Clinical trial results:
An Open-Label Study with TMC278 25 mg q.d. in Combination with a Background Regimen Containing 2 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors in HIV-1 Infected Subjects, Who Participated in TMC278 clinical studies

Summary

EudraCT number	2010-021209-18
Trial protocol	BE DE GB SE ES IT DK AT NL
Global end of trial date	28 February 2020

Results information

Result version number	v1 (current)
This version publication date	26 February 2021
First version publication date	26 February 2021

Trial information

Trial identification

Sponsor protocol code	TMC278-TiDP6-C222

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01266902
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202, Raritan, United States, NJ 08869
Public contact	Janssen Research & Development, LLC, Clinical Registry group, ClinicalTrialsEU@its.jnj.com
Scientific contact	Janssen Research & Development, LLC, Clinical Registry group, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to provide continued access to rilpivirine (RPV) for subjects who were randomized and treated with RPV in the Phase 2b (TMC278-C204 [C204]) or Phase 3 studies (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215]), and who, at the time of roll-over, experienced and were expected to continue experiencing clinical benefit from RPV treatment.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and applicable regulatory requirements. Serious Adverse Events (SAEs), Adverse events (AEs) leading to discontinuation, any grade 3/4 events of rash (irrespective of causality), AEs considered at least possibly related to RPV, human immunodeficiency virus (HIV)-related AEs, and pregnancies were collected from signing of the informed consent form (ICF) until the data cut-off date and were followed up by the investigator.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 February 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	9 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 35
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Chile: 12
Country: Number of subjects enrolled	China: 26
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Netherlands: 3

Country: Number of subjects enrolled	Puerto Rico: 7
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Russian Federation: 38
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Thailand: 65
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	United States: 85
Country: Number of subjects enrolled	South Africa: 48
Worldwide total number of subjects	482
EEA total number of subjects	107

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	479
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total of 482 subjects were treated and 437 discontinued at data cut-off date (8 Feb 2018): 371 switched to commercially available RPV and 6 discontinued as they reached a virologic endpoint. At last visit of last subject (28 February 2020), out of 45 subjects 37 switched to commercially available RPV and 6 lost to follow-up.

Period 1

Period 1 title	Period 1 (Main Study)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not Applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Rilpivirine (RPV) (TMC278-C204 [C204])

Arm description:

Subjects who rolled over from trial C204 continued to receive RPV 25 milligrams (mg) once daily (qd) in combination with an investigator-selected background regimen consisting of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI)s starting Day 1.

Arm type	Experimental
Investigational medicinal product name	Rilpivirine
Investigational medicinal product code	
Other name	TMC278
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

RPV 25 mg oral tablets were administered orally.

Investigational medicinal product name	Nucleos(t)ide Reverse Transcriptase Inhibitors
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two N(t)RTIs were administered as the investigator-selected background regimen.

Arm title	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])

Arm description:

Subjects who rolled over from trial C209 and C215 continued to receive RPV 25 mg qd in combination with an investigator-selected background regimen consisting of 2 N(t)RTIs starting Day 1. In trial C209, the background regimen was fixed to tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) and in trial C215, the background regimen was selected by the investigator and contained either abacavir (ABC)/lamivudine (3TC), zidovudine (AZT)/3TC, or TDF/FTC.

Arm type	Experimental

Investigational medicinal product name	Nucleos(t)ide Reverse Transcriptase Inhibitors
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two N(t)RTIs were administered as the investigator-selected background regimen.

Investigational medicinal product name	Rilpivirine
Investigational medicinal product code	
Other name	TMC278
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

RPV 25 mg oral tablets were administered orally.

Number of subjects in period 1	Rilpivirine (RPV) (TMC278-C204 [C204])	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])
Started	119	363
Completed	89	282
Not completed	30	81
Consent withdrawn by subject	2	12
Adverse events	3	11
Continued to RPV treatment	11	34
Investigator's/Subject's decision	2	3
Subject non-compliant	3	7
Lost to follow-up	5	12
Lack of efficacy	4	2

Period 2

Period 2 title	Period 2 (After Protocol Amendment 3)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not Applicable

Arms

Arm title	RPV 25 mg (After Protocol Amendment 3)

Arm description:

All subjects who were continued under a simplified study setting with only a minimum of study-related activities, as per Protocol Amendment 3 continued to receive RPV 25 mg and followed up for safety.

Arm type	Experimental
Investigational medicinal product name	Rilpivirine
Investigational medicinal product code	
Other name	TMC278
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

RPV 25 mg oral tablets were administered orally.

Number of subjects in period 2[1]	RPV 25 mg (After Protocol Amendment 3)
Started	45
Completed	37
Not completed	8
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Lost to follow-up	6

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only 45 subjects continued Rilpivirine (RPV) treatment per Protocol Amendment 3.

