SYNOPSIS

SPONSOR Vertex Pharmaceuticals Incorporated 130 Waverly Street Cambridge, MA 02139-4242, USA	~~*(For Regulatory Authority Use Only)*~~
NAME OF FINISHED PRODUCT VX-787	
NAME OF ACTIVE INGREDIENT VX-787	
TITLE OF STUDY A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Effects of VX-787 Administered to Adult Volunteers Experimentally Inoculated With Live Influenza Virus	
INVESTIGATOR(S) AND STUDY CENTERS [redacted] MBBCh [redacted] London, [redacted]	
PUBLICATION REFERENCE There were no publications at the time this clinical study report was finalized.	
STUDY PERIOD Study initiation: 19 March 2012 (date first eligible subject signed informed consent form) Study completion: 05 October 2012 (date last subject completed the last scheduled Follow-up Visit)	**PHASE OF DEVELOPMENT** Phase 2a

OBJECTIVES

Primary Objective

To determine the effect of oral administration of VX-787 (administered post inoculation) on the area under the concentration versus time curve (AUC) of viral titers quantified by nasal swab tissue culture in a human challenge model of influenza

Secondary Objectives

To evaluate:

- Safety and tolerability of VX-787 in healthy adult subjects inoculated with live influenza virus
- Safety of the GMP-manufactured influenza virus inoculum strain in susceptible, healthy subjects receiving either VX-787 or placebo
- Influenza viral kinetics from nasal swabs by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR)
- Change and severity of clinical symptoms
- Changes in the sequence of the relevant target region of influenza in nasal swabs
- Pharmacokinetics (PK) of VX-787

[redacted]

METHODOLOGY

This was a randomized, double-blinded, placebo-controlled study of VX-787 in a human challenge model of influenza.

Subjects attended a Screening Visit no more than 49 days before planned viral inoculation, and must have been serosuitable to the challenge virus at the Screening Visit. If there were unexpected operational delays or a subject was qualified but not enrolled in an earlier quarantine session, the subject could have been enrolled without rescreening within 80 days if the Day -2 (or Day -1) laboratory results met eligibility criteria. Subjects were admitted to the quarantine unit on Day -2 (or Day -1, if they were late entries) and were intranasally inoculated with 1.0 mL of a 50% tissue culture infective dose [$TCID_{50}$] of 5.0 to 5.5 $\log_{10}$/mL live influenza A/Wisconsin/67/2005 (H3N2) challenge strain virus on Day 0. Subjects were randomized to either placebo or VX-787 in 1 of 6 quarantine sessions (Table 2-1) and were administered the first dose of placebo or VX-787 at 24 hours after viral inoculation.

Table 2-1 Quarantine Sessions

Quarantine[a]	Randomization of Subjects, N	Day 0	Days 1 Through 5[b]
1, 2, and 3	27 placebo, 16 VX-787[c]	Viral Inoculation (Flu Challenge)	Study drug (100 mg qd)
4	2 placebo, 19 VX-787	Viral Inoculation (Flu Challenge)	Study drug (400 mg qd)
5	2 placebo, 20 VX-787	Viral Inoculation (Flu Challenge)	Study drug (900/600 mg qd[d])
6	2 placebo, 18 VX-787	Viral Inoculation (Flu Challenge)	Study drug (1200/600 mg qd[e])

N: number of subjects; qd: daily

[a] After the first 4 quarantines, an interim analysis was conducted to evaluate efficacy and safety across the 100-mg and 400-mg VX-787 treatment groups and was used to choose dosages for Quarantines 5 and 6.

[b] The first dose of study drug was administered 24 hours after viral inoculation.

[c] Number of the subjects enrolled in the first 3 quarantines. Subjects in each quarantine were randomized to receive VX-787 (Quarantine 1, n = 5; Quarantine 2, n = 6; Quarantine 3, n = 5) or placebo (Quarantine 1, n = 9; Quarantine 2, n = 10; Quarantine 3, n = 8).

[d] The dosage of VX-787 for Quarantine 5 was a single loading dose of 900 mg on Day 1 and 600 mg qd from Days 2 through 5.

[e] The dosage of VX-787 for Quarantine 6 was a single loading dose of 1200 mg on Day 1 and 600 mg qd from Days 2 through 5.

