SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals **Trade Name**: - **Indication**: HCV-infection	**Drug Substance**: TMC435 **Trial no**.: TMC435-TiDP16-C110 **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 pharmacokinetic interaction between TMC435 and methadone, at steady-state.	
Investigator: M. Romach, M.D., Kendle Early Phase, 720 King Street West, 7th floor, Toronto, Ontario M5V 2T3, Canada	**Country**: Canada
Trial Period: Start: 28-Sep-2009 End: 06-Jan-2010	**No. of Investigators**: 1 **No. of Subjects**: 12 subjects

Objectives:

The primary objective was:

- to evaluate the effect of steady-state TMC435 150 mg q.d. on the steady-state pharmacokinetics of R- and S-methadone.

The secondary objectives were:

- to evaluate the potential pharmacodynamic effects of concurrent use of TMC435 and methadone, i.e., symptoms of methadone toxicity or withdrawal via pupillometry and the "Short Opiate Withdrawal" and "Desires for Drugs" questionnaires;
- to evaluate the steady-state pharmacokinetics of TMC435 150 mg q.d. in subjects on stable methadone maintenance therapy;
- to evaluate the short-term safety and tolerability of coadministration of TMC435 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 TMC435 150 mg q.d. and methadone, both at steady-state.

The trial population consisted of 12 HCV-negative opioid-dependent subjects on stable methadone maintenance therapy.

The methadone therapy (dosage and formulation) was not to be changed from Day -14 until Day 8 inclusive, unless warranted for safety reasons. Methadone dose was individualized for each subject and had to be between 30 and 150 mg daily (extremes included). Subjects received TMC435 150 mg q.d. for 7 days, added to their methadone therapy. All intakes of TMC435 (Days 1 to 7) and methadone (Days -14 to 8) were supervised.

Full 24-hour pharmacokinetic profiles of R- and S-methadone were determined on Day -1 (methadone alone) and on Day 7 (methadone + TMC435). A full 24-hour pharmacokinetic profile of TMC435 was determined on Day 7 (methadone + TMC435).

Pharmacodynamic assessments of the effects of concurrent use of TMC435 and methadone, i.e., methadone withdrawal or toxicity symptoms (Short Opiate Withdrawal Scale [SOWS], Desires for Drugs Questionnaire [DDQ] and pupillometry) were performed on Day -7, daily from Day -2 until Day 7 within 2 hours before the intake of methadone, and on Days -1 and 7 at 4 hours after methadone intake.

Safety and tolerability were evaluated continuously throughout the trial.

Subject Selection

Inclusion Criteria

1. Aged between 18 and 55 years, extremes included;
2. Normal weight as defined by a Body Mass Index (BMI, weight in kg divided by the square of height in meters) of 18.0 to 32.0 kg/m^2, extremes included;
3. Informed Consent Form (ICF) signed voluntarily before the start of any study specific procedures;
4. Able to comply with protocol requirements and restrictions;
5. Opioid-dependent, as determined by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Version IV, Revised (DSM-IV-R);
6. Receiving once daily oral methadone maintenance therapy at a stable individualized dose of 30 to 150 mg q.d. for at least 30 days prior to screening;
7. The subject agreed:
   - not to change the methadone dose from Day -14 until Day 8 included;
   - to have a daily observed and documented methadone intake from Day -14 until Day 8, and a daily observed and documented TMC435 intake from Day 1 until Day 7;
8. Normal 12-lead electrocardiogram (ECG) (in triplicate) at screening including:
   a. Normal sinus rhythm (heart rate [HR] between 50 and 120 beats per minute [bpm; extremes not included]);
   b. QTc interval ≤ 450 ms;
   c. QRS interval < 120 ms;
   d. PR interval ≤ 210 ms.
9. If the subject was recruited from another site, the subject had obtained approval from his/her addiction physician for participation in this trial. Furthermore, the addiction physician agreed to provide medical care for the subject after discharge from the testing facility;
10. General medical condition, which in the investigator's opinion, did not interfere with the assessments and the completion of the trial;
11. Otherwise healthy on the basis of a physical examination, medical history (except drug abuse), vital signs and the results of blood biochemistry, blood coagulation and hematology tests and a urinalysis (except positive drug screen for substances that were not exclusionary) carried out at screening.

