SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec BVBA **Trade Name**: - **Indication**: Chronic hepatitis C virus infection	**Drug Substance**: VX-950 (telaprevir) **Trial no**.: VX-950-TiDP24-C135 **Clinical Phase**: I
Title: A Phase I, open-label, single-sequence drug-drug interaction trial in subjects on stable methadone maintenance therapy, to investigate the potential interaction between telaprevir 750 mg q8h and methadone, at steady-state	
Investigator: E. Sellers, MD, PhD, Kendle Early Stage, 720 King Street West, 7th Floor, Toronto, Ontario, Canada, M5V 2T3	**Country**: Canada
Trial Period: Start: 31-Jul-2009 End: 16-Dec-2009	**No. of Investigators**: 1 **No. of Subjects**: 16

Objectives:

The primary objective of the trial was to evaluate the effect of steady-state telaprevir 750 mg every 8 hours (q8h) on the steady-state pharmacokinetics of R- and S-methadone.

Secondary objectives of the trial were to evaluate the potential effect of telaprevir on the pharmacodynamic effects of methadone therapy, to evaluate the steady-state pharmacokinetics of telaprevir 750 mg q8h in subjects on stable methadone maintenance therapy in comparison with historical controls, and to evaluate the short-term safety and tolerability of coadministration of telaprevir and methadone in subjects on stable methadone maintenance therapy.

Design:

This was a Phase I, open-label, single-sequence drug-drug interaction trial in subjects on stable methadone maintenance therapy to investigate the potential interaction between telaprevir 750 mg every 8 hours (q8h) and methadone, at steady-state. Telaprevir is being investigated for the treatment of chronic hepatitis C virus (HCV) infection.

It was planned to enroll 16 subjects who were on stable methadone maintenance therapy.

Telaprevir 750 mg q8h was added for 7 days to subjects' current methadone therapy. The methadone dosage was not to be changed from screening until Day 7 (inclusive).

Full 24-hour pharmacokinetic profiles of both isomers of methadone (R-methadone and S-methadone) were determined on Day -1 (methadone alone) and on Day 7 (methadone plus telaprevir). Profiles of both isomers were determined as R-methadone is mainly responsible for the opioid effect and S-methadone has been linked to the QTc prolongation effect of methadone. A full 8-hour pharmacokinetic profile of telaprevir was determined on Day 7 (methadone plus telaprevir).

All intakes of methadone (Day -14 until Day 8) and telaprevir (Day 1 until Day 7) were supervised. From Day -2 until Day 8, methadone was taken after completion of breakfast, immediately after the morning dose of telaprevir, if applicable. Telaprevir was taken with food.

Pharmacodynamic assessments of the symptoms of methadone withdrawal (by means of the Short Opiate Withdrawal Scale [SOWS], Desires for Drugs Questionnaire [DDQ], and pupillometry) were performed on Day -7 and daily from Day -2 until Day 7, within 2 hours before the intake of methadone. On Days -1, 2, 4, and 7, pupillometry was also performed 2 and 4 hours after intake of methadone.

Safety and tolerability were evaluated throughout the trial.

Subject Selection

Inclusion Criteria:

1. Male or female, aged between 18 and 55 years of age, extremes included.
2. Females were to be post-menopausal for at least 2 years (amenorrheal for at least 3 years), or were to have undergone bilateral tubal ligation (or other permanent birth control methods), or hysterectomy (total), or oophorectomy (bilateral). A pregnancy test performed at screening had to be negative for females (not applicable for females with hysterectomy or oopherectomy).
3. Signed Informed Consent Form (ICF) voluntarily before the first trial-related activity.
4. Subjects were to be receiving once daily (q.d.) oral methadone maintenance therapy at a stable individualized dose of 30 to 130 mg q.d. for at least 2 weeks prior to screening, formulated as commercially available tablets or solution.
5. The subject was to agree:
   - not to change the current methadone dose from screening until Day 7 included;
   - to have a daily observed and documented methadone intake from Day –14 until Day 8 and a daily observed and documented telaprevir intake from Day 1 until Day 7.
6. A body mass index (BMI) of 18.0 to 30.0 kg/m2, extremes included, at screening.
7. The subject had to have obtained approval for his/her participation in this trial from his/her addiction physician. Furthermore, the addiction physician had to agree to provide medical care for the subject after discharge from trial center.
8. General medical condition, in the investigator's opinion, was not to interfere with the assessments and the completion of the trial.
9. Otherwise healthy on the basis of a physical examination, medical history (except drug abuse), electrocardiogram (ECG), vital signs and the results of blood biochemistry, blood coagulation and hematology tests and a urinalysis carried out at screening.
10. Subject was willing and able to refrain from the concomitant use of any disallowed medications from Day –14 until Day 8.
11. Able to comply with the protocol requirements and restrictions.

