SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals **Trade Name**: - **Indication**: HIV-1 infection	**Drug Substance**: TMC278 **Trial no.**: TMC278-TiDP38-C145 **Clinical Phase**: I
Title: A Phase I, open-label, randomized, crossover trial in healthy adults to compare the oral bioavailability of 3 concept pediatric formulations of TMC278 (solution, suspension, granules) to that of the adult 25 mg Phase III tablet formulation, and to assess the food effect for each concept formulation.	
Investigator: F.N.B. Cohen, M.D., Kendle International B.V., Clinical Pharmacology Unit, Bolognalaan 40, 3584 CJ Utrecht, The Netherlands.	**Country**: The Netherlands
Trial Period: Start: 13-Jan-2009 End: 02-May-2009	**No. of Investigators**: 1 **No. of Subjects**: 36

Objectives: The primary objectives of this trial were: to compare the rate and extent of absorption of TMC278 when administered as a single 25 mg dose of the 3 concept pediatric formulations (solution [10 mg/mL], suspension [5 mg/mL], granules [2.5 mg/g]), under fed and fasted conditions, to that when administered as the 25 mg TMC278 Phase III tablet formulation, under fed conditions, in healthy adults; and to assess the effect of food on the bioavailability of TMC278 after a single 25 mg dose of the concept pediatric formulations in healthy adults.

The secondary objectives were: to evaluate short-term safety and tolerability of TMC278 following administration of 3 single oral doses of 25 mg, formulated as one of the concept pediatric formulations (under fed and fasted conditions) and as the Phase III tablet (under fed conditions), in healthy adults; and to evaluate the palatability of each concept pediatric formulation in healthy adults under fasted conditions.

Design: This was a Phase I, open-label, randomized, 3-way crossover trial to compare the oral bioavailability of TMC278 after administration as 1 of 3 concept pediatric formulations (a solution [10 mg/mL], a suspension [5 mg/mL], or granules [2.5 mg/g]) to that when administered as the adult 25 mg Phase III tablet formulation, and to assess the food effect for each concept formulation. The palatability of each concept formulation was assessed as well, under fasted conditions.

TMC278 is being investigated for the treatment of HIV-1 infected subjects.

The trial population consisted of 36 healthy adults, divided over 3 panels of 12 subjects each, 1 panel for each concept pediatric formulation.

In each of the 3 panels, subjects received 3 different TMC278 treatments in a randomized fashion, in 3 subsequent sessions, separated by a washout period of at least 14 days.

The different treatments were:

Panel 1: single 25 mg TMC278 dose (2.5 mL) of oral solution (10 mg base/mL) in fed (Treatment A1) and fasted (Treatment B1) condition;

Panel 2: single 25 mg TMC278 dose (5 mL) of oral suspension (5 mg base equivalents/mL) in fed (Treatment A2) and fasted (Treatment B2) condition;

Panel 3: single 25 mg TMC278 dose (10 g) of granules (2.5 mg base equivalents/g) in fed (Treatment A3) and fasted (Treatment B3) condition;

Panels 1, 2, and 3: single 25 mg TMC278 dose as a tablet (25 mg base equivalents/tablet) in fed condition

(Treatment C).

In each treatment session, full pharmacokinetic profiles of TMC278 were measured up to 168 hours after intake.

Safety and tolerability were monitored throughout the trial.

Subject Selection

Inclusion Criteria

1. Aged between 18 and 55 years, extremes included.
2. Non-smoking or smoking no more than 10 cigarettes, or 2 cigars, or 2 pipes per day for at least 3 months prior to selection.
3. A Body Mass Index (weight in kg divided by the square of height in meters) of 18.0 to 30.0 kg/m^2, extremes included.
4. Informed Consent Form (ICF) signed voluntarily before the first trial-related activity.
5. Able to comply with protocol requirements.
6. Healthy on the basis of a medical evaluation that revealed the absence of any clinically relevant abnormality and included a physical examination, medical history, electrocardiogram (ECG), vital signs, and the results of blood biochemistry and hematology tests and a urinalysis carried out at screening.

