.2)
	≥80	79 (17.3)	41 (17.7)	71 (18.8)
BMI (kg/m^2)	n	456	231	377
	Mean	23.60	24.33	24.39
	SD	4.63	5.07	4.97
	Min	15.3	15.8	15.7
	Median	22.45	23.50	23.20
	Max	39.9	57.1	43.4

		S-033188 N=456 n (%)	Placebo N=231 n (%)	Oseltamivir N=377 n (%)
Sex	Male	232 (50.9)	120 (51.9)	218 (57.8)
	Female	224 (49.1)	111 (48.1)	159 (42.2)
Region	Japan/Asia	343 (75.2)	175 (75.8)	303 (80.4)
	Rest of the world	113 (24.8)	56 (24.2)	74 (19.6)
Race	American Indian or Alaska Native	0	0	0
	Asian	349 (76.5)	178 (77.1)	305 (80.9)
	Black or African American	18 (3.9)	11 (4.8)	9 (2.4)
	Native Hawaiian or Other Pacific Islander	0	0	1 (0.3)
	White	85 (18.6)	40 (17.3)	60 (15.9)
	Other	4 (0.9)	2 (0.9)	2 (0.5)
Ethnicity	Hispanic or Latino	32 (7.0)	11 (4.8)	25 (6.6)
	Not Hispanic or Latino	424 (93.0)	220 (95.2)	352 (93.4)
	Not reported	0	0	0
	Unknown	0	0	0
Prior drug	Yes	165 (36.2)	84 (36.4)	148 (39.3)
	No	291 (63.8)	147 (63.6)	229 (60.7)
Prior therapy	Yes	1 (0.2)	0	4 (1.1)
	No	455 (99.8)	231 (100.0)	373 (98.9)
Medical history	Yes	197 (43.2)	114 (49.4)	170 (45.1)
	No	259 (56.8)	117 (50.6)	207 (54.9)
Smoking habits	Yes	94 (20.6)	56 (24.2)	103 (27.3)
	No	362 (79.4)	175 (75.8)	274 (72.7)
Composite symptom scores at baseline	n	456	231	377
	Mean	13.2	13.5	13.2
	SD	3.2	3.3	3.1
	Min	5	5	6
	Median	13.0	13.0	13.0
	Max	21	21	21
	≤11	144 (31.6)	72 (31.2)	119 (31.6)
	≥12	312 (68.4)	159 (68.8)	258 (68.4)
Body temperature (degrees Celsius) at baseline	n	453	231	374
	Mean	38.47	38.39	38.49
	SD	0.52	0.50	0.48
	Min	36.3	35.3	37.0
	Median	38.30	38.30	38.30
	Max	40.7	41.0	40.6
Time to treatment from flu onset (hours)	≥0 to ≤12	60 (13.2)	34 (14.7)	41 (10.9)
	>12 to ≤24	178 (39.0)	87 (37.7)	163 (43.2)
	>24 to ≤36	139 (30.5)	67 (29.0)	94 (24.9)
	>36 to ≤48	79 (17.3)	43 (18.6)	79 (21.0)
	Missing	0	0	0

		S-033188 N=456 n (%)	Placebo N=231 n (%)	Oseltamivir N=377 n (%)
Influenza virus subtype by rapid influenza diagnostic test	A	371 (81.4)	182 (78.8)	317 (84.1)
	B	40 (8.8)	19 (8.2)	34 (9.0)
	A and B	1 (0.2)	2 (0.9)	0
	Negative	42 (9.2)	28 (12.1)	26 (6.9)
	Unknown	2 (0.4)	0	0
Influenza virus subtype based on RT-PCR	A/H1N1pdm	7 (1.5)	7 (3.0)	2 (0.5)
	A/H3	393 (86.2)	196 (84.8)	332 (88.1)
	B	38 (8.3)	20 (8.7)	34 (9.0)
	Mixed infection	8 (1.8)	3 (1.3)	6 (1.6)
	Other	10 (2.2)	5 (2.2)	3 (0.8)
	Negative	0	0	0
Influenza vaccination	Yes	108 (23.7)	55 (23.8)	98 (26.0)
	No	348 (76.3)	176 (76.2)	279 (74.0)

BMI = body mass index; RT-PCR = reverse transcription polymerase chain reaction; SD = standard deviation

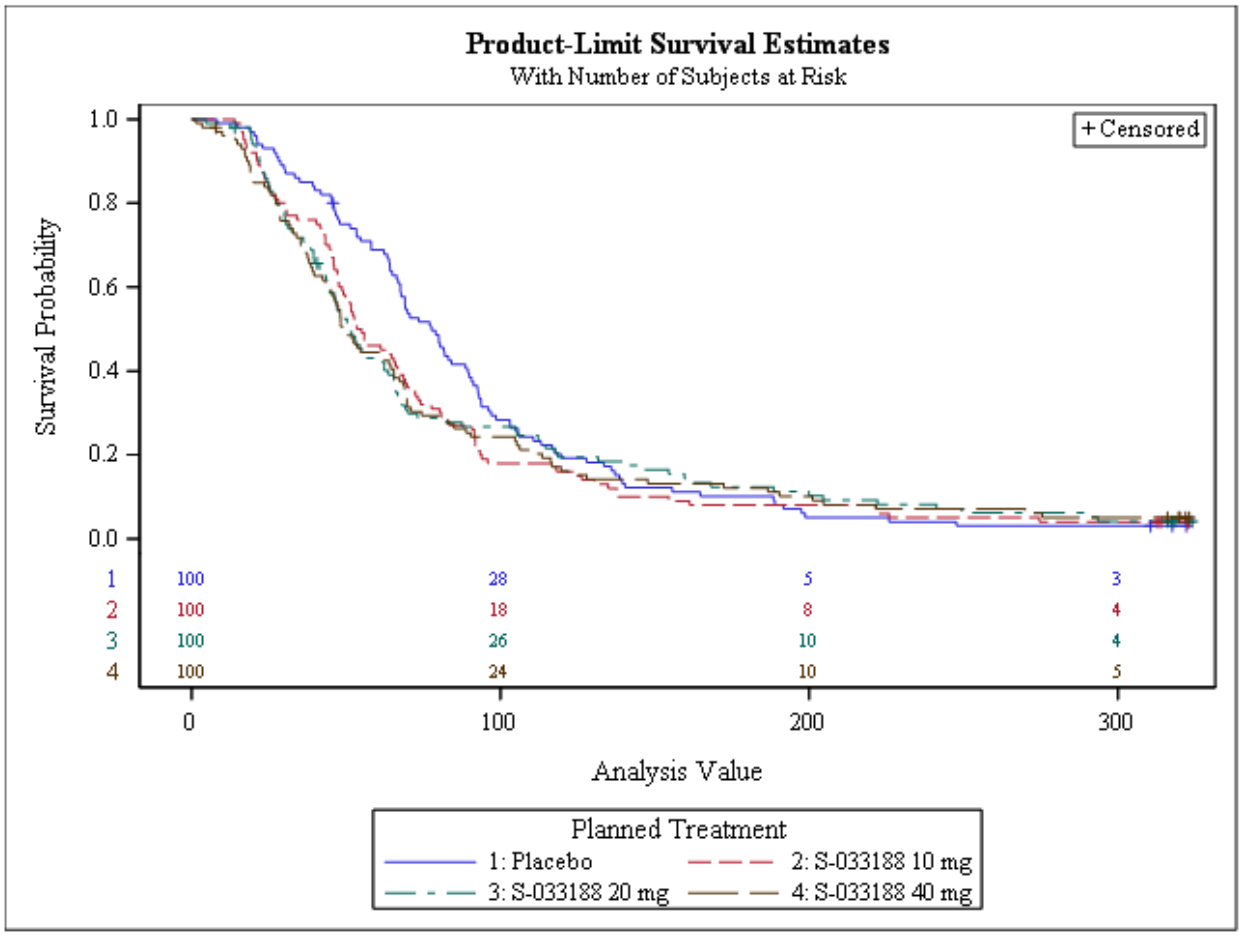
Source: Table 11-2 in the Clinical Study Report for T0831

3.2.4 Results and Conclusions

3.2.4.1 Phase 2b trial results for Time to Alleviation of Symptoms

Based on the reviewer's analysis, the responses in T0821 for each dose of S-033188 appeared similar and each had earlier TTAS than placebo. The findings for each dose shown below the figure were statistically significant and remained significant after adjusting for multiplicity.

Figure 5: Kaplan-Meier plot for the Primary Efficacy Analysis of Study T0821



p-values for stratified Gehan Wilcoxon test:
S-033188 10 mg vs. placebo p=0.009
S-033188 20 mg vs. placebo p=0.018
S-033188 40 mg vs. placebo p=0.005

Source: Reviewer's analysis

None of the applicant's statistical comparisons of each dose of S-033188 against placebo were statistically significant using the Cox proportional hazards model. This was most likely due to the lack of proportional hazards as statistical significance was achieved using the Gehan Wilcoxon test. The applicant performed a post-hoc analysis and found that the hazards were not proportional. The applicant concluded that the stratified generalized Wilcoxon test was more appropriate for evaluating treatment group differences because the Wilcoxon test does not require the proportional hazards assumption. Median TTAS ranged from 50 to 54 hours for the active treatment arms compared to 78 hours for the placebo subjects.

Table 4: Applicant's Analysis of Time to Alleviation of Symptoms using the Cox Proportional Hazards Model for Study T0821

(Details of Maximum Likelihood Estimates)	Estimate	SE	P-value	P value Adjusted by Hommel Method	Hazard Ratio	95% Confidence Interval of Hazard Ratio
S-033188 10 mg	-0.2770	0.1450	0.0561	0.1650	0.758	0.571, 1.007
S-033188 20 mg	-0.2109	0.1461	0.1488	0.1650	0.810	0.608, 1.078
S-033188 40 mg	-0.2024	0.1458	0.1650	0.1650	0.817	0.614, 1.087
Placebo	---	---	---	---	---	---
Smoking habits Yes	0.0452	0.1101	0.6813	---	1.046	0.843, 1.298
Smoking habits No	---	---	---	---	---	---
Composite symptom scores at baseline	0.0864	0.0178	<.0001	---	1.090	1.053, 1.129

Note: Covariates: smoking habit, composite symptom scores at baseline.
SE: Standard error.
Source: Table 11-4 of the Clinical Study Report for T0821

Table 5: Applicant's Secondary Analyses of Time to Alleviation of Symptoms for Study T0821

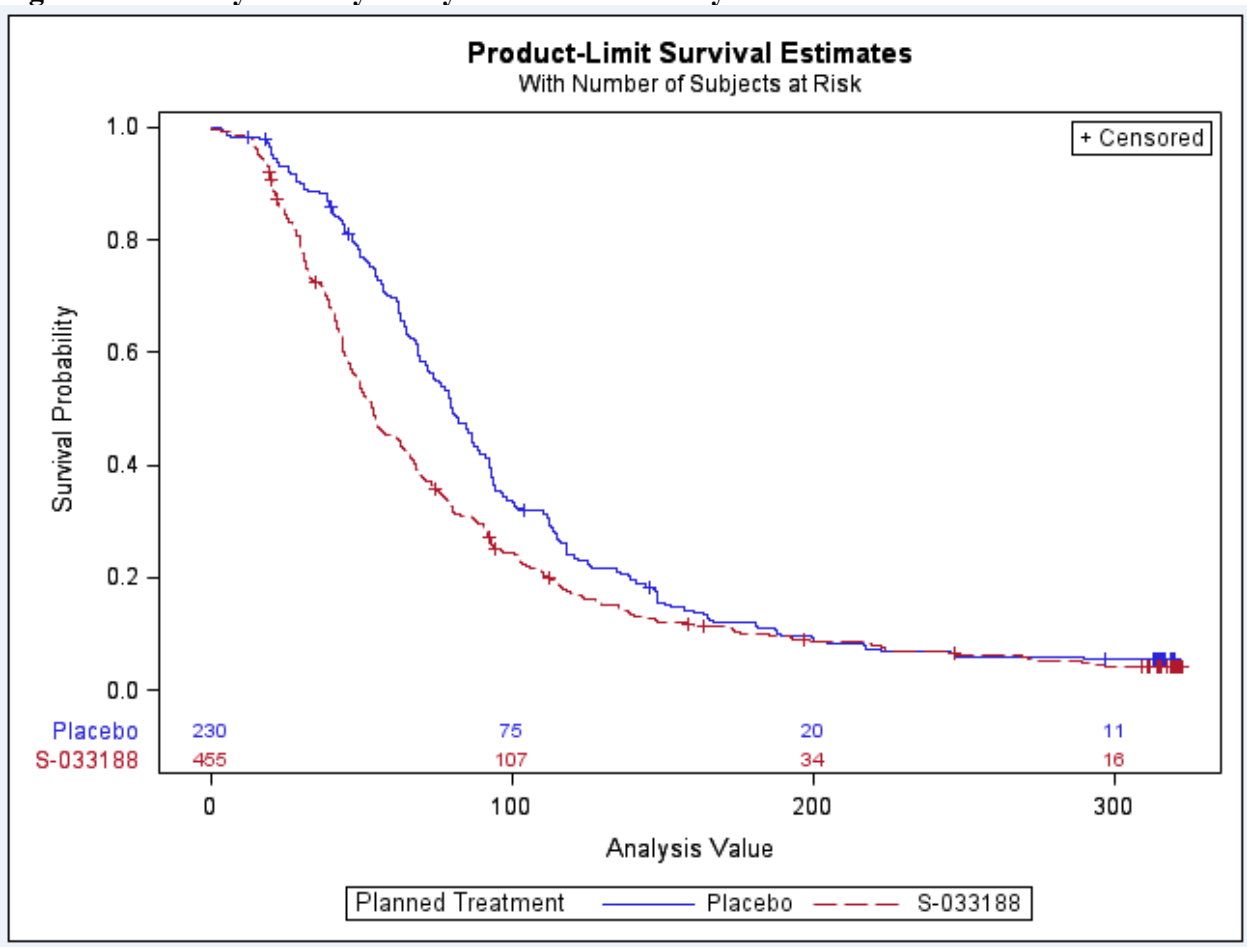
	S-033188 10 mg	S-033188 20 mg	S-033188 40 mg	Placebo
Summary statistics				
- n	100	100	100	100
- Median (hrs)	54.2	51.0	49.5	77.7
- 95% confidence interval (hrs)	47.7, 66.8	44.5, 62.4	44.5, 64.4	67.6, 88.7
- Difference (vs Placebo) (hrs)	-23.4	-26.6	-28.2	---
Stratified Generalized Wilcoxon test vs placebo [a]				
- P-value	0.0085	0.0182	0.0046	---
Cox proportional hazards model vs placebo [b]				
- Hazard ratio	0.758	0.810	0.817	---
- 95% confidence interval	0.571, 1.007	0.608, 1.078	0.614, 1.087	---
- P-value	0.0561	0.1488	0.1650	---

a Stratified factors: smoking habit, composite symptom scores at baseline.
b Covariates: smoking habit, composite symptom scores at baseline.
Source: Table 11-6 of the Clinical Study Report for T0821

3.2.4.2 Phase 3 trial results for Time to Alleviation of Symptoms

Statistical significance between S-033188 and placebo was achieved in the phase 3 trial ($p<0.001$ using the Gehan Wilcoxon and log rank tests). Medan times to alleviation of symptoms were 54 hours for S-033188 subjects and 80 hours for placebo subjects. The median difference in TTAS between S-033188 and placebo subjects was 21 hours using the Hodges-Lehmann approach.

Figure 6: Primary Efficacy Analysis of Phase 3 Study T0831



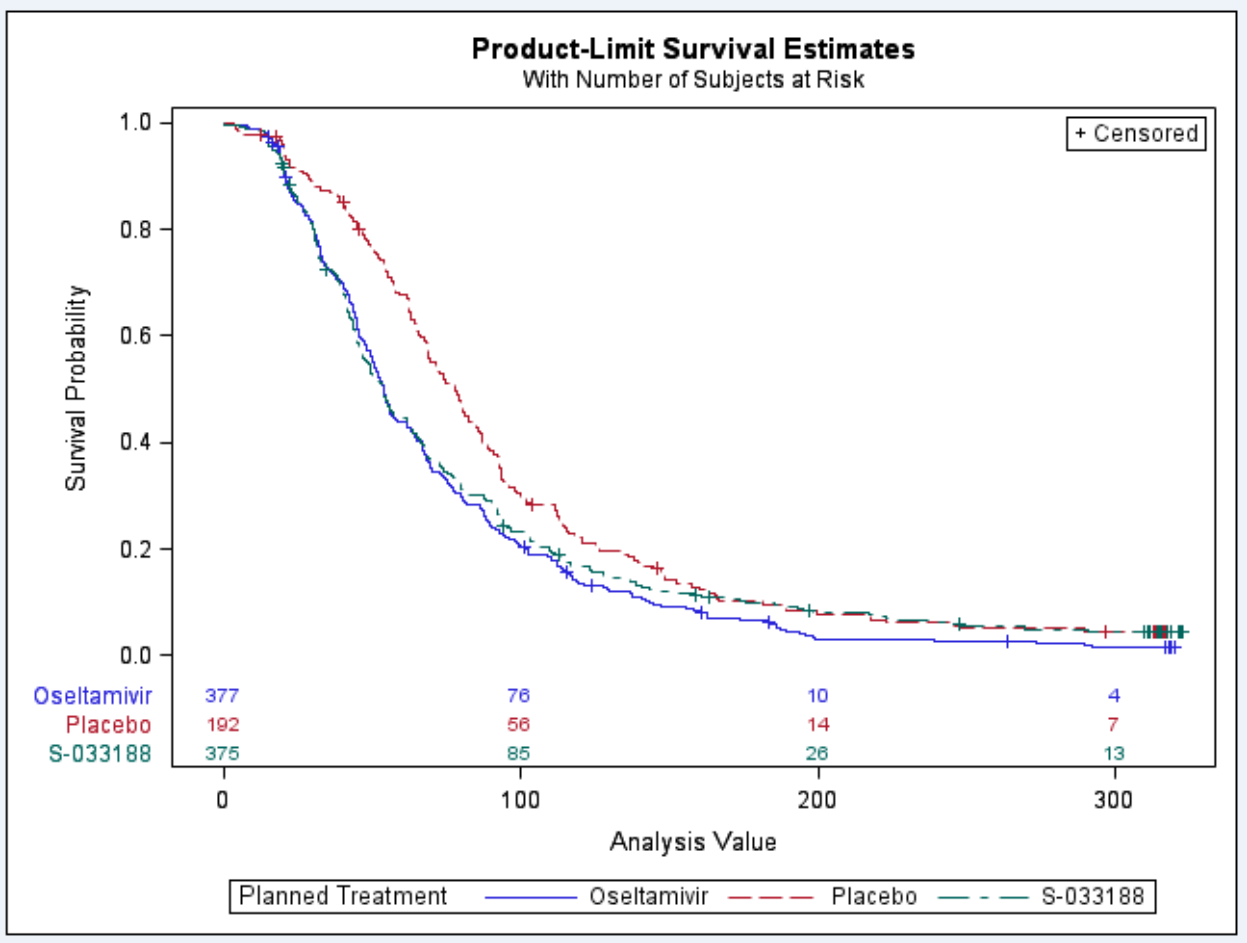
p-value for stratified Gehan Wilcoxon test <0.001
p-value for stratified log rank test <0.001
p-values were stratified by composite symptom score at baseline (q11, ≥12) and region (US, Japan)

Treatment Group	Median (hours)	95% CI
S-033188	54	(50,59)
Placebo	80	(73, 87)
Placebo – S-033188	+21	(13, 28)

Median differences were computed using Hodges-Lehmann estimates
Source: Reviewer's analysis

Since there was no oseltamivir arm for subjects less than 20 years of age the reviewer repeated the primary efficacy analysis for subjects 20 years of age and older in order to compare the TTAS in oseltamivir subjects with the TTAS in the other two treatment groups. Statistical significance between S-033188 and placebo and between oseltamivir and placebo were clearly achieved ($p<0.001$ for both comparisons using the Gehan Wilcoxon and log rank tests). Medan times to alleviation of symptoms for subjects 20 years of age and older were 54 hours for S-033188 and oseltamivir subjects and 78 hours for placebo subjects. The median difference in TTAS between S-033188 and placebo subjects was 19 hours.

Figure 7: Kaplan-Meier plots for subjects 20 years of age and older in Phase 3 Study T0831



Treatment Group	Median (hours)	95% CI	Gehan Wilcoxon p-value
S-033188	54	(48, 59)	
Oseltamivir	54	(50, 56)	
Placebo	78	(69, 85)	
Placebo – S-033188	+19	(10, 26)	<0.001
Placebo - Oseltamivir	+20	(12, 27)	<0.001
Oseltamivir – S-033188	+0.3	(-4, +6)	0.63

Median differences were computed using Hodges-Lehmann estimates
p-values were stratified by composite symptom score at baseline (q11, ≥12) and region (US, Japan)
Source: Reviewer's analysis

The applicant computed differences in medians instead of median differences and proposed using difference between the placebo median and S-033188 median of 26.5 hours in the label instead of the median difference of 21 hours. Otherwise similar results were obtained by the applicant compared to those obtained by the reviewer.

Table 6: Applicant's Analysis of Time to Alleviation of Symptoms for Study T0831

	S-033188	Placebo
Summary statistics		
- n	455	230
- Median (hours)	53.7	80.2
- 95% confidence interval (hours)	49.5, 58.5	72.6, 87.1
- Difference (vs Placebo) (hours)	-26.5	---
- 95% confidence interval for median difference (hours) [a]	-35.8, -17.8	---
Stratified Generalized Wilcoxon test vs Placebo [b]		
- P value	<.0001	---
Stratified Log rank test vs Placebo [b]		
- P value	<.0001	---

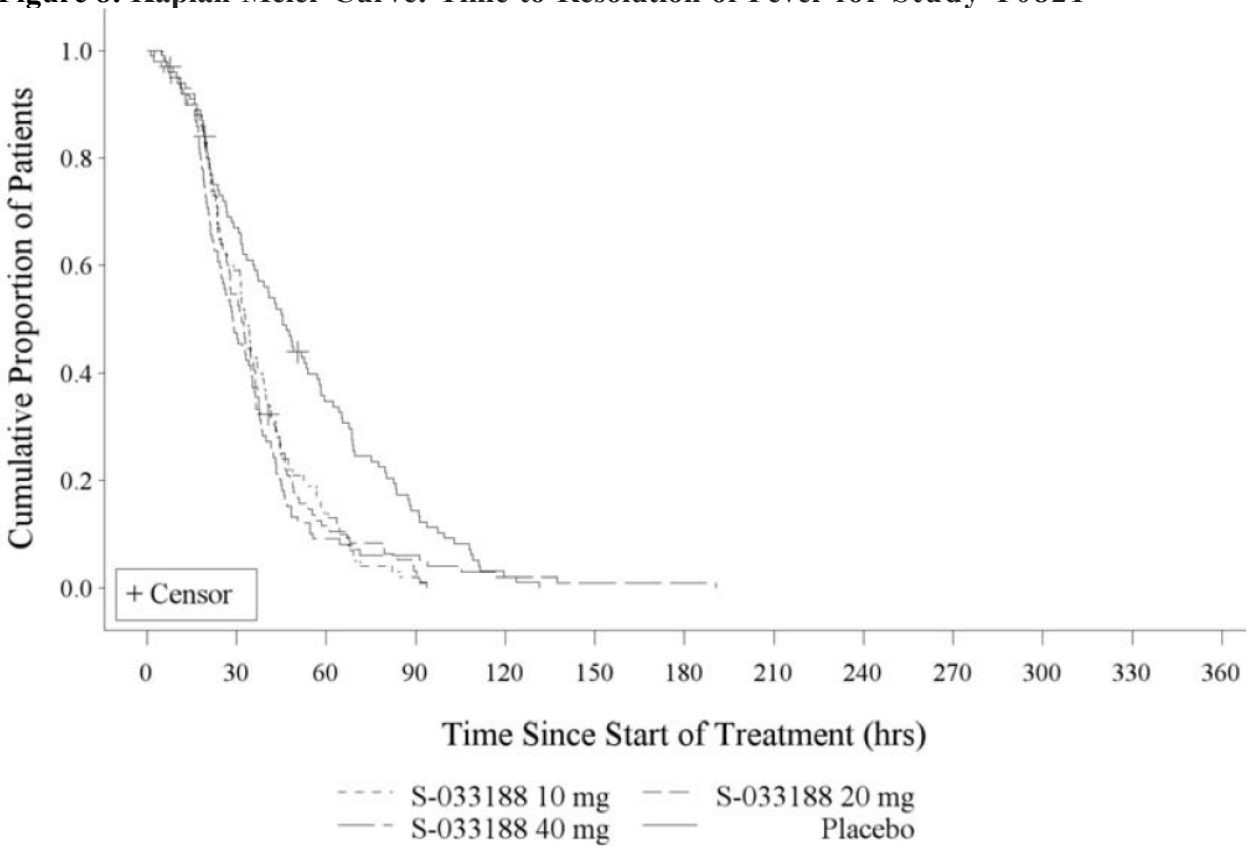
	S-033188 (≥ 20 years of age stratum)	Oseltamivir
Summary statistics		
- n	375	377
- Median (hours)	53.5	53.8
- 95% confidence interval (hours)	48.0, 58.5	50.2, 56.4
- Difference (vs Oseltamivir) (hours)	-0.3	---
- 95% confidence interval for median difference (hours) [a]	-6.6, 6.6	---
Stratified Generalized Wilcoxon test vs Oseltamivir [b]		
- P value	0.7560	---
Stratified Log rank test vs Oseltamivir [b]		
- P value	0.3761	---

[a] Bootstrap estimates
[b] Stratification factors: composite symptom scores at baseline and region
Patients who did not experience alleviation of symptoms were censored at the last observation time point.
Subset of patients whose time to alleviation of symptoms was not missing was included in this analysis.
Applicant used the Peto version of the Wilcoxon test instead of the Gehan Wilcoxon test
Source: Table 11-4 of the Clinical Study Report for T0831

3.2.4.3 Phase 2b trial results for Time to Resolution of Fever

The superiority of S-033188 compared to placebo was also demonstrated in the phase 2b trial for the secondary efficacy endpoint of time to resolution of fever where results for the Wilcoxon test and the Cox proportional hazards model were both statistically significant.