Exclusion Criteria:

1. History of any illness that, in the opinion of the investigator or the subject's general practitioner or addiction physician, could confound the results of the trial or pose an additional risk in administering study drug(s) to the subject. This could include but was not limited to: a history of relevant drug or food allergies; history of cardiovascular or central nervous system disease; history or presence of clinically significant pathology; or history of mental disease.
2. Consumption of herbal medications or dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, and grapefruit or grapefruit juice, apple juice or orange juice within 14 days before Day –1.
3. Current alcohol use, which, in the assessment of the investigator, could compromise subject's safety or compliance with the study protocol procedures.
4. Test positive for drugs of abuse such as cocaine, amphetamines, barbiturates, benzodiazepines, or opiates on Day -2 unless explained by allowed concomitant medications.

   Note: Positive drug screening tests for the following did not result in exclusion of a subject:
   - cannabinoids, when used via inhalation (smoking);
   - temazepam, oxazepam, lorazepam, chlordiazepoxide, and codeine, when used in a prescribed dose.
5. Participation in a clinical study involving administration of an investigational drug within 60 days or 5 half-lives (whichever was longer) prior to the screening visit.
6. Donation of blood or having had a significant loss of blood within 2 months (500 mL or more), or donation of more than 1 unit of plasma within 7 days before the first dose of telaprevir (Day 1).

Exclusion Criteria (Cont'd):

7. Hemoglobin level of <12.0 g/dL at screening.
8. Positive test for any of the following infectious disease tests: hepatitis A infection (confirmed by hepatitis A antibody immunoglobulin M [IgM]), hepatitis B antigen (HBsAg), hepatitis C infection (confirmed by hepatitis C virus antibody [HCVAb]), human immunodeficiency virus type 1 antibody (HIV1Ab), or human immunodeficiency virus type 2 antibody (HIV2Ab). Note: In case of a positive HCV antibody test, a PCR test could be performed to assess if the subject was HCV ribonucleic acid (RNA) negative. HCV RNA negative subjects were allowed to participate in the trial.
9. Male subject with female partner planning to become pregnant during the trial or within 90 days of the last dose of telaprevir.
10. Having participated previously in a trial with telaprevir.

Treatment	**Telaprevir**	**Methadone**
Concentration	375 mg	Commercially available solution, final dose preparation done by the on-site pharmacist
Dosage Form (F No.)	Tablet (F004)	Solution
Usage	Oral	Oral
Batch Number	3066476R	-
Dose Regimen	Screening phase:	subjects included in the trial were on stable oral methadone therapy (individualized dose of 30 to 130 mg q.d.) for at least 2 weeks prior to screening.
	Run-in phase:	supervised intake of methadone at stable individualized dose of 30 to 130 mg q.d. from Day -14 to Day -1.
	Methadone + telaprevir phase:	supervised intake of methadone at stable individualized dose of 30 to 130 mg q.d. + treatment with telaprevir 750 mg q8h from Day 1 to Day 7.
	Follow-up phase:	continued intake of methadone at individualized dose for an additional 30 to 32 days.
Duration of Treatment	telaprevir and methadone were coadministered for 7 days.	
Duration of Trial	Screening phase: maximum 21 days Run-in phase: 14 days Methadone + telaprevir phase: 7 days Follow-up phase: 30 to 32 days	
Disallowed Medication	All investigational drugs (except telaprevir) were disallowed from 60 days or 5 half-lives (whichever was longer) prior to the screening visit until the end of the trial. Any other medication the subject was using had to be discussed prior to inclusion with the sponsor on a case-by-case basis, except for ibuprofen and paracetamol (acetaminophen). Preferably, concomitant therapy that was not disallowed was not to be changed (started, stopped, or change in regimen) between Day -14 and Day 8, except for ibuprofen and paracetamol. However, if there was a need to change (start, stop, or change in regimen) concomitant therapies during the trial, dosage and regimen had to be discussed in advance with the sponsor. Ibuprofen and paracetamol could be used up to 3 days before the first intake of telaprevir. After that, the clinical investigator could permit the use of ibuprofen or paracetamol (from 3 days before the first intake of telaprevir until Day 7) at no more than 1200 mg per day for ibuprofen, and at no more than 2000 mg per day for paracetamol. In case of rash, the use of medications including topical corticosteroids and the topical and systemic antihistaminic agents diphenhydramine, fexofenadine, hydroxyzine, levocetirizine, or desloratadine, were allowed at the investigator's discretion.	