Exclusion Criteria

1. Female subject of childbearing potential without use of effective birth control methods, or not willing to continue practicing these birth control methods during the trial and for at least 30 days after the end of the treatment period. Women of childbearing potential either had to:
   - use a double barrier method (i.e., using a condom with either diaphragm or cervical cap)* or;
   - use hormone-based contraceptives in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap, or female condom) or;
   - use a intrauterine device in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap, or female condom) or;
   - be only nonheterosexually active, practice heterosexual abstinence, or had a vasectomized partner (confirmed sterile);

     * A male and female condom were not to be used together due to risk of breakage or damage caused by latex friction.

     Women who were postmenopausal since more than 2 years (amenorrheal for at least 3 years), or post-hysterectomy (total) or post-oophorectomy (bilateral), or post-surgical sterilization (without reversal operation) were considered of non-childbearing potential.
2. Tested positive for drugs of abuse such as barbiturates, amphetamines, benzodiazepines, cocaine, and opioids, with the exception of methadone, at screening, unless the positive test results were explained by allowed concomitant medications.

   Note: Positive drug screening tests for the following did not result in exclusion of a subject:
   - cannabinoids;
   - temazepam, oxazepam, lorazepam, clonazepam, chlordiazepoxide, and codeine, when prescribed.
3. Use of alcohol at the moment of screening (and Day -2), which in the investigator's opinion could compromise subject's safety and/or compliance with the trial procedures;

4. Positive test for any of the following infectious disease tests: hepatitis A infection (confirmed by hepatitis A antibody immunoglobulin [IgM]), hepatitis B antigen (HBsAg), hepatitis C infection (confirmed by hepatitis C virus [HCV] antibody), human immunodeficiency virus 1 antibody (HIV1Ab), or human immunodeficiency virus 2 antibody (HIV2Ab). *Note:* In case of a positive HCV antibody test, a polymerase chain reaction (PCR) test could be performed to assess if the subject was HCV-RNA negative (HCV-RNA negative subjects could participate in the trial);
5. Decompensated liver function defined as clinical or laboratory evidence of significantly decreased hepatic function or decompensation, irrespective of liver enzyme levels (international normalized ratio [INR] > 1.5 or albumin < 30 g/L or total bilirubin ≥ 2.5 x upper limit of laboratory normal range [ULN]);
6. At the moment of screening, active or underlying clinically significant gastrointestinal, cardiovascular, neurologic, psychiatric (other than drug dependency), metabolic (including Gilbert syndrome), renal, hepatic, respiratory, inflammatory, or infectious disease;
7. At the moment of screening, significant diarrhea, gastric stasis, or constipation (other than the pharmacodynamic effects of methadone) that in the investigator's opinion could have influenced drug absorption or bioavailability;
8. Past history of heart arrhythmias (extrasystole, tachycardia at rest) or having baseline prolongation of QTc interval > 450 ms, history of risk factors for Torsade de Pointes syndrome (hypokalemia, family history of long QT syndrome);
9. Any history of significant skin disease such as, but not limited to, drug rash or eruptions, drug allergies, food allergy, dermatitis, eczema, psoriasis, or urticaria;
10. History of drug allergy such as, but not limited to, sulfonamides and penicillins, or drug allergy witnessed in previous trials with experimental drugs;
11. Previously demonstrated clinically significant allergy, hypersensitivity or photosensitivity to any of the excipients of the investigational medication administered in this trial (i.e., TMC435: lactose, sodium lauryl sulphate, aerosil, and magnesium stearate);
12. Use of disallowed concomitant therapy during the 14 days prior to the first dose of TMC435. Concomitant therapy that was not disallowed was not to be changed between Day -14 and Day 7, except for ibuprofen and acetaminophen (paracetamol);
13. Lack of good/reasonable venous access;
14. Participation in an investigational drug trial within 60 days prior to Day -14;
15. Donation of blood or plasma or having had a significant loss of blood within 60 days prior to Day -14 (500 mL or more);
16. A positive serum pregnancy test or breastfeeding at screening;
17. Subjects with one or more of the following laboratory abnormalities at screening as defined by the World Health Organization (WHO) Adult Toxicity and in accordance with the normal ranges of the clinical laboratory:
    - Serum creatinine grade 1 or greater (≥ 1.1 x ULN);
    - Lipase > 1.5 x ULN;
    - Hemoglobin grade 1 or greater (≤ 10.5 g/dL);
    - Platelet count grade 1 or greater (≤ 99,000/mm^3);
    - Absolute neutrophil count grade 1 or greater (≤ 1500/mm^3);
    - Alanine aminotranferase (ALT) or aspartate aminotransferase (AST) grade 1 or greater (≥ 1.25 x ULN);
    - Total bilirubin grade 1 or greater (≥ 1.1 x ULN);
    - Any other toxicity grade 2 or above.