Exclusion Criteria

1. A positive human immunodeficiency virus (HIV)-1 or HIV-2 test at screening.
2. Female, except if postmenopausal since more than 2 years, or posthysterectomy, or postsurgical sterilization (without reversal operation).
3. History or evidence of current use of alcohol, barbiturate, amphetamine, recreational, or narcotic drug use, which in the investigator's opinion would compromise subject's safety and/or compliance with the trial procedures.
4. Hepatitis A, B, or C infection (confirmed by hepatitis A antibody IgM, hepatitis B surface antigen, or hepatitis C virus antibody, respectively) at screening.
5. A positive urine drug test at screening. Urine was tested to check the current use of methadone, barbiturates, amphetamines, benzodiazepines, cocaine, cannabinoids, and opioids. Note: a positive test could be repeated once to exclude a technical error.
6. Currently active or underlying gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, endocrinologic, genitourinary, renal, hepatic, respiratory, inflammatory, or infectious disease.
7. Currently significant diarrhea, gastric stasis, or constipation that in the investigator's opinion could influence drug absorption or bioavailability.
8. Any history of significant skin disease such as, but not limited to, rash or eruptions, drug allergies, food allergy, dermatitis, eczema, psoriasis, or urticaria.
9. Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medication administered in this trial (i.e., TMC278).
10. Use of concomitant medication, including over-the-counter products, herbal medications, and dietary supplements. Over-the-counter medication had to be discontinued at least 7 days prior to the first administration of trial medication and prescribed medication had to be discontinued at least 14 days before the first intake of trial medication, except for ibuprofen and acetaminophen.
11. Participation in an investigational drug trial within 60 days prior to the first intake of trial medication.
12. Donation of blood or plasma or significant blood loss within the 60 days preceding the first intake of trial medication.

13. Subjects with the following laboratory abnormalities at screening, as defined by the Division of Acquired Immunodeficiency Syndrome Table for Grading the Severity of Adult and Pediatric Adverse Events and in accordance with the normal ranges of the clinical laboratory: serum lipase grade 1 or greater (≥ 1.1 x upper limit of laboratory range [ULN]); hemoglobin toxicity 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); aspartate aminotransferase or alanine aminotransferase grade 1 or greater (≥ 1.25 x ULN); total bilirubin grade 1 or greater (≥ 1.1 x ULN); any other laboratory abnormality of grade 2 or above, including proteinuria (spot urine) ≥ 2+, and microscopic hematuria (> 10 red blood cells/high power field), with the exception of grade 2 low density lipoprotein cholesterol or grade 2 total cholesterol values if < ULN of the local laboratory.
14. Having participated in more than 1 trial (single or multiple dose) with TMC125 (etravirine), TMC120 (dapivirine), and/or TMC278 (rilpivirine, formerly known as R278474), or having developed rash, erythema, or urticaria while participating in a trial with the aforementioned compounds.
15. History of clinically relevant heart rhythm disturbances or grade 2 or above electrolyte abnormalities (hypokalemia, hypocalcemia, hypomagnesemia) at screening.
16. Subjects with ageusia, hypogeusia, or dysgeusia.
17. Renal impairment: calculated creatinine clearance (CL_{Cr}) < 80 mL/min. Note: The site was to calculate CL_{Cr} using the Cockroft-Gault formula.

Treatment	Treatment A1, B1	Treatment A2, B2	Treatment A3, B3	Treatment C
Concentration	TMC278 10 mg/mL	TMC278 5 mg base equivalents/mL	TMC278 2.5 mg base equivalents/g	TMC278 25 mg base equivalents/tablet
Dosage	25 mg TMC278 (base)	25 mg TMC278 (HCl salt)	25 mg TMC278 (HCl salt)	25 mg TMC278 (HCl salt)
Dosage Form (TF No.)	Solution (R278474-F008)	Suspension (R314585-F014)	Granules (R314585-F015)	Tablets (R314585-F006)
Usage	Treatment A1: 25 mg on Day 1 of session (fed) Treatment B1: 25 mg on Day 1 of session (fasted) 2.5 mL orally single dose	Treatment A2: 25 mg on Day 1 of session (fed) Treatment B2: 25 mg on Day 1 of session (fasted) 5 mL orally single dose	Treatment A3: 25 mg on Day 1 of session (fed) Treatment B3: 25 mg on Day 1 of session (fasted) 10 g orally single dose	25 mg on Day 1 of session (fed) 1 tablet orally single dose
Batch Number	08K13	08K17	08K17	8BL2H