Assessments	
Pharmacokinetics	Blood samples for determination of telaprevir plasma concentrations were taken on Days 2, 3, 4, 5, and 6 (immediately before intake of telaprevir), on Day 7 (immediately before morning intake of telaprevir and at several time points after morning intake of telaprevir), and at time of dropout or the following morning. Blood samples for determination of R- and S-methadone plasma concentrations were taken on Days -4, -3, -2, 1, 2, 3, 4, 5, 6, and 8 (immediately before intake of methadone), on Days -1 and 7 (immediately before intake of methadone and at several time points after intake of methadone), and at time of dropout or the following morning.
Safety Adverse Events	Adverse events (AEs) were checked at every visit and reported from signing of the ICF onwards until the last trial-related visit. Management of rash was at the discretion of the investigator and was to follow generally accepted medical standards taking into account the protocol-defined procedures.
Clinical Laboratory	Blood samples for biochemistry and hematology measurements were taken at screening; on Days -14, -1, 1, 3, 5, 7, and 8 (predose); 7 days and 30, 31, or 32 days after last study medication intake or dropout; and at time of dropout or the following morning. Urine samples for urinalysis were taken at screening; on Days -14, -7, -4, -3, -2, -1, 1, 2, 3, 4, 5, 6, 7, and 8; 7 days and 30, 31, or 32 days after last study medication intake or dropout; and at time of dropout or the following morning.
Cardiovascular Safety	ECG was measured at screening; on Days -1 and 7 (predose and 4 hours after methadone intake [and telaprevir intake, if applicable]); on Days 1, 3, 5, and 8 (predose); 7 days after last study medication intake or dropout; and at time of dropout or the following morning. Vital signs (heart rate and blood pressure) were measured at screening; on Days -14, 1, 3, 5, and 8 (predose); on Days -1 and 7 (predose and 2 and 4 hours after methadone intake [and telaprevir intake, if applicable]); on Days 2 and 4 (2 and 4 hours after methadone and telaprevir intake); 7 days and 30, 31, or 32 days after last study medication intake or dropout, and at time of dropout or the following morning.
Pharmacodynamic Assessments of Methadone	Pharmacodynamic assessments of the symptoms of methadone withdrawal by means of the SOWS, DDQ, and pupillometry were performed on Day -7 and daily from Day -2 until Day 7 (within 2 hours before the intake of methadone). On Days –1, 2, 4, and 7, pupillometry was also performed 2 and 4 hours after intake of methadone.
Physical Examination	A physical examination was performed at screening; on Days -2, 1, and 6 (immediately before intake of methadone); 7 days and 30, 31, or 32 days after last study medication intake or dropout; and at time of dropout or the following morning.