Baseline characteristics

Reporting groups	
Reporting group title	Rilpivirine (RPV) (TMC278-C204 [C204])
Reporting group description:	
Subjects who rolled over from trial C204 continued to receive RPV 25 milligrams (mg) once daily (qd) in combination with an investigator-selected background regimen consisting of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI)s starting Day 1.	
Reporting group title	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])
Reporting group description:	
Subjects who rolled over from trial C209 and C215 continued to receive RPV 25 mg qd in combination with an investigator-selected background regimen consisting of 2 N(t)RTIs starting Day 1. In trial C209, the background regimen was fixed to tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) and in trial C215, the background regimen was selected by the investigator and contained either abacavir (ABC)/lamivudine (3TC), zidovudine (AZT)/3TC, or TDF/FTC.	

Reporting group values	Rilpivirine (RPV) (TMC278-C204 [C204])	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])	Total
Number of subjects	119	363	482
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	118	361	479
From 65 to 84 years	1	2	3
85 years and over	0	0	0
Title for AgeContinuous Units: years			
median	40	39	
full range (min-max)	28 to 66	22 to 69	-
Title for Gender Units: subjects			
Female	41	84	125
Male	78	279	357

End points

End points reporting groups

Reporting group title	Rilpivirine (RPV) (TMC278-C204 [C204])

Reporting group description:

Subjects who rolled over from trial C204 continued to receive RPV 25 milligrams (mg) once daily (qd) in combination with an investigator-selected background regimen consisting of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI)s starting Day 1.

Reporting group title	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])

Reporting group description:

Subjects who rolled over from trial C209 and C215 continued to receive RPV 25 mg qd in combination with an investigator-selected background regimen consisting of 2 N(t)RTIs starting Day 1. In trial C209, the background regimen was fixed to tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) and in trial C215, the background regimen was selected by the investigator and contained either abacavir (ABC)/lamivudine (3TC), zidovudine (AZT)/3TC, or TDF/FTC.

Reporting group title	RPV 25 mg (After Protocol Amendment 3)

Reporting group description:

All subjects who were continued under a simplified study setting with only a minimum of study-related activities, as per Protocol Amendment 3 continued to receive RPV 25 mg and followed up for safety.

Primary: Number of Subjects with Adverse Events (AEs)

End point title	Number of Subjects with Adverse Events (AEs)[1]

End point description:

An AE can be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non investigational) product, whether or not related to that medicinal (investigational or non investigational) product. The intent-to-treat (ITT) population included all subjects who have taken at least 1 dose of rilpivirine (RPV), regardless of their compliance with the protocol and adherence to the dosing regimen.

End point type	Primary

End point timeframe:

Up to 7 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Inferential statistical analysis was planned for the Primary Endpoint.

End point values	Rilpivirine (RPV) (TMC278-C204 [C204])	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	363		
Units: Subjects	32	70		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Grade 3/4 Events of Rash irrespective of

Causality

End point title	Number of Subjects with Grade 3/4 Events of Rash irrespective of Causality[2]

End point description:

Subjects with grade 3/4 events of rash irrespective of causality were assessed. A grade 3 rash defined as diffuse macular, maculopapular or morbilliform rash with vesicles or limited number of bullae or; rash with superficial ulcerations of mucous membranes limited to 1 anatomical site or; rash with at least one of following: elevations in aspartate aminotransferase (AST)/alanine aminotransferase (ALT) more than 2*baseline value and at least 5 times upper limit of normal; fever greater than (>) 38 degree celsius or 100 degree fahrenheit; eosinophils > 1000/millimeter (mm)^3; serum sickness-like reaction. A grade 4 rash defined as following: extensive or generalized bullous lesions or; Stevens-Johnsons Syndrome (SJS) or ulceration of mucous membrane involving 2 or more distinct mucosal sites or toxic epidermal necrolysis. The ITT population included all subjects who have taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen.

End point type	Primary

End point timeframe:

Up to 7 years

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Inferential statistical analysis was planned for the Primary Endpoint.

End point values	Rilpivirine (RPV) (TMC278-C204 [C204])	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	363		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Virologic Rebound

End point title	Time to Virologic Rebound

End point description:

Time to virologic rebound was time to (first) human immunodeficiency virus type 1 (HIV-1) ribonucleic acid (RNA) greater than or equal to (>=) 50 or >= 200 copies/milliliter (copies/mL). The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time. The ITT population included all subjects who have taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen.

End point type	Secondary

End point timeframe:

Up to Week 360

End point values	Rilpivirine (RPV) (TMC278-C204 [C204])	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	363		
Units: days				
arithmetic mean (standard error)				
>= 50 copies/mL	1670.6 (± 51.32)	1939.3 (± 52.43)		
>= 200 copies/mL	1901.3 (± 47.19)	1877.3 (± 25.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time To Treatment Failure

End point title	Time To Treatment Failure

End point description:

Time to treatment failure was defined as time to virologic rebound (time to first HIV-1 RNA >= 50 or >= 200 copies/mL) or discontinuation for reason other than RPV having become commercially available in the participating country, whichever came first, calculated as the time (in days) from baseline until treatment failure. The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time. The ITT population included all subjects who have taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen.