An additional quarantine (#7) with a delayed VX-787 treatment (72 to 96 hours post inoculation) was planned, but was not performed due to logistical issues.

Subjects remained at the study site from admission through Day 8 (the quarantine period). Before discharge from the quarantine facility (Days 7 and 8), 3 doses of oseltamivir were administered to all subjects according to the prescribing information. Subjects completed their course of medication at home (a full 10-dose course).

This medication was given to prevent any potential spread of the challenge virus to subject contacts.

Subjects returned to the clinic approximately 23 days after the last dose of study drug (Day 28 ±3 days) for a Safety Follow-up Visit.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED)

Approximately 140 subjects were planned for enrollment (20 in each of 7 quarantine sessions). A total of 106 subjects were enrolled in 6 quarantine sessions; all 106 were inoculated with influenza virus. Study drug was administered to 104 subjects: 72 subjects received at least 1 dose of VX-787 and 32 subjects received placebo.

PK Set

The PK Set included all subjects who received at least 1 dose of active study drug and had sufficient PK samples collected for the determination of VX-787 parameters (N = 71).

Efficacy Sets

The Full Analysis (FA) Set included all randomized subjects who received at least 1 dose of study drug (VX-787 or placebo) and whose viral concentrations were above or equal to lower limit of quantification (LLOQ) for the $TCID_{50}$ assay at any time point within 48 hours post inoculation, or whose hemagglutination inhibition (HAI) titer raised 4-fold or greater from baseline (Day -1) in the post inoculation period (N = 74).

The Per Protocol (PP) Set included all subjects in the FA Set who did not have major protocol deviations that had an impact on the efficacy analysis (N = 74). Decisions regarding which subjects were included in the PP Set were made before database lock. The PP Set was identical to the FA Set, because there were no major protocol deviations that had an impact on the efficacy analysis.

The Tissue Culture Positive Within 48 Hours Post-Inoculation Set (TCP_{48hr}) included all subjects who received at least 1 dose of study drug (i.e., VX-787 or placebo) and whose viral concentrations were ≥LLOQ for the $TCID_{50}$ assay at any time point within 48 hours after inoculation with the challenge virus (N = 42).

The qRT-PCR Positive Within 48 Hours Post-Inoculation Set (PCR_{48hr}) included all subjects who received at least 1 dose of study drug (i.e., VX-787 or placebo) and whose viral concentrations were ≥LLOQ of the qRT-PCR assay (4 $\log_{10}$ copies/mL) at any time point within 48 hours after inoculation with the challenge virus (N = 39).

The Tissue Culture Positive Within 8 Days Post-Inoculation Set (TCP_{8day}) included all subjects who received at least 1 dose of study drug (i.e., VX-787 or placebo) and whose viral concentrations were ≥LLOQ for the $TCID_{50}$ assay at any time point within 8 days after inoculation with the challenge virus (N = 55).

The qRT-PCR Positive Within 8 Days Post-Inoculation Set (PCR_{8day}) included all subjects who received at least 1 dose of study drug (i.e., VX-787 or placebo) and whose viral concentrations were ≥LLOQ of the qRT-PCR assay (4 $\log_{10}$ copies/mL) at any time point within 8 days after inoculation with the challenge virus (N = 55).

The Sequence Analysis Set included all randomized subjects who received at least 1 dose of study drug (i.e., VX-787 or Placebo) and had at least 1 sequence measurement post treatment initiation (N = 57).

Safety Sets

The Safety Set included all subjects who were inoculated with influenza virus (N = 106).

The Study Drug Safety Set included subjects who were inoculated with influenza virus and received at least 1 dose of VX-787 (N = 72) or placebo (N = 32), for a total of N = 104.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Healthy male and female subjects between 18 to 45 years of age (inclusive), with serosuitability to the inoculating virus, influenza A/Wisconsin/67/2005 (H3N2)

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS

VX-787 (batch numbers 37577.1/A4099-111 and 38581.1/A4099 -111) was orally administered in capsules at 100 mg daily (qd), 400 mg qd, a single loading dose of 900 mg on Day 1 and 600 mg qd on Days 2 through 5 (900/600), or a single loading dose of 1200 mg on Day 1 and 600 mg qd on Days 2 through 5 (1200/600).