Figure 8: Kaplan-Meier Curve: Time to Resolution of Fever for Study T0821



Source: Figure 11-3 of the Clinical Study Report for T0821

The applicant computed median times to resolution of fever of 33, 32 and 29 hours for subjects in the S-033188 10, 20 and 40 mg treatment groups respectively and 45 hours for subjects in the placebo treatment group.

Table 7: Analysis of Time to Resolution of Fever for Study T0821

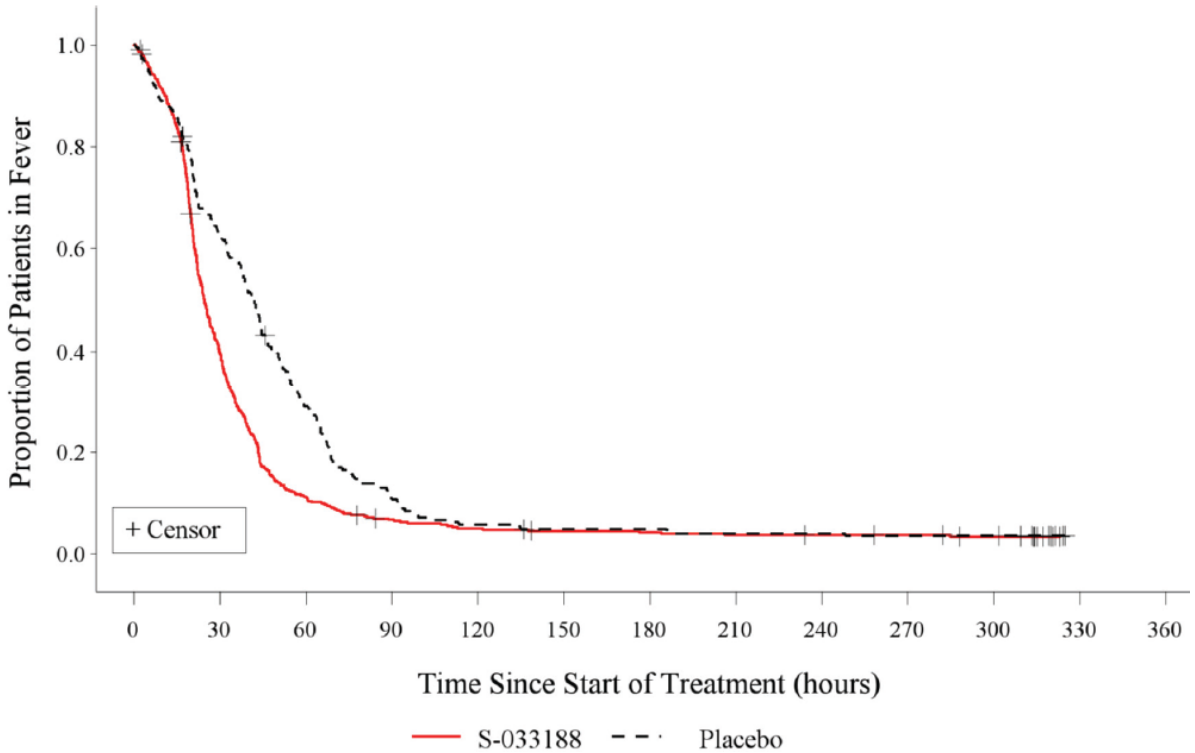
	S-033188 10 mg	S-033188 20 mg	S-033188 40 mg	Placebo
Summary statistics				
- n	100	100	100	100
- Median (hrs)	33.4	31.6	28.9	45.3
- 95% confidence interval (hrs)	26.9, 38.1	26.9, 35.8	24.5, 34.7	35.6, 54.0
- Difference (vs Placebo) (hrs)	-11.9	-13.7	-16.5	---
Stratified Generalized Wilcoxon test vs placebo [a]				
- P-value	0.0128	0.0034	0.0003	---
Cox proportional hazards model vs placebo [b]				
- Hazard ratio	0.538	0.546	0.554	---
- 95% confidence interval	0.403, 0.720	0.409, 0.728	0.417, 0.737	---
- P-value	<.0001	<.0001	<.0001	---

a Stratified factors: smoking habit, composite symptom scores at baseline.
b Covariates: smoking habit, composite symptom scores at baseline, body temperature at baseline.
Source: Table 11-9 of the Clinical Study Report for T0821

3.2.4.4 Phase 3 trial results for Time to Resolution of Fever

The superiority of S-033188 compared to placebo was demonstrated in T0831 for the secondary efficacy endpoint of time to resolution of fever where the p-value for the Wilcoxon and the log rank tests were both highly statistically significant ($p<0.001$) in the phase 3 trial.

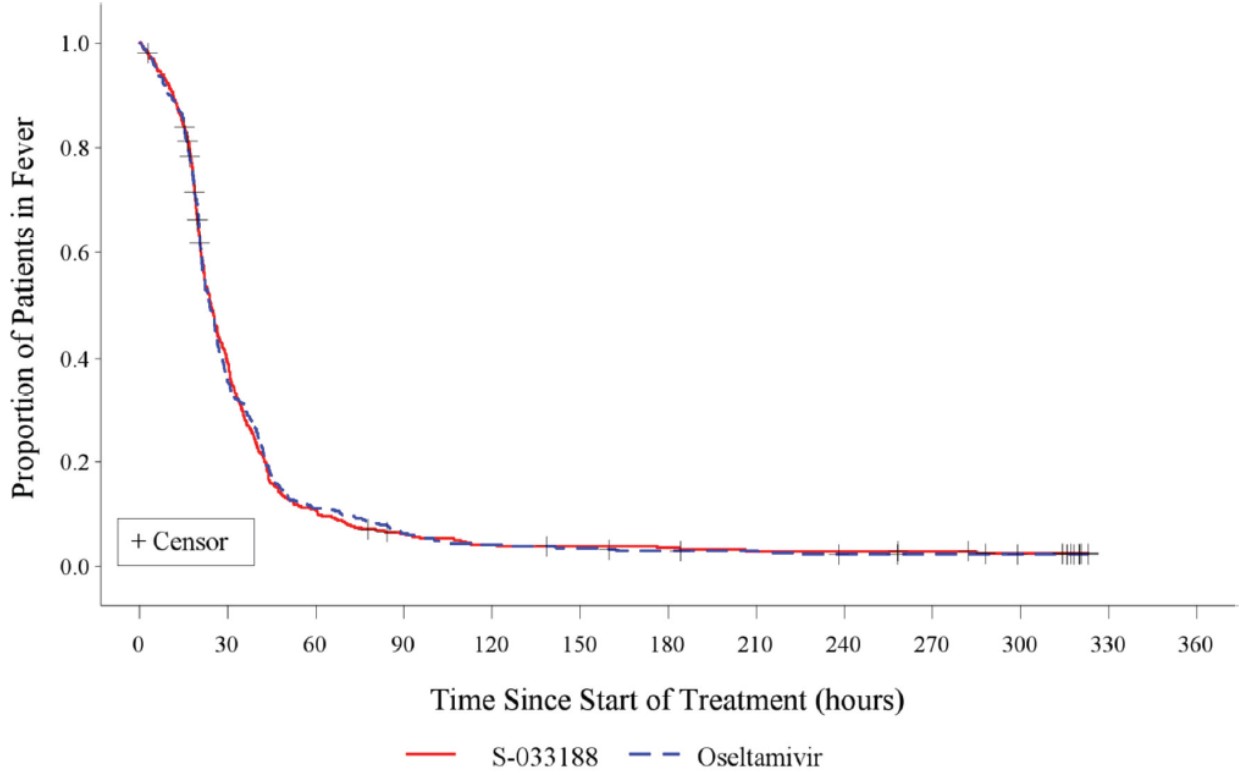
Figure 9: Kaplan-Meier Curve: Time to Resolution of Fever for Study T0831



Source: Figure 11-11 of the Clinical Study Report for T0831

In subjects at least 20 years of age similar trends for the time to resolution of fever were observed for both active drugs and there was no statistically significant difference between them (p=0.92).

Figure 10: Kaplan-Meier Curve: Time to Resolution of Fever (≥ 20 Years of Age Stratum) for Study T0831



Source: Figure 11-12 of the Clinical Study Report for T0831

The applicant computed median times to resolution of fever of 24.5 hours for subjects in the S-033188 treatment group and 42 hours for subjects in the placebo treatment group. In subjects who were at least 20 years of age the applicant computed median times of 24 hours for both S-033188 and oseltamivir treatment groups.

Table 8: Analysis of Time to Resolution of Fever for Study T0831

	S-033188	Placebo
Summary statistics		
- n	448	230
- Median (hours)	24.5	42.0
- 95% confidence interval (hours)	22.6, 26.6	37.4, 44.6
- Difference (vs Placebo) (hours)	-17.5	---
- 95% confidence interval for median difference (hours) [a]	-21.1, -11.9	---
Stratified Generalized Wilcoxon test vs Placebo [b]		
- P value	<.0001	---
Stratified Log rank test vs Placebo [b]		
- P value	<.0001	---

	S-033188 (≥ 20 years of age stratum)	Oseltamivir
Summary statistics		
- n	369	374
- Median (hours)	24.4	24.0
- 95% confidence interval (hours)	22.2, 26.5	22.1, 25.9
- Difference (vs Oseltamivir) (hours)	0.5	---
- 95% confidence interval for median difference (hours) [a]	-2.8, 3.4	---
Stratified Generalized Wilcoxon test vs Oseltamivir [b]		
- P value	0.9225	---
Stratified Log rank test vs Oseltamivir [b]		
- P value	0.9225	---

[a] Bootstrap estimates.
[b] Stratification factors: composite symptom scores at baseline and region.
Subset of patients whose body temperature at baseline was more than 37°C and time to resolution of fever was not missing was included in this analysis.
Source: Table 11-34 of the Clinical Study Report for T0831

3.2.4.5 Secondary efficacy results for individual symptoms

Phase 2b and 3 results for the individual seven symptoms that are included in the primary efficacy endpoint are shown below. In the phase 3 trial, comparisons of the TTAS between S-033188 and placebo using the stratified Peto-Prentice Gehan Wilcoxon test for each of the individual seven symptoms in the phase 3 trial were all statistically significant. There were no statistically significant differences between S-033188 and oseltamivir for any of the seven individual symptoms.

In the phase 2b trial, there were statistically significant differences favoring at least the 40 mg dose compared to placebo for nasal congestion, aches or pains of the muscle or joints, fatigue and for feeling feverishness or having chills and for headaches (Cox model only for headaches) without adjustment for multiplicity for the three doses. There were no statistically significant differences between any dose of S-033188 and placebo for cough or sore throat.

Table 9: Analyses of Time to Alleviation of Individual Symptoms in Study T0821

	S-033188 10 mg	S-033188 20 mg	S-033188 40 mg	Placebo
Nasal congestion				
n	49	38	45	47
Median (95% CI) (hrs)	25.2 (19.0, 47.2)	21.6 (13.4, 30.5)	21.9 (16.0, 28.7)	42.8 (22.9, 68.3)
Difference (vs Placebo) (hrs)	-17.6	-21.3	-21.0	---
P-value (G. Wilcoxon test) [a]	0.0430	0.0516	0.0003	---
Hazard ratio (95% CI) [b]	0.742 (0.494, 1.114)	0.590 (0.379, 0.920)	0.564 (0.369, 0.862)	---
P-value (Cox model) [b]	0.1500	0.0199	0.0081	---
Aches or pains of the muscle or joints				
n	73	77	71	71
Median (95% CI) (hrs)	31.2 (24.9, 39.9)	29.9 (22.8, 37.0)	25.4 (20.5, 28.9)	41.9 (28.7, 48.6)
Difference (vs Placebo) (hrs)	-10.7	-12.0	-16.4	---
P-value (G. Wilcoxon test) [a]	0.2153	0.0346	0.0048	---
Hazard ratio (95% CI) [b]	0.770 (0.553, 1.072)	0.687 (0.494, 0.955)	0.657 (0.469, 0.920)	---
P-value (Cox model) [b]	0.1217	0.0255	0.0145	---
Fatigue				
n	82	82	77	79
Median (95% CI) (hrs)	32.0 (29.2, 39.9)	31.3 (26.7, 42.4)	31.1 (24.6, 38.6)	42.7 (30.3, 53.2)
Difference (vs Placebo) (hrs)	-10.7	-11.5	-11.7	---
P-value (G. Wilcoxon test) [a]	0.1221	0.0594	0.0224	---
Hazard ratio (95% CI) [b]	0.783 (0.574, 1.069)	0.876 (0.637, 1.203)	0.724 (0.527, 0.995)	---
P-value (Cox model) [b]	0.1236	0.4120	0.0463	---
Feeling feverishness or having chills				
n	97	93	94	95
Median (95% CI) (hrs)	24.7 (21.3, 28.4)	29.4 (22.0, 34.8)	23.0 (19.8, 28.6)	28.8 (21.1, 33.4)
Difference (vs Placebo) (hrs)	-4.1	0.6	-5.8	---
P-value (G. Wilcoxon test) [a]	0.0602	0.3774	0.0258	---
Hazard ratio (95% CI) [b]	0.635 (0.475, 0.850)	0.848 (0.634, 1.133)	0.710 (0.529, 0.951)	---
P-value (Cox model) [b]	0.0023	0.2642	0.0216	---
Headache				
n	61	58	54	57
Median (95% CI) (hrs)	42.2 (29.8, 47.3)	37.0 (28.5, 43.5)	37.9 (28.6, 44.5)	43.7 (29.7, 53.6)
Difference (vs Placebo) (hrs)	-1.5	-6.7	-5.8	---
P-value (G. Wilcoxon test) [a]	0.6846	0.7741	0.0904	---
Hazard ratio (95% CI) [b]	0.803 (0.557, 1.157)	0.936 (0.635, 1.381)	0.655 (0.447, 0.961)	---
P-value (Cox model) [b]	0.2388	0.7404	0.0304	---
Cough				
n	74	74	78	75
Median (95% CI) (hrs)	31.1 (21.3, 41.5)	29.8 (21.9, 32.9)	24.6 (16.1, 29.4)	31.2 (20.9, 51.4)
Difference (vs Placebo) (hrs)	-0.1	-1.4	-6.6	---
P-value (G. Wilcoxon test) [a]	0.6643	0.8536	0.1551	---
Hazard ratio (95% CI) [b]	0.941 (0.675, 1.312)	0.883 (0.636, 1.226)	0.865 (0.626, 1.196)	---
P-value (Cox model) [b]	0.7188	0.4569	0.3796	---
Sore throat				
n	56	64	55	46
Median (95% CI) (hrs)	35.3 (21.2, 49.8)	27.8 (19.9, 32.1)	31.9 (17.3, 43.0)	26.3 (16.5, 45.2)
Difference (vs Placebo) (hrs)	9.1	1.5	5.6	---
P-value (G. Wilcoxon test) [a]	0.2905	0.6293	0.9930	---
Hazard ratio (95% CI) [b]	1.312 (0.882, 1.951)	1.050 (0.713, 1.547)	1.092 (0.738, 1.617)	---
P-value (Cox model) [b]	0.1800	0.8047	0.6602	---

a Stratified Generalized Wilcoxon test vs placebo. Stratified factors: smoking habit, composite symptom scores at baseline.

b Cox proportional hazards model vs placebo. Covariates: smoking habit, composite symptom scores at baseline.

Subset of patients whose symptom scores at baseline were moderate or severe. CI: Confidence Interval

Source: Table 11-8 of the Clinical Study Report for T0821

Table 10: Analyses of Time to Alleviation of Individual Symptoms in Study T0831

	S-033188	Placebo
Cough		
Summary statistics		
- n	308	171
- Median (hours)	38.3	61.4
- 95% confidence interval (hours)	30.3, 43.5	44.8, 69.5
- Difference (vs Placebo) (hours)	-23.1	---
Stratified Generalized Wilcoxon test vs Placebo [a]		
- P value	0.0001	---
Sore throat		
Summary statistics		
- n	249	119
- Median (hours)	31.5	40.5
- 95% confidence interval (hours)	27.3, 39.2	31.8, 48.3
- Difference (vs Placebo) (hours)	-9.0	---
Stratified Generalized Wilcoxon test vs Placebo [a]		
- P value	0.0298	---
Headache		
Summary statistics		
- n	296	153
- Median (hours)	26.1	37.9
- 95% confidence interval (hours)	22.9, 29.8	25.8, 42.2
- Difference (vs Placebo) (hours)	-11.8	---
Stratified Generalized Wilcoxon test vs Placebo [a]		
- P value	0.0297	---
Nasal congestion		
Summary statistics		
- n	277	153
- Median (hours)	31.8	52.5
- 95% confidence interval (hours)	29.9, 38.7	41.5, 62.7
- Difference (vs Placebo) (hours)	-20.7	---
Stratified Generalized Wilcoxon test vs Placebo [a]		
- P value	0.0027	---
Feverishness or chills		
Summary statistics		
- n	408	214
- Median (hours)	20.9	25.8
- 95% confidence interval (hours)	20.0, 21.9	21.7, 31.5
- Difference (vs Placebo) (hours)	-4.9	---
Stratified Generalized Wilcoxon test vs Placebo [a]		
- P value	0.0003	---
Muscle or joint pain		
Summary statistics		
- n	353	169
- Median (hours)	23.2	31.3
- 95% confidence interval (hours)	21.4, 26.3	25.5, 39.2
- Difference (vs Placebo) (hours)	-8.1	---
Stratified Generalized Wilcoxon test vs Placebo [a]		
- P value	0.0094	---

	S-033188	Placebo
Fatigue		
Summary statistics		
- n	361	188
- Median (hours)	25.3	40.5
- 95% confidence interval (hours)	22.0, 29.2	31.2, 46.8
- Difference (vs Placebo) (hours)	-15.3	---
Stratified Generalized Wilcoxon test vs Placebo [a]		
- P value	0.0007	---

	S-033188 (≥ 20 years of age stratum)	Oseltamivir
Cough		
Summary statistics		
- n	250	262
- Median (hours)	38.2	31.4
- 95% confidence interval (hours)	30.3, 43.4	28.6, 36.8
- Difference (vs Oseltamivir) (hours)	6.8	---
Stratified Generalized Wilcoxon test vs Oseltamivir [a]		
- P value	0.6623	---
Sore throat		
Summary statistics		
- n	211	198
- Median (hours)	32.1	30.4
- 95% confidence interval (hours)	27.6, 39.8	25.0, 43.9
- Difference (vs Oseltamivir) (hours)	1.8	---
Stratified Generalized Wilcoxon test vs Oseltamivir [a]		
- P value	0.8184	---
Headache		
Summary statistics		
- n	246	239
- Median (hours)	26.9	25.6
- 95% confidence interval (hours)	24.5, 30.8	21.9, 30.4
- Difference (vs Oseltamivir) (hours)	1.3	---
Stratified Generalized Wilcoxon test vs Oseltamivir [a]		
- P value	0.9989	---
Nasal congestion		
Summary statistics		
- n	217	230
- Median (hours)	33.0	31.3
- 95% confidence interval (hours)	30.5, 40.4	26.8, 39.8
- Difference (vs Oseltamivir) (hours)	1.7	---
Stratified Generalized Wilcoxon test vs Oseltamivir [a]		
- P value	0.3706	---
Feverishness or chills		
Summary statistics		
- n	337	341
- Median (hours)	21.0	21.2
- 95% confidence interval (hours)	20.0, 22.0	20.3, 22.0
- Difference (vs Oseltamivir) (hours)	-0.1	---
Stratified Generalized Wilcoxon test vs Oseltamivir [a]		
- P value	0.9973	---
Muscle or joint pain		
Summary statistics		
- n	300	291

	S-033188 (≥ 20 years of age stratum)	Oseltamivir
- Median (hours)	23.3	24.0
- 95% confidence interval (hours)	21.6, 26.7	21.6, 27.1
- Difference (vs Oseltamivir) (hours)	-0.7	---
Stratified Generalized Wilcoxon test vs Oseltamivir [a]		
- P value	0.6760	---
Fatigue		
Summary statistics		
- n	293	308
- Median (hours)	28.9	26.6
- 95% confidence interval (hours)	23.2, 30.5	23.0, 30.8
- Difference (vs Oseltamivir) (hours)	2.2	---
Stratified Generalized Wilcoxon test vs Oseltamivir [a]		
- P value	0.4241	---

[a] Stratification factors: composite symptom scores at baseline and region.
Subset of patients whose symptom score at baseline was moderate or severe and time to alleviation of symptom was not missing was included in this analysis.
Patients who did not experience alleviation of symptom were censored at the last observation time point.