Dose Regimen	Panel 1: Group 1: treatment sequence A1/B1/C in 3 separate sessions. Group 2: treatment sequence B1/C/A1 in 3 separate sessions. Group 3: treatment sequence C/A1/B1 in 3 separate sessions. Group 4: treatment sequence C/B1/A1 in 3 separate sessions. Group 5: treatment sequence B1/A1/C in 3 separate sessions. Group 6: treatment sequence A1/C/B1 in 3 separate sessions. Panel 2: Groups 1 – 6: Same treatment sequences in 3 separate sessions as Panel 1, but with suspension formulation. Panel 3: Groups 1 – 6: Same treatment sequences in 3 separate sessions as Panel 1, but with granules formulation. Note: all sessions were separated by a 14-day washout period.
Duration of Treatment	Treatments A1, A2, A3, B1, B2, B3, and C: 1 day (single dose) each. Assessments were performed up to Day 8 (inclusive).
Duration of Trial	For each panel, 3 treatment periods of 1 day (single dose) each, with a washout period of 14 days in between each period (excluding screening and follow-up).
Disallowed Medication	All systemic over-the-counter medication had to be discontinued at least 7 days before the first administration of trial medication and all prescribed medication had to be discontinued at least 14 days before the first administration of trial medication, except for ibuprofen or acetaminophen. Subjects were not to use any medication other than the trial medication up to 14 days after the last intake of trial medication, except for ibuprofen or acetaminophen. Subjects were also not to use any systemic herbal medications or dietary supplements, including products containing *Hypericum perforatum* (e.g., St. John's wort) from 14 days before the first trial medication intake up to 14 days after the last trial medication intake. Ibuprofen or acetaminophen could be used up to 3 days before the intake of trial medication in each treatment session. After that, the clinical investigator could permit the use of ibuprofen or acetaminophen from 3 days before the intake of trial medication until the last pharmacokinetic sample had been taken in each treatment session, at no more than 400 mg per day for ibuprofen, and at no more than 1000 mg per day for acetaminophen. Hormone replacement therapy was allowed in postmenopausal women. 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 was permitted. In case of diarrhea, the use of loperamide was permitted.

Assessments	**Screening**[a]	**Treatments** **A1 (Panel 1), A2 (Panel 2), A3 (Panel 3), and C (Panels 1, 2, and 3): fed conditions** **B1 (Panel 1), B2 (Panel 2), and B3 (Panel 3): fasted conditions** **(Session I, II, or III)**[b]							**Follow-up**
	≤21 days	Day -1[c]	Day 1[d]	Day 2[e]	Day 3	Day 4	Day 6	Day 8[f]	Day 8[f] and 30, 31, or 32
Pharmacokinetics									
Blood sample[g]			X[h]	X	X	X	X	X	
Safety									
AEs and concomitant medication[i]	X	X	X	X	X	X	X	X	X
Hematology & biochemistry[j]	X		X[k]	X				X	X
Urinalysis	X		X[k]	X				X	X
Urine drug screen	X	X							
Serum pregnancy test, females only	X								X[l]
Urine pregnancy test, females only		X							
ECG	X		X[k]						
Vital signs[m]	X		X[k]	X				X	X
Skin examination	X	X						X	X
Physical examination	X	X						X	X
Other									
Taste questionnaire			X[n]						

AE = adverse event; ECG = electrocardiogram.

[a] Informed consent, smoking habits, inclusion/exclusion criteria, concomitant diseases, height, weight, subject characteristics and demographics, and medical and surgical history were recorded, and HIV-1 & -2 tests and hepatitis A, B, and C tests were performed before Day 1 of Session I.

[b] Treatments were separated by a washout period of at least 14 days.

[c] Subjects were admitted to the unit in the evening before Day 1.

[d] Start of water restriction began 2 hours before intake of trial medication and stopped 2 hours postdose.

[e] Subjects were discharged from the unit on this day.

[f] In Session III for each subject, Day 8 coincided with the first follow-up visit; therefore these investigations were only performed once.

[g] For determination of TMC278 plasma concentrations.

[h] Pharmacokinetic samples were taken predose (within 2 hours before intake of trial medication), 0.5, 1, 2, 3, 4, 5, 6, 9, 12, and 16 hours postdose on Day 1. Further pharmacokinetic samples were taken at 24, 48, 72, 120, and 168 hours postdose.