End point type	Secondary

End point timeframe:

Up to Week 360

End point values	Rilpivirine (RPV) (TMC278-C204 [C204])	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	363		
Units: days				
arithmetic mean (standard error)				
>= 50 copies/mL	1795.7 (± 70.03)	1694.1 (± 59.42)		
>= 200 copies/mL	1868.7 (± 63.29)	1637.5 (± 42.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Cluster of Differentiation 4 (CD4+) Cell Count for Observed Case Approach until Week 336

End point title	Change from Baseline in Cluster of Differentiation 4 (CD4+) Cell Count for Observed Case Approach until Week 336

End point description:

Change from baseline in CD4+ cell count were reported for observed case approach. The immunologic assessment was determined by changes in Cluster of CD4+ cell count for observed case approach. The ITT population included all subjects who have taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen. Here 'n' (number analyzed) included all subjects who were evaluable for specified time point categories.

End point type	Secondary

End point timeframe:

Baseline up to Weeks 96, 192, 288, 336

End point values	Rilpivirine (RPV) (TMC278-C204 [C204])	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	363		
Units: cells/microliter (cells/mcL)				
arithmetic mean (standard error)				
Week 96: Observed Case (n= 74, 149)	72.63 (± 20.581)	55.91 (± 13.425)		
Week 192: Observed Case (n= 68, 100)	148.76 (± 24.111)	132.73 (± 21.989)		
Week 288: Observed Case (n= 45, 89)	122.29 (± 29.628)	101.50 (± 24.108)		
Week 336: Observed Case (n= 12, 30)	161.73 (± 39.851)	76.49 (± 40.484)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CD4+ Cell Count for Non-Completer Equals Failure (NC=F) Approach until Week 336

End point title	Change from Baseline in CD4+ Cell Count for Non-Completer Equals Failure (NC=F) Approach until Week 336

End point description:

Change from baseline in CD4+ cell count were reported for NC=F approach (subjects who discontinued because RPV became commercially available or could be accessed through another source or because the subjects switched to other local [RPV-based] treatment options or local standard of care, were censored at that time; other subjects after discontinuation had their CD4+ values imputed with baseline value. Intermittently missing values were imputed with a last observation carried-forward approach). The ITT population included all subjects who have taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regime. Here 'n' (number analyzed) included all subjects who were evaluable for specified time point categories.

End point type	Secondary

End point timeframe:

Baseline up to weeks 96, 192, 288, 336

End point values	Rilpivirine (RPV) (TMC278-C204 [C204])	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	363		
Units: cells/mcL				
arithmetic mean (standard error)				
Week 96 (n= 79, 196)	69.76 (± 19.372)	42.19 (± 11.525)		
Week 192 (n= 77, 153)	133.56 (± 21.906)	91.69 (± 15.563)		
Week 288 (n= 61, 134)	92.12 (± 22.809)	63.33 (± 17.132)		
Week 336 (n= 27, 86)	70.69 (± 23.558)	49.24 (± 16.688)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Serious Adverse Events (SAEs)

End point title	Number of Subjects with Serious Adverse Events (SAEs)

End point description:

A SAE is any untoward medical occurrence that at any dose: results in death; is life threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect. The ITT population included all subjects who have taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen.

End point type	Secondary

End point timeframe:

Up to 7 years

End point values	Rilpivirine (RPV) (TMC278-C204 [C204])	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	363		
Units: Subjects	9	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with AEs related to Rilpivirine (RPV)

End point title	Number of Subjects with AEs related to Rilpivirine (RPV)

End point description:

Number of subjects with AEs related to RPV were assessed. An AE can be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non investigational) product, whether or not related to that medicinal (investigational or non investigational) product. The ITT population included all subjects who have taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen.

End point type	Secondary

End point timeframe:

Up to 7 years

End point values	Rilpivirine (RPV) (TMC278-C204 [C204])	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	363		
Units: Subjects	7	16		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 7 years

Adverse event reporting additional description:

The safety analysis set included all subjects who have taken at least 1 dose of rilpivirine (RPV), regardless of their compliance with the protocol and adherence to the dosing regimen.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Rilpivirine (RPV) (TMC278-C204 [C204])

Reporting group description:

Subjects who rolled over from trial C204 continued to receive RPV 25 milligrams (mg) once daily (qd) in combination with an investigator-selected background regimen consisting of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI)s starting Day 1.