Source: Table 11-32 of the Clinical Study Report for T0831

3.3 Evaluation of Safety

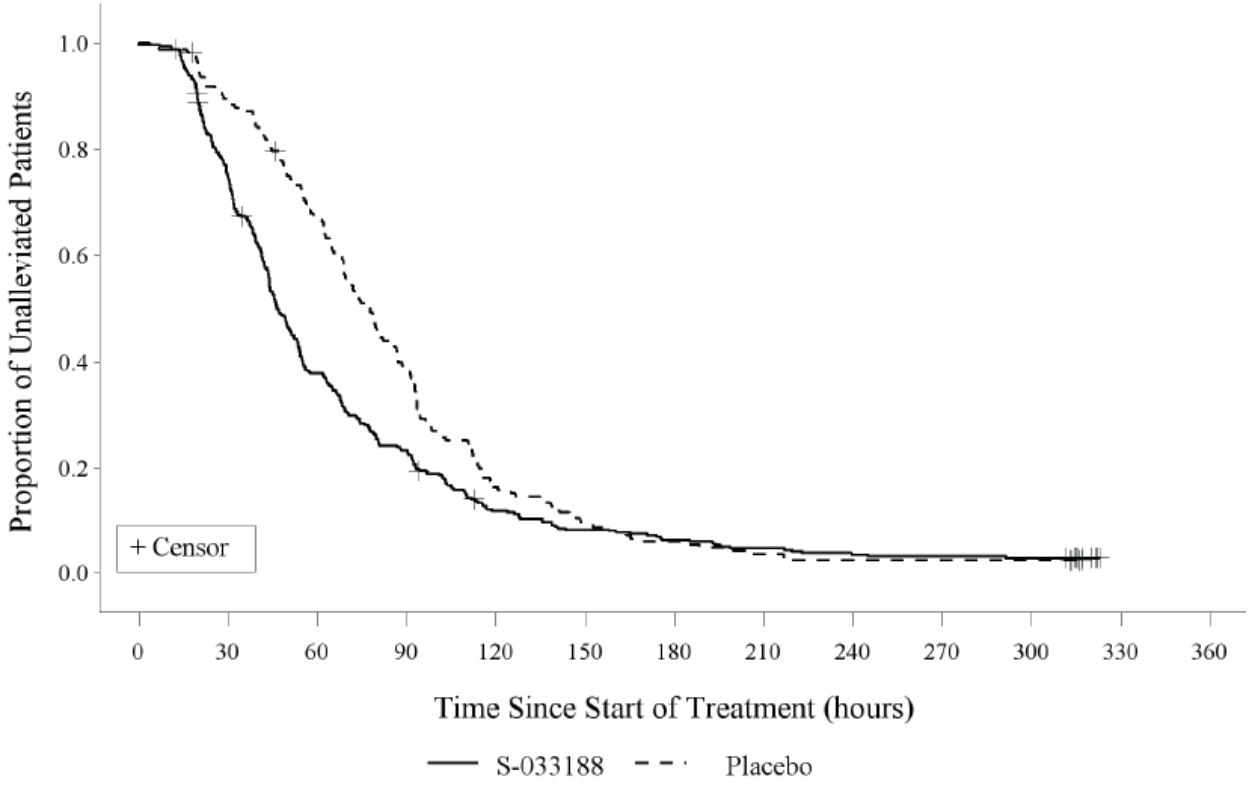
See the clinical review for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Statistically significant differences ($p<0.001$) were most apparent for the primary efficacy analysis in favor of S-033188 in Japan in the phase 3 trial. The same trend was apparent for the pooled analysis. (Pooled analyses are shown in the Appendix.)

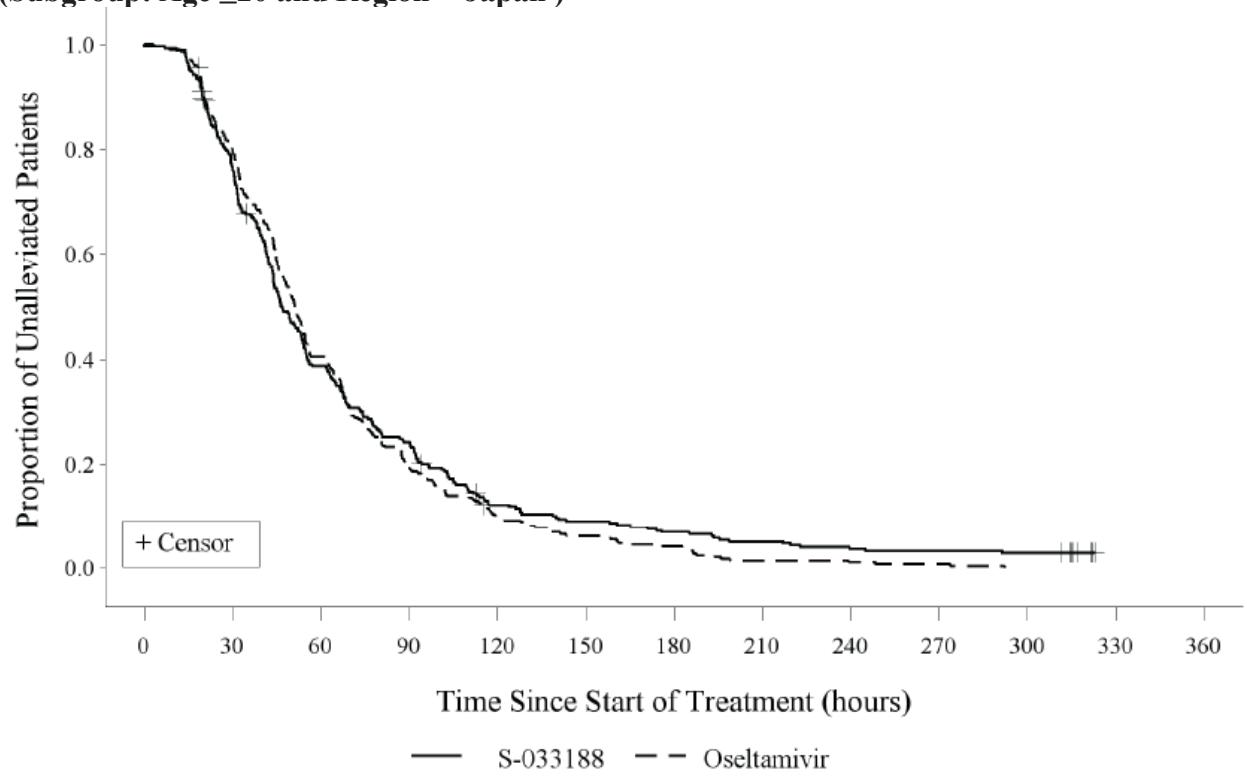
Figure 11: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Study T0831 (Subgroup: Region = Japan)



Source: Figure 14.4.7 of the Clinical Study Report for T0831

The applicant's Kaplan-Meier plot comparing S-033188 to oseltamivir showed similar trends for TTAS in both treatment groups in Japanese and U.S. subjects.

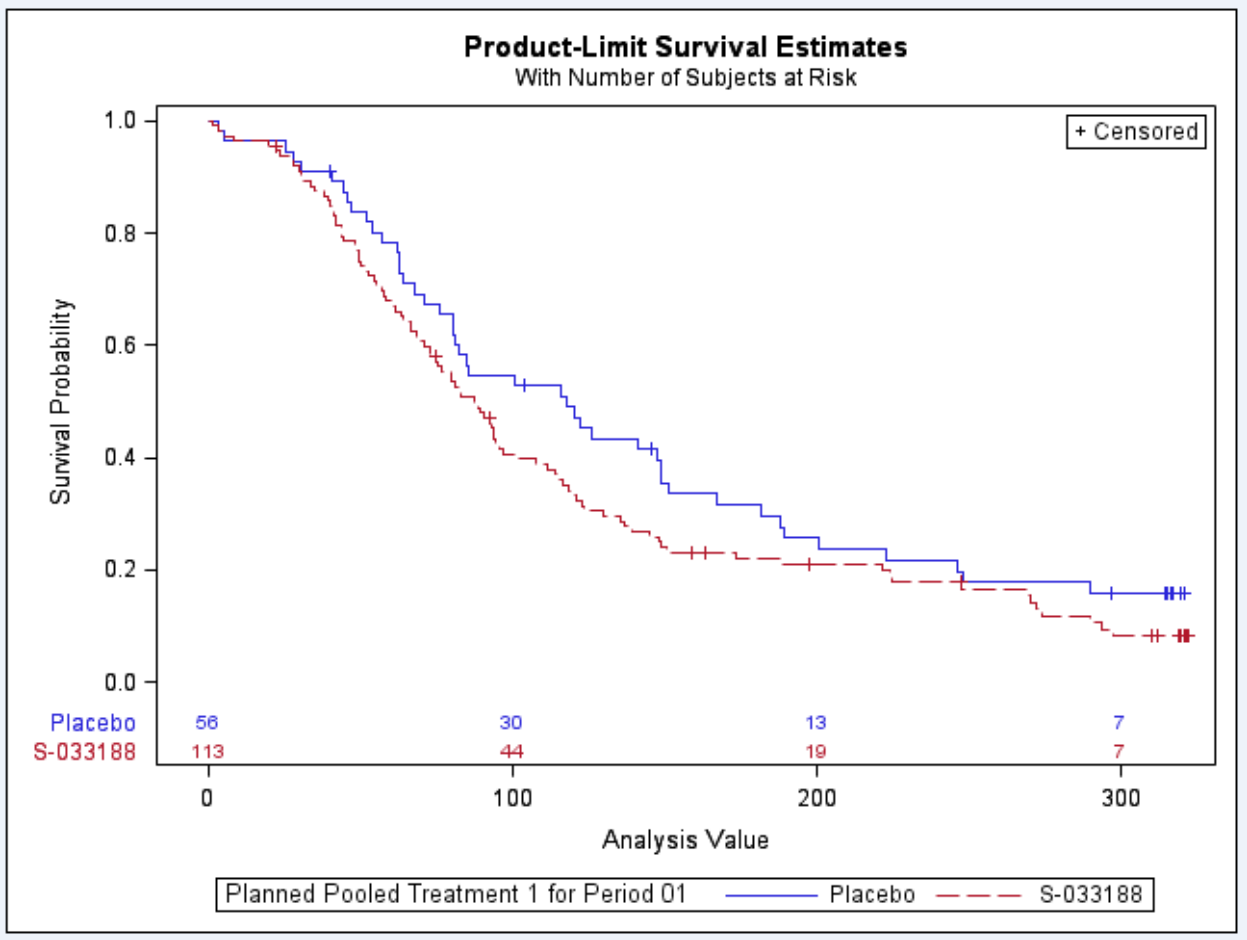
Figure 12: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Study T0831 (Subgroup: Age ≥20 and Region = Japan)



Source Figure 14.4.8 of the Clinical Study Report for T0831

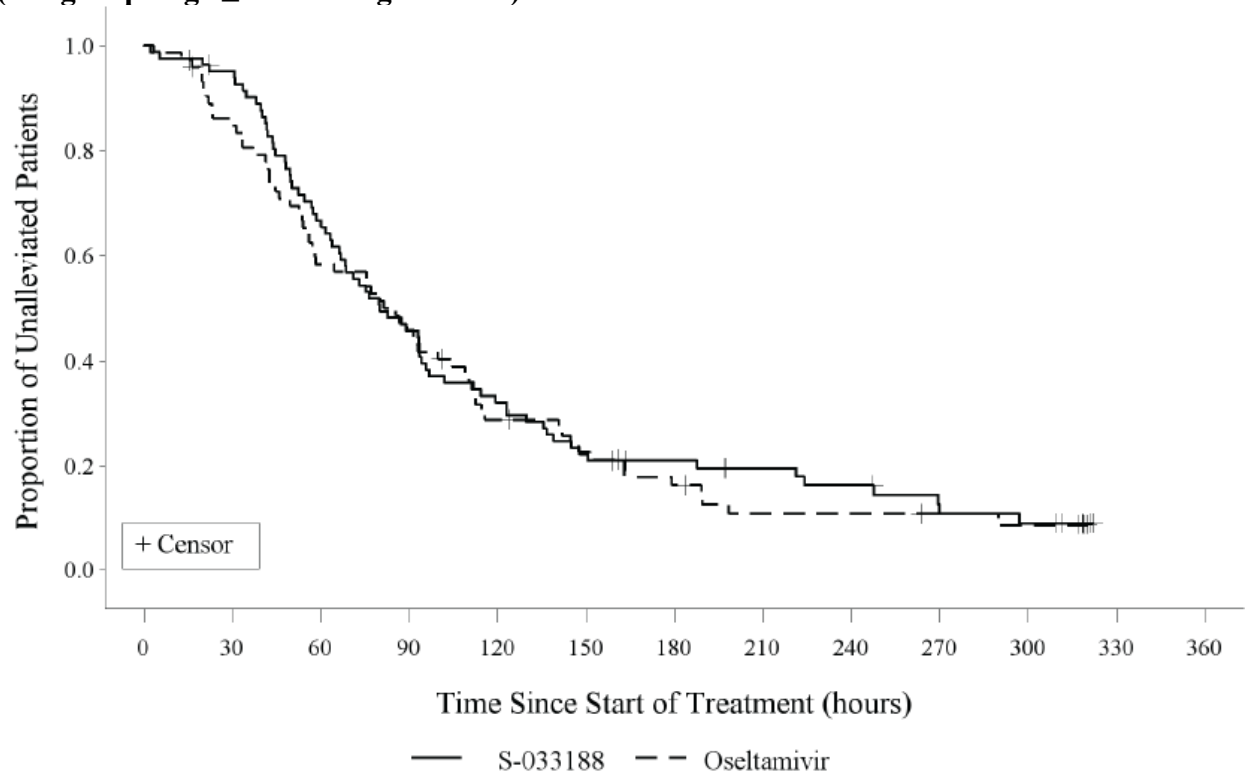
Statistical significance at the two-sided 0.05 level was not achieved in U.S. subjects (p=0.08). However similar trends appeared to exist in U.S. subjects and the sample size for U.S. subjects was much smaller than for Japanese subjects. Since all of the subjects in T0821 were from Japan, the U.S. subgroup consisted only of subjects from T0831.

Figure 13: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Study T0831 (Subgroup: Region = U.S.)



Gehan Wilcoxon p-value stratified by TSS (q11 vs. ≥12) =0.08
Source: Reviewer's analysis

Figure 14: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Study T0831 (Subgroup: Age ≥20 and Region = US)



Source Figure 14.4.10 of the Clinical Study Report for T0831

Table 11: Time to Alleviation of Symptoms by Region in Study T0831

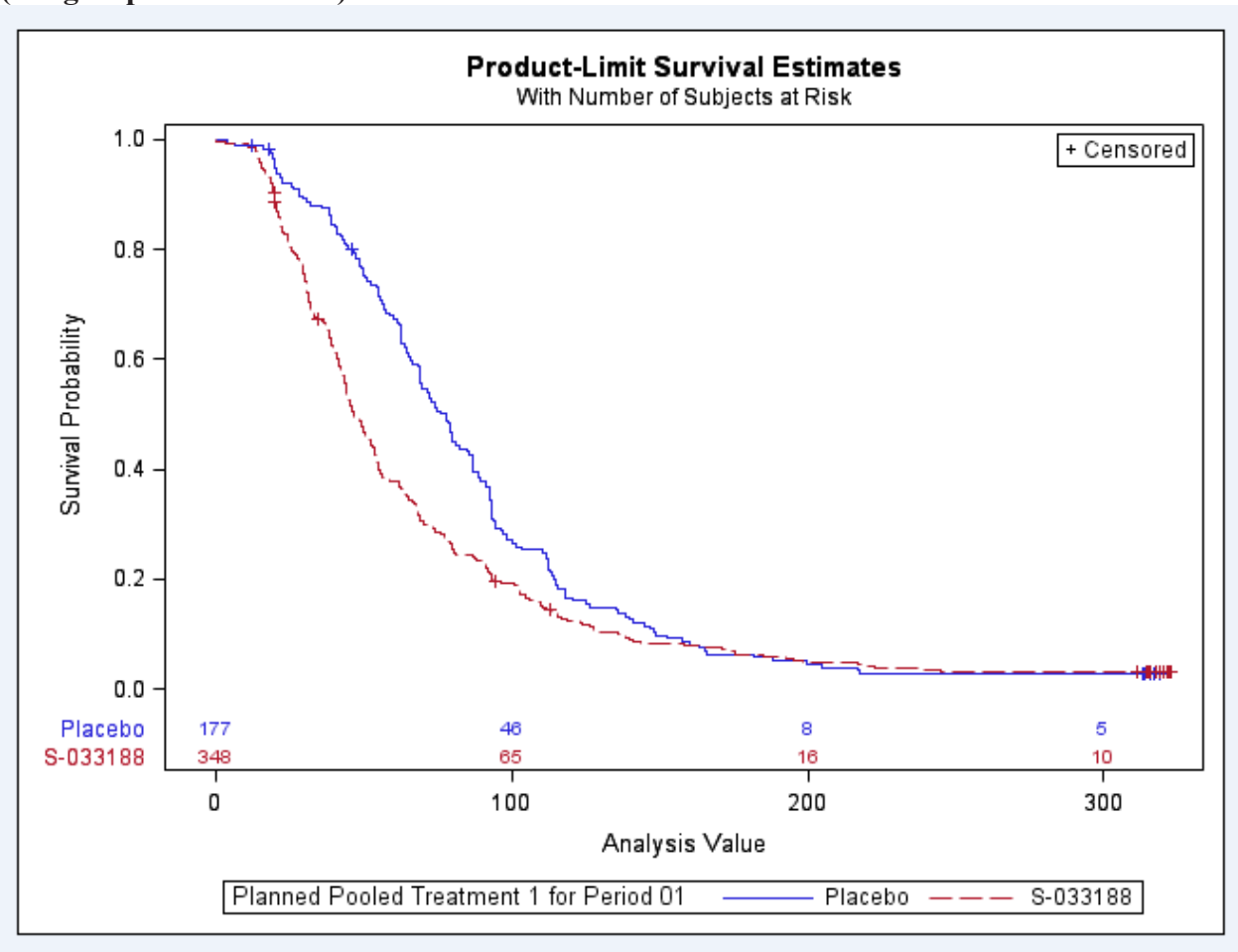
	S-033188	Placebo
Region: Japan/Asia		
Summary statistics		
- n	342	174
- Median (hours)	46.4	77.7
- 95% confidence interval (hours)	43.8, 52.1	68.8, 86.5
- Difference (vs Placebo) (hours)	-31.3	---
Stratified Generalized Wilcoxon test vs Placebo [a]		
- P value	<.0001	---
Region: Rest of the world		
Summary statistics		
- n	113	56
- Median (hours)	87.3	117.9
- 95% confidence interval (hours)	72.9, 96.8	80.2, 148.5
- Difference (vs Placebo) (hours)	-30.6	---
Stratified Generalized Wilcoxon test vs Placebo [a]		
- P value	0.1373	---

	S-033188 (≥ 20 years of age stratum)	Oseltamivir
Region: Japan/Asia		
Summary statistics		
- n	293	303
- Median (hours)	46.8	51.1
- 95% confidence interval (hours)	43.8, 53.4	47.2, 54.6
- Difference (vs Oseltamivir) (hours)	-4.3	---
Stratified Generalized Wilcoxon test vs Oseltamivir [a]		
- P value	0.4961	---
Region: Rest of the world		
Summary statistics		
- n	82	74
- Median (hours)	80.0	85.4
- 95% confidence interval (hours)	66.2, 94.0	57.1, 104.4
- Difference (vs Oseltamivir) (hours)	-5.4	---
Stratified Generalized Wilcoxon test vs Oseltamivir [a]		
- P value	0.5087	---

[a] Stratification factors: composite symptom scores at baseline.
Subset of patients whose time to alleviation of symptoms was not missing was included in this analysis.
Source: Table 11-40 of the Clinical Study Report for T0831

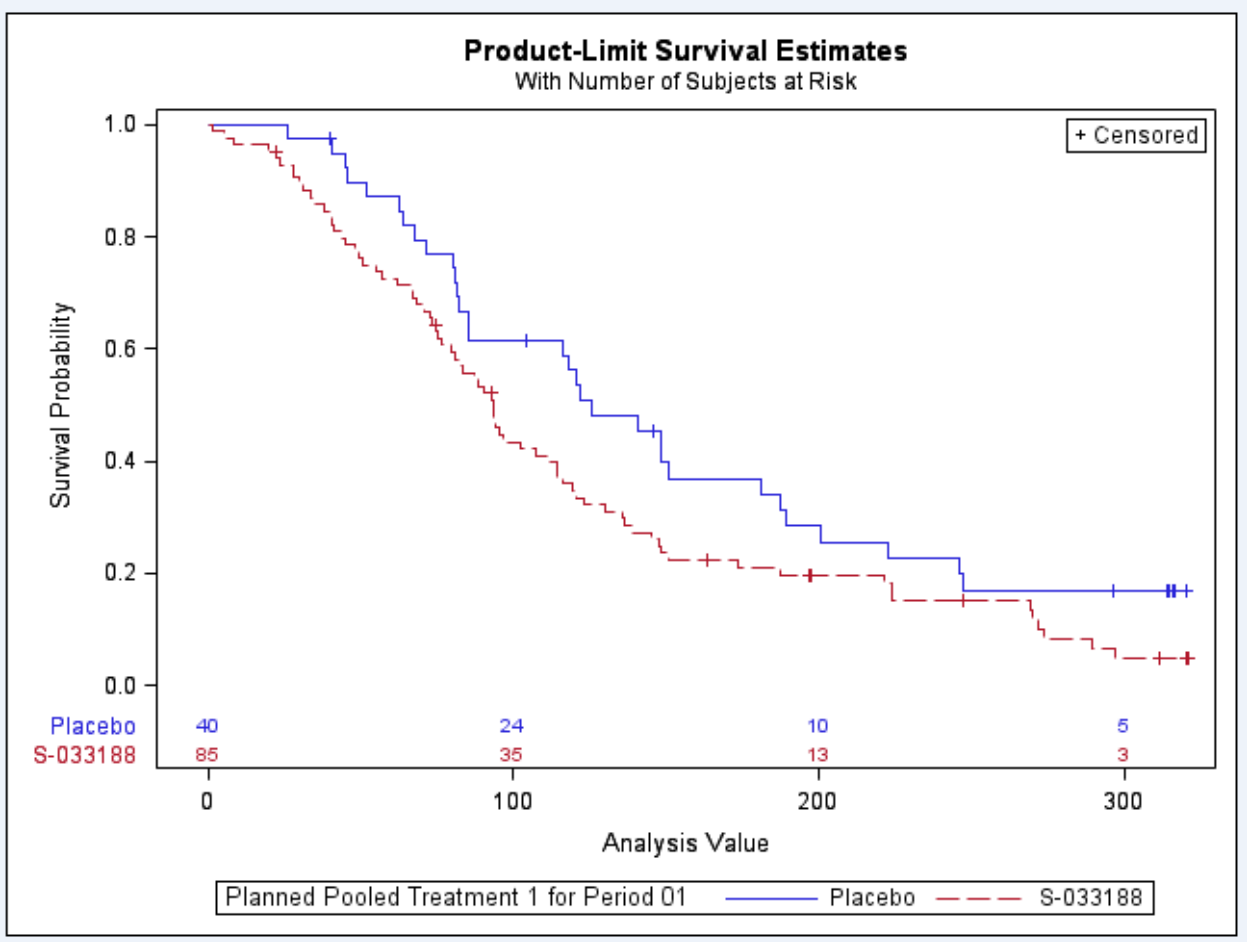
Statistically significant differences were most apparent for the primary efficacy analysis in favor of S-033188 in Asians ($p<0.001$) and were also statistically significant in Whites ($p=0.035$). Statistical significance was not observed in Other Races but this subgroup only had 22 subjects in the S-033188 arm and 13 subjects in the placebo arm.