[i] Adverse events and concomitant medication were monitored continuously from signing the ICF until the last trial related activity.

[j] Biochemistry samples were taken fasted for at least 10 hours, before breakfast.

[k] Within 2 hours before intake of trial medication.

[l] Performed on Day 30, 31, or 32.

[m] Blood pressure and pulse rate: supine after 5 minutes, standing after 1 minute.

[n] Taste questionnaire to be completed by the subject within 5 to 15 minutes after TMC278 intake in Treatments B1, B2, and B3 only.

Statistical Methods	Descriptive statistics, graphical presentations, frequency tabulations including 90% confidence limits, intent-to-treat analysis, linear mixed effects modeling, Mann-Whitney U-Test.

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics - Subject Disposition	**Panel 1 Solution N = 12**	**Panel 2 Suspension N = 12**	**Panel 3 Granules N = 12**
Number of Subjects Entered (M/F)	8/4	10/2	11/1
Age: median (range), yrs	43.5 (22-54)	39.5 (21-54)	39.5 (20-54)
Race, n (%)			
Caucasian	10 (83.3)	10 (83.3)	9 (75.0)
Asian	1 (8.3)	1 (8.3)	1 (8.3)
Black	1 (8.3)	1 (8.3)	2 (16.7)
Drop-Outs – Reason			
Any reason	1 (8.3)	0	1 (8.3)
AEs	1 (8.3)	0	0
Non-compliance	0	0	1 (8.3)

Panel 1: oral solution, single dose of 25 mg TMC278			
Pharmacokinetics of TMC278 (mean ± SD, t_{max}: median [range])	**Tablet under fed conditions (reference)**	**Oral solution under fed conditions (test 1)**	**Oral solution under fasted conditions (test 2)**
n	12	12	11
C_{max}, ng/mL	113.8 ± 30.00	137.9 ± 30.14	184.9 ± 28.82
t_{max}, h	4.0 (4.0-5.0)	4.0 (3.0-6.0)	1.0 (1.0-2.0)
AUC_{last}, ng.h/mL	2910 ± 1150	3878 ± 890.9	3663 ± 561.4
AUC_{∞}, ng.h/mL	3338 ± 1332	4204 ± 1072	3964 ± 730.7
$t_{1/2term}$, h	46.59 ± 14.23	42.71 ± 12.87	44.46 ± 14.27
LS mean ratio (90% CI), %			
	-	**Test 1 vs reference**	**Test 2 vs reference**
n	-	12 vs 12	11 vs 12
C_{max}	-	122.6 (102.8 - 146.3)	169.7 (153.3 - 187.8)
AUC_{last}	-	138.7 (118.9 - 161.7)	129.5 (114.7 - 146.3)
AUC_{∞}	-	129.8 (111.5 - 151.1)	125.6 (110.9 - 142.1)
	-	-	**Test 2 vs test 1**
n	-	-	11 vs 12
C_{max}	-	-	131.6 (119.2 - 145.3)
AUC_{last}	-	-	92.94 (86.71 - 99.61)
AUC_{∞}	-	-	92.72 (85.74 - 100.3)

Panel 2: oral suspension, single dose of 25 mg TMC278			
Pharmacokinetics of TMC278 (mean ± SD, t_{max}: median [range])	**Tablet under fed conditions (reference)**	**Oral suspension under fed conditions (test 1)**	**Oral suspension under fasted conditions (test 2)**
n	12	12	12
C_{max}, ng/mL	108.7 ± 34.92	115.5 ± 26.12	130.4 ± 32.82
t_{max}, h	4.5 (3.0-9.0)	4.0 (3.0-5.0)	2.0 (1.0-4.0)
AUC_{last}, ng.h/mL	3127 ± 1129	3390 ± 1161	3263 ± 1291
AUC_{∞}, ng.h/mL	3597 ± 1768	4005 ± 1897	3671 ± 1703
$t_{1/2term}$, h	47.81 ± 21.87	54.17 ± 29.73	47.77 ± 18.01
LS mean ratio (90% CI), %			
	-	**Test 1 vs reference**	**Test 2 vs reference**
n	-	12 vs 12	12 vs 12
C_{max}	-	108.4 (98.09 - 119.9)	121.6 (107.7 - 137.2)
AUC_{last}	-	108.4 (98.30 - 119.4)	103.4 (92.90 - 115.0)
AUC_{∞}	-	111.4 (102.1 - 121.5)	102.4 (92.69 - 113.2)
	-	-	**Test 2 vs test 1**
n	-	-	12 vs 12
C_{max}	-	-	112.1 (104.8 - 120.0)
AUC_{last}	-	-	95.40 (91.09 - 99.91)
AUC_{∞}	-	-	91.92 (87.45 - 96.62)