Statistical Methods	All analyses, except for the pharmacokinetic analysis, were performed on the full analysis (FA) set, which was defined as all enrolled subjects who used telaprevir at least once. The pharmacokinetic analysis was performed on all enrolled subjects who took supervised methadone at least once. All demographic and other initial subject characteristics were tabulated and analyzed descriptively. Descriptive statistics were calculated for the plasma concentrations of telaprevir, and R- and S-methadone at each time point, and for the derived pharmacokinetic parameters. For each subject, plasma concentration-time data were graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and graphs with combined individual plasma concentration-time profiles were produced. Pharmacokinetic parameters were subjected to an exploratory graphical analysis including various transformations in order to get a general overview. To assess the effect of telaprevir on R- and S-methadone, statistical analysis was performed for R- and S-methadone comparing Day 7 (test: methadone + telaprevir) versus Day -1 (reference: methadone alone). The primary pharmacokinetic parameters for R- and S-methadone were the minimum plasma concentration in the dosing interval (C_{min}), the maximum plasma concentration (C_{max}), and the area under the plasma concentration-time curve from time of administration up to 24 hours postdose (AUC_{24h}) on the logarithmic scale. Additionally, statistical analysis was performed for the ratio of the individual AUC_{24h} values of S-methadone and R-methadone (Ratio $AUC_{24h,\ S-/\ R-methadone}$) comparing Day 7 (test: methadone + telaprevir) versus Day -1 (reference: methadone alone). All observations for test and reference, paired and unpaired, were included in the statistical analysis. The least square (LS) means of the primary parameters for each treatment group (day) were estimated with a linear mixed effects model, controlling for treatment as a fixed effect, and subject as a random effect. A 90% confidence interval (CI) was constructed around the difference between the LS means of test and reference. Both the difference between the LS means and the 90% CIs were retransformed to the original scale. Telaprevir pharmacokinetic parameters were summarized with descriptive statistics, and compared to historical controls. Predose plasma concentrations of telaprevir in the morning of Days 2 to 7 were compared graphically to assess the achievement of steady-state conditions of telaprevir on Day 7. Predose plasma concentrations of R- and S-methadone on Days -4 to -1 and on Days 2 to 7 were compared graphically to assess the achievement of steady-state conditions of R- and S-methadone on Days -1 and 7, respectively. Safety data summaries were provided for AEs, laboratory, ECG, vital signs, and physical examination data. Changes versus reference were determined for laboratory, ECG, and vital signs assessments. The reference assessment time point was Day -14 (or earlier if the assessment on Day -14 was missing) for all assessments during the run-in phase and the follow-up phase. The last assessment during the run-in phase was the reference assessment time point for all assessments during the methadone + telaprevir phase. The pharmacodynamic assessment of methadone was evaluated by means of descriptive statistics (pupillometry) and frequency tabulations (SOWS and DDQ).

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics - Subject Disposition	FA Set[a] N = 16
Number of subjects treated (male/female)	14/2
Age: median (range), years	33.0 (23; 45)
BMI: median (range), kg/m^2	25.25 (20.7; 30.0)
Total number (%) of subjects who prematurely discontinued the trial	1 (6.3)[b]
Reason: withdrawal of consent	1 (6.3)[b]

N: number of subjects with data in FA set

[a] All analyses, except for the pharmacokinetic analysis, were performed on the FA set, i.e., all enrolled subjects who used telaprevir at least once. The pharmacokinetic analysis was performed on all subjects who were enrolled in the trial and took supervised methadone at least once. In total, 18 subjects took supervised methadone at least once, i.e., the 16 subjects from the FA set and 2 additional subjects who withdrew consent before the first intake of telaprevir.

[b] This subject prematurely discontinued the trial during treatment with methadone and telaprevir.