DURATION OF TREATMENT

Excluding the Screening Visit, the duration of the study was approximately 30 days (from admittance to the clinic on Day -2 to the Safety Follow-up Visit on Day 28 [± 3 days]). The duration of VX-787 treatment was 5 days (beginning on Day 1 and continuing through Day 5).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS

Placebo (weight-matched microcrystalline cellulose) administered in capsules

CRITERIA FOR EVALUATION

Pharmacokinetics Assessments

Blood samples for VX-787 PK analysis:

Day 1: predose (-1 to 0 hours) and 1, 2, 4, 6, and 12 hours after study drug administration

Days 2 through 4: predose (-1 to 0 hours)

Day 5: predose (-1 to 0 hours) and 1, 2, 4, 6, 12, 24 hours (Day 6), 48 hours (Day 7), and 72 hours (Day 8) after study drug administration

Efficacy Assessments

Viral shedding: Nasal swabs were collected 3 times per day; every 8 hours ± 30 minutes, starting predose on Day 1. Viral loads were measured using tissue culture and qRT-PCR for Days 1 through 7.

Clinical symptoms (diary cards and directed physical examination): Subjects assessed viral inoculation-related signs and symptoms and associated severity (3 times a day, starting on Day -1 or Day -2) using a symptom questionnaire in the subject diary card. Physicians also performed a directed physical examination (DPE) for defined clinical symptoms.

Tissue count and mucus weight: Subjects were given preweighed packets of paper tissues which were collected for each 24 hour period throughout the quarantine period, starting on Day -1, to determine daily mucus weight and number of tissues used.

Virus sequencing: Nasal swab samples were used for analysis of the nucleotide sequence of the PB2 segment of influenza A virus from Days 1 through 7.

Serology: Blood was collected Day-1, Day 8, and at Follow-up Visit (Day 28±3) for analysis of influenza virus A antibodies using HAI assay.

Safety Assessments

Monitoring of adverse events (AEs), clinical laboratory testing (serum chemistry, hematology, coagulation, and urinalysis), vital signs, 12-lead electrocardiograms (ECGs), physical examinations, and spirometry.

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DATA ANALYSIS AND STATISTICAL METHODS

Pharmacokinetic Analyses

The PK Set was used for PK analysis. No formal statistical analysis was performed on PK parameters.

Descriptive statistics for VX-787 concentrations by treatment group and nominal time point were calculated and included arithmetic mean, arithmetic % coefficient of variation (CV%), median, minimum, maximum, number of subjects (N), and arithmetic standard deviation (SD). PK parameters of VX-787 were determined using standard noncompartmental methods. PK parameters included AUC from time of dosing extrapolated to infinity ($AUC_{0-\infty}$), AUC from time of dosing to last time point with a concentration above the lower limit of quantitation ($AUC_{0-tlast}$), maximum observed concentration (C_{max}), time of the C_{max} (t_{max}), and half-life ($t_{1/2}$). AUC was computed using the linear/logarithmic trapezoidal rule and at least 4 quantifiable concentration-time values had to be available.

The PK of VX-787 was summarized in tables and figures.

Efficacy Analyses

The FA Set was used for efficacy analyses.

All primary and secondary endpoints were summarized using descriptive statistics (number of observations, mean, SD, median, minimum values, and/or maximum value).

Primary Endpoint:

The primary efficacy endpoint was AUC of viral shedding by $TCID_{50}$ from Days 1 through 7. A dose response trend test (Jonckheere-Terpstra dose trend test) was performed on the 4 VX-787 treatment groups. Pairwise comparisons using the Wilcoxon rank-sum test were performed for the pooled placebo group (subjects who received placebo in all quarantine periods) with either each individual VX-787 dose group or the pooled VX-787 group (all dosing groups of VX-787).