Panel 3: oral granules, a single dose of 25 mg TMC278			
Pharmacokinetics of TMC278 (mean ± SD, t_{max}: median [range])	**Tablet under fed conditions (reference)**	**Granules under fed conditions (test 1)**	**Granules under fasted conditions (test 2)**
n	11	11	11[a]
C_{max}, ng/mL	102.9 ± 33.16	119.3 ± 26.81	85.95 ± 22.07
t_{max}, h	5.0 (2.0-5.0)	4.0 (3.0-5.0)	4.0 (2.0-5.0)
AUC_{last}, ng.h/mL	2922 ± 1220	3665 ± 1273	2479 ± 1097
AUC_{∞}, ng.h/mL	3263 ± 1467	3990 ± 1425	2740 ± 1192
$t_{1/2term}$, h	43.34 ± 23.23	40.00 ± 16.89	45.90 ± 22.98
LS mean ratio (90% CI), %			
	-	**Test 1 vs reference**	**Test 2 vs reference**
n	-	11 vs 11	11 vs 11
C_{max}	-	118.4 (100.0 - 140.3)	87.02 (78.55 - 96.41)
AUC_{last}	-	127.7 (110.6 - 147.6)	93.09 (84.94 - 102.0)
AUC_{∞}	-	125.8 (108.6 - 145.8)	92.70 (85.96 - 99.98)
	-	-	**Test 2 vs test 1**
n	-	-	11 vs 11
C_{max}	-	-	70.05 (58.94 - 83.24)
AUC_{last}	-	-	71.08 (63.35 - 79.75)
AUC_{∞}	-	-	72.04 (64.34 - 80.67)

[a] n=12 for $t_{1/2term}$

Panel 1: oral solution, single dose of 25 mg TMC278			
Safety (n = number of subjects with data)	**TMC278 25 mg solution**		**TMC278 25 mg tablet**
	Fed N=12	**Fasted N=11**	**Fed N=12**
Adverse Events (AEs)			
n (%) with 1 or more AEs	6 (50.0)	4 (36.4)	8 (66.7)
n (%) of deaths	0	0	0
n (%) with 1 or more other serious AEs	0	0	0
n (%) of treatment stopped due to AEs	0	0	1 (8.3)
n (%) with 1 or more grade 3 or 4 AEs	0	0	0
Most frequently reported treatment-emergent AEs (reported in ≥ 2 subjects with any treatment), n (%)			
Headache	2 (16.7)	2 (18.2)	4 (33.3)
Myalgia	2 (16.7)	1 (9.1)	0
Fatigue	2 (16.7)	0	2 (16.7)

Panel 2: oral suspension, single dose of 25 mg TMC278			
Safety (n = number of subjects with data)	**TMC278 25 mg suspension**		**TMC278 25 mg tablet**
	Fed N=12	**Fasted N=12**	**Fed N=12**
Adverse Events (AEs)			
n (%) with 1 or more AEs	6 (50.0)	5 (41.7)	6 (50.0)
n (%) of deaths	0	0	0
n (%) with 1 or more other serious AEs	0	0	0
n (%) of treatment stopped due to AEs	0	0	0
n (%) with 1 or more grade 3 or 4 AEs	0	0	0
Most frequently reported treatment-emergent AEs (reported in ≥ 2 subjects with any treatment), n (%)			
Headache	4 (33.3)	2 (16.7)	2 (16.7)
Nasopharyngitis	1 (8.3)	2 (16.7)	2 (16.7)
Oropharyngeal Pain	0	0	2 (16.7)