Pharmacokinetics of R-Methadone **Time Point Reference/Test** Pharmacokinetic Parameter: mean ± SD, t_{max}: median (range)	Individualized Methadone Therapy (Reference)	Individualized Methadone Therapy + 750 mg Telaprevir q8h (Test)
Day -4/Day 4		
N	18	16
C_{0h}, ng/mL	143.0 ± 53.28	108.1 ± 34.76
Day -3/Day 5		
N	18	15
C_{0h}, ng/mL	145.2 ± 58.11	108.8 ± 32.95
Day -2/Day 6		
N	17	15
C_{0h}, ng/mL	142.7 ± 46.43	108.4 ± 35.46
Day -1/Day 7		
N	17	15
C_{0h}, ng/mL	146.3 ± 49.78	96.98 ± 31.38
C_{min}, ng/mL	139.2 ± 45.31	93.47 ± 28.63
C_{max}, ng/mL	257.7 ± 92.69	189.8 ± 113.8
t_{max}, h	2.5 (1.5 - 16.0)	3.0 (1.5 - 4.0)
AUC_{24h}, ng.h/mL	4334 ± 1542	2991 ± 959.6
$C_{ss,av}$, ng/mL	180.6 ± 64.24	124.6 ± 39.98
Fluctuation index, %	65.55 ± 15.58	70.91 ± 38.90

Pharmacokinetic Parameter	LSmeans Ratio (90% CI), Test (on Day 7) Versus Reference (on Day -1)
N	15 versus 17
C_{min}	0.69 (0.64 - 0.75)
C_{max}	0.71 (0.66 - 0.76)
AUC_{24h}	0.71 (0.66 - 0.76)

SD: standard deviation; t_{max}: time to reach the maximum plasma concentration; C_{0h}: predose plasma concentration; $C_{ss,av}$: average steady-state plasma concentration

The median methadone dose used on Day -1 (N = 17) and Day 7 (N = 15) was 85 mg (range: 40 – 120 mg).

Pharmacokinetics of S-Methadone **Time Point Reference/Test** Pharmacokinetic Parameter: mean ± SD, t_{max}: median (range)	**Individualized Methadone Therapy (Reference)**	**Individualized Methadone Therapy + 750 mg Telaprevir q8h (Test)**
Day -4/Day 4		
N	18	16
C_{0h}, ng/mL	137.6 ± 62.70	98.73 ± 42.40
Day -3/Day 5		
N	18	15
C_{0h}, ng/mL	142.0 ± 69.74	100.7 ± 47.28
Day -2/Day 6		
N	17	15
C_{0h}, ng/mL	139.2 ± 58.14	96.49 ± 45.37
Day -1/Day 7		
N	17	15
C_{0h}, ng/mL	141.2 ± 64.10	84.55 ± 44.40
C_{min}, ng/mL	132.8 ± 57.12	81.97 ± 42.79
C_{max}, ng/mL	301.8 ± 114.4	211.9 ± 145.3
t_{max}, h	2.5 (1.5 - 16.0)	2.5 (1.0 - 4.0)
AUC_{24h}, ng.h/mL	4562 ± 1982	2941 ± 1378
$C_{ss,av}$, ng/mL	190.1 ± 82.59	122.5 ± 57.41
Fluctuation index, %	92.82 ± 27.95	103.1 ± 46.60

Pharmacokinetic Parameter	**LSmeans Ratio (90% CI), Test (on Day 7) Versus Reference (on Day -1)**
N	15 versus 17
C_{min}	0.60 (0.54 - 0.67)
C_{max}	0.65 (0.60 - 0.71)
AUC_{24h}	0.64 (0.58 - 0.70)
Ratio $AUC_{24h,\ S\text{-}/R\text{-methadone}}$	0.90 (0.86 - 0.94)

The median methadone dose used on Day -1 (N = 17) and Day 7 (N = 15) was 85 mg (range: 40 – 120 mg).

Pharmacokinetics of Telaprevir[a] **Time Point** Pharmacokinetic Parameter: mean ± SD, t_{max}: median (range)	**Individualized Methadone Therapy + 750 mg Telaprevir q8h**
Day 7	
N	15
C_{0h}, ng/mL	2476 ± 1021
C_{min}, ng/mL	1894 ± 904.7
C_{max}, ng/mL	3376 ± 1260
t_{max}, h	4.0 (2.5 - 8.0)
AUC_{8h}, ng.h/mL	20480 ± 7628
$C_{ss,av}$, ng/mL	2561 ± 953.4
Fluctuation index, %	61.10 ± 19.68

[a] The steady-state pharmacokinetic parameters for telaprevir were compared to those observed after intake of telaprevir alone (750 mg q8h) in healthy subjects in Trials VX-950-C123 and VX-950-C133. In these trials, mean C_{min} values of 1903 ng/mL and 2073 ng/mL, respectively, mean C_{max} values of 3338 ng/mL and 3236 ng/mL, respectively, and mean AUC_{8h} values of 20810 ng.h/mL and 21190 ng.h/mL, respectively, were observed.