Secondary Efficacy Endpoints:

- Viral kinetics (median [range] viral AUC calculated by qRT-PCR of nasal swabs, from Day 1through Day 7; mean [SD] duration of viral shedding by tissue culture and qRT-PCR; median [95% confidence interval, CI] peak viral shedding titer by tissue culture and qRT-PCR, and time to resolution from peak viral shedding by tissue culture and qRT-PCR)
- Composite clinical symptom scores (median [range] AUC of composite score from Days 1 through 7; mean [SD] duration of clinical symptoms; median [95% CI] peak composite score). Individual symptom scores were recorded by subjects on diary cards and included 10 symptoms (runny nose, stuffy nose, sneezing, sore throat, earache, malaise, cough, shortness of breath, headache, and muscle and/or joint ache).
- Influenza-like symptom scores (median [range] AUC of composite score from Days 1 through 7; mean [SD] duration of symptoms, and median [95% CI] peak composite score). Individual influenza-like symptoms were recorded by subjects on diary cards and included 7 symptoms (runny nose, stuffy nose, sore throat, malaise, cough, headache, and muscle and/or joint ache).
- Total tissue count and total mucus weight after viral inoculation
- Sequence analysis of the relevant target region of influenza

For the analysis of secondary endpoints, pairwise comparisons of the pooled placebo group with either each individual VX-787 dose group or the pooled VX-787 group were performed using analysis of variance (ANOVA; peak scores, tissue count, and mucus weight), the log-rank test (durations), or the Wilcoxon rank-sum test (viral AUC).

Other Efficacy Endpoints:

Other efficacy endpoints were described using descriptive statistics (number and percentage of observations).

- Individual clinical symptom scores (from diary cards; individual symptom AUC from Days 1 through 7; duration of individual symptom; and peak individual symptom)
- Presence of influenza-like illness (fever, upper respiratory illness, lower respiratory illness, systemic illness), challenge virus-like illness (upper respiratory illness, lower respiratory illness, or systemic illness), laboratory-confirmed challenge virus infection ($\geq$LLOQ [0.8 $\log_{10}$ $TCID_{50}$/mL] or HAI titer more than 4-fold increase from baseline), or challenge virus-like illness with laboratory-confirmed challenge virus infection
- Directed physical examination scores (upper [DPE-URI] or lower [DPE-LRI] respiratory illness scores)
- Serum anti-influenza A virus antibody titer (HAI) on Day -1, Day 8, and the Follow-up Visit

Safety Analyses

Safety analyses were conducted using the Study Drug Safety Set. Descriptive statistics (number of observations, mean, SD, median, minimum values, and maximum values) were used to summarize safety variables, including AEs, clinical laboratory assessments, 12-lead ECG measurements, vital signs, and spirometry. Categorical data were summarized using counts and percentages.

Safety data were analyzed for 2 periods: (1) Viral inoculation period, defined as time from the viral inoculation to first dose of study drug (referred to as post-inoculation AEs), and (2) Post-treatment-initiation period, defined as from first dose of study drug through the Follow-up Visit or Day 28, whichever was later (referred to as AEs).

SUMMARY OF RESULTS

Pharmacokinetics Results

VX-787 exposure (C_{max} and $AUC_{0\text{-}tlast}$) on Day 1 was roughly dose proportional from 100 mg to 400 mg and slightly less than dose proportional from 400 mg to 1200 mg. However, exposure following a 900 mg dose was greater than dose proportional and largely overlapped the exposure observed following a 1200 mg dose. Similar to Day 1, VX-787 exposure on Day 5 was roughly dose proportional from 100 mg to 400 mg. The trend in non-dose proportionality for the 900/600-mg and 1200/600-mg dose groups observed on Day 1 appeared to continue at Day 5, despite the same maintenance dose of 600 mg qd on Days 2 through 5. Exposure in the 1200/600-mg dose group was less than dose proportional and exposure in the 900/600-mg group was greater than dose proportional relative to 400-mg group. Exposure in the 900/600-mg dose group largely overlapped that of the 1200/600-mg dose group, with a 1.7-fold higher mean C_{max} and $AUC_{0\text{-}24h}$ on Day 5. Across Days 2 through 6 mean trough concentrations largely overlapped in the 900/600-mg (159 to 239 ng/mL) and 1200/600-mg (143 to 162 ng/mL) groups. The mean terminal elimination half-life ranged from 16 to 45 hours across the cohorts and was longer and more variable in the 900/600-mg dose group relative to the others. Intersubject variability (%CV) was similar on Days 1 and 5, ranging from 29% to 67% for AUC and 46% to 94% for C_{max}.