Figure 15: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Study T0831 (Subgroup: Race = Asian)



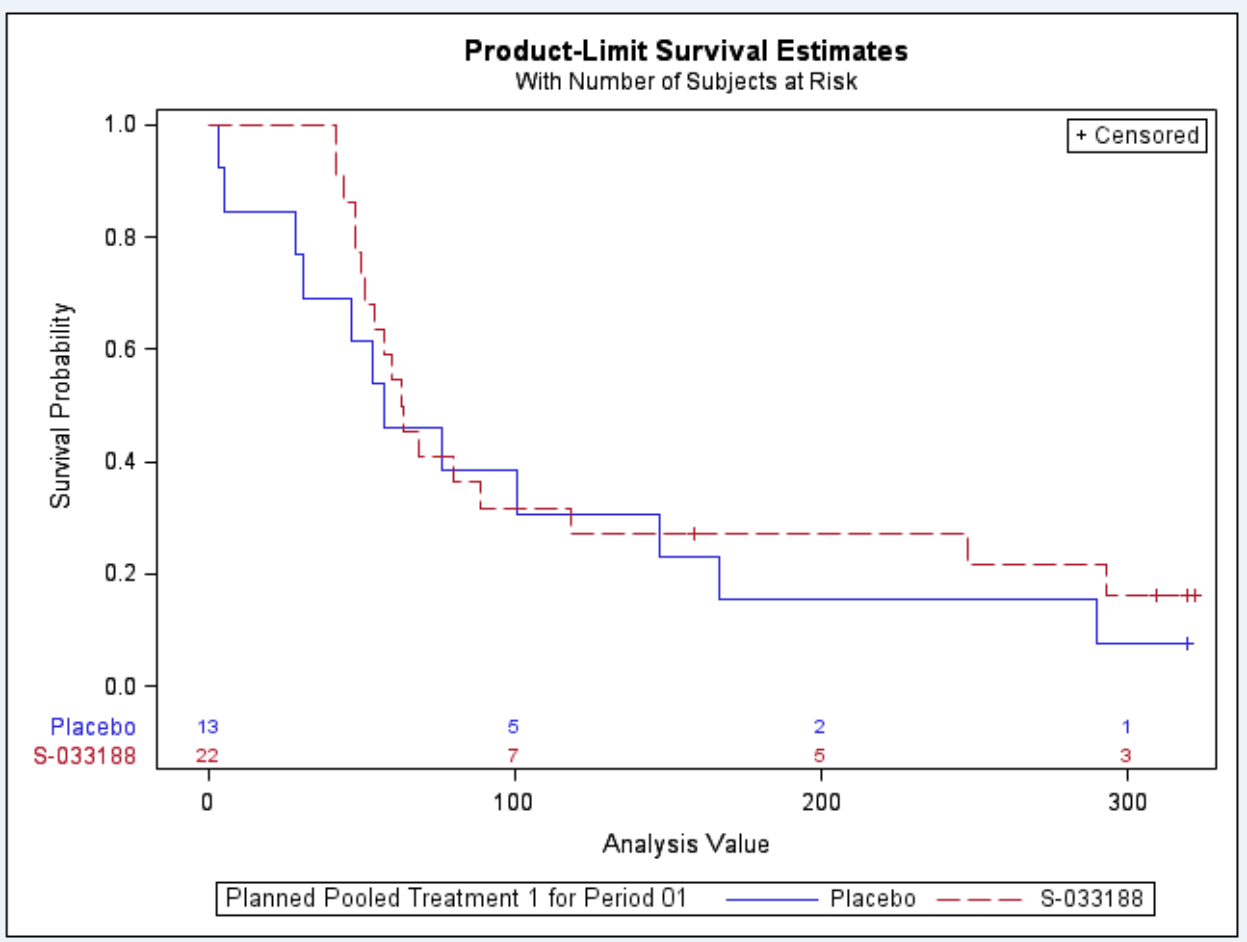
Gehan Wilcoxon p-value stratified by geographic region (Japan vs. U.S.) and TSS (q11 vs. ≥12) <0.001
Source: Reviewer's analysis

Figure 16: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Study T0831 (Subgroup: Race = White)



Gehan Wilcoxon p-value stratified by TSS (q11 vs. ≥12) =0.035
Source: Reviewer's analysis

Figure 17: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Study T0831 (Subgroup: Race = Other)

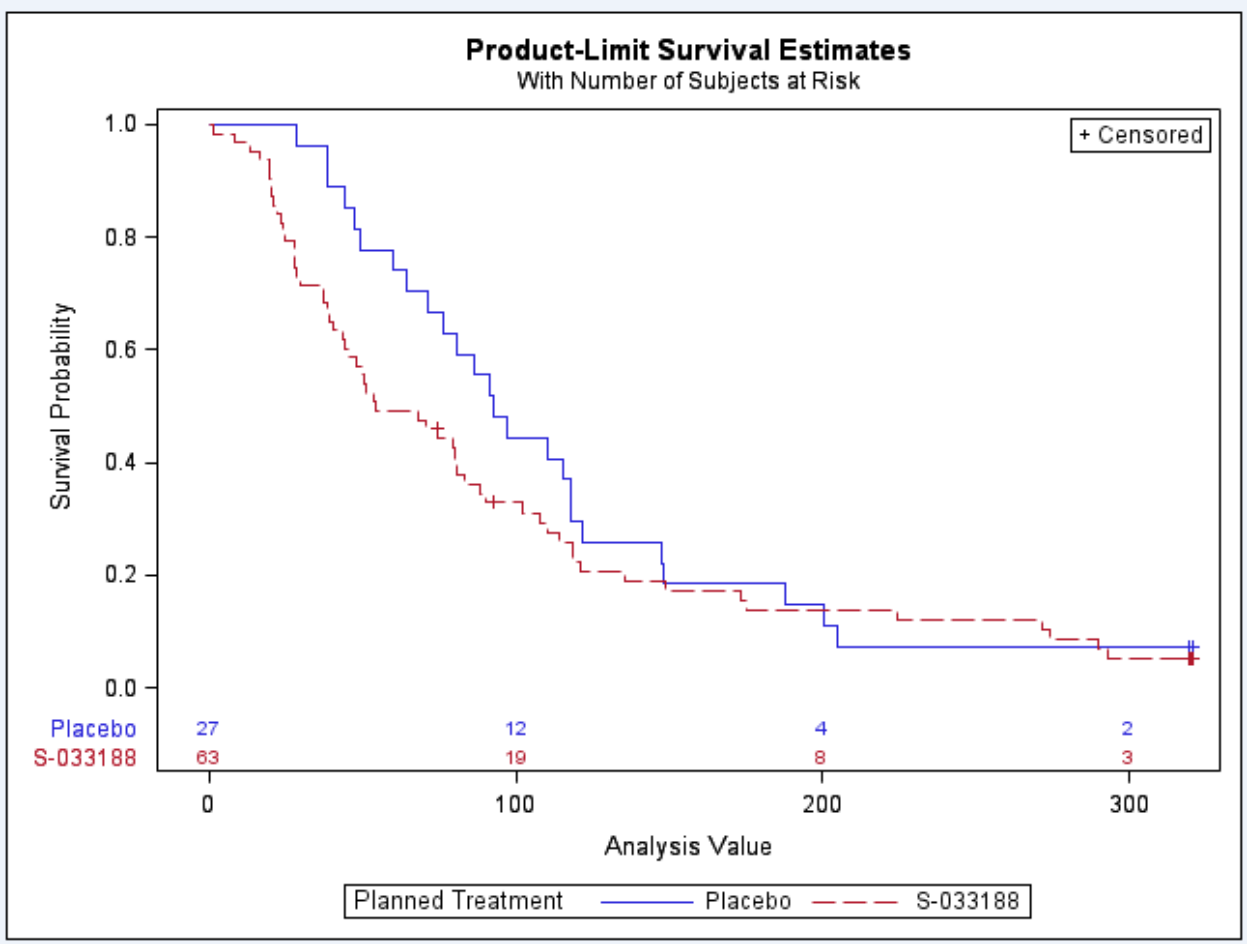


Gehan Wilcoxon p-value stratified by geographic region (Japan vs. U.S.) and TSS (q11 vs. ≥12) =0.42

Source: Reviewer's analysis

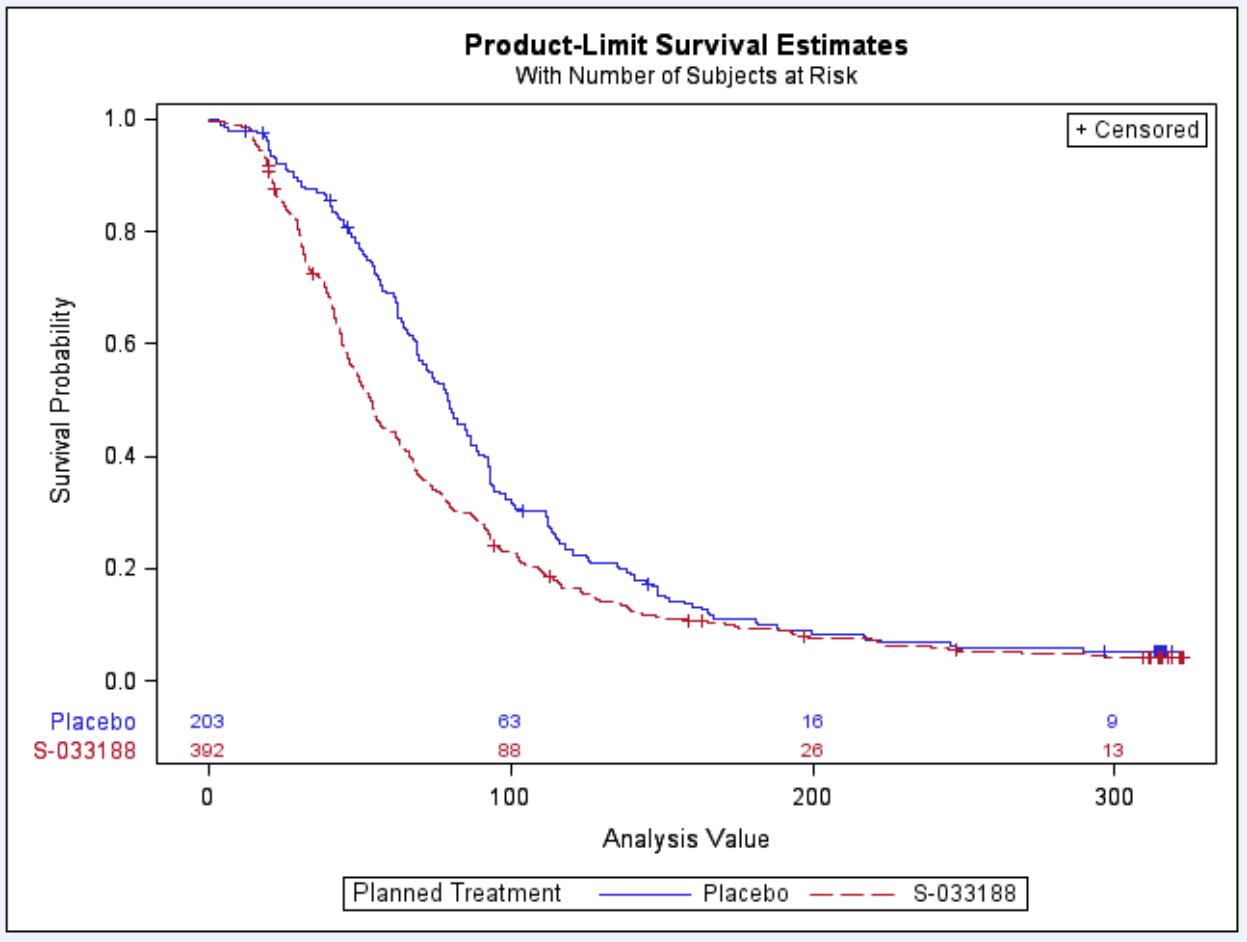
The applicant analyzed age subgroups for adolescents who were 12-17 years of age and the remaining adult subgroup (18 years of age and older) in study T0831, as shown in the reviewer's Kaplan-Meier plots and in the applicant's table below. Since all of the subjects in T0821 were at least 20 years of age, the adolescent subgroup consisted only of subjects from T0831. The comparison between S-033188 and placebo was statistically significant in favor of S-033188 in both adolescents and adults.

Figure 18: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Adolescents (Age<18) in Study T0831



Gehan Wilcoxon p-value stratified by geographic region (Japan vs. U.S.) and TSS (q11 vs. ≥12) = 0.01
Source: Reviewer's analysis

Figure 19: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Adults Subjects (Age ≥18) in Study T0831



Gehan Wilcoxon p-value stratified by geographic region (Japan vs. U.S.) and TSS (q11 vs. ≥12) < 0.001
Source: Reviewer's analysis

Since adolescent results were also included in Section 14 of the label, median differences between S-033188 and placebo treatment responses were calculated by the reviewer and found to be less than the differences in medians (27 hours vs. 39 hours for adolescents and 21 vs 26 hours for adults).

Subgroup	Treatment Group	Median (hours)	95% CI
Adolescents (Age<18 years)	S-033188	54	(43,81)
	Placebo	93	(64, 118)
	Placebo – S-033188	+27	(0, 53)
Adults (Age≥18 years)	S-033188	54	(49, 58)
	Placebo	79	(70, 87)
	Placebo – S-033188	21	(12, 28)

Median differences were computed using Hodges-Lehmann estimates
Source: Reviewer's analysis

Table 12: Time to Alleviation of Symptoms by Adolescents and Adults in Study T0831

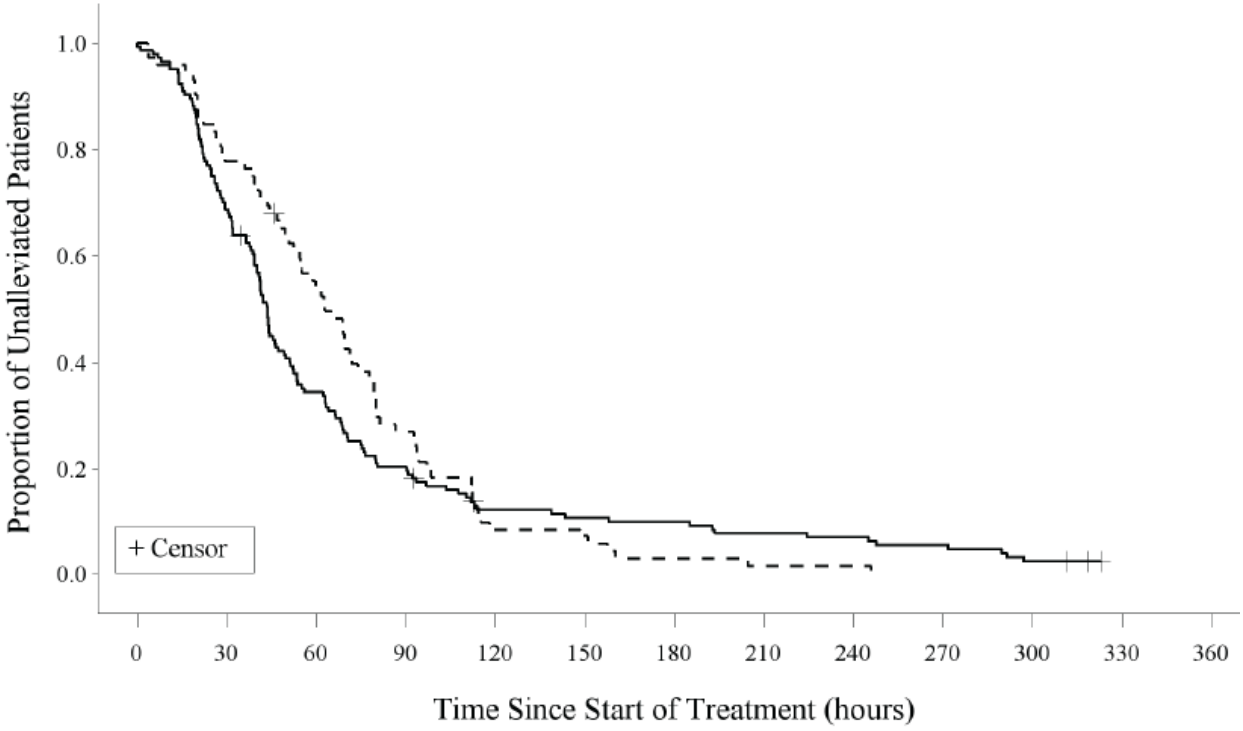
	S-033188	Placebo	Oseltamivir
Age: <18 years			
Summary statistics			
- n	63	27	---
- Median (hours)	54.1	92.7	---
- 95% confidence interval (hours)	43.5, 80.7	64.1, 118.0	---
- Difference (vs Placebo) (hours)	-38.6	---	---
Stratified Generalized Wilcoxon test vs Placebo [a]			
- P value	0.0055	---	---
Age: ≥18 years			
Summary statistics			
- n	392	203	377
- Median (hours)	53.7	79.4	53.8
- 95% confidence interval (hours)	49.1, 57.5	69.5, 86.8	50.2, 56.4
- Difference (vs Placebo) (hours)	-25.6	---	---
- Difference (vs Oseltamivir) (hours)	-0.1	---	---
Stratified Generalized Wilcoxon test vs Placebo [a]			
- P value	<.0001	---	---
Stratified Generalized Wilcoxon test vs Oseltamivir [a]			
- P value	0.7179	---	---

[a] Stratification factors: composite symptom scores at baseline and region.
Subset of patients whose time to alleviation of symptoms was not missing was included in this analysis.
Source: Table 11-46 of the Clinical Study Report for T0831

4.2 Other Special/Subgroup Populations

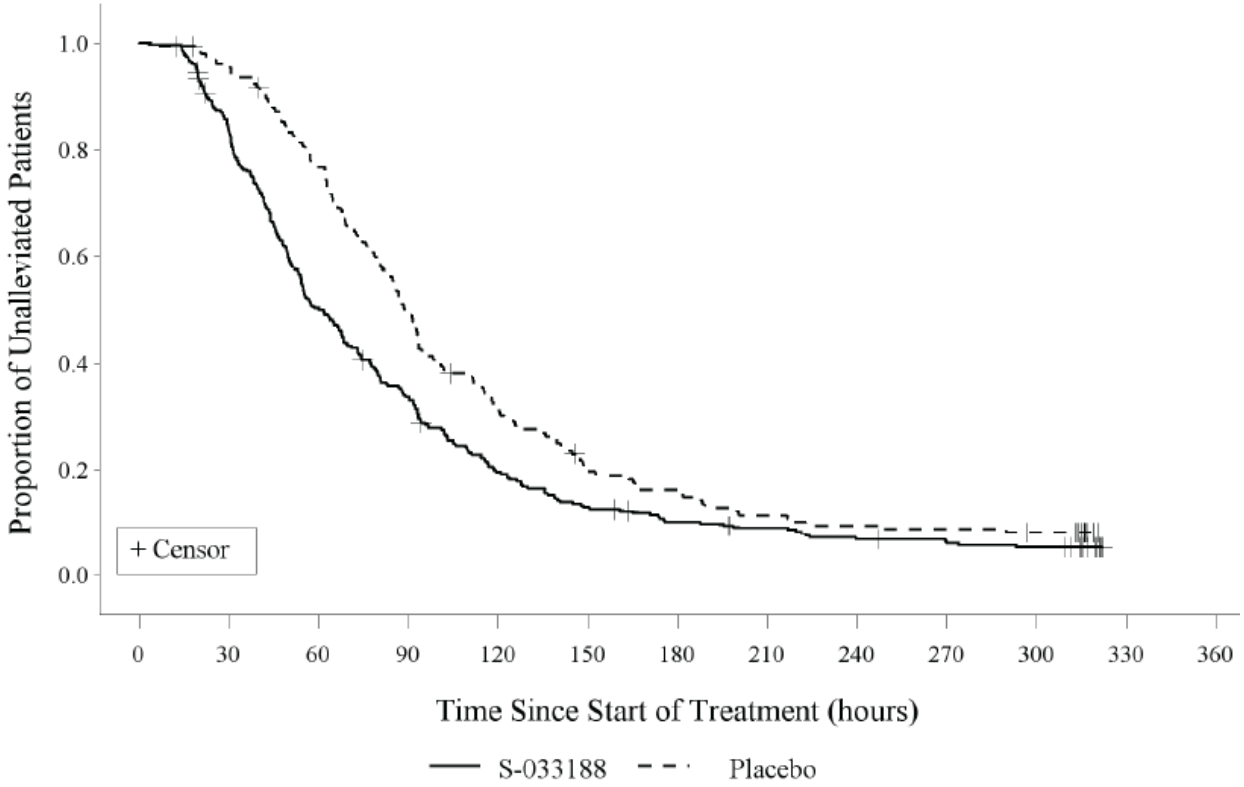
Compared to placebo, statistically significant differences were observed for the primary efficacy analysis in favor of S-033188 in for both subgroups for the two composite symptom score strata used at randomization.

Figure 20: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Study T0831 (Subgroup: Composite Symptom Scores at Baseline q11)



Source: Table 14.4.3 of the Clinical Study Report for T0831

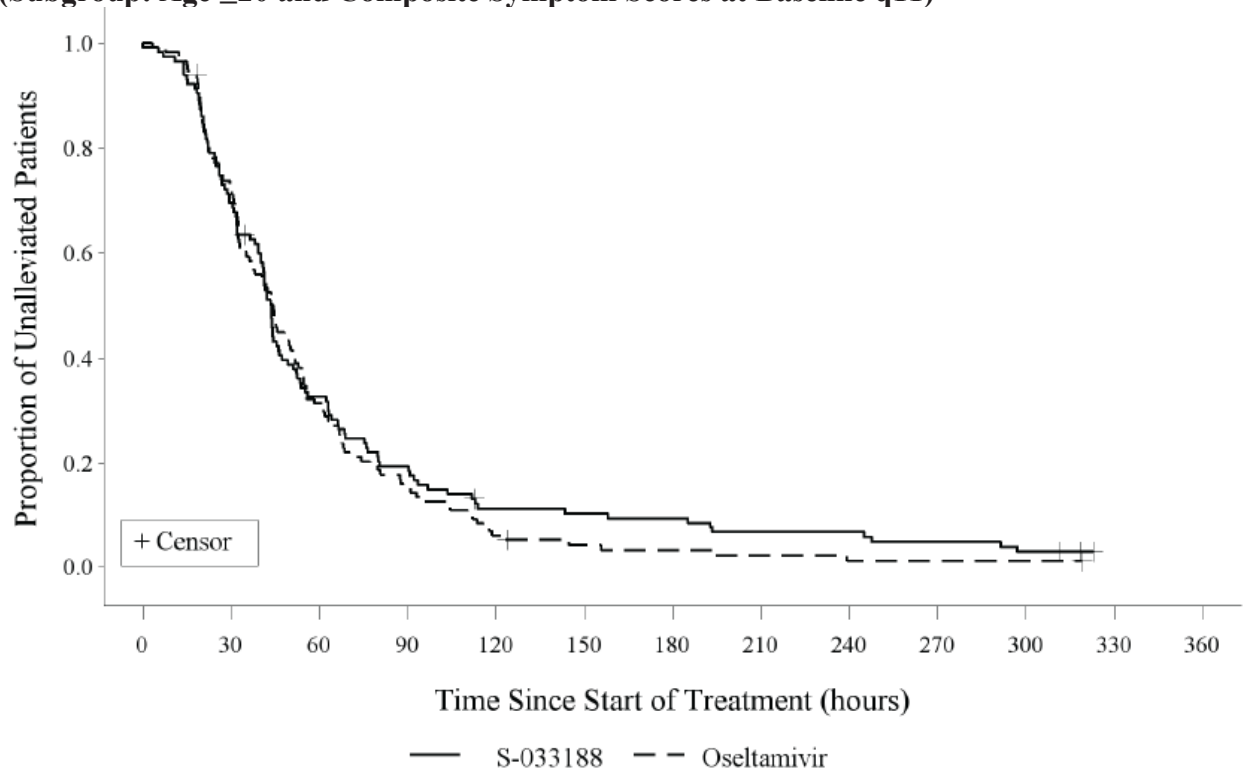
Figure 21: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Study T0831 (Subgroup: Composite Symptom Scores at Baseline ≥12)



Source: Table 14.4.4 of the Clinical Study Report for T0831

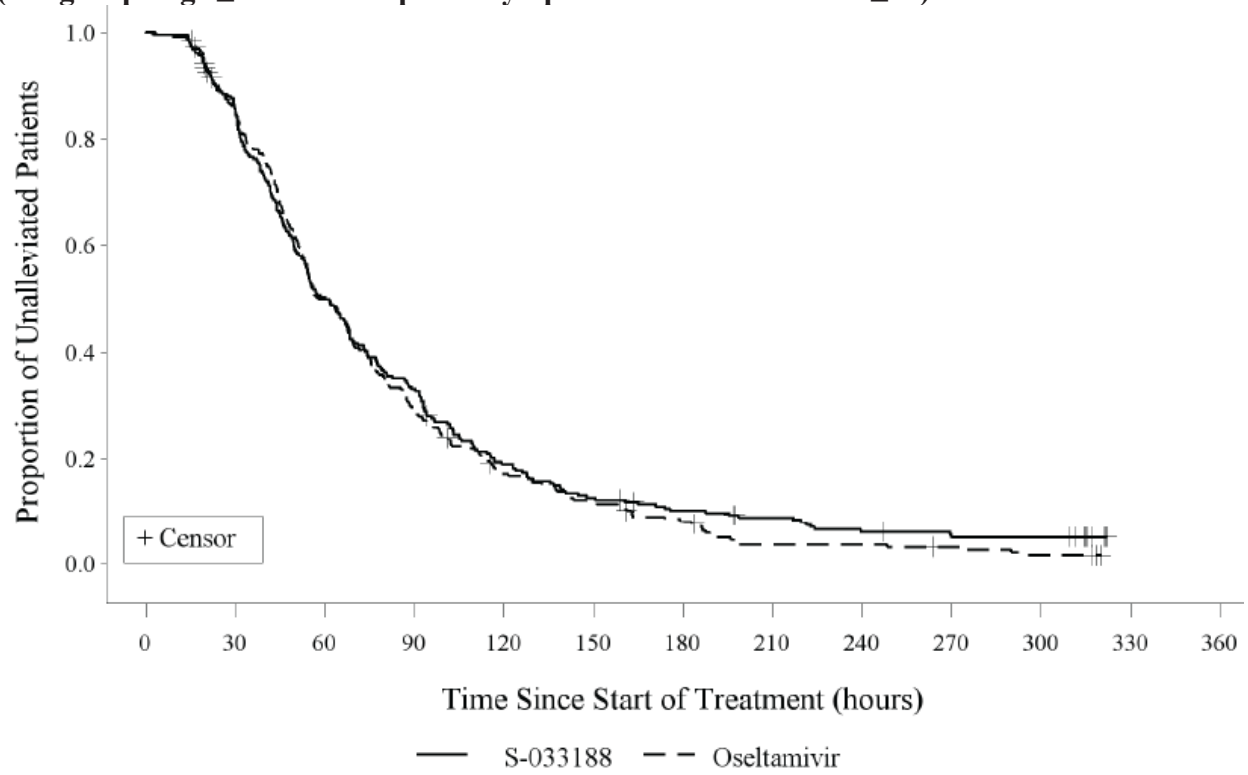
Similar trends were observed for the primary efficacy analysis for S-033188 and oseltamivir in for both subgroups for the two composite symptom score strata used at randomization.