Safety (N = number of subjects with data in FA set)	**Run-in (Methadone) N = 16[a]**	**Methadone + telaprevir N = 16**	**Follow-up (Methadone) N = 16**	**Whole Trial N = 16**
AEs				
Most frequently reported AEs (reported in > 2 subjects during any of the phases), n (%)				
Headache	4 (25.0)	6 (37.5)	0	7 (43.8)
Nausea	0	6 (37.5)	0	6 (37.5)
Euphoric mood	0	5 (31.3)	0	5 (31.3)
Pruritus SSC events[b] (pruritus in all 3 subjects)	0	3 (18.8)	0	3 (18.8)
Somnolence	3 (18.8)	2 (12.5)	0	5 (31.3)
Dizziness	3 (18.8)	0	0	3 (18.8)
N (%) with 1 or more AEs	12 (75.0)	13 (81.3)	3 (18.8)	15 (93.8)
N (%) of deaths	0	0	0	0
N (%) with 1 or more other serious AEs (SAEs)	0	0	0	0
N (%) with 1 or more AEs leading to permanent discontinuation of telaprevir	0	0	0	0
N (%) with 1 or more AEs leading to permanent discontinuation of methadone	0	0	0	0
N (%) with 1 or more grade 3 AEs	0	0	1 (6.3)	1 (6.3)
N (%) with 1 or more AEs considered at least possibly related to telaprevir by the investigator	0	10 (62.5)	1 (6.3)	10 (62.5)
N (%) with 1 or more AEs considered at least possibly related to methadone by the investigator	6 (37.5)	10 (62.5)	2 (12.5)	12 (75.0)

[a] Two additional subjects took supervised methadone during the run-in phase. They discontinued the trial before the first intake of telaprevir due to withdrawal of consent and not due to AEs. These subjects had no SAEs.

[b] Special search categories (SSC) for rash- and pruritus-related AEs were created by grouping AE terms that represent similar medical concepts, from the same or different system organ classes, to ensure that each subject with an event included within a pre-defined SSC was counted but counted only once.

No deaths or other SAEs occurred in this trial. None of the subjects permanently discontinued telaprevir and/or methadone treatment prematurely due to an AE.

Overall, 15 (93.8%) subjects experienced at least 1 AE during this trial. Twelve (75.0%) subjects experienced at least 1 AE during the run-in phase and 13 (81.3%) subjects during the methadone + telaprevir phase.

The most frequently reported AEs by preferred term during the methadone + telaprevir phase were headache (in 6 [37.5%] subjects), nausea (in 6 [37.5%] subjects), euphoric mood (in 5 [31.3%] subjects), and pruritus (in 3 [18.8%] subjects). Other AEs were reported in at most 2 subjects during the methadone + telaprevir phase.

Nausea, euphoric mood, and pruritus were only reported during the methadone + telaprevir phase and not during the run-in phase. The incidence of headache in the methadone + telaprevir phase (6 [37.5%] subjects) was similar to the incidence in the run-in phase (4 [25.0%] subjects). Somnolence also occurred in a similar number of subjects in both phases (in 2 [12.5%] subjects during the methadone + telaprevir phase and in 3 [18.8%] subjects during the run-in phase). Dizziness did not occur during the methadone + telaprevir phase, while this AE was reported in 3 (18.8%) subjects during the run-in phase.

All AEs occurring in this trial were grade 1 or 2 in severity, except for AST increased reported as grade 3 AE during follow-up in 1 (6.3%) subject. This grade 3 AE was considered possibly related to telaprevir and not related to methadone.