Efficacy Results

Key efficacy results are summarized in Table 2-2.There was a statistically significant effect on the primary endpoint, AUC of viral shedding by tissue culture (dose response trend of reduction; $P = 0.036$), supported by the similar result for the analysis by qRT-PCR ($P = 0.031$). Compared with the pooled placebo group, the VX-787 1200/600-mg group also demonstrated a statistically significant reduction of the AUC of viral shedding by tissue culture ($P = 0.010$) and by qRT-PCR ($P = 0.014$); furthermore, this group had a statistically significant reduction in the duration of composite clinical symptoms ($P = 0.001$), the AUC of influenza-like symptoms ($P = 0.040$), and the duration of influenza-like symptoms ($P<0.001$). Compared with the pooled placebo group, there was no statistically significant difference in the percentage of subjects with sero-conversion in the pooled VX-787 group ($P = 0.828$).

Table 2-2 Summary of Key Efficacy Results, Full Analysis Set

Endpoint [units]		Pooled Placebo (N = 22)	VX-787 100 mg (N = 12)	VX-787 400 mg (N = 12)	VX-787 900/600 mg (N = 14)	VX-787 1200/600 mg (N = 14)	VX-787 Pooled (N = 52)
Viral Shedding by Tissue Culture[a]	AUC, median (range) [log_{10} $TCID_{50}$/mL*Day]	5.85 (0.0, 17.1)	1.25 (0.0, 16.1)	0.70 (0.0, 18.0)	3.20 (0.0, 16.1)	0.35 (0.0, 8.4)	0.65 (0.0, 18.0)
	P Value[b]	NA	0.269	0.206	0.723	**0.010**	0.057
	Duration, median (95%CI) [Day]	2.38 (0.03, 4.63)	0.96 (0.00, 3.39)	1.60 (0.00, NA)	2.71 (0.00, 4.68)	0.00 (0.00, 1.33)	0.71 (0.00, 2.43)
	P Value[d]	NA	0.331	0.831	0.893	0.169	0.487
	Peak, mean (SD) [log_{10} $TCID_{50}$/mL]	3.13 (1.878)	2.09 (2.209)	1.73 (1.976)	2.68 (2.201)	1.00 (1.365)	1.87 (2.002)

	***P* Value[c]**	NA	0.139	**0.049**	0.505	**0.002**	**0.015**
Viral Shedding by qRT-PCR[e]	**AUC, median (range) [log_{10} copies/mL*Day]**	18.40 (0.0, 42.1)	6.05 (0.0, 41.9)	4.90 (0.0, 36.9)	10.65 (0.0, 37.1)	0.45 (0.0, 24.7)	3.45 (0.0, 41.9)
	***P* Value[b]**	NA	0.218	0.306	0.821	**0.014**	0.075
	Duration, median (95%CI) [Day]	2.91 (0.03, 5.35)	0.96 (0.00, 3.39)	1.36 (0.00, NA)	2.39 (0.00, 5.01)	0.00 (0.00, 0.66)	0.71 (0.00, 2.38)
	***P* Value[d]**	NA	0.318	0.753	0.602	0.084	0.240
	Peak, mean (SD) [log_{10} copies]	5.36 (3.108)	4.36 (3.379)	3.90 (3.514)	5.08 (3.097)	2.37 (2.861)	3.91 (3.276)
	***P* Value[c]**	NA	0.380	0.202	0.794	**0.007**	0.081
Composite Clinical Symptom	**AUC, median(range) [Grade*Day]**	4.85 (0.0, 23.5)	1.85 (0.0, 25.3)	4.70 (0.0, 16.0)	1.75 (0.0, 32.3)	1.95 (0.0, 5.5)	2.15 (0.0, 32.3)
	***P* Value[b]**	NA	0.422	0.694	0.595	0.083	0.211
	Duration, median (95%CI) [Day]	3.69 (2.04, 4.73)	3.21 (0.03, 5.43)	3.34 (1.28, 4.63)	2.69 (0.00, 4.61)	1.88 (0.00, 2.24)	2.34 (1.87, 3.06)
	***P* Value[d]**	NA	0.946	0.994	0.686	**0.001**	0.355
	Peak, mean (SD) [Grade]	3.91 (3.637)	3.17 (3.881)	2.83 (2.167)	3.71 (4.232)	1.50 (1.286)	2.79 (3.158)
	***P* Value[c]**	NA	0.532	0.366	0.863	**0.036**	0.187
Influenza-like Symptom	**AUC, median(range) [Grade*Day]**	4.05 (0.0, 17.7)	1.85 (0.0, 21.3)	3.80 (0.0, 14.0)	1.75 (0.0, 28.6)	1.75 (0.0, 4.4)	2.05 (0.0, 28.6)
	***P* Value[b]**	NA	0.363	0.617	0.595	**0.040**	0.149
	Duration, median (95%CI) [Day]	3.69 (2.04, 4.73)	3.21 (0.00, 5.40)	3.34 (1.28, 4.63)	2.69 (0.00, 4.61)	1.88 (0.00, 2.24)	2.34 (1.87, 3.00)
	***P* Value[d]**	NA	0.957	0.994	0.653	**<0.001**	0.342
	Peak, mean (SD) [Grade]	3.41 (3.003)	2.75 (3.361)	2.42 (1.832)	3.21 (3.534)	1.36 (1.216)	2.42 (2.689)
	***P* Value[c]**	NA	0.511	0.323	0.838	**0.034**	0.168
Serology[f]	**Sero-conversion, n/N (%)**	21/32 (66%)	11/16 (69%)	9/19 (47%)	13/19 (68%)	12/18 (67%)	45/72 (63%)
	***P* Value**	NA	>0.999	0.247	>0.999	>0.999	0.828