Figure 22: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Study T0831 (Subgroup: Age ≥20 and Composite Symptom Scores at Baseline q11)



Source: Table 14.4.5 of the Clinical Study Report for T0831

Figure 23: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Study T0831 (Subgroup: Age ≥20 and Composite Symptom Scores at Baseline ≥12)



Source: Table 14.4.6 of the Clinical Study Report for T0831

Table 13: Time to Alleviation of Symptoms by Composite Symptom Score at Baseline in Study T0831

	S-033188	Placebo
Composite Symptom Scores at Baseline ≤ 11		
Summary statistics		
- n	144	72
- Median (hours)	43.6	62.7
- 95% confidence interval (hours)	39.2, 49.1	52.5, 73.9
- Difference (vs Placebo) (hours)	-19.1	---
Stratified Generalized Wilcoxon test vs Placebo [a]		
- P value	0.0078	---
Composite Symptom Scores at Baseline ≥ 12		
Summary statistics		
- n	311	158
- Median (hours)	61.6	88.7
- 95% confidence interval (hours)	54.1, 68.2	80.6, 94.5
- Difference (vs Placebo) (hours)	-27.0	---
Stratified Generalized Wilcoxon test vs Placebo [a]		
- P value	<.0001	---

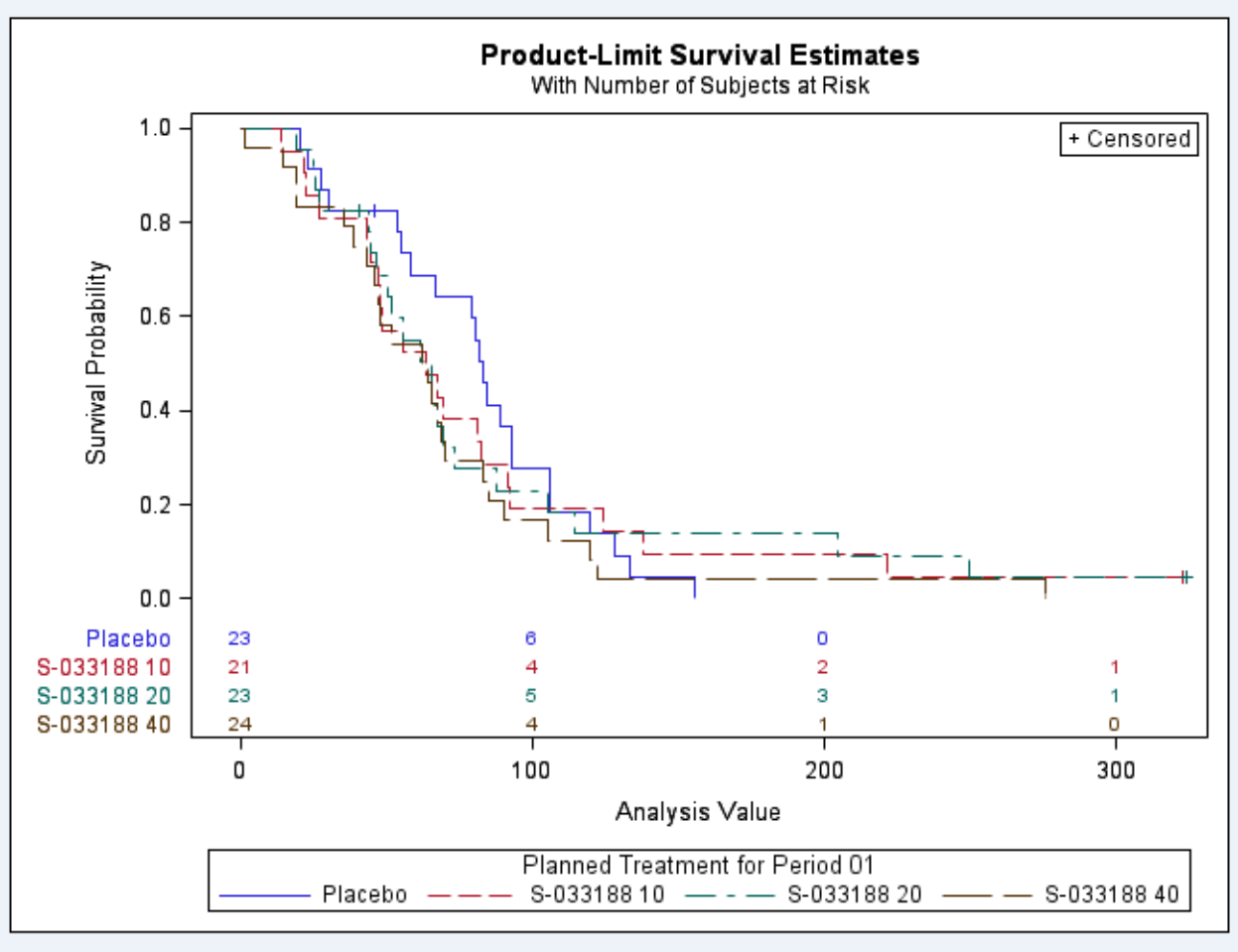
	S-033188 (≥ 20 years of age stratum)	Oseltamivir
Composite Symptom Scores at Baseline ≤ 11		
Summary statistics		
- n	115	119
- Median (hours)	43.6	44.4
- 95% confidence interval (hours)	40.0, 46.3	35.2, 50.7
- Difference (vs Oseltamivir) (hours)	-0.8	---
Stratified Generalized Wilcoxon test vs Oseltamivir [a]		
- P value	0.7367	---
Composite Symptom Scores at Baseline ≥ 12		
Summary statistics		
- n	260	258
- Median (hours)	60.1	58.0
- 95% confidence interval (hours)	54.0, 67.7	53.7, 68.3
- Difference (vs Oseltamivir) (hours)	2.1	---
Stratified Generalized Wilcoxon test vs Oseltamivir [a]		
- P value	0.8817	---

[a] Stratification factors: region.

Subset of patients whose time to alleviation of symptoms was not missing was included in this analysis.
Source: Table 11-39 of the Clinical Study Report for T0831

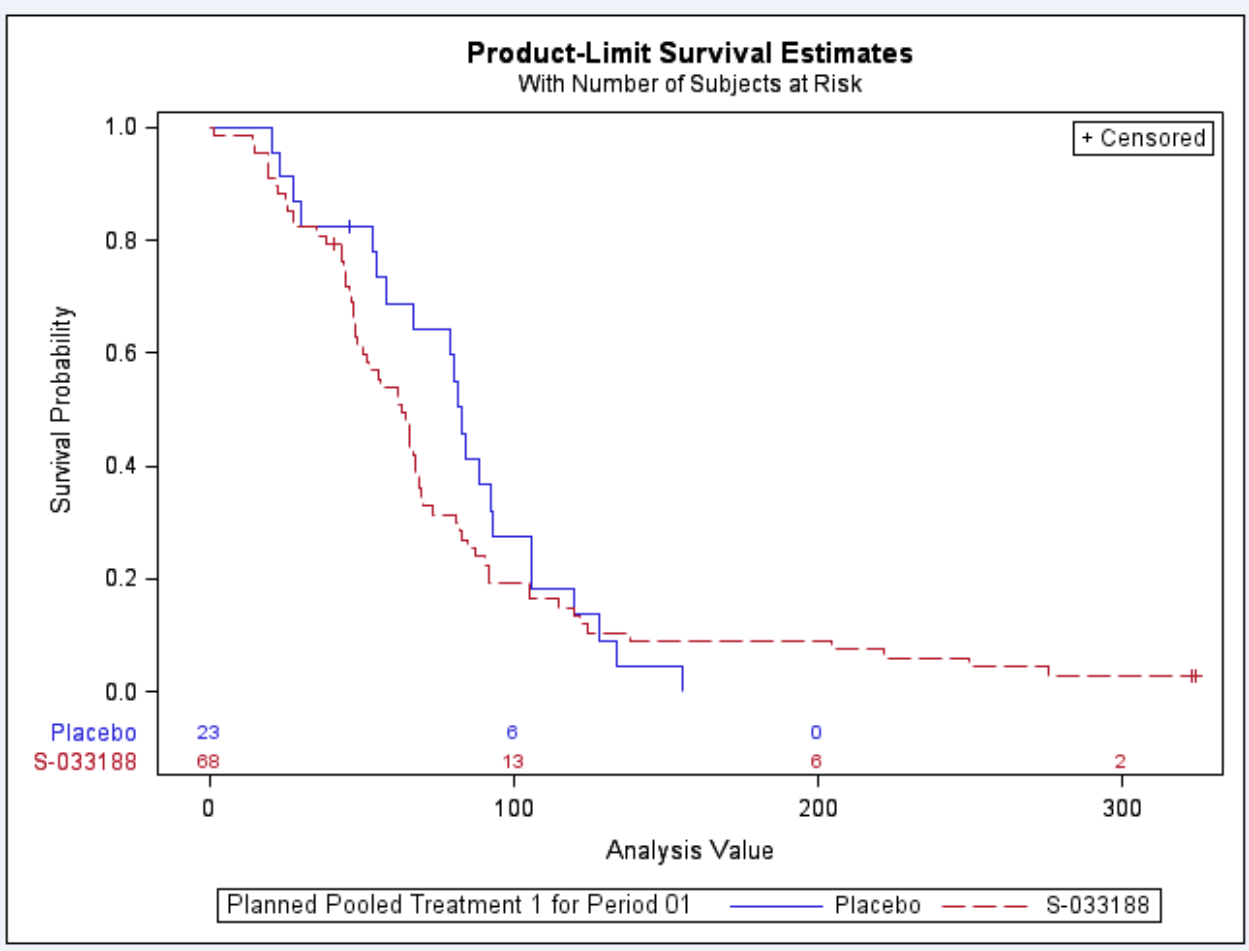
In T0821 the TTAS was lower for each dose of S-033188 than it was for placebo. Statistical significance at the two-sided 0.05 level was not achieved in Influenza B subjects in the analysis comparing pooled S-033188 doses against placebo (p=0.10) and in the analysis comparing the 40 mg dose that was selected for phase 3 against placebo (p=0.16).

Figure 24: Kaplan-Meier plot for the Time to Alleviation of Symptoms in Subjects with Influenza Type B in Study T0821 plotting each dose of S-033188



Gehan Wilcoxon p-value stratified by TSS (q 11 vs. ≥12) and smoking habit (Yes/No) for the 40 mg vs placebo comparison =0.16
Source: Reviewer's analysis

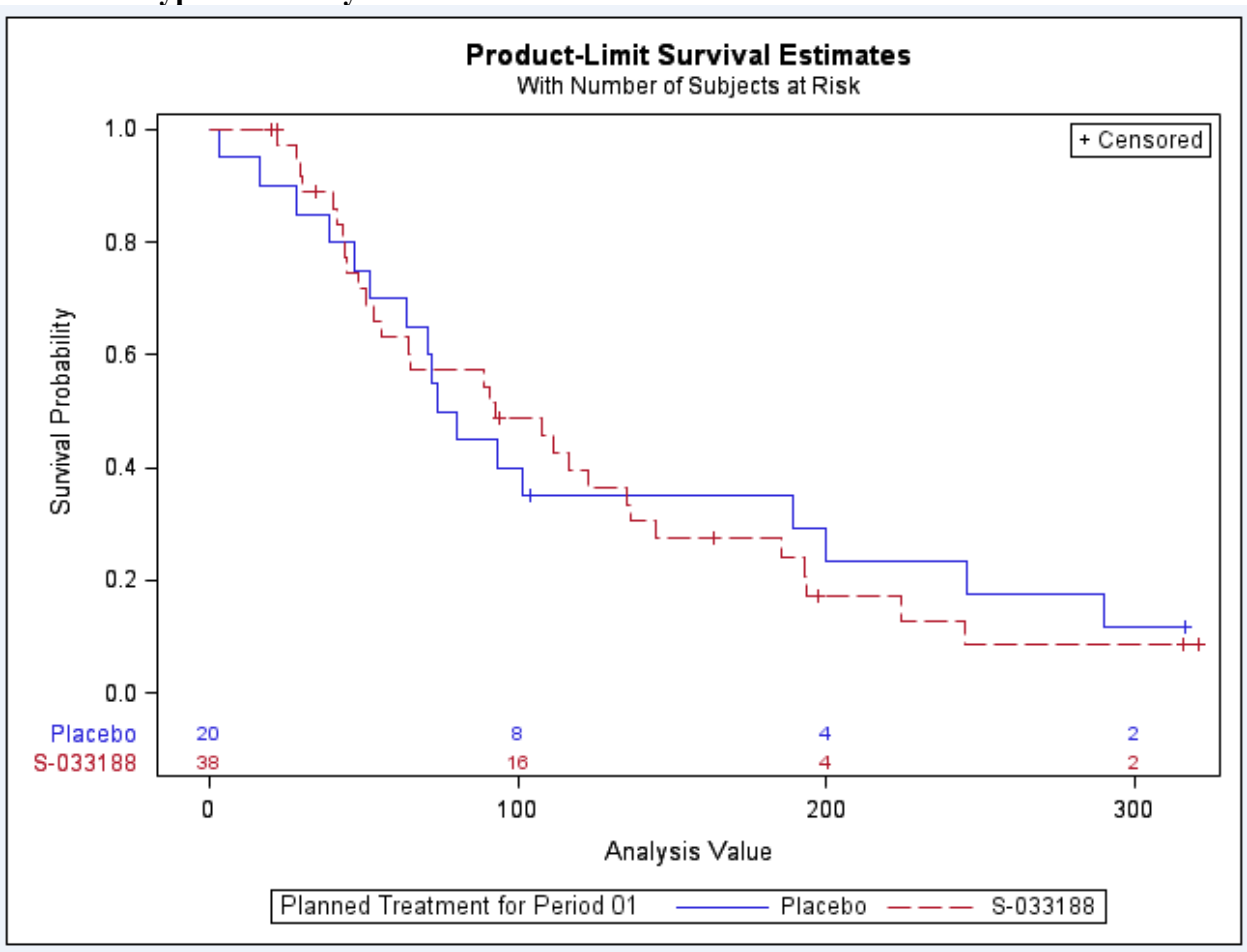
Figure 25: Kaplan-Meier plot for the Time to Alleviation of Symptoms in Subjects with Influenza Type B in Study T0821 pooling three individual doses of S-033188



Gehan Wilcoxon p-value stratified by TSS (q 11 vs. ≥12) and smoking habit (Yes/No) =0.10
Source: Reviewer's analysis

In T0831 the TTAS was comparable in both placebo and S-033188 arms where the Kaplan-Meier curves for the two treatment groups crossed.

Figure 26: Kaplan-Meier plot for the Time to Alleviation of Symptoms in Subjects with Influenza Type B in Study T0831



Gehan Wilcoxon p-value stratified by geographic region (Japan vs. U.S.) and TSS (q 11 vs. ≥12) =0.66
Source: Reviewer's analysis

The applicant performed similar analyses of the TTAS for each influenza viral subtype where the median TTAS was consistently lower for each dose of S-033188 compared to placebo in T0821.

Table 14: Analysis of Time to Alleviation of Symptoms by Influenza Virus Subtype in Study T0821

	S-033188 10 mg	S-033188 20 mg	S-033188 40 mg	Placebo
A/H1N1pdm				
n	66	71	61	69
Median (95% CI) (hrs)	52.9 (45.9, 65.6)	47.1 (39.4, 55.3)	48.2 (35.2, 65.5)	70.6 (64.9, 89.9)
Difference (vs Placebo) (hrs)	-17.7	-23.5	-22.4	---
P-value (G. Wilcoxon test) [a]	0.0084	0.0083	0.0049	---
Hazard ratio (95% CI) [b]	0.732 (0.518, 1.036)	0.751 (0.534, 1.057)	0.754 (0.528, 1.077)	---
P-value (Cox model) [b]	0.0780	0.1007	0.1212	---
A/H3N2				
n	13	5	12	6
Median (95% CI) (hrs)	66.0 (28.1, 83.5)	65.8 (21.3, 188.5)	45.4 (23.5, 113.4)	100.0 (18.9, 113.1)
Difference (vs Placebo) (hrs)	-34.0	-34.2	-54.6	---
P-value (G. Wilcoxon test) [a]	0.1254	0.4913	0.2689	---
Hazard ratio (95% CI) [b]	0.565 (0.202, 1.575)	0.864 (0.227, 3.294)	0.743 (0.250, 2.205)	---
P-value (Cox model) [b]	0.2747	0.8305	0.5925	---
B				
n	21	23	24	23
Median (95% CI) (hrs)	63.3 (44.5, 82.3)	65.4 (46.4, 73.2)	63.3 (43.3, 69.8)	83.1 (58.1, 92.8)
Difference (vs Placebo) (hrs)	-19.8	-17.8	-19.9	---
P-value (G. Wilcoxon test) [a]	0.2152	0.6608	0.1604	---
Hazard ratio (95% CI) [b]	0.867 (0.470, 1.597)	0.844 (0.457, 1.559)	0.722 (0.399, 1.306)	---
P-value (Cox model) [b]	0.6459	0.5888	0.2811	---

a Stratified Generalized Wilcoxon test vs placebo. Stratified factors: smoking habit, composite symptom scores at baseline.

b Cox proportional hazards model vs placebo. Covariates: smoking habit, composite symptom scores at baseline.

Source: Table 11-26 of the Clinical Study Report for T0821

In T0831 the median TTAS was observed to be lower for S-033188 than for placebo in the influenza A viral subtypes while the reverse trend was observed for subjects with type B influenza.

Table 15: Time to Alleviation of Symptoms by Influenza Virus Subtype in Study T0831

Influenza Virus Type Based on PCR		S-033188	Placebo
A/H3	Summary statistics		
	- n	392	195
	- Median (hours)	52.2	79.5
	- 95% confidence interval (hours)	47.0, 56.8	69.5, 86.8
	- Difference (vs Placebo) (hours)	-27.3	---
	Stratified Generalized Wilcoxon test vs Placebo [a]		
	- P value	<.0001	---
A/H1N1pdm	Summary statistics		
	- n	7	7
	- Median (hours)	43.7	141.0
	- 95% confidence interval (hours)	22.0, 109.1	82.1, ---
	- Difference (vs Placebo) (hours)	-97.3	---
	Stratified Generalized Wilcoxon test vs Placebo [a]		
	- P value	0.4212	---
B	Summary statistics		
	- n	38	20
	- Median (hours)	93.0	77.1
	- 95% confidence interval (hours)	53.4, 135.4	46.8, 189.0
	- Difference (vs Placebo) (hours)	15.9	---
	Stratified Generalized Wilcoxon test vs Placebo [a]		
	- P value	0.8568	---

PCR = polymerase chain reaction

[a] Stratification factors: composite symptom scores at baseline and region

Patients who did not experience alleviation of symptoms were censored at the last observation time point. Subset of patients whose time to alleviation of symptoms was not missing was included in this analysis.

The applicant used Peto's Wilcoxon test instead of the Gehan Wilcoxon test.

Source: Table 11-6 in the Clinical Study Report for T0831

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The applicant pre-specified using the Cox proportional hazards analysis for the primary efficacy analysis in the phase 2b trial and used the Gehan Wilcoxon test as a secondary analysis. The proportional hazards assumption does not hold for acute uncomplicated influenza because it is an illness of limited duration and survival curves converge after a few days. Therefore, a version of the generalized Wilcoxon test is typically used for the primary efficacy analysis for drugs intended to treat uncomplicated influenza and this approach demonstrated statistically significant results for each dose compared to placebo.

Due to the lack of proportional hazards in the phase 2b trial and the resulting lack of statistical significance using the Cox proportional hazards analysis, the applicant pre-specified the Peto-Prentice version of the Wilcoxon test for the primary efficacy analysis of the phase 3 trial. The statistical reviewer used the Gehan Wilcoxon test for primary efficacy analyses of both trials. The reviewer chose to use the more common Gehan version of the Wilcoxon test in part because the applicant used this version in their phase 2b trial and because it has been more commonly used than the other versions. In contrast, the log rank test can yield quite different results from the Wilcoxon tests when hazards are not proportional. The reviewer was open to accepting the applicant's phase 3 results (where they pre-specified using the Peto-Prentice approach) for labeling purposes but all of the statistical tests were highly significant for the primary efficacy analysis in the phase 3 trial.

The median difference in clinical responses between treatment groups is a measure of the treatment effect size. The applicant calculated the difference in medians between treatment groups A and B as the difference between the median response of all individuals in group A minus the median responses of all subjects in group B. This calculation only considers the difference between the 50^{th} percentile of each group A and group B. From the reviewer's perspective, the median difference should be calculated as the median of all pairwise differences in responses between individuals in group A and B. This methodology is more appropriate since the difference in medians of treatment groups is not always equal to the median difference between treatment groups. This is in contrast to the mean difference which is equal to the difference in means.

The median difference between subjects in S-033188 and placebo subjects in the phase 3 trial was 21 hours while the difference in the median of the S-033188 subjects and the median of placebo subjects was 26.5 hours. The median difference is preferred over the difference in medians because the median difference compares the entire distribution of each treatment arm by computing all pairwise differences between patients in group A and patients in group B.

However, the difference in medians only considers the difference between a single percentile in each treatment group.

5.2 Collective Evidence

Median TTAS values in the phase 2b trial were similar to those observed in the phase 3 trial. Unlike the phase 3 trial, the statistical significance of the primary efficacy analysis in the phase 2b trial depended on which statistical test was used. There were no statistically significant differences observed between any one of the three S-033188 treatment groups and placebo using the pre-specified Cox proportional hazards model. However, the phase 2b trial was considered to be supportive of the phase 3 trial results by the statistics reviewer because there were statistically significant differences favoring each dose compared to placebo using the Wilcoxon test. The Wilcoxon test is typically used for the primary analysis for acute uncomplicated influenza trials as it puts more weight on earlier events than the Cox proportional hazards model, while the Cox proportional hazards model is more powerful when there are proportional hazards which is not usually the case in these types of trials with self-limiting response after a few days.

A highly statistically significant difference in TTAS was observed between S-033188 and placebo subjects who were infected with the type A strain of influenza while there was no statistically significance between the TTAS in S-0331888 and placebo subjects with the type B strain. In addition, an earlier median TTAS was observed in the placebo subjects than in S-033188 subjects in the phase 3 trial while the opposite trend was observed in the phase 2b trial. S-033188 does not appear to work as well in Influenza B subjects. However due to the small number of subjects with type B influenza in both trials, the conflicting results in the two trials could have been observed by chance, although this is unknown. In addition, if there is reduced efficacy in Type B subjects, it is unlikely that statistically significance would be detected in such a small number of subjects.

5.3 Conclusions and Recommendations

The majority of subjects in the phase 2b and 3 trials were infected with type A strain of the influenza virus where there was clear evidence of a treatment effect for S-033188. There were far fewer subjects with the type B strain and the efficacy of S-033188 compared to placebo appeared to be less evident in these patients. There were also discordant results between the phase 2b and 3 trials for subjects infected with type B influenza. Therefore, how effective S-033188 is for the treatment of the type B strain of influenza is unclear. However, since it is infeasible wait for test results to see what strain of influenza subjects have prior to treatment, the label will not restrict the use of the product to subjects with the Influenza A viral strain.