Treatment	TMC435
Concentration Dosage Form (F No.) Usage	75 mg/capsule Capsule (F021) Oral
Batch Number	09C09/F021
Dose Regimen	TMC435 150 mg q.d. from Day 1 to Day 7 as add-on to subject's stable individualized methadone maintenance therapy (Metadol™) 30 to 150 mg q.d. from Day -14 to Day 8
Duration of Treatment	7 days (excluding screening and follow-up)
Duration of Trial	22 days (excluding screening and follow-up)

Disallowed Medication	All investigational drugs were disallowed from 60 days prior to the first supervised methadone intake (Day -14) until the end of the trial (except for TMC435 from Day 1 to Day 7). The following medications were not allowed from Day -14 until Day 8: - Cytochrome P450 inducers (rifamycins: rifabutin, rifampin, rifapentin; anticonvulsants: phenobarbital, phenytoin, carbamazepine, oxcarbazepine; systemic dexamethasone and other systemic glucocorticoids; all products containing *Hypericum perforatum* [St. John's Wort]; modafinil; pioglitazone and troglitazone); - Cytochrome P450 inhibitors and inhibitors of transporting proteins (systemic azole antifungals: ketoconazole, itraconazole and voriconazole; fluconazole [except if not exceeding 200 mg/day]; macrolide antibiotics: erythromycin, clarithromycin, troleandomycin, roxithromycin; and telithromycin); - Cytochrome P450 substrates (cisapride, terfenadine, and astemizole; aprepitant; felodipine, nifedipine, nicardipine, amlodipine, verapamil, diltiazem; pimozide); - the antiarrhythmics bepridil, flecainide, propafenone, systemic lidocaine, mexilitine, disopyramide, amiodarone and quinidine; - the antimigraines ergotamine, dihydroergotamine, ergonovine, methylergonovine, ergometrine, methylergonovine and other ergot derivatives; - megestrol acetate; - nefazodone; - proton pump inhibitors; - H_2 blockers (except if taken at least 12 hours before or 4 hours after intake of TMC435 medication) and antacids (except if taken at least 2 hours before or 4 hours after intake of TMC435); - the immunomodulators cyclosporin, tacrolimus, sirolimus, rapamycin, thalidomide; - the anticoagulants warfarin, phenprocoumon and acenocoumarol. Any other medication the subject was using had to be discussed prior to inclusion with the sponsor on a case-by-case basis. Preferably, concomitant therapy that was allowed was not to be changed (started, stopped, or change in regimen) between Day -14 and Day 8, except for ibuprofen and acetaminophen. However, if there was a need to change concomitant therapies during the trial, dosage and regimen had to be discussed in advance with the sponsor. Ibuprofen and acetaminophen could be used up to 3 days before the first intake of TMC435 investigational medication. After that, the clinical investigator could permit the use of ibuprofen (at no more than 400 mg per day) or acetaminophen (at no more than 1000 mg per day). Other comedication was allowed in the following cases: - In case of cutaneous reaction/rash and/or an allergic reaction, the use of cetirizine (Reactine®), fexofenadine (Allegra®), loratadine (Claritin®), desloratadine (Aerius®), topical corticosteroids, or antipruritic agents in the recommended dosing scheme was permitted. - In case of nausea, the use of antiemetics was permitted. - In case of diarrhea, the use of loperamide was permitted. Hormone replacement therapy was allowed in postmenopausal women. Applicable procedures and treatment guidance based on package inserts had to be respected. In case any of these medications were used, the indication, the dose and dose regimen had to be recorded in the Concomitant Therapy section of the CRF. For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition, the condition had to be documented in the Adverse Event section of the CRF.

Assessments	
Pharmacokinetics	Blood samples were taken for measurement of the concentration of the following drugs during treatment: TMC435 - on Day 4 to 6 (predose[a]); - on Day 7 (predose[a] and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 5h, 6h, 8h, and 12h postdose); - on Day 8 (24h postdose); - at time of dropout or the following morning[b]. R-and S-methadone: - on Day -4, Day -3, and Day -2 (all predose[a]); - on Day -1 (predose[a] and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 5h, 6h, 8h, and 12h postdose); - on Day 1, Day 2[c], Day 3[c] (all predose[a]); - on Day 4 to 6 (predose[a]); - on Day 7 (predose[a] and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 5h, 6h, 8h, and 12h postdose); - on Day 8 (predose[a]); - at time of dropout or the following morning[b]. [a] Immediately before intake of methadone and TMC435, as applicable. [b] For determination of TMC435, and methadone R- and S-isomer concentrations, if applicable. In case of dropout prior to Day 1, no pharmacokinetic blood sample needed to be taken. [c] Upon discretion of the investigator a predose pharmacokinetic sample could be taken when the subject demonstrated clinical withdrawal or toxicity symptoms.
Safety Adverse Events	Adverse events were monitored continuously from signing of the ICF onwards until the last trial-related activity.

Clinical Laboratory	Blood samples for biochemistry[a] and hematology measurements and urine samples for urinalysis were taken:
	
	- at screening;
	- on Day –14[b];
	- on Day -7, Day -4, Day -3, and Day -2 (all predose[b] and all urine samples only);
	- on Day -1 and Day 7 (2h predose[b] and 4h postdose);
	- on Day 1, Day 3, and Day 8 (predose[b]);
	- at dropout;
	  - at time of dropout or the following morning;
	  - 10 to 14 days and 30 to 32 days after dropout.
	- at follow-up.
	  - 7 days and 30 to 32 days after last drug intake.
	
	[a] All biochemistry samples had to be taken fasted for at least 10 hours, except for the samples taken 4 hours postdose on Days -1 and 7. Coagulation was included in the safety samples of screening, Days 3, 7, and 8 and in the safety sample of the first post-treatment visit if effects on coagulation were seen during the dosing period.
	[b] Within 2 hours before intake of methadone and TMC435, as applicable.

Cardiovascular Safety	Triplicate ECGs and vital signs[a] were measured:
	- at screening;
	- on Day -14[b, c];
	- on Day -1 and Day 7 (2h predose[b, c] and 4h postdose[b]);
	- on Day 1, Day 3, and Day 8 (predose[b, c]);
	- at dropout;
	  - at time of dropout or the following morning;
	  - 10 to 14 days and 30 to 32 days after dropout.
	- at follow-up.
	  - 7 days and 30 to 32 days after last drug intake.
	[a] Blood pressure and pulse: supine after 5 min, standing after 1 min.
	[b] For ECG: Within 2 hours before breakfast. On Days -1 and 7, the ECG scheduled 4 hours postdose had to be performed within 10 minutes before pharmacokinetic blood sampling at the corresponding time point.
	[c] For vital signs: Within 2 hours before intake of methadone and TMC435, as applicable.

Physical Examination	Physical examinations were performed:
	- at screening;
	- on Day -2;
	- on Day 8;
	- at dropout;
	  - at time of dropout or the following morning;
	  - 10 to 14 days and 30 to 32 days after dropout.
	- at follow-up.
	  - 7 days and 30 to 32 days after last drug intake.

Pharmacodynamic Assessments of Methadone	SOWS, DDQ, and pupillometry were completed: - on Day -7 and Day -2 (both predose[a]); - on Day -1 (2h predose[a] and 4h postdose); - on Day 1 to Day 6 (all predose[a]); - on Day 7 (2h predose[a] and 4h postdose). [a] Within 2 hours before intake of methadone.
Pharmacogenetic/genomic testing	For subjects who consented, blood samples for pharmacogenetic/genomic testing were collected on Day -2. The samples were stored and could be analyzed as part of future exploratory analyses.
Statistical Methods	Intent-to-Treat analysis, descriptive statistics, frequency tabulations, linear mixed effects modeling

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics - Subject Disposition	**All subjects N = 12**
Number of Subjects Entered (M/F)	10/2
Age: median (range), yrs	30.5 (21-43)
Weight: median (range), kg	71.0 (52-91)
Ethnic Origin, n (%)	
White (not Hispanic or Latino)	11 (91.7)
American Indian or Alaska Native	1 (8.3)
Dropouts - Reason	
AE (rash)	1 (8.3)

Pharmacokinetics of R-methadone (mean ± SD, t_{max}: median [range])	**Individualized methadone therapy[a] (reference)**	**Individualized methadone therapy[a] + 150 mg TMC435 q.d. on Days 1-7 (test)**
Day -4 / Day 4		
n	12	12
C_{0h}, ng/mL	172.0 ± 58.81	167.5 ± 70.10
Day -3 / Day 5		
n	12	12
C_{0h}, ng/mL	172.6 ± 59.34	169.9 ± 71.48
Day -2 / Day 6		
n	12	12
C_{0h}, ng/mL	161.5 ± 59.48	161.8 ± 72.68
Day -1 / Day 7		
n	12	11[b]
C_{0h}, ng/mL	167.9 ± 61.01	163.9 ± 74.38
C_{min}, ng/mL	157.0 ± 58.89	162.8 ± 73.81
C_{max}, ng/mL	295.0 ± 102.4	307.8 ± 126.2
t_{max}, h	3.0 (1.5-4.0)	2.0 (1.0-4.0)
AUC_{24h}, ng.h/mL	5023 ± 1720	5464 ± 1942
$C_{ss,av}$, ng/mL	209.3 ± 71.68	227.7 ± 80.93
FI, %	66.13 ± 9.203	70.76 ± 14.27
LSmean ratio[c] (90% CI)		
		Test vs reference
n		11[b] vs 12
C_{min}	-	1.021 (0.9284 - 1.122)
C_{max}	-	1.028 (0.9669 - 1.094)
AUC_{24h}	-	0.9948 (0.9108 - 1.086)

[a] Methadone doses ranged from 30 mg to 145 mg q.d. (1 subject each used a dose of 30 mg, 50 mg, 80 mg, 90 mg, 100 mg, 110 mg, and 145 mg, 2 subjects used a dose of 95 mg and 3 subjects used a dose of 115 mg). Methadone doses were not changed during the trial.
[b] n = 10 for AUC_{24h}, $C_{ss,av}$ and FI
[c] Day -1 vs Day 7

Pharmacokinetics of S-methadone (mean ± SD, t_{max}: median [range])	**Individualized methadone therapy[a] (reference)**	**Individualized methadone therapy[a] + 150 mg TMC435 q.d. on Days 1-7 (test)**
Day -4 / Day 4		
n	12	12
C_{0h}, ng/mL	165.0 ± 67.45	172.1 ± 96.54
Day -3 / Day 5		
n	12	12
C_{0h}, ng/mL	166.7 ± 73.76	176.7 ± 103.5
Day -2 / Day 6		
n	12	12
C_{0h}, ng/mL	154.6 ± 73.49	164.7 ± 99.27
Day -1 / Day 7		
n	12	11[b]
C_{0h}, ng/mL	160.5 ± 71.04	166.8 ± 103.5
C_{min}, ng/mL	151.1 ± 69.79	164.6 ± 101.4
C_{max}, ng/mL	359.3 ± 135.6	398.5 ± 178.4
t_{max}, h	3.0 (1.5-4.0)	1.5 (0.5-4.0)
AUC_{24h}, ng.h/mL	5414 ± 2146	6234 ± 2846
$C_{ss,av}$, ng/mL	225.6 ± 89.40	259.8 ± 118.6
FI, %	94.07 ± 19.33	107.7 ± 37.60
LSmean ratio[c] (90% CI)		
		Test vs reference
n		11[b] vs 12
C_{min}	-	1.020 (0.8921 - 1.166)
C_{max}	-	1.087 (1.017 - 1.162)
AUC_{24h}	-	1.026 (0.9052 - 1.163)

[a] Methadone doses ranged from 30 mg to 145 mg q.d. (1 subject each used a dose of 30 mg, 50 mg, 80 mg, 90 mg, 100 mg, 110 mg, and 145 mg, 2 subjects used a dose of 95 mg and 3 subjects used a dose of 115 mg). Methadone doses were not changed during the trial.

[b] n = 10 for AUC_{24h}, $C_{ss,av}$ and FI

[c] Day -1 vs Day 7

Pharmacokinetics of TMC435 (mean ± SD, t_{max}: median [range])	**150 mg TMC435 q.d. on Days 1-7 + individualized methadone therapy**	**150 mg TMC435 q.d. on Days 1-11 + a single dose of cocktail of probe drugs on Days 10 and 11[b] (historical control[c])**
n	11[a]	16
Day 4/Day 8		
C_{0h}, ng/mL	183.4 ± 160.2	-
Day 5/Day 9		
C_{0h}, ng/mL	173.9 ± 147.3	1183 ± 1003
Day 6/Day 10		
C_{0h}, ng/mL	188.0 ± 158.4	1347 ± 1176
Day 7/Day 11		
C_{0h}, ng/mL	168.8 ± 137.8	1491 ± 1287
C_{min}, ng/mL	152.4 ± 130.5	1180 ± 1050
C_{max}, ng/mL	965.7 ± 429.1	5209 ± 2334
t_{max}, h	5.0 (4.0-8.0)	5.08 (3.08-12.08)
AUC_{24h}, ng.h/mL	12110 ± 7704	67000 ± 36610
$C_{ss,av}$, ng/mL	504.5 ± 321.0	-
FI, %	180.4 ± 60.86	-

[a] n = 12 for Day 4, 5 and 6
[b] A single dose of oral midazolam (0.075 mg/kg) on Day 10 and a single dose of drug cocktail (midazolam [0.025 mg/kg i.v.], dextromethorphan [30 mg], caffeine [150 mg], omeprazole [40 mg] and warfarin [10 mg], all given orally) on Day 11
[c] Data are obtained from trial TMC435-TiDP16-C107

	Screening and Run-in	**Treatment**	**Follow-up**	
Safety (n = number of subjects with data)	**Methadone** **N = 12**	**Methadone + TMC435** **N = 12**	**Methadone** **N = 12**	**All Periods** **N = 12**
Adverse Events (AEs)				
Most frequently reported AEs (reported in > 1 subject per treatment phase), n (%)				
Headache	5 (41.7)	5 (41.7)	0	7 (58.3)
Anxiety	3 (25.0)	0	0	3 (25.0)
Constipation	2 (16.7)	1 (8.3)	0	3 (25.0)
Lethargy	1 (8.3)	3 (25.0)	0	3 (25.0)
Back pain	1 (8.3)	2 (16.7)	0	2 (16.7)
n (%) with 1 or more AEs	10 (83.3)	10 (83.3)	1 (8.3)	12 (100.0)
n (%) of deaths	0	0	0	0
n (%) with 1 or more other serious AEs	0	0	0	0
n (%) of treatment stopped due to AEs	0	1 (8.3)	0	1 (8.3)
n (%) with 1 or more grade 3 or 4 AEs	0	0	0	0
No deaths, other SAEs, or grade 3 or 4 AEs were reported during the trial. Adverse events leading to treatment discontinuation were reported in 1 subject who prematurely discontinued study medication after 6 days of methadone + TMC435 intake due to grade 2 rash considered probably related to TMC435 and doubtfully related to methadone by the investigator.				

Clinical Laboratory Tests	Median changes in laboratory parameters were generally small and not considered clinically relevant. No grade 3 or grade 4 treatment-emergent individual laboratory abnormalities were observed. All graded laboratory abnormalities were observed in at most 2 subjects per treatment phase. No differences between the treatment phases in the incidence and severity of laboratory abnormalities were observed. The most frequent non-graded laboratory abnormalities were albumin, monocytes, total cholesterol, and triglycerides above normal.
Cardiovascular Safety	Median changes in vital signs and ECG parameters were generally small, except for increases in supine and standing pulse rate, observed in both the treatment phase and during follow-up. One subject was observed with grade 3 increased supine DBP and standing SBP on Day 7 of methadone + TMC435 intake and with grade 2 increased standing DBP and supine SBP at several time points during the methadone + TMC435 treatment phase. All other graded treatment-emergent vital signs-related abnormalities observed during treatment were grade 1. No QTcF values above 500 ms were observed. One subject was observed with QTcF values between 480 and 500 ms during methadone + TMC435 intake (corresponding with increases from baseline of more than 60 ms). No other QTcF values above 480 ms or QTcF increases of more than 60 ms were observed.
Physical Examination	Two subjects were observed with at least one abnormal new finding (i.e., not present at screening) in physical examination. These findings were reported as AEs, i.e., rash (grade 2) in one subject and catheter site hematoma (grade 1) and laceration (grade 2) in the second subject.
Pharmacodynamic Assessments of Methadone	No consistent trends or clinically relevant changes in SOWS and DDQ scores or pupil diameter were observed.

Conclusions - Removed from document

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