AUC: area under the value versus time curve; CI: confidence interval; NA: not applicable; qRT-PCR: quantitative reverse transcriptase polymerase chain reaction; SD: standard deviation; $TCID_{50}$: 50% tissue culture infective dose

Note: Statistically significant *P* values (*P*<0.05) are in bold font.

[a] *P* = 0.036 for the dose response trend of AUC from Jonckheere-Terpstra trend test

[b] *P* value calculated from Wilcoxon rank-sum test

[c] *P* value calculated from ANOVA

[d] *P* value calculated from log-rank test

[e] *P* = 0.031 for the dose response trend of AUC from Jonckheere-Terpstra trend test

[f] Sero-conversion defined as ≥4-fold increase in anti-influenza antibody titer at Follow-up Visit compared with baseline. *P* value calculated using Fisher's Exact Test

Similar results for viral shedding were also observed for the subgroup of subjects in the FA Set with

influenza-positive tissue culture within 48 hours post inoculation. The dose-response trend test in AUC of viral shedding by tissue culture and qRT-PCR and the comparison of the VX-787 1200/600-mg group with the pooled placebo were statistically significant (Table 2-3).

Table 2-3 Summary of Key Efficacy Results for Subgroup of Full Analysis Set Subjects With Influenza Positive Tissue Culture Within 48 Hours Post Inoculation

Effects [units]		Placebo Pooled (N = 11)	VX-787 100 mg (N = 5)	VX-787 400 mg (N = 7)	VX-787 900/600 mg (N = 11)	VX-787 1200/600 mg (N = 8)	VX-787 Pooled (N = 31)
Viral Shedding by Tissue Culture[a]	**AUC, median (range) [log_{10} $TCID_{50}$/mL*Day]**	11.1 (1.1, 17.1)	5.90 (1.8, 16.1)	6.30 (0.6, 18.0)	6.10 (0.1, 16.1)	1.65 (0.3, 8.4)	5.20 (0.1, 18.0)
	***P* Value**	NA	0.659	0.378	0.305	**<0.001**	0.062
Viral Shedding by qRT-PCR[b]	**AUC, median (range) [log_{10} copies/mL*Day]**	25.3 (3.5, 42.1)	15.0 (8.6, 41.9)	15.8 (0.0, 36.9)	19.8 (0.0, 37.1)	2.40 (0.0, 24.7)	13.5 (0.0, 41.9)
	***P* Value**	NA	0.231	0.355	0.277	**0.011**	**0.039**

AUC: area under the value versus time curve; qRT-PCR: quantitative reverse transcriptase- polymerase chain reaction; $TCID_{50}$: 50% tissue culture infective dose

[a] $P = 0.008$ for the dose response (Jonckheere-Terpstra dose trend test). Individual *P* values were calculated using the Wilcoxon rank-sum test.

[b] $P = 0.005$ for the dose response (Jonckheere-Terpstra dose trend test). Individual *P* values were calculated using the Wilcoxon rank-sum test.

Viral Sequencing Results

The amino acid substitution M431I in the RNA-dependent RNA polymerase subunit PB2, which previously has been associated with decreased sensitivity to VX-787 in in vitro studies, was observed in 4 subjects treated withVX-787. This mutation was observed at multiple time points in 2 subjects, and at a single time point in 2 subjects.

Safety Results

Safety analyses used the Study Drug Safety Set (N=104; n = 32, pooled placebo; n = 72, pooled VX-787).

- VX-787 was generally safe and well tolerated. There were no SAEs or AEs leading to discontinuation of study drug.
- Influenza-like illness was the most frequent AE (pooled placebo, 12/32, 37.5%; pooled VX-787, 34/72, 42.2%), as expected due to viral inoculation.
- Adverse events that occurred in ≥10% of subjects and ≥10% difference in the pooled VX-787 group than in the pooled placebo group were decreased blood phosphorus level (0%, placebo; 18.1%, VX-787), rhinorrhea (18.8%, placebo; 4.2%, VX-787), and nasal congestion (15.6% placebo; 1.4%, VX-787).
- The majority of AEs that occurred in subjects treated with VX-787 did not exceed mild or moderate in severity. Eight severe AEs occurred among 5 subjects (decreased blood phosphorus, [redacted]; increased blood creatine kinase, [redacted]; increased blood myoglobin, [redacted]; and severe headache, [redacted]). [redacted]
- Increased ALT was observed in some subjects (placebo, 15.6%; VX-787, 13.9%). Six subjects had increases of >2 times the ULN with complete resolution on follow-up [redacted]

- Both ALT elevation and serum phosphate decrease have been previously described in influenza and upper respiratory infections. Evidence of infection with challenge virus (sero-conversion or tissue culture positive) was observed in 13 of 17 subjects with an AE of increased ALT or AST, and 13 of 16 subjects with decreased blood phosphorous. Liver enzyme abnormalities have also been observed following administration of oseltamivir, and the ALT elevation AE occurred on or after the date that the first dose of oseltamivir was administered in 12 of the 17 subjects with the increased ALT AE.
- There was no evidence of other clinically meaningful trends in the clinical chemistry, hematology, coagulation profiles, ECG, or spirometry measurements for any of the VX-787 dose groups.

CONCLUSIONS

Pharmacokinetics

- VX-787 exposure was roughly dose proportional from 100 mg to 400 mg on Days 1(single dose) and 5 (multiple dose), while exposure was greater than dose proportional in the 900/600-mg dose group and less than dose proportional in the 1200/600--mg group. Exposure in the 900/600-mg and 1200/600-mg dose groups largely overlapped throughout the 5 days of dosing.
- After reaching steady-state on Day 3, mean trough (predose) VX-787 concentrations were ~100 ng/mL in the 400-mg dose group. Across Days 2 through 6, mean trough concentrations were similar in the 900/600-mg (159 to 239 ng/mL) and 1200/600-mg (143 to 162 ng/mL) groups.

Efficacy

VX-787 was effective in decreasing viral shedding in subjects with an active influenza A infection, with a concomitant reduction in symptoms.

- A statistically significant dose response trend was observed on the AUC of viral shedding by tissue culture assay ($P = 0.036$) and qRT-PCR ($P = 0.031$).
- The 1200/600-mg treatment group had a statistically significant reduction of the AUC of viral shedding by tissue culture ($P = 0.010$) and by qRT-PCR ($P = 0.014$) compared with placebo.
- The 1200/600-mg treatment group had a statistically significant reduction of the AUC ($P = 0.040$), peak ($P = 0.034$), and duration ($P < 0.001$) of patient-reported influenza-like symptom scores compared with placebo.
- The 1200/600-mg treatment group had a statistically significant decrease in the duration ($P = 0.001$) of patient-reported composite clinical symptom score compared with placebo.

Safety

VX-787 was generally safe and well tolerated. There were no SAEs or AEs leading to discontinuation of the study drug.

These results suggested that VX-787, alone or in combination with other antivirals, has the potential to be a novel treatment for patients with influenza A infection.

Date of Report:

15 May 2013