5.4 Labeling Recommendations (as applicable)

APPENDIX 1: Additional Details about Statistical Methods

The following SAS code was used by the reviewer for the comparison between the S-033188 group and the placebo group for the primary efficacy analysis in T0831:

```
proc lifetest data = analysisdata;
where (TRTPN=1 or TRTPN=2);
    {e.g., for a comparison of S-033188 and placebo}
time AVAL * CNSR (x);
strata TSSGR REGION / group = TRTPN test = (logrank wilcoxon peto modpeto);
run; quit;
```

- TRTPN/TRT01PN: Treatment group
- AVAL: Time to alleviation of symptoms
- CNSR: =1/0 if censored, 0/1 otherwise in T0831/T0821
- TSSGR: Category of baseline composite symptom score (≤ 11 or ≥ 12)
- REGION: Category of region (Japan/Asia or USA/Rest of the world)

Subjects in the primary efficacy analysis were selected using the parameter code (paramcd)='ALLEDES' for T0831 and paramcd='TTAS' for T0821.

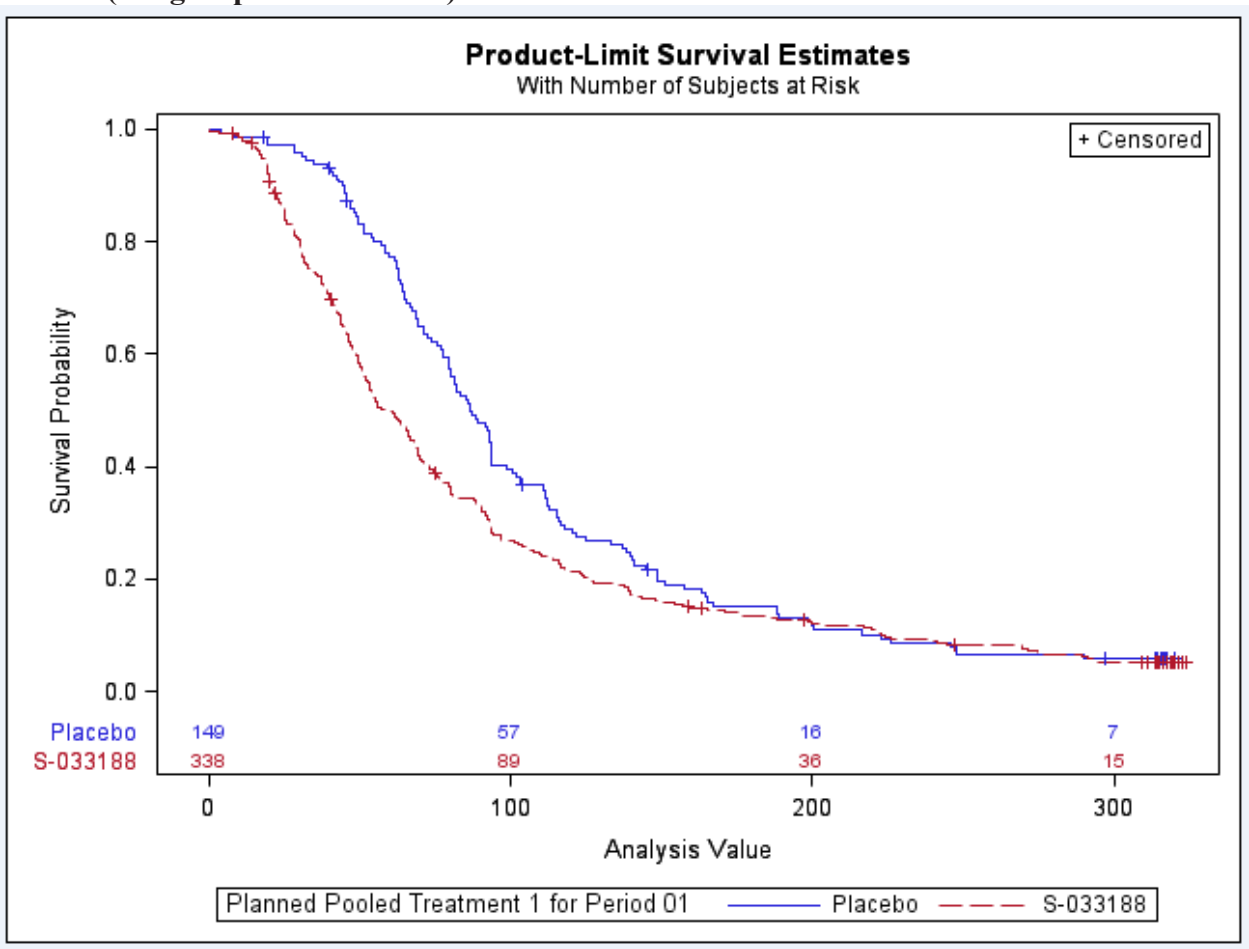
The 10,000 bootstrap samples were generated by the following SAS code. A random seed of 16010831 and 16010832 was used for comparisons between the S-033188 and the Placebo or Oseltamivir, respectively. Then, the treatment group difference in median time was calculated by each bootstrapped sample and its 95% CI was constructed using percentiles of the bootstrap distribution.

```
proc surveyselect data = analysisdata seed = 16010831 out = bootstrap method = urs
rate = 1.0 rep = 10000 outhits;
strata TRT01PN;
run; quit;
```

APPENDIX 2: Pooled Subgroup Analyses

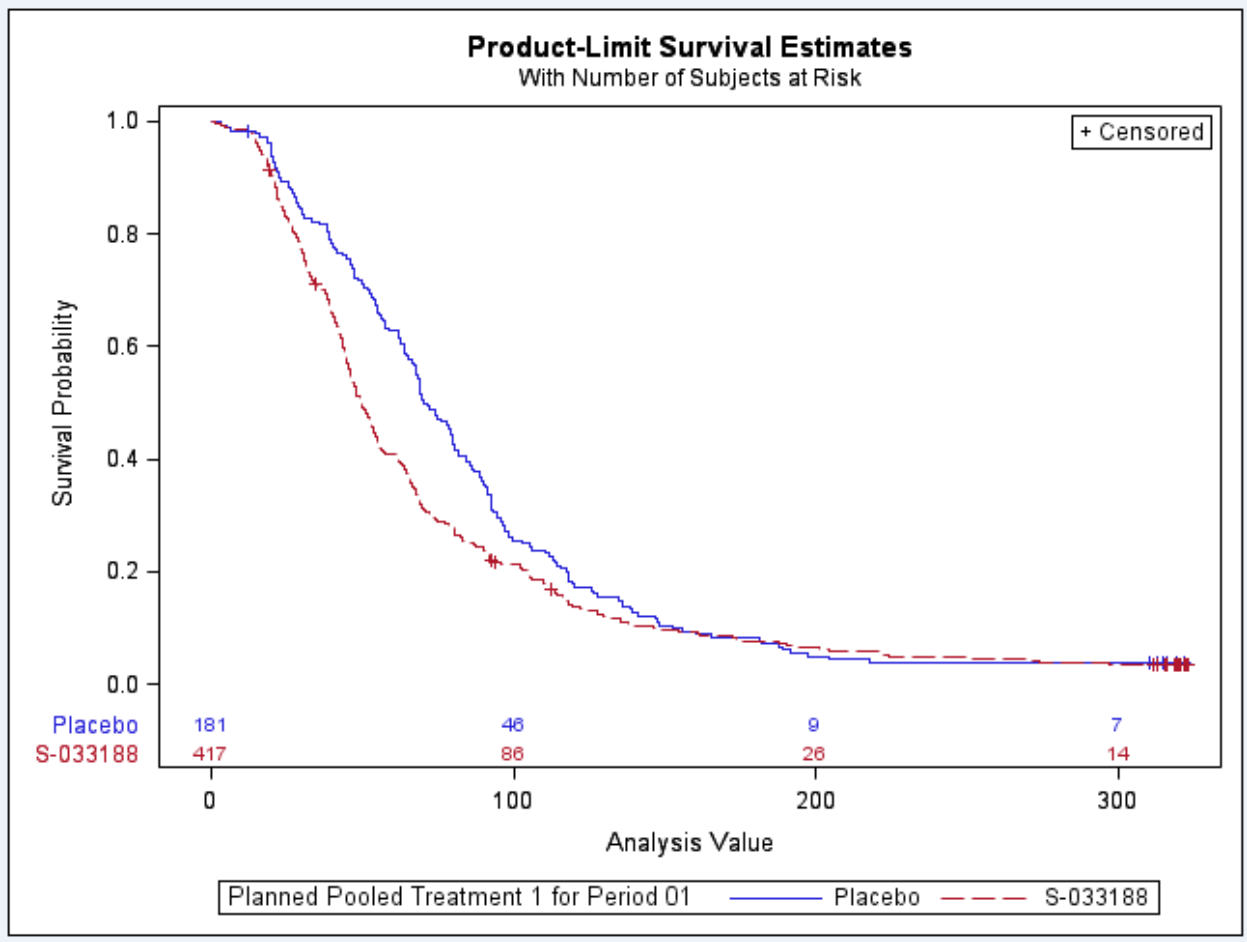
Statistically significant differences ($p<0.001$) were observed for the primary efficacy analysis in favor of S-033188 in both genders.

Figure 27: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Phase 2 and 3 Studies (Subgroup: Sex = Female)



Gehan Wilcoxon p-value stratified by study, geographic region (Japan vs. U.S.) and TSS (q11 vs. ≥12) <0.001
Source: Reviewer's analysis

Figure 28: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Phase 2 and 3 Studies (Subgroup: Sex = Male)

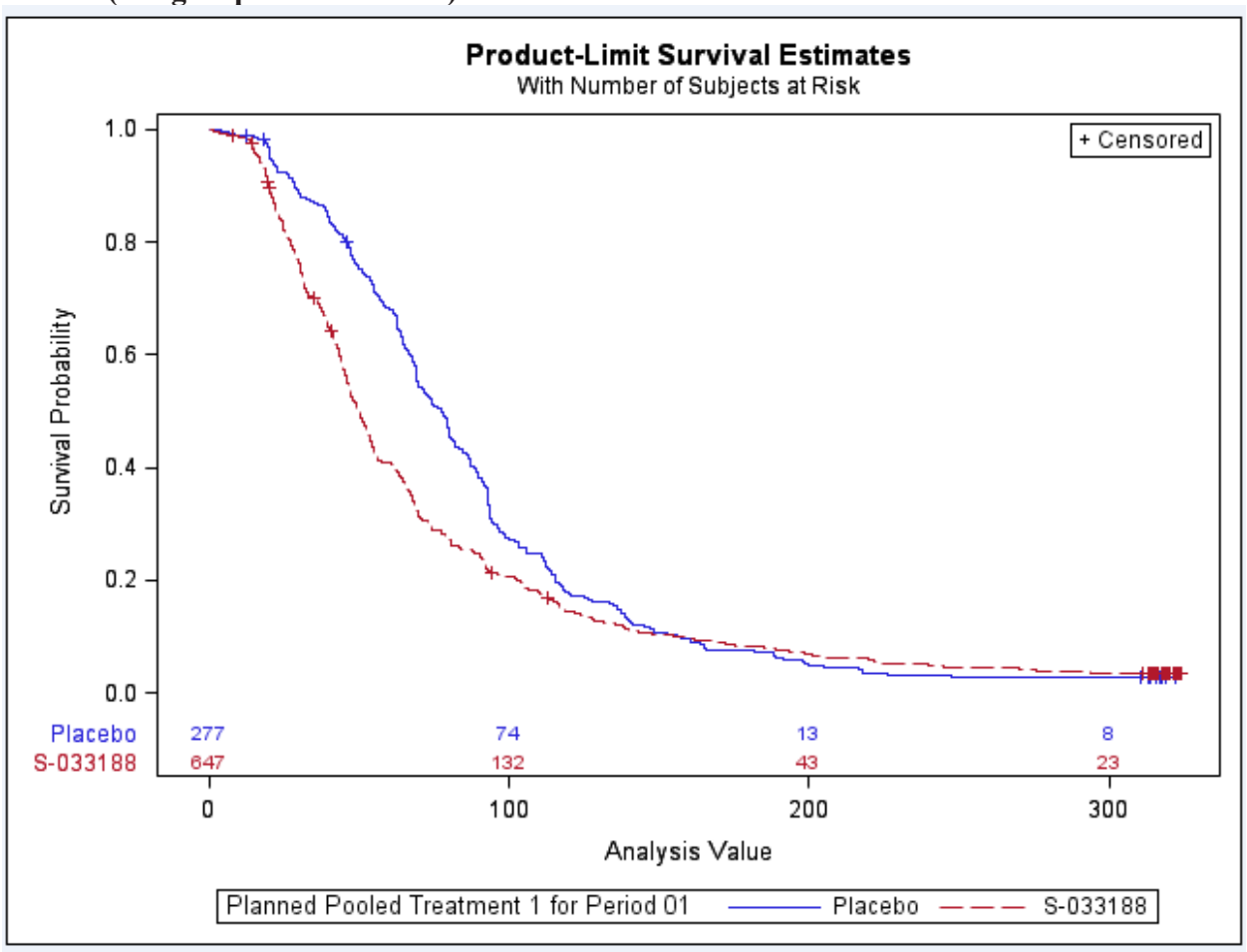


Gehan Wilcoxon p-value stratified by study, geographic region (Japan vs. U.S.) and TSS (q11 vs. ≥12) <0.001

Source: Reviewer's analysis

Statistically significant differences were most apparent for the primary efficacy analysis in favor of S-033188 in Asians (p<0.001).

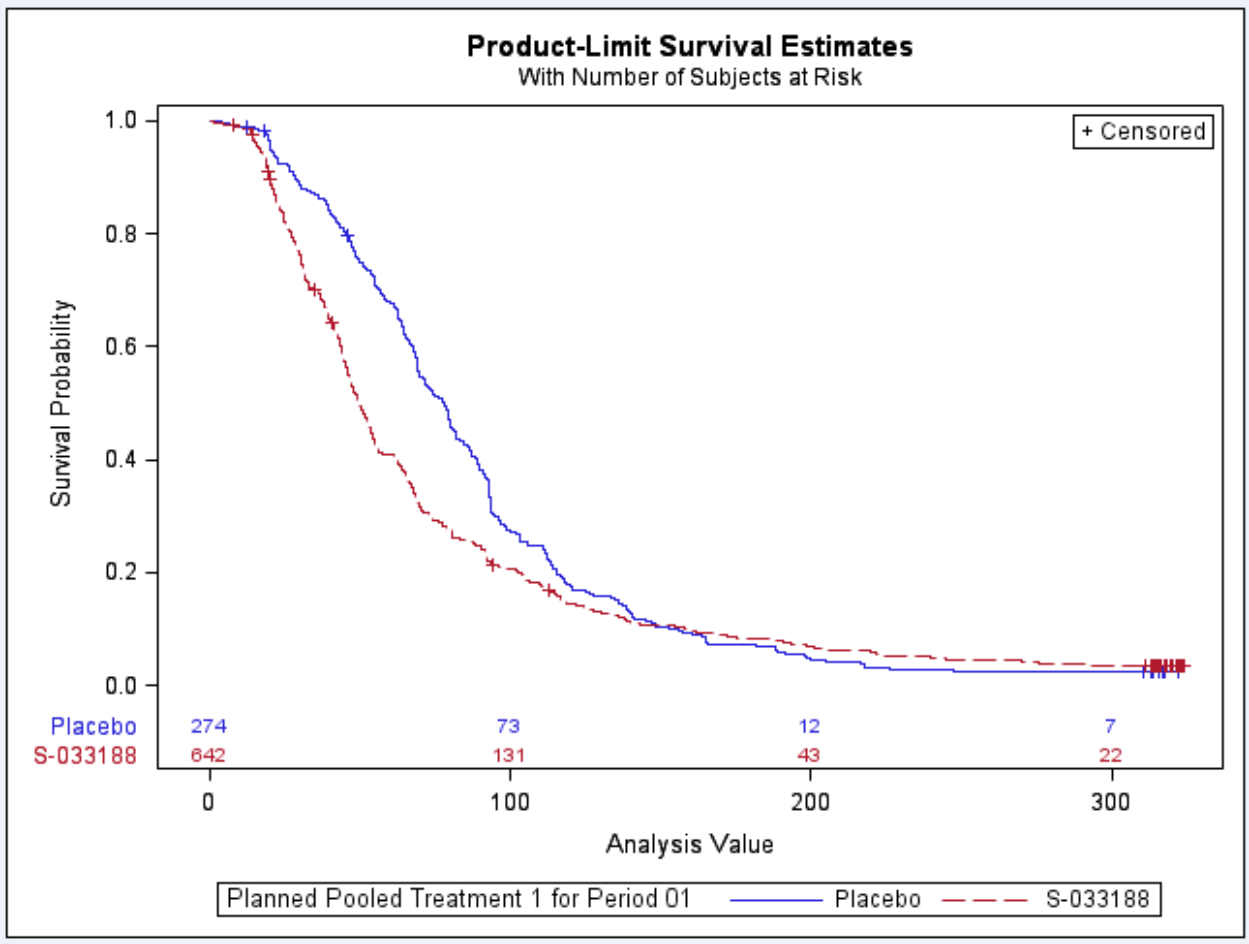
Figure 29: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Phase 2 and 3 Studies (Subgroup: Race = Asian)



Gehan Wilcoxon p-value stratified by study, geographic region (Japan vs. U.S.) and TSS (q11 vs. ≥12) <0.001
Source: Reviewer's analysis

Statistically significant differences ($p<0.001$) were most apparent for the primary efficacy analysis in favor of S-033188 in Japan.

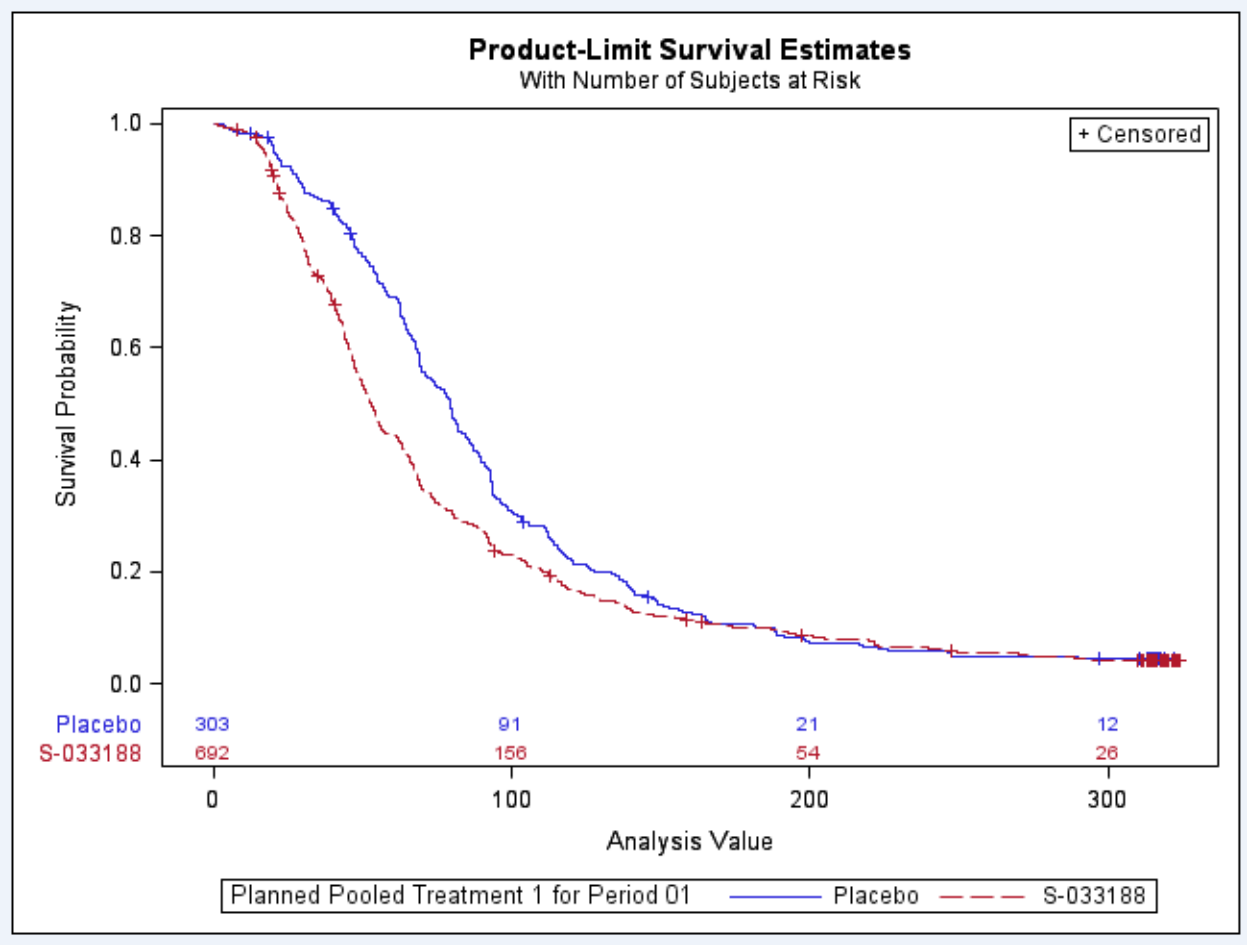
Figure 30: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Phase 2 and 3 Studies (Subgroup: Region = Japan)



Gehan Wilcoxon p-value stratified by study and TSS (q11 vs. ≥12) <0.001
Source: Reviewer's analysis

Similar trends were observed for adult subjects after combining data from the phase 2b and 3 trials as were seen in the Kaplan-Meier plot for T0831.

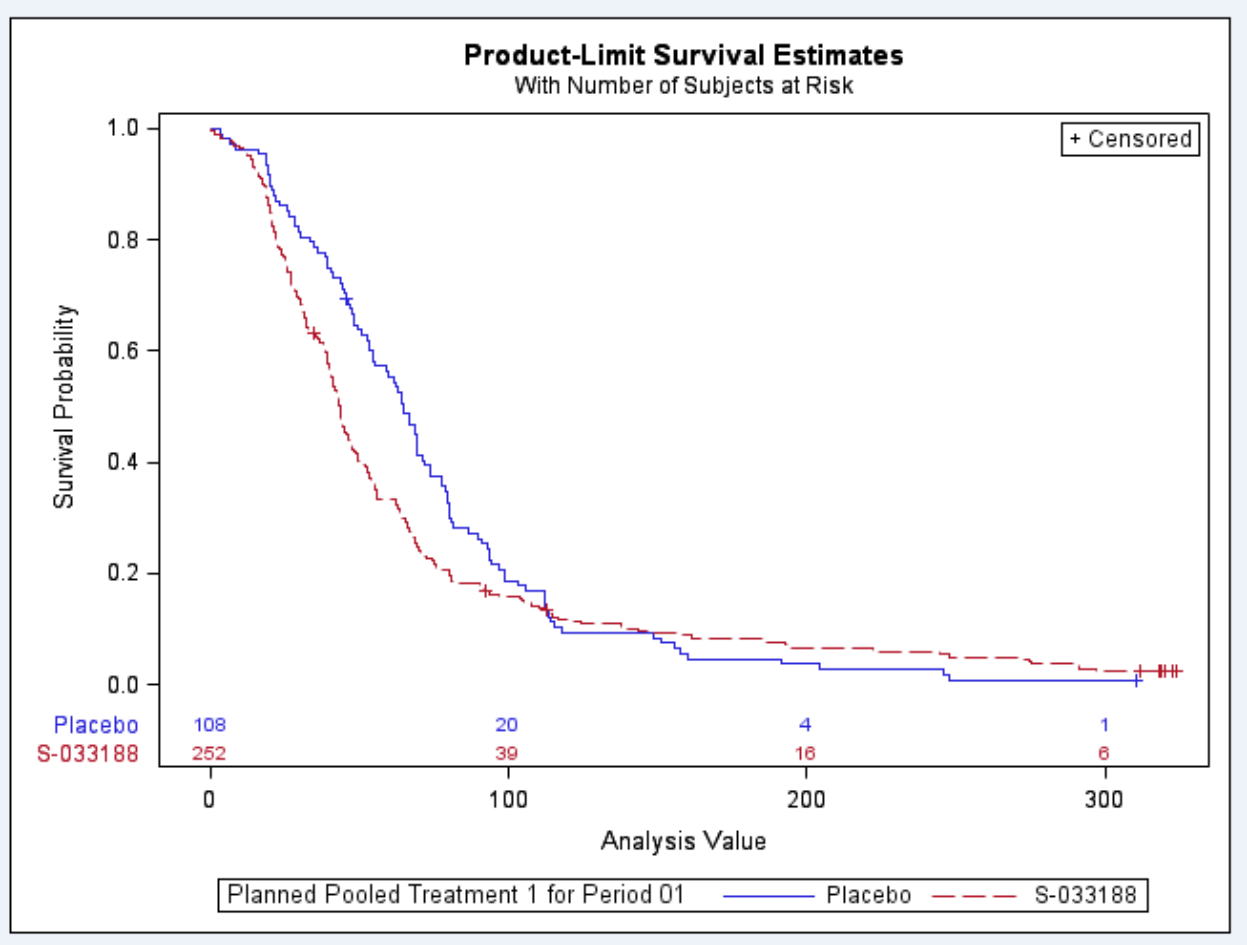
Figure 31: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Adults Subjects (Age ≥18) in Phase 2 and 3 Studies



Gehan Wilcoxon p-value stratified by study, geographic region (Japan vs. U.S.) and TSS (q11 vs. ≥12) < 0.001
Source: Reviewer's analysis

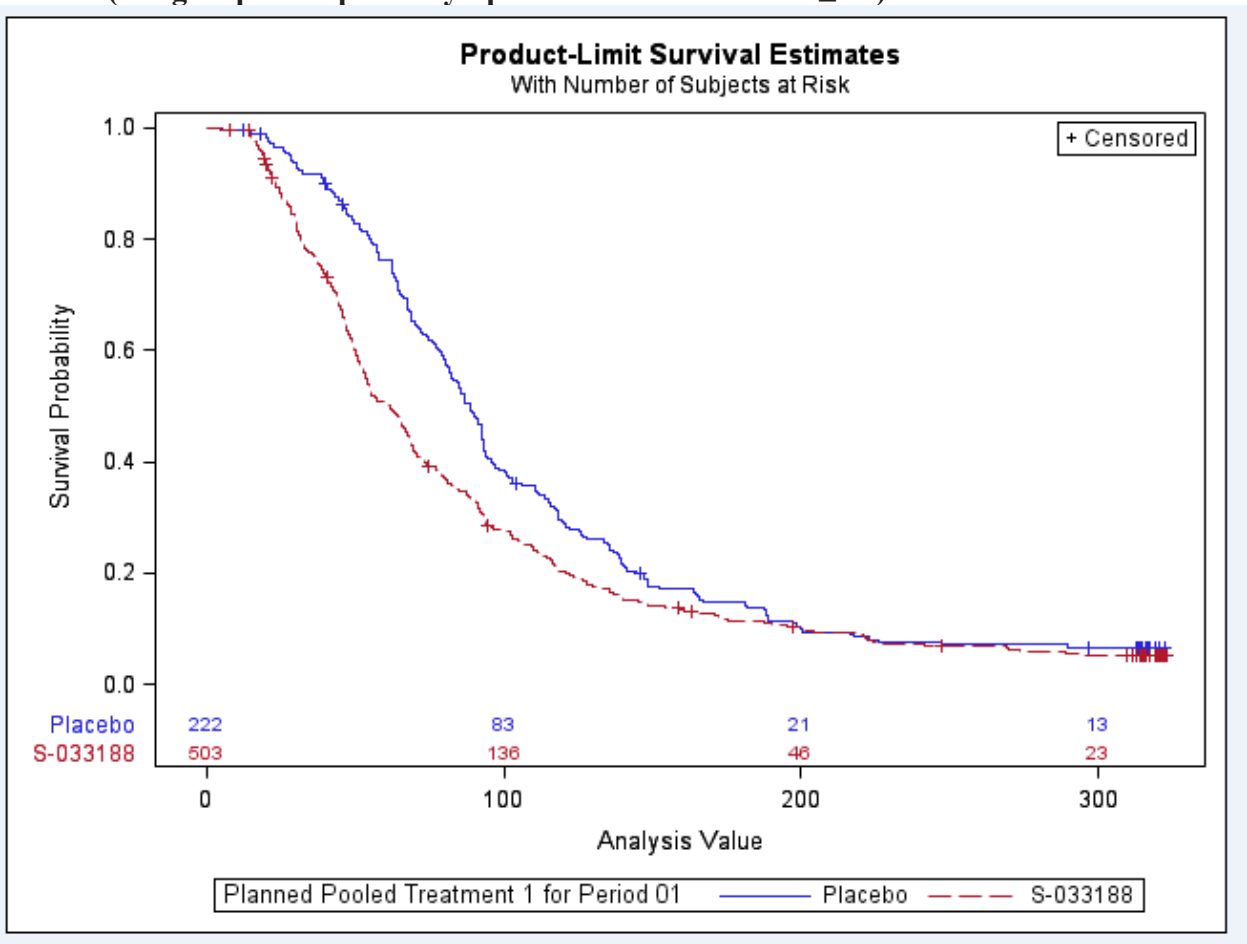
Statistically significant differences ($p<0.001$) were observed for the primary efficacy analysis in favor of S-033188 in for both subgroups for the two composite symptom score strata used at randomization.

Figure 32: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Phase 2 and 3 Studies (Subgroup: Composite Symptom Scores at Baseline q 11)



Gehan Wilcoxon p-value stratified by study and geographic region (Japan vs. U.S.) <0.001
Source: Reviewer's analysis

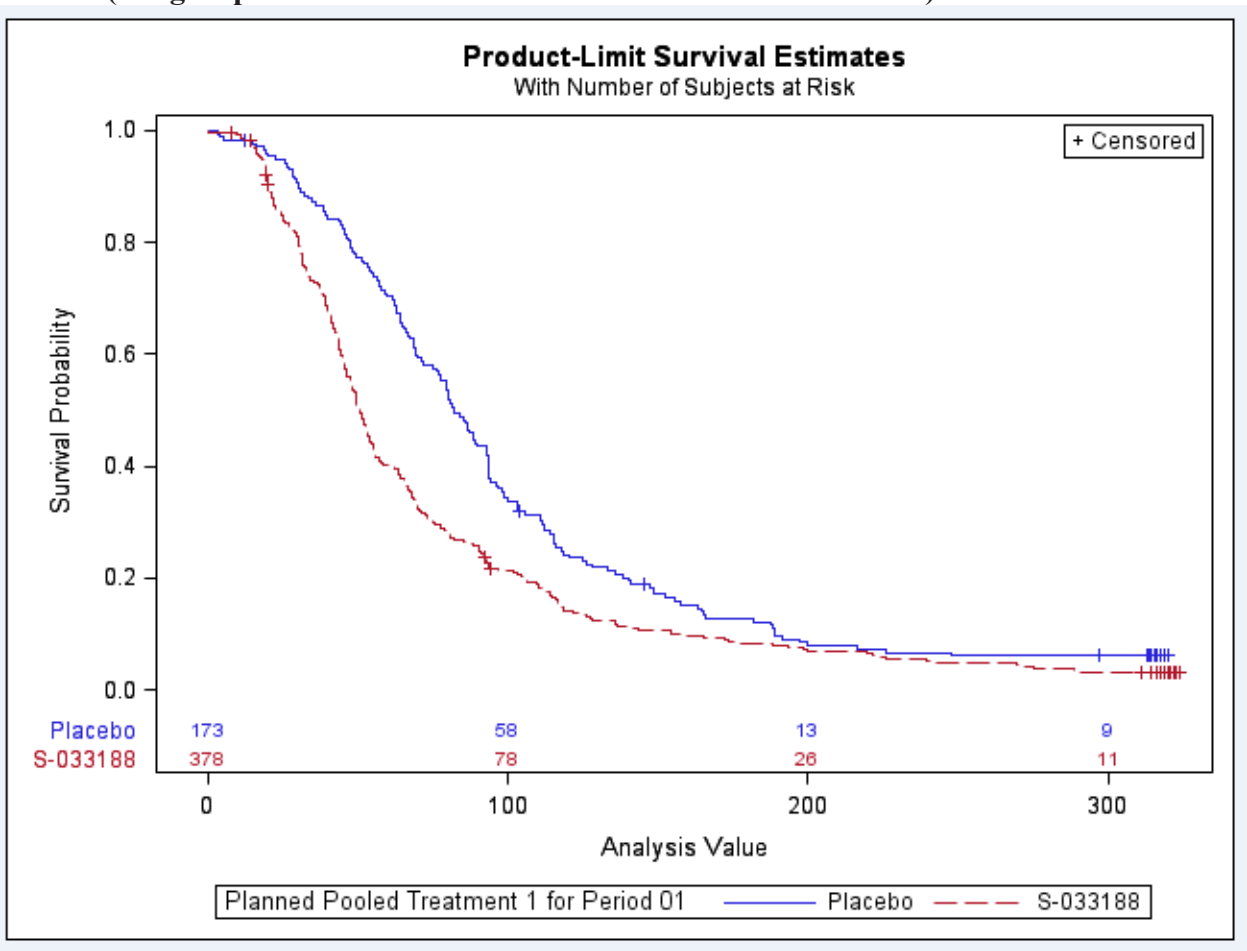
Figure 33: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Phase 2 and 3 Studies (Subgroup: Composite Symptom Scores at Baseline ≥ 12)



Gehan Wilcoxon p-value stratified by study and geographic region (Japan vs. U.S.) <0.001
Source: Reviewer's analysis

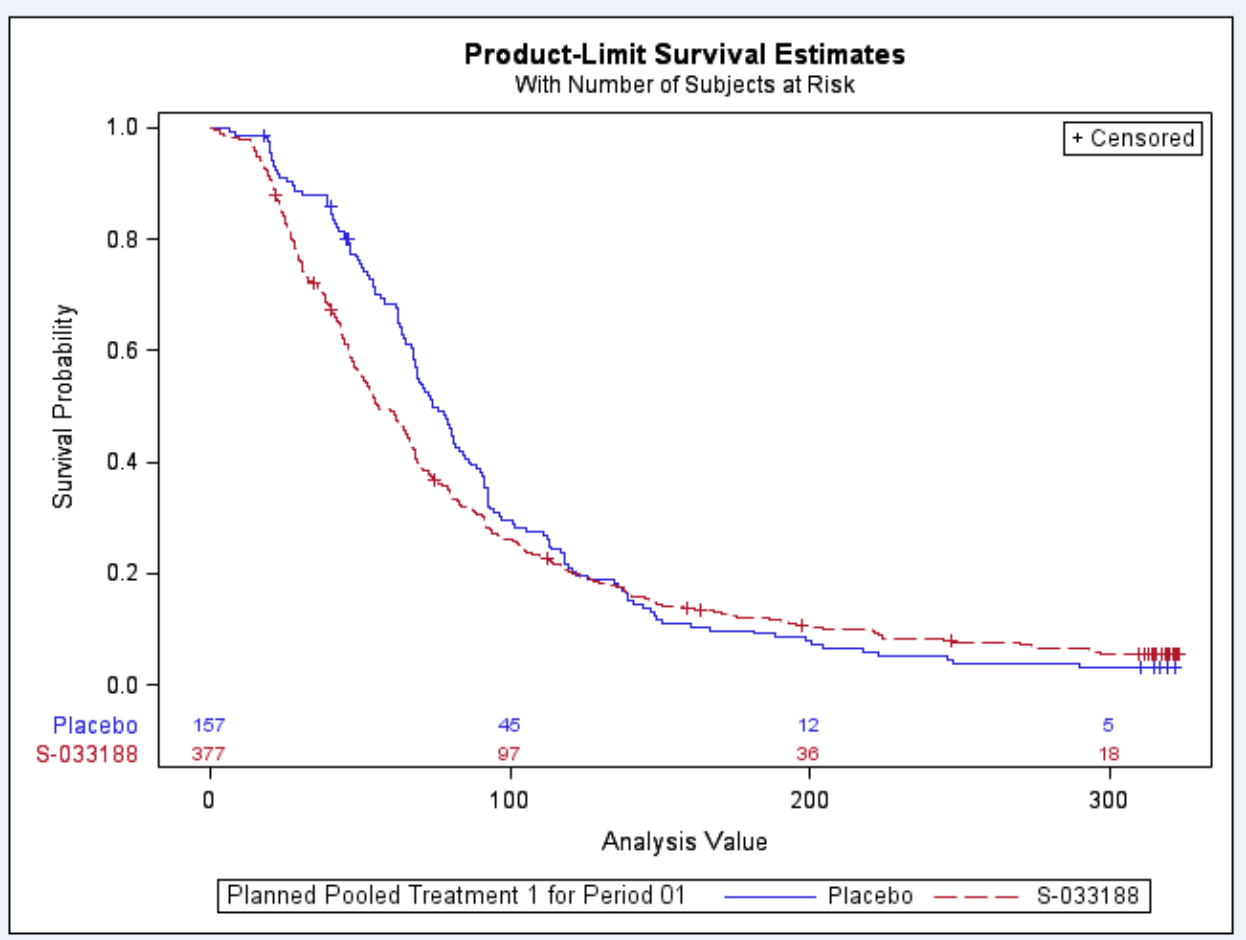
Statistically significant differences (p<0.001) were observed for the primary efficacy analysis in favor of S-033188 in for both subgroups of patients treated 0 to 24 hours and >24 to 48 hours from flu onset.

Figure 34: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Phase 2 and 3 Studies (Subgroup: Time to Treatment from Flu Onset 0 to 24 hours)



Gehan Wilcoxon p-value stratified by study, geographic region (Japan vs. U.S.) and TSS (q 11 vs. ≥12) <0.001
Source: Reviewer's analysis

Figure 35: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Phase 2 and 3 Studies (Subgroup: Time to Treatment from Flu Onset >24 to 48 hours)

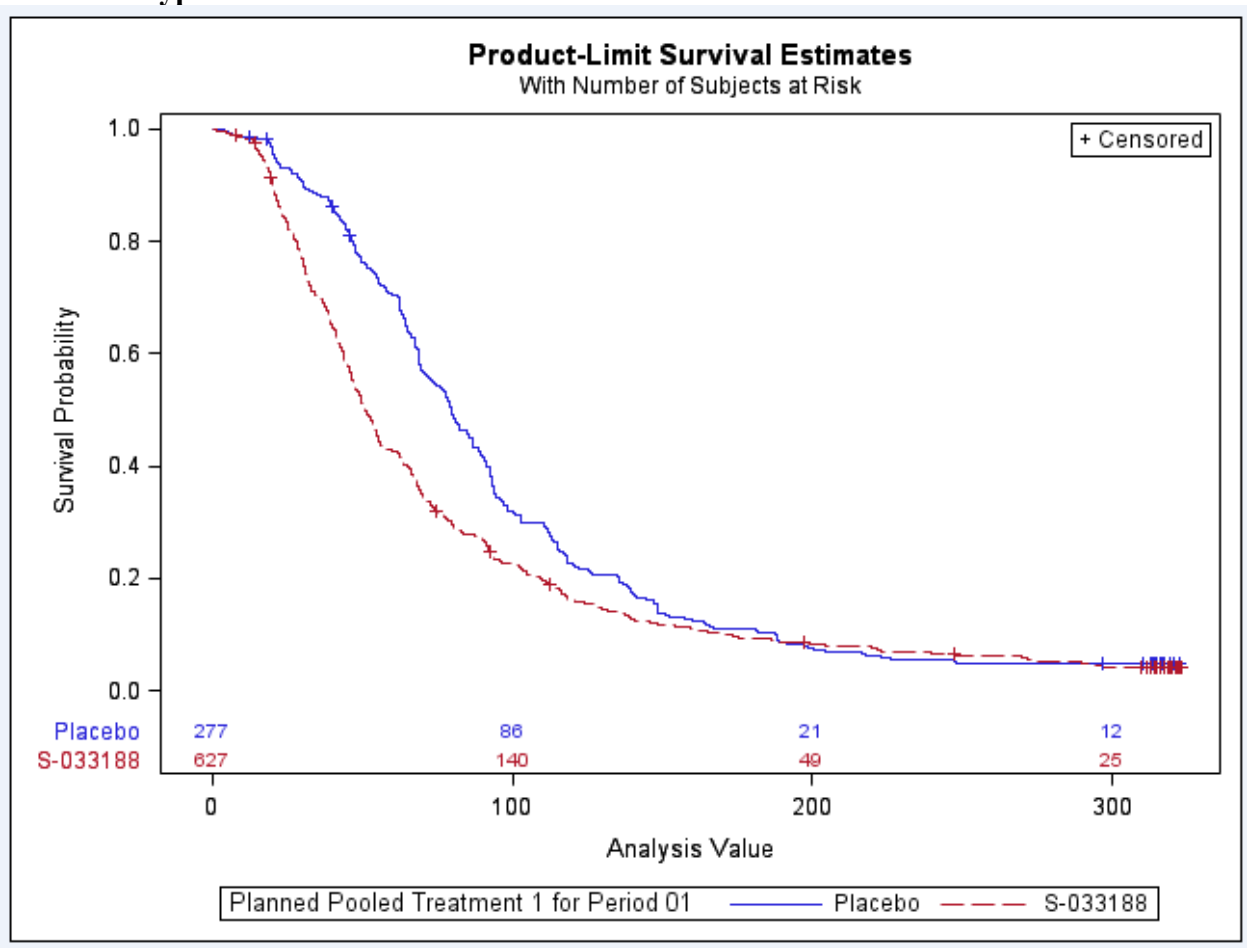


Gehan Wilcoxon p-value stratified by study, geographic region (Japan vs. U.S.) and TSS (q 11 vs. ≥12) <0.001

Source: Reviewer's analysis

Statistically significant differences ($p<0.001$) were most apparent for the primary efficacy analysis in favor of S-033188 in Influenza A subjects.

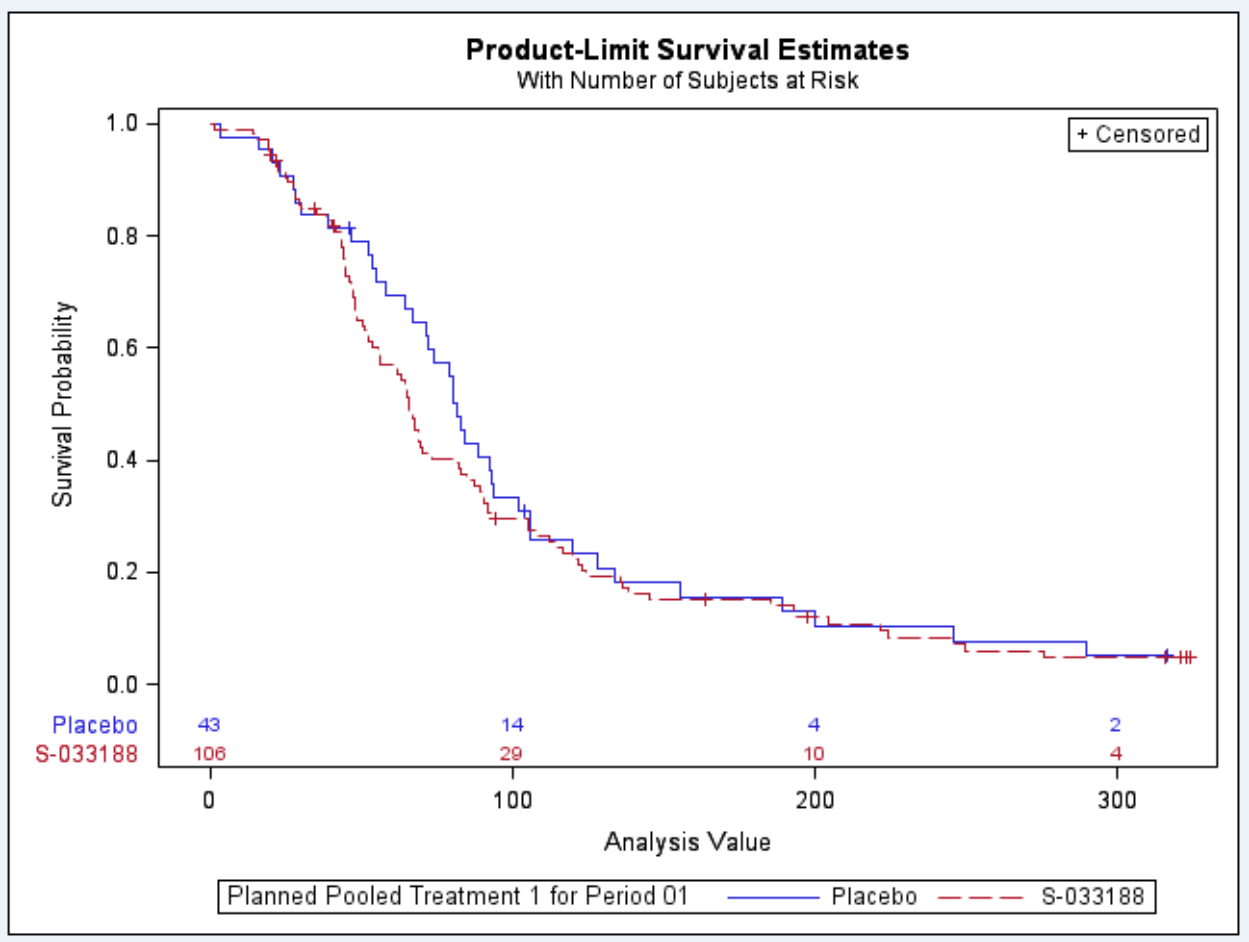
Figure 36: Kaplan-Meier plot for the Time to Alleviation of Symptoms in Subjects with Influenza Type A in Phase 2 and 3 Studies



Gehan Wilcoxon p-value stratified by study, geographic region (Japan vs. U.S.) and TSS (q 11 vs. ≥12) <0.001
Source: Reviewer's analysis

Statistical significance at the two-sided 0.05 level was not achieved in Influenza B subjects (p=0.09) where there appeared to be less separation of the Kaplan-Meier curves than for Influenza A subjects in addition to a much smaller sample size.

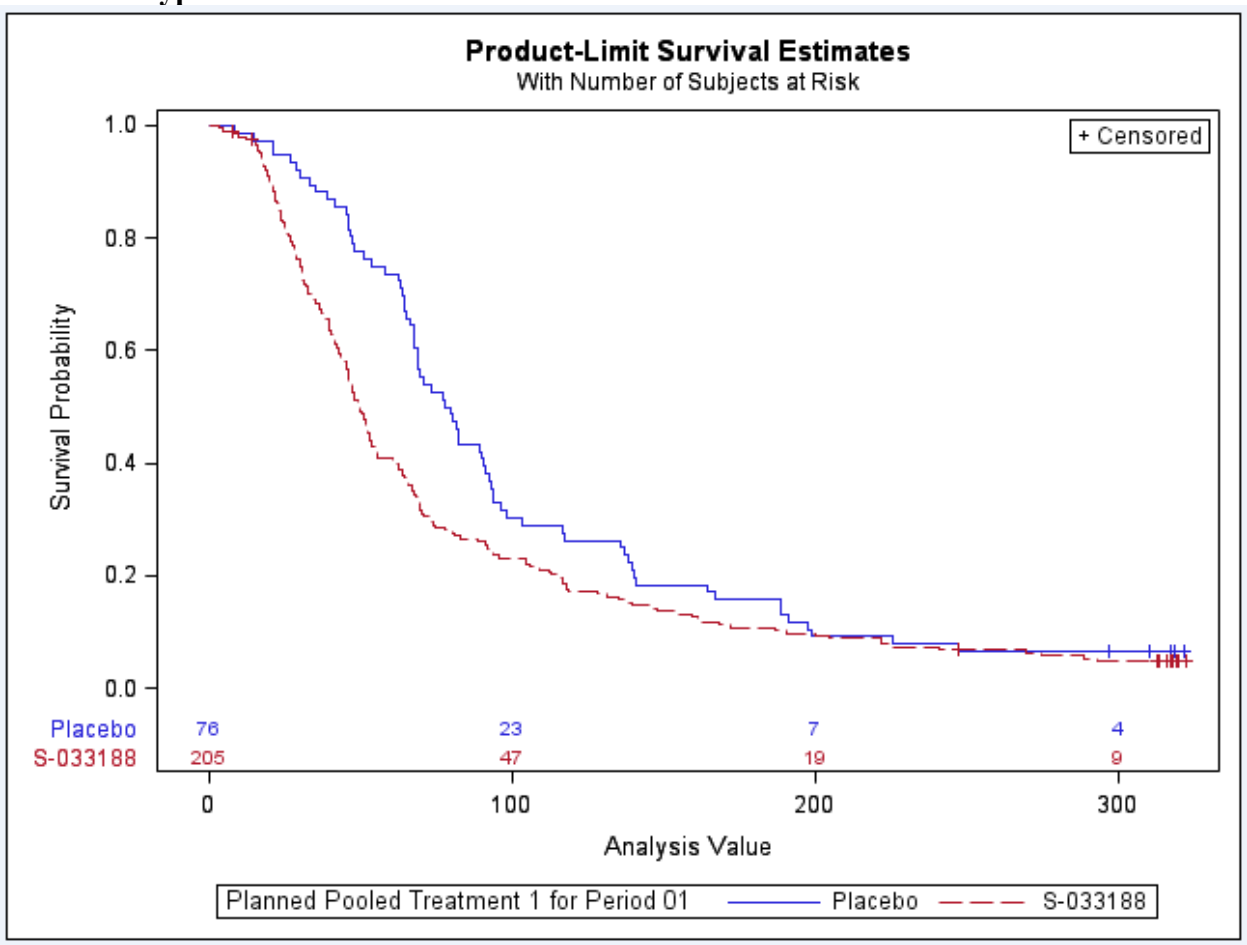
Figure 37: Kaplan-Meier plot for the Time to Alleviation of Symptoms in Subjects with Influenza Type B in Phase 2 and 3 Studies



Gehan Wilcoxon p-value stratified by study, geographic region (Japan vs. U.S.) and TSS (q 11 vs. ≥12) =0.09
Source: Reviewer's analysis

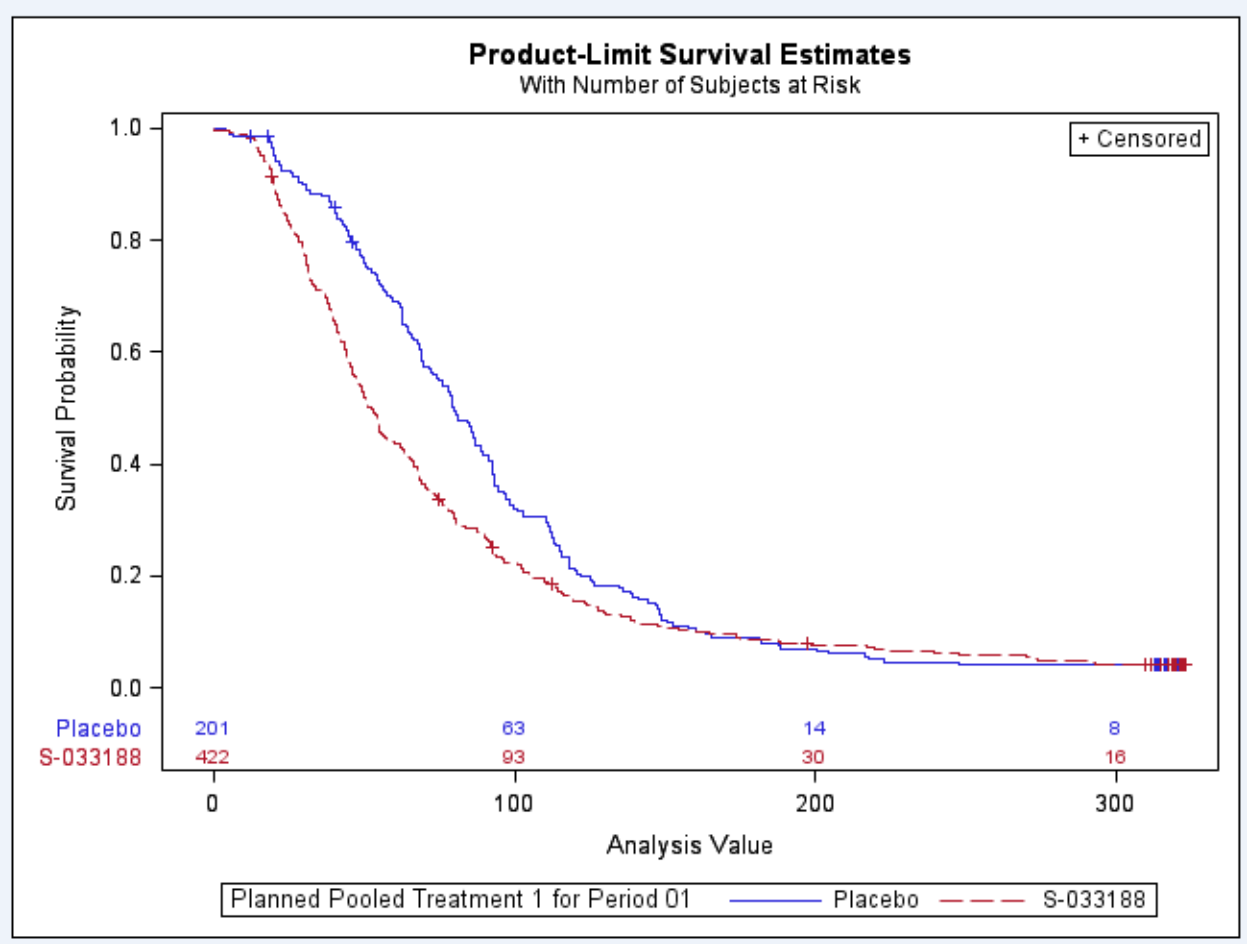
Statistically significant differences ($p<0.001$) were observed for the primary efficacy analysis in favor of S-033188 in for both Influenza A subtypes (H1N1 and H3N2).

Figure 38: Kaplan-Meier plot for the Time to Alleviation of Symptoms in Subjects with Influenza Type A/H1N1 in Phase 2 and 3 Studies



Gehan Wilcoxon p-value stratified by study, geographic region (Japan vs. U.S.) and TSS (q 11 vs. ≥12) =0.001
Source: Reviewer's analysis

Figure 39: Kaplan-Meier plot for the Time to Alleviation of Symptoms in Subjects with Influenza Type A/H3N2 in Phase 2 and 3 Studies

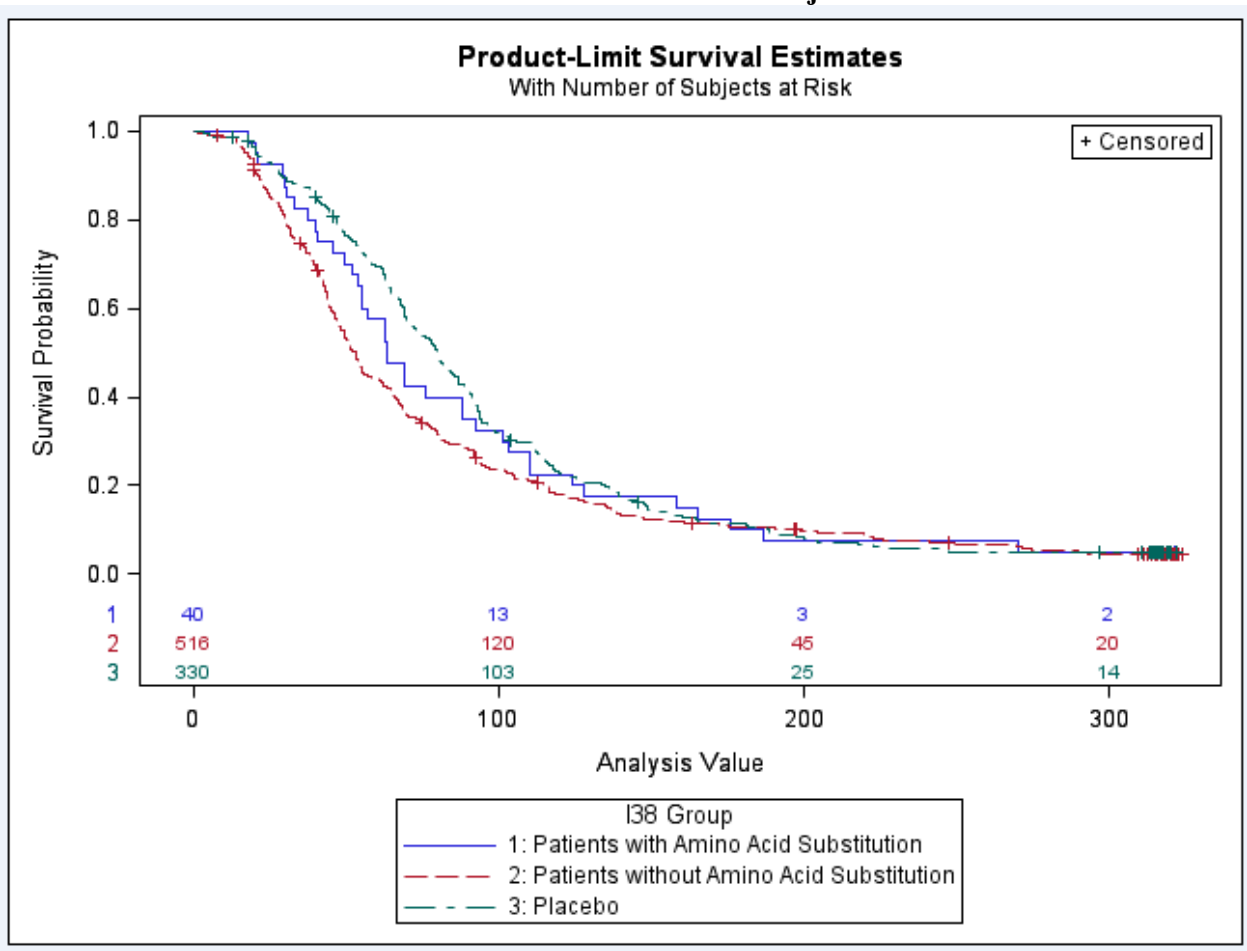


Gehan Wilcoxon p-value stratified by study, geographic region (Japan vs. U.S.) and TSS (q11 vs. ≥12) <0.001

Source: Reviewer's analysis

There was a statistically significant difference ($p<0.001$) for the primary efficacy analysis comparison between S-033188 patients without the amino acid substitution and placebo but no statistically significant difference ($p=0.22$) for the comparison between S-033188 patients with the amino acid substitution and placebo.

Figure 40: Kaplan-Meier Curve of Time to Alleviation of Symptoms in S-033188 subjects with and without Amino Acid Substitutions vs. Placebo subjects in Phase 2 and 3 Studies

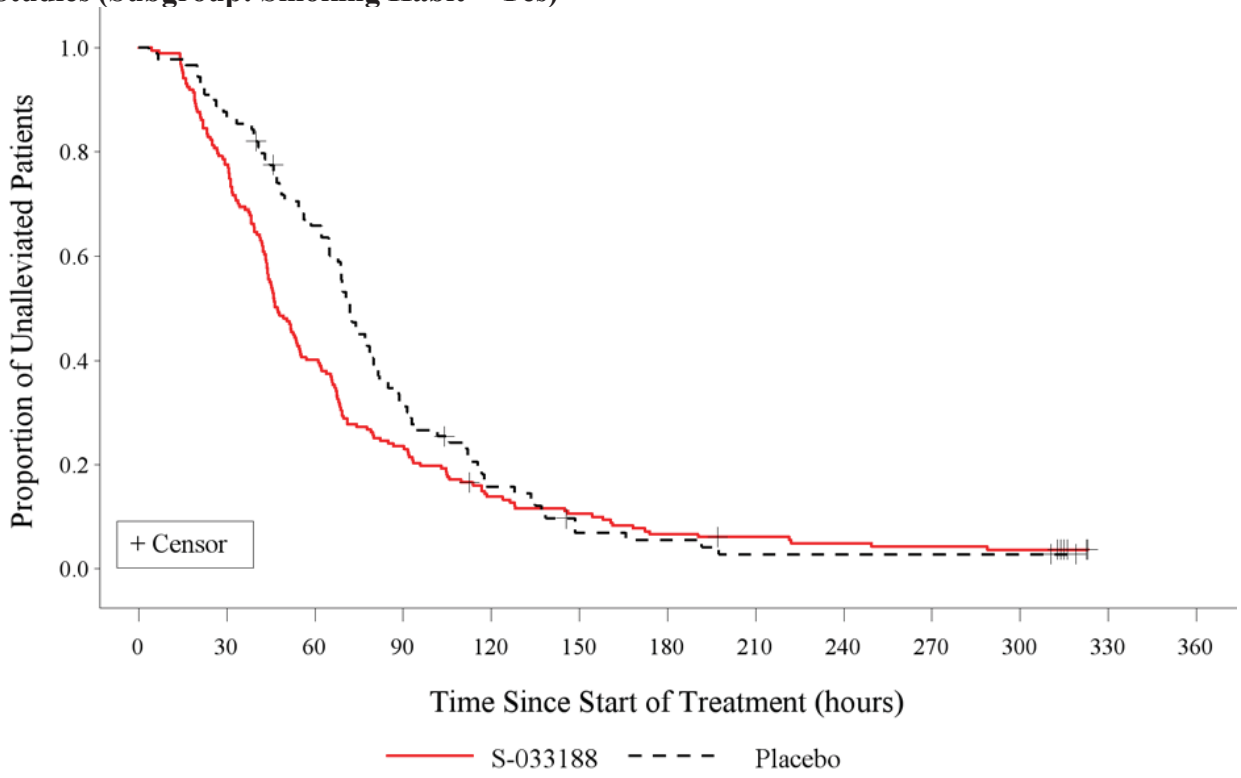


p-value stratified by study, geographic region (Japan vs. U.S.) and TSS (q11 vs. ≥12)
Source: Statistics Reviewer's analysis

Note that the I38X amino acid substitutions that define the subsets analyzed do not account for all treatment-emergent substitution events that could have affected outcomes, although they represent the majority of treatment-emergent resistance events (See the Clinical Virology review for details.)

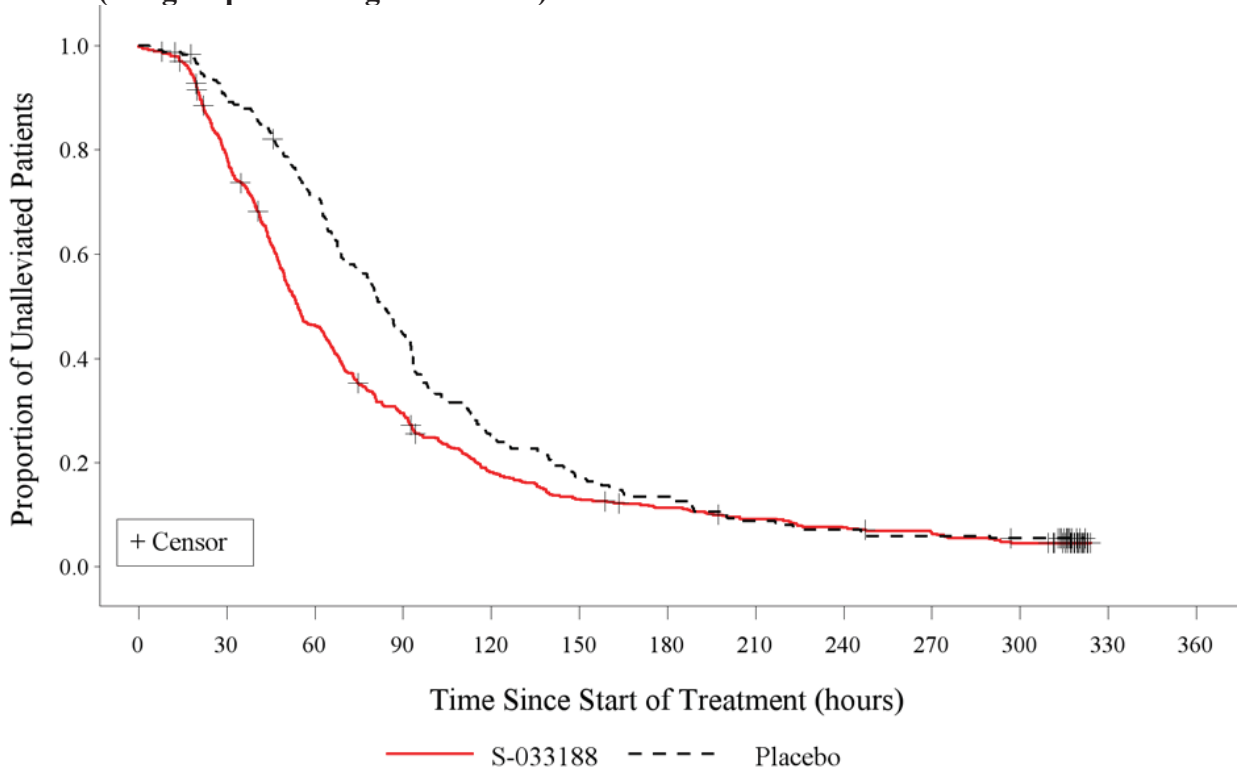
Additional Kaplan-Meier analyses were performed by the applicant for smoking habit in the ISE. Consistent trends appear to exist in both smoking habit strata with shorter TTAS for subjects in the S-033188 treatment group than for placebo subjects.

Figure 41: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Phase 2 and 3 Studies (Subgroup: Smoking Habit = Yes)



Source: Figure 1.1.11 of the ISE, Tables and Figures document

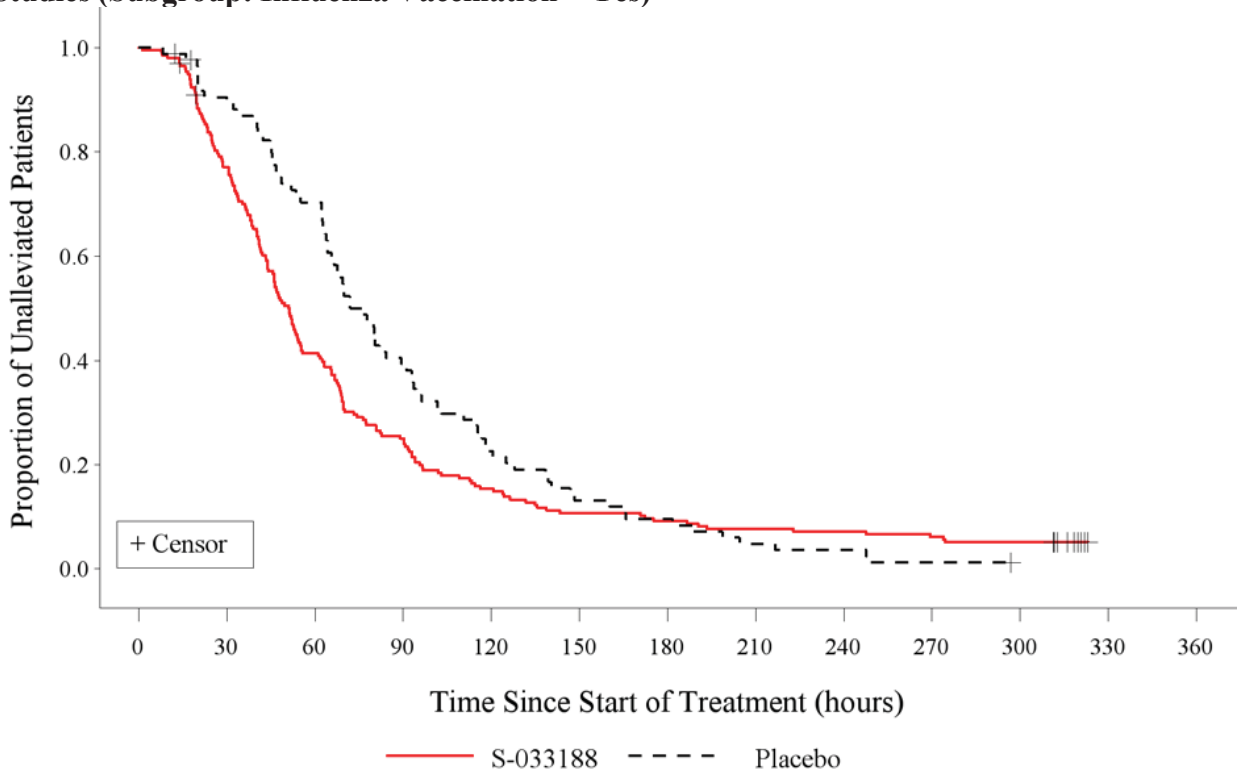
Figure 42: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Phase 2 and 3 Studies (Subgroup: Smoking Habit = No)



Source: Figure 1.1.12 of the ISE, Tables and Figures document

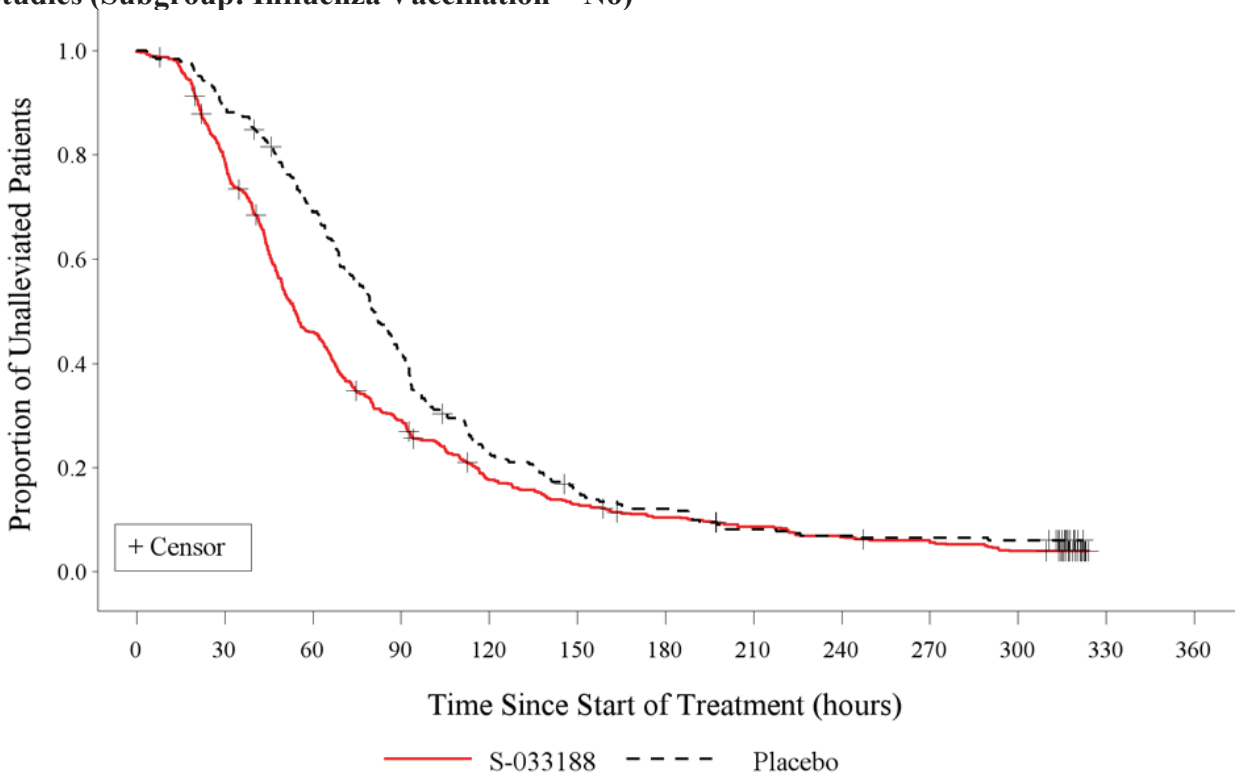
Additional Kaplan-Meier analyses were performed by the applicant for influenza vaccination in the ISE. Consistent trends appear to exist in both of the influenza vaccination strata in with shorter TTAS for subjects in the S-033188 treatment group than for placebo subjects.

Figure 43: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Phase 2 and 3 Studies (Subgroup: Influenza Vaccination = Yes)



Source: Figure 1.1.19 of the ISE, Tables and Figures document

Figure 44: Kaplan-Meier Curve of Time to Alleviation of Symptoms in Phase 2 and 3 Studies (Subgroup: Influenza Vaccination = No)



Source: Figure 1.1.20 of the ISE, Tables and Figures document

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/s/

FRASER B SMITH
09/24/2018

THAMBAN I VALAPPIL
09/24/2018