Panel 3: oral granules, a single dose of 25 mg TMC278			
Safety (n = number of subjects with data)	**TMC278 25 mg granules**		**TMC278 25 mg tablet**
	Fed N=11	**Fasted N=12**	**Fed N=11**
Adverse Events (AEs)			
n (%) with 1 or more AEs	7 (63.6)	5 (41.7)	3 (27.3)
n (%) of deaths	0	0	0
n (%) with 1 or more other serious AEs	0	0	0
n (%) of treatment stopped due to AEs	0	0	0
n (%) with 1 or more grade 3 or 4 AEs	0	0	0
Most frequently reported treatment-emergent AEs (reported in ≥ 2 subjects with any treatment), n (%)			
Headache	3 (27.3)	1 (8.3)	1 (9.1)
Nasopharyngitis	0	0	2 (18.2)

There were no notable differences in the incidences of AEs across the panels. Within the solution, suspension, and granule treatment groups, a slightly higher incidence of AEs was observed under fed conditions, compared to fasted conditions. The most commonly reported AE during the trial was headache. One subject was reported with a grade 2 AE of rash maculo-papular during treatment with the TMC278 tablet (fed), which led to the withdrawal of the subject from the trial. No grade 3 (severe) or grade 4 (life-threatening) treatment-emergent AEs were reported. There were no deaths or SAEs reported in this trial.
Skin events of interest were reported for 2 subjects during the trial: 1 (8.3%) subject during treatment with the TMC278 solution (fed) (rash papular) and 1 (8.3%) subject with a grade 2 AE of rash maculo-papular as mentioned above.

Clinical Laboratory Tests

No clinically meaningful changes over time were observed in the hematology, biochemistry, and urinalysis parameters in any treatment group. The majority of treatment-emergent abnormalities were DAIDS grade 1. The most common treatment-emergent grade 2 abnormalities were decreased phosphorus, hyperglycemia, increased lipase, and increased total bilirubin; reported in no more than 2 subjects in any session. No grade 3 or 4 treatment-emergent laboratory abnormalities were observed during the trial. No subjects were observed with treatment-emergent AEs related to laboratory parameters or discontinued the trial for this reason.

Vital Signs

There were no consistent or clinically relevant changes in vital signs parameters, and no clinically relevant individual abnormalities were observed.

Physical Examination

No clinically relevant new physical examination findings were reported. No new physical examination abnormalities were reported as AEs.

Taste Questionnaire

A higher proportion of subjects rated the overall palatability of the TMC278 suspension and granule formulation as "acceptable" or "good" (83.3% and 8.3% [suspension], and 66.7% and 16.7% [granules], respectively), compared to the solution (25.0% and 16.7%, respectively). The results of the visual analogue scale revealed that a higher proportion (58.3%) of subjects in the TMC278 solution group expressed a dislike (very much or a little) to the solution compared to the suspension or granule groups (16.7% each).

Conclusions

Pharmacokinetics

The results of the present trial demonstrate that all 3 concept pediatric formulations of TMC278 have an acceptable oral bioavailability when administered as a single dose of 25 mg.

Oral Solution
Both in fed and fasted conditions, the TMC278 exposure (C_{max}, AUC) for the oral solution was higher as compared to the tablet formulation in fed conditions, and this was especially apparent for C_{max} of the solution in fasted conditions (70% higher). While the AUC for the solution was similar in fasted and fed conditions, the C_{max} was 32% higher in the fasted as compared to the fed condition.

Oral Suspension
The exposure for the oral suspension, both under fed and fasted conditions, was comparable to that of the tablet formulation under fed conditions, except for a higher C_{max} (22%) when the oral suspension was administered under fasted conditions. There was no food effect for the suspension formulation.

Oral Granules
When administered in fed conditions, the exposure (C_{max}, AUC) for the granules was about 20-30% higher as compared to the tablet formulation in fed conditions. Under fasted conditions, the exposure (AUC) for the granules was similar, with a lower C_{max} as compared to the tablet formulation in fed conditions. There was a food effect for the granules, with a 28-30% lower exposure (C_{max}, AUC) when administered under fasted as compared to fed conditions.

Safety

No new safety signals for AEs, laboratory parameters, vital signs, or ECG were observed.

Taste Questionnaire

The proportion of subjects in each panel that rated the concept formulation as "acceptable" or "good" was 41.7%, 91.7%, and 83.3% for the TMC278 solution, suspension, and granule formulations, respectively.

Disclaimer

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