For all subjects with euphoric mood and pruritus during the methadone + telaprevir phase, these AEs were considered at least possibly related to telaprevir and methadone by the investigator. Nausea was considered at least possibly related to telaprevir in 5 of the 6 subjects with nausea during the methadone + telaprevir phase, while this AE was only considered at least possibly related to methadone in 2 of these 6 subjects. Headache was considered at least possibly related to telaprevir in 2 (12.5%) subjects and to methadone in 1 (6.3%) subject during the methadone + telaprevir treatment phase.

Five (31.3%) subjects had rash and/or pruritus SSC events. Pruritus occurred in 3 (18.8%) subjects and folliculitis, skin reaction, and rash were each reported in 1 (6.3%) subject. All rash and pruritus SSC events occurred during the methadone + telaprevir phase, except for folliculitis. All rash and pruritus SSC events were grade 1 in severity.

Clinical Laboratory Tests	No clinically relevant trends or changes over time in laboratory values were observed. The most frequent treatment-emergent (i.e., worsened versus reference) graded laboratory abnormalities during the methadone + telaprevir phase (observed in more than 1 subject) were hypertriglyceridemia (in 3 [18.8%] subjects), hemoglobin decreased (in 3 [18.8%] subjects), WBC count increased (in 3 [18.8%] subjects), and hypercholesterolemia (in 2 [12.5%] subjects). There were no treatment-emergent graded laboratory abnormalities that occurred in more than 1 (6.3%) subject during the run-in phase. All treatment-emergent graded laboratory abnormalities in this trial were grade 1 or 2 in toxicity, except for grade 3 increased AST in 1 (6.3%) subject during follow-up. This laboratory abnormality was reported as a grade 3 AE. No other laboratory abnormalities were reported as AE.
Cardiovascular Safety	Although there was a trend towards a lower pulse and heart rate in the run-in phase than in the methadone + telaprevir phase, median changes from reference in vital signs and ECG parameters were generally small and none of the median changes were considered clinically relevant. All treatment-emergent (i.e., worsened versus reference) vital signs abnormalities were observed in at most 2 subjects during the methadone + telaprevir phase. None of the subjects had a QTcF value above 450 ms or increase in QTcF versus reference of more than 60 ms during the methadone + telaprevir phase. None of the abnormalities related to vital signs or ECG were reported as AE.
Pharmacodynamic Assessments of Methadone	During coadministration of telaprevir and methadone, fewer subjects experienced withdrawal symptoms than during treatment with methadone alone (as measured by means of the SOWS). The desire for heroin was comparable (as measured by means of the DDQ). Overall, the median resting pupil diameter was smaller during coadministration of telaprevir and methadone than when subjects only received methadone, indicating that there were no signs of opiate withdrawal.

Conclusions

In the presence of telaprevir at 750 mg q8h, R-methadone C_{min}, C_{max}, and AUC_{24h} were decreased by 31%, 29%, and 29%, respectively, compared to methadone maintenance treatment alone. S-methadone C_{min}, C_{max}, and AUC_{24h} were decreased by 40%, 35%, and 36%, respectively. The S-/R-methadone ratio of AUC_{24h} was comparable in the presence of telaprevir compared to methadone maintenance treatment alone, suggesting lack of a stereo-specific effect.

Telaprevir pharmacokinetics were comparable to historical data (Trials VX-950-C123 and VX-950-C133), suggesting absence of an effect of methadone on the pharmacokinetics of telaprevir.

During coadministration of telaprevir and methadone, fewer subjects experienced withdrawal symptoms than during treatment with methadone alone (as measured by means of the SOWS). The desire for heroin was comparable (as measured by means of the DDQ). Overall, the median resting pupil diameter was smaller during coadministration of telaprevir and methadone than when subjects only received methadone, indicating that there were no signs of opiate withdrawal. These results suggest that the decreased concentrations of methadone observed during coadministration with telaprevir did not result in clinically significant changes in withdrawal symptoms.

Telaprevir (750 mg q8h) in combination with methadone was generally safe and well-tolerated in subjects on stable methadone maintenance therapy. The most frequently reported AEs during coadministration were headache, nausea, euphoric mood, and pruritus.

No adjustment of the methadone dose is required when initiating coadministration of telaprevir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients.