SYNOPSIS

Trial Identification and Protocol Summary

Company: Janssen Research and Development* **Trade Name**: Edurant® **Indication**: HIV infection	**Drug Substance**: TMC278 (rilpivirine) **Trial no**.: TMC278IFD1001 **Clinical Phase**: I
Title: A Phase I, open-label, randomized, crossover trial in healthy subjects to investigate the effect of steady-state TMC278 on the pharmacokinetics of a single dose of digoxin.	
Investigator: S. Deleu, M.D., GCPCP, Clinical Pharmacology Unit, AZ Jan Palfijn, Lange Bremstraat 70, 2170 Merksem, Belgium	**Country**: Belgium
Trial Period: Start: 31-Jan-2012 End: 05-Apr-2012#	**No. of Investigators**: 1 **No. of Subjects**: 22

Objectives:

The primary objective was:

- To investigate the effect of steady-state TMC278 on the single dose pharmacokinetics of digoxin.

The secondary objective was:

- To determine the short-term safety and tolerability of coadministration of steady-state TMC278 and single dose digoxin.

Design:

This was a Phase I, open-label, randomized, crossover study in 22 healthy adult subjects to investigate the potential drug-drug interaction between steady-state TMC278 and single dose digoxin.

Subjects were randomized to one of 2 treatment sequences consisting of Treatments A and B (11 subjects to Sequence A-B and 11 subjects to Sequence B-A) on Day 1 of Session 1, prior to the first drug intake. In Treatment A, digoxin 0.5 mg (single oral dose) was administered. In Treatment B, TMC278 25 mg q.d. (oral doses) was administered for 16 days, with digoxin 0.5 mg (single oral dose) administered in the morning on Day 11. All treatments were administered under fed conditions, within 10 minutes after breakfast. The 2 consecutive sessions were separated by a washout of at least 14 days. The study duration (including Day -1 of Treatment A and B) was at least 26 days, screening and follow-up phase excluded.

On Days 1 and 11 of Treatments A and B, pharmacokinetic assessments of digoxin in plasma and urine were determined over 144 hours after dosing. A full pharmacokinetic profile of TMC278 in plasma was determined over 24 hours starting on Day 11 of Treatment B and additional predose samples were taken from Day 11 until Day 16. Safety and tolerability were monitored throughout the study.

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Note that the analysis output erroneously states 11 May 2012 as end of the study. On this day, a remark was entered in the database concerning a screening failure (Subject 1001-3234). The actual last subject visit was on 05 April 2012 (Subject 1001-0639).

Subject Selection

Inclusion Criteria

Each potential subject had to satisfy all of the following criteria to be enrolled in the study.

1. Subjects had to have signed an informed consent form (ICF) indicating that they understood the purpose of and procedures required for the study and were willing to participate in the study.
2. Subjects had to be men or women between 18 and 55 years of age, extremes included.
3. Subjects had to be healthy on the basis of physical examination, medical history, vital signs, electrocardiogram (ECG), and the results of blood biochemistry and hematology tests and a urinalysis performed at screening. If the results were outside the normal reference ranges, the subject could have been included only if the investigator judged the abnormalities or deviations from normal to be not clinically significant (with exception of the graded abnormalities mentioned in exclusion criterion 15). This determination had to be recorded in the subject's source documents and initialed and dated by the investigator.

   Note: Retesting of ECG recordings with abnormal values that could have led to exclusion was allowed once. Retesting took place before baseline (= Day 1 of Session 1).
4. Men had to agree to use a highly effective method of birth control (i.e., male condom with either female intrauterine device, diaphragm, cervical cap or hormone based contraceptives used by their female partner) when having sexual intercourse with a female partner of childbearing potential, and to not donate sperm during the study and for 3 months after receiving the last dose of study medication.

   Men who had had a vasectomy and had a female partner of childbearing potential had to agree to use a male condom during the study and for 3 months after receiving the last dose of study medication.

   If the female sexual partner was postmenopausal for at least 2 years or was surgically sterile (had had a total hysterectomy or bilateral oophorectomy, bilateral tubal ligation/clips without reversal operation, or otherwise be incapable of becoming pregnant), she was not considered to be of childbearing potential and hence the birth control methods mentioned were not applicable.

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

   If a subject's partner became pregnant in the time between when the subject started taking the study medication until 1 month after the last dose, the investigator had to be informed immediately.
5. Women had to:
   - be postmenopausal for at least 2 years, OR
   - be surgically sterile (had had a total hysterectomy or bilateral oophorectomy, bilateral tubal ligation/clips without reversal operation, or otherwise be incapable of becoming pregnant).
6. Women had to have a negative pregnancy test at screening.
7. Subjects had to be willing/able to adhere to the prohibitions and restrictions specified in this protocol.
8. Subjects had to be non-smoking.
9. Subject had to have a Body Mass Index (BMI) of 18.5 to 30.0 kg/m^2, extremes included.

Exclusion Criteria

Any potential subject who met any of the following criteria was excluded from participating in the study.

1. A positive HIV-1 or HIV-2 test at screening.
2. History or suspicion of alcohol or barbiturates, amphetamines, recreational or narcotic drug use which in the investigator's opinion would have compromised subject safety and/or compliance with study procedures.
3. Hepatitis A, B or C infection (confirmed by hepatitis A immunoglobulin, Hepatitis B surface Antigen, or hepatitis C virus antibody, respectively) at screening.
4. A positive urine drug test at screening or on Day -1 (Treatment A and Treatment B). Urine was tested for the presence of amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, methadone, and opioids.
   Note: a positive test could have been repeated once to exclude a technical error. Retesting took place during the same visit. Subjects with a confirmed positive urine drug test at screening or on Day -1 (Treatment A and Treatment B) were excluded.
5. Female subjects were not to be breastfeeding.
6. Currently active or underlying gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, endocrine, renal, hepatic, respiratory, inflammatory or infectious disease.
7. Currently significant diarrhea or gastric stasis that in the investigator's opinion could influence drug absorption or bioavailability.
8. Less than 2 or 3 bowel movements on average per week.
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. Previously demonstrated clinically significant allergy or hypersensitivity to the drug or any of the excipients of the drug administered in this study (i.e., TMC278, digoxin or digitalis preparations).
11. Use of concomitant medication, including over-the-counter (OTC) products, herbal medications, and dietary supplements.
12. Having previously participated in more than 1 study (single or multiple dose) with TMC125 (etravirine), TMC120 (dapivirine) and/or TMC278 (rilpivirine) or having developed a rash, erythema or urticaria while participating in a study with the aforementioned compounds.
13. Received an investigational product (including investigational vaccines) or used an investigational medical device within 60 days before the planned start of treatment or currently enrolled in an investigational study.
14. Donation of blood or plasma or significant blood loss within the 60 days preceding the first administration of study medication.
15. Subjects with the following laboratory abnormalities at screening as defined by the Division of Acquired Immune Deficiency Syndrome (AIDS)(DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events and in accordance with the normal ranges of the laboratory:
    - serum creatinine grade 1 or greater (≥ 1.1 x upper limit of laborat ory normal range [ULN]); or estimated creatinine clearance < 90 mL/min.
    - lipase grade 1 or greater (≥ 1.1 x ULN);
    - hemoglobin grade 1 or greater (≤ 10.9 g/dL).
    - platelet count grade 1 or greater (≤ 124.999 x 10^9/L);
    - absolute neutrophil count grade 1 or greater (≤ 1.3 x 10^9/L);
    - AST or ALT grade 1 or greater (≥ 1.25 x ULN);
    - total bilirubin grade 1 or greater (≥ 1.1 x ULN);
    - grade 1 or above electrolyte abnormalities (hypokalemia, hypocalcemia, hyperkalemia, hypercalcemia, hypomagnesemia);
    - any other laboratory abnormality of grade 2 or above. With the exception of low-density lipoprotein (LDL) cholesterol, this was not to be higher than ULN of the local lab.
      Note: Retesting of abnormal lab values that could have led to exclusion was allowed once. Retesting took place during an unscheduled visit in the screening phase (before baseline [= Day 1 of Session 1]).
16. History of clinically relevant heart rhythm disturbances.
17. History of idiopathic hypertrophic subaortic stenosis (IHSS), hypertrophic cardiomyopathy, atrioventricular block, ventricular tachycardia/ventricular fibrillation or family history of sudden cardiac death.
18. Wolff (Wolfe)-Parkinson-White (WPW) syndrome or any other clinically relevant abnormality on ECG on Day 1 of Session 1.

Treatment	Digoxin (Lanoxin ®)	TMC278
Dose Strength Dosage Form (F Number) Usage	0.25 mg tablet oral	25 mg tablet (F006) oral
Batch Number	1D002	AJL2L
Dose and Dose Regimen	Treatment A: A single oral dose of digoxin 0.5 mg (2 tablets, taken together) on Day 1 Treatment B: TMC278 25 mg q.d. oral doses on Days 1 to 16 with a single oral dose of digoxin 0.5 mg on Day 11	
Duration of Treatment	Treatment A: 1 day. Treatment B: 16 days.	
Duration of Trial	The study duration (including Day -1 of Treatment A and B) was at least 26 days, screening (maximum 20 days) and follow-up phase (5 – 7 days after last study medication intake) excluded.	
Disallowed Medication	Grapefruit and grapefruit juice were not allowed between 14 days before the first intake of study medication until the last pharmacokinetic blood sample had been taken in each session. All OTC medication had to be discontinued at least 7 days before the first intake of study medication and prescribed medication had to be discontinued at least 14 days before the first intake of study medication, except for paracetamol (acetaminophen), ibuprofen and hormone replacement therapy. Subjects were not allowed to use any medication other than the study medication up to 14 days after the last intake of study medication except for paracetamol, ibuprofen and hormone replacement therapy. Subjects were also not to use any systemic herbal medications or dietary supplements including products containing *Hypericum perforatum* (St. John's wort) from 14 days before the first intake of study medication up to 14 days after the last intake of study medication. Paracetamol/acetaminophen or ibuprofen could be used up to 3 days before the intake of study medication in each session. After that, the investigator could permit the use of paracetamol or ibuprofen from 3 days before the intake of study medication until last pharmacokinetic sample had been taken in each session, at ≤ 3 x 500 mg per day or 2 x 200 mg per day, respectively, and ≤ 3 g per week (for paracetamol). Hormone replacement therapy was allowed in postmenopausal women. Other co-medication was allowed in the following cases: • In case of cutaneous reaction/rash and/or an allergic reaction, the use of cetirizine (Zyrtec®), levocetirizine (Xyzal®), topical corticosteroids, or antipruritic agents in the recommended dosing scheme was permitted. • In case of nausea, the use of antiemetics (domperidone, metoclopramide) was permitted. • In case of diarrhea, the use of loperamide was permitted.	

Assessments	
Pharmacokinetics	At the following time points blood samples for pharmacokinetic analysis were taken: - Treatment A: o For determination of TMC278: Day 1: predose o For determination of digoxin : ▪ Day 1: predose and 20 minutes (min), 40 min, 1 hour (h), 1.5 h, 2 h, 3 h, 4 h, 5 h, 6 h, 9 h, 12 h and 16 h postdose; ▪ Days 2 - 7: at 24 h, 48 h, 72 h, 96 h, 120 h and 144 h postdose, respectively. - Treatment B: o For determination of TMC278: ▪ Days 1, 8, 9 and 10: predose ▪ Day 11: predose and 20 min, 40 min, 1 h, 1.5 h, 2 h to 6 h hourly, 9 h, 12 h and 16 h postdose; ▪ Days 12 -17: 24 h, 48 h, 72 h, 96 h, 120 h, and 144 h postdose relative to study medication intake on Day 11; o For determination of digoxin: ▪ Day 11: predose and 20 min, 40 min, 1 h, 1.5 h, 2 h to 6 h hourly, 9 h, 12h and 16 h postdose; ▪ Days 12 -17: 24 h, 48 h, 72 h, 96 h, 120 h, and 144 h postdose relative to study medication intake on Day 11; ▪ at time of dropout or the following morning for determination of TMC278 and/or digoxin, as applicable. The complete urinary output was collected during the intervals 0-12, 12-24, 24-48, 48-72, 72-96, 96-120 and 120-144 hours after intake of digoxin in the morning on Day 1 (Treatment A) and after intake in the morning on Day 11 (Treatment B).
Safety Adverse Events	Adverse events (AEs) were checked at every visit and reported from signing of the ICF onwards until the last study related visit. Severity and medication relationship of AEs towards TMC278 was recorded.
Clinical Laboratory Safety	Blood[a] and urine samples were taken: - at screening; - Treatment A: o on Day 1, predose[b]; o on Day 7[c], 144 h postdose; - Treatment B: o on Day 1: predose[b]; o on Day 11: predose[b,d]; o on Day 17[c], 144 h postdose relative to study medication intake on Day 11. - at follow-up: 5 - 7 days after last intake of study medication; - at time of dropout or the following morning and 5 – 7 days after dropout. [a] Biochemistry samples were taken fasted for at least 10 hours. At time of dropout biochemistry samples were also taken fasted for at least 10 hours, if possible. [b] Within 2 hours before study medication intake. [c] Safety urine sample was taken from the collected volume of the 120 - 144 hour time point after it had been measured for the total volume. [d] Only blood sample taken.

Cardiovascular safety	ECG and vital signs[a] were recorded: - at screening; - Treatment A: o on Day 1: predose[b]; o on Day 7: 144 h postdose; - Treatment B: o on Day 1 and 11: predose[b]; o on Day 17; - at follow-up: 5 - 7 days after last intake of study medication; - at time of dropout or the following morning; - 5 – 7 days after dropout (only vital signs). [a] Blood pressure (BP) and pulse rate: supine after 5 minutes, standing after 1 minute. [b] Within 2 hours before study medication intake, if applicable.
Physical examination	Physical examinations (skin examination included) were performed: - at screening - Treatment A: o on Day 7: 144 h postdose; - Treatment B: o on Day 17. - at follow-up: 5 - 7 days after last intake of study medication. - at time of dropout or the following morning and 5 – 7 days after dropout.
Statistical Methods	Intent-to-Treat (ITT) analysis, Descriptive statistics, and frequency tabulations.

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics – Subject Disposition	**Sequence A-B**	**Sequence B-A**	**Whole study**
Number of Subjects Entered (Male/Female)	11 (5/6)	11 (6/5)	22 (11/11)
Age: median (range), years	48.0 (32 - 55)	44.0 (34 - 54)	46.0 (32 - 55)
Weight: median (range)	73.8 (60 - 92)	80.1 (56 - 99)	75.4 (56 - 99)
BMI: median (range)	25.7 (21 - 28)	26.6 (22 - 30)	26.1 (21 - 30)
Race			
White	11	11	22
Discontinuations - Reason			
Other	0	1	1

Pharmacokinetics of Digoxin in Plasma (mean ± SD, t_{max}: median [range])	**Single oral dose of 0.5 mg digoxin on Day 1** (reference)			**25 mg TMC278 q.d. on Days 1 to 16 + single oral dose of 0.5 mg digoxin on Day 11** (test)		
Day 1/Day 11						
n	21			22[a]		
C_{max}, ng/mL	1.93	±	0.637	2.05	±	0.678
t_{max}, h	1.50 (0.68-3.00)			1.74 (0.65-3.02)		
AUC_{4h}, ng.h/mL	4.44	±	1.21	4.46	±	1.31
AUC_{last}, ng.h/mL	26.6	±	7.38	26.0	±	7.86
AUC_{∞}, ng.h/mL	33.8[b]	±	7.09[b]	33.5	±	7.93
λ_z, 1/h	0.0184	±	0.00312	0.0189	±	0.00392
$t_{1/2,term}$, h	38.8	±	6.30	38.3	±	8.17
CL/F, L/h	15.4[b]	±	3.00[b]	15.7	±	3.50
LSmean ratio (90% CI)						
				Test vs reference		
n				22 vs 21		
C_{max}	-			1.06 (0.97 - 1.17)		
AUC_{last}	-			0.98 (0.93 - 1.04)		

SD = Standard Deviation; CI = Confidence Interval; LSmean = Least Square mean; n = number of subjects with that event; C_{max} = maximum observed plasma concentration; t_{max} = time to reach C_{max}; AUC_{4h} = area under the plasma concentration-time curve from time of administration up to 4 hours post dosing; AUC_{last} = AUC from time of administration up to the last time point with a measurable concentration post dosing; AUC_{∞} = AUC extrapolated to infinity; λ_z = terminal elimination rate constant; $t_{1/2,term}$ = terminal elimination half-life; CL/F = apparent systemic drug clearance

[a] n = 21 for AUC_{∞}, λ_z, $t_{1/2term}$ and CL/F

[b] Approximation, as accurate determination of AUC_{∞}, not possible (%$AUC_{\infty,ex}$ [extrapolated percentage of AUC_{∞}] > 20%) for > 50% of the subjects

Pharmacokinetics of Digoxin in Urine (mean ± SD)	**Single oral dose of 0.5 mg digoxin on Day 1** (reference)			**25 mg TMC278 q.d. on Days 1 to 16 + single oral dose of 0.5 mg digoxin on Day 11** (test)		
Day 1/Day 11						
n	21[a]			22		
Ae_{total}, mg	0.238	±	0.0475	0.278	±	0.0610
$D_{urine,total}$, %	47.7	±	9.51	55.7	±	12.2
GFR_{CystC}[b], L/h	6.65	±	1.01	6.89	±	0.973
$CL_{R, digoxin}$, L/h	9.46	±	2.54	11.2	±	2.66
$CL_{GFR, digoxin}$, L/h	1.78	±	0.483	1.84	±	0.450
$CL_{nonGFR, digoxin}$, L/h	7.73	±	2.49	9.38	±	2.61
LSmean ratio (90% CI)						
				Test vs reference		
n				22 vs 18		
$CL_{R, digoxin}$	-			1.16 (1.07 - 1.25)[c]		

n = number of subjects with that event; SD = Standard Deviation; CI = Confidence Interval; LSmean = Least Square mean; Ae_{total} = total amount excreted in the urine; $D_{urine,total}$ = total percentage of the dose excreted in urine; GFR_{CystC} = glomerular filtration rate calculated based on serum cystatin C levels; $CL_{GFR, digoxin}$ = glomerular renal clearance of digoxin, calculated as fraction unbound of digoxin x GFRCystC; $CL_{nonGFR, digoxin}$ = nonglomerular renal clearance of digoxin, calculated as $CL_{R,digoxin} - CL_{GFR, digoxin}$.

[a] n = 18 for Ae_{total}, $D_{urine,total}$, CL_R, and CL_{nonGFR}

[b] GFR_{CystC} was calculated using the Hoek formula: GFR = -4.32 + 80.35 x 1/CystC (units of cystatin C should be mg/L) (**Note**: GFR can be determined based on serum creatinine, however, because TMC278 has some effect on creatinine clearance, cystatin C was used instead to calculate GFR)

[c] Upper limit of CI was 1.247227 rounded to 1.25.

Pharmacokinetics of TMC278 in Plasma (mean ± SD, t_{max}: median [range])	**25 mg TMC278 q.d. on Days 1 to 16 + single oral dose of 0.5 mg digoxin on Day 11**		
n	22		
Day 11			
C_{0h}, ng/mL	111	±	41.8
C_{min}, ng/mL	80.1	±	28.5
C_{max}, ng/mL	210	±	53.5
t_{max}, h	5.00 (4.00-16.00)		
AUC_{24h}, ng.h/mL	3177	±	899
$C_{ss,av}$, ng/mL	133	±	37.6
FI, %	101	±	23.3

n = number of subjects with that event; SD = Standard Deviation; C_{0h} = predose plasma concentration; C_{min} = minimum observed plasma concentration; C_{max} = maximum observed plasma concentration; t_{max} = time to reach C_{max}; AUC_{24h} = AUC from time of administration up to 24 hours post dosing; $C_{ss,av}$ = average steady-state plasma concentration; FI = fluctuation index.

Safety	**TMC278 alone**	**TMC278 + Digoxin**	**Digoxin alone**	**Whole study**
n (%) with at least 1 AE	10 (45.5)	7 (31.8)	5 (23.8)	16 (72.7)
n (%) with at least 1 grade 3 or 4 AE	0	0	0	0
n (%) with at least 1 SAE	0	0	0	0
n (%) with at least 1 AE leading to discontinuation	0	0	0	0
n (%) of deaths	0	0	0	0
Most frequent AEs (reported in > 1 subject in whole study), n (%)				
Headache	3 (13.6)	3 (13.6)	3 (14.3)	7 (31.8)
Back Pain	2 (9.1)	1 (4.5)	0	3 (13.6)
Abdominal Pain	0	0	2 (9.5)	2 (9.1)
Dry Mouth	1 (4.5)	1 (4.5)	0	2 (9.1)
Tooth Abscess	2 (9.1)	0	0	2 (9.1)
Oropharyngeal Pain	1 (4.5)	0	1 (4.8)	2 (9.1)

n = number of subjects with that event; SAE = serious AE
Whole study includes screening, all treatment phases, and follow-up

None of the subjects experienced an SAE, a grade 3 or 4 AE or discontinued due to an AE.
The most frequently reported AEs (reported in > 1 subject in any study phase) were headache, back pain, abdominal pain, and tooth abscess. None of the most frequently reported AEs were considered related to the study medication by the investigator.

Clinical Laboratory Tests	No grade 3 or grade 4 laboratory abnormalities were observed during any study phase. No AEs related to laboratory or urinalysis abnormalities were reported.
Cardiovascular Safety	Abnormalities in ECG parameters were infrequent and were observed in at most 2 subjects during any study phase. No QTc values > 500 ms, no QTc changes of > 60 ms from baseline and no AEs related to ECG parameters were reported.
Vital Signs and physical examination	No AEs related to vital sign parameters were reported. Physical examination abnormalities were considered clinically significant by the investigator in 2 subjects and reported as AE: Subject 1001-1094 experienced rhinitis and reduced spinal mobility due to pain during the TMC278 + digoxin treatment phase. Subject 1001-1101 experienced rhinitis during the TMC278 + digoxin treatment phase.

Conclusions

This was a Phase I, open-label, randomized, crossover study in 22 healthy adult subjects to investigate the potential drug-drug interaction between TMC278 and digoxin.

The plasma and urine pharmacokinetics of the prototype permeability glycoprotein (P-gp) substrate digoxin were unaffected by coadministration of steady-state rilpivirine. The 90% CIs of the LSmeans ratios of the main pharmacokinetic parameters were contained within the 0.80 – 1.25 boundaries of no effect.

These results indicate that TMC278 at the recommended dose of 25 mg q.d. does not influence P-gp activity in vivo.

TMC278 steady-state pharmacokinetics were in line with those previously observed in other studies in healthy adults.

A single dose of digoxin with TMC278 at steady-state was generally safe and well tolerated in healthy adults.