Reporting group title	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])

Reporting group description:

Subjects who rolled over from trial C209 and C215 continued to receive RPV 25 mg qd in combination with an investigator-selected background regimen consisting of 2 N(t)RTIs starting Day 1. In trial C209, the background regimen was fixed to tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) and in trial C215, the background regimen was selected by the investigator and contained either abacavir (ABC)/lamivudine (3TC), zidovudine (AZT)/3TC, or TDF/FTC.

Serious adverse events	Rilpivirine (RPV) (TMC278-C204 [C204])	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 119 (7.56%)	14 / 363 (3.86%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal Adenoma			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon Cancer			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastric Cancer			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose Vein			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood Glucose Increased			

subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Foot Fracture			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand Fracture			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb Injury			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stab Wound			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac Hypertrophy			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ischaemic Stroke			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemolytic Anaemia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	1 / 119 (0.84%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal Failure			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue Fever			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Abscess			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syphilis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Rilpivirine (RPV) (TMC278-C204 [C204])	RPV (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215])	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 119 (20.17%)	61 / 363 (16.80%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital Warts			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	2 / 119 (1.68%)	0 / 363 (0.00%)	
occurrences (all)	2	0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 119 (0.00%)	7 / 363 (1.93%)	
occurrences (all)	0	7	
General disorders and administration site conditions			
Chest Discomfort			
subjects affected / exposed	1 / 119 (0.84%)	1 / 363 (0.28%)	
occurrences (all)	1	1	
Chest Pain			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	1	0	
Feeling Hot			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Nodule			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Oedema Peripheral			

subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 119 (0.00%)	2 / 363 (0.55%)	
occurrences (all)	0	2	
Epistaxis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Nasal Congestion			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal Pain			
subjects affected / exposed	0 / 119 (0.00%)	3 / 363 (0.83%)	
occurrences (all)	0	3	
Productive Cough			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Psychiatric disorders			
Abnormal Dreams			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Anxiety			
subjects affected / exposed	0 / 119 (0.00%)	2 / 363 (0.55%)	
occurrences (all)	0	2	
Depression			

subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 119 (0.00%)	3 / 363 (0.83%)	
occurrences (all)	0	3	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 119 (0.84%)	3 / 363 (0.83%)	
occurrences (all)	1	4	
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	2	
Blood Cholesterol Increased			
subjects affected / exposed	0 / 119 (0.00%)	2 / 363 (0.55%)	
occurrences (all)	0	2	
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	1	0	
Blood Creatinine Increased			
subjects affected / exposed	0 / 119 (0.00%)	2 / 363 (0.55%)	
occurrences (all)	0	2	
Blood Lactic Acid Increased			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Blood Triglycerides Increased			
subjects affected / exposed	0 / 119 (0.00%)	3 / 363 (0.83%)	
occurrences (all)	0	3	
Liver Function Test Abnormal			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Bone Fissure			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Injury			

subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	1	0	
Joint Injury			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Laceration			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Skin Injury			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Nervous system disorders			
Carpal Tunnel Syndrome			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Cluster Headache			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Disturbance in Attention			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	0 / 119 (0.00%)	4 / 363 (1.10%)	
occurrences (all)	0	4	
Paraesthesia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Eye disorders			

Conjunctivitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Eye Pain			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Abdominal Pain			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	1	0	
Abdominal Pain Lower			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Abdominal Pain Upper			
subjects affected / exposed	1 / 119 (0.84%)	2 / 363 (0.55%)	
occurrences (all)	1	3	
Anal Pruritus			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Cheilitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	0 / 119 (0.00%)	2 / 363 (0.55%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	0 / 119 (0.00%)	2 / 363 (0.55%)	
occurrences (all)	0	2	
Enteritis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Gastritis			

subjects affected / exposed	1 / 119 (0.84%)	1 / 363 (0.28%)	
occurrences (all)	1	1	
Gingivitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Oesophagitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Alopecia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Dermal Cyst			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Dermatitis Allergic			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	3	
Dyshidrosis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Facial Wasting			

subjects affected / exposed	2 / 119 (1.68%)	0 / 363 (0.00%)	
occurrences (all)	2	0	
Lipoatrophy			
subjects affected / exposed	1 / 119 (0.84%)	1 / 363 (0.28%)	
occurrences (all)	1	1	
Lipodystrophy Acquired			
subjects affected / exposed	2 / 119 (1.68%)	0 / 363 (0.00%)	
occurrences (all)	2	0	
Pruritus			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	1	0	
Seborrhoeic Dermatitis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	1	0	
Skin Plaque			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 119 (0.00%)	2 / 363 (0.55%)	
occurrences (all)	0	2	
Osteopenia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Trismus			

subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Infections and infestations			
Body Tinea			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	2	0	
Chlamydial Infection			
subjects affected / exposed	1 / 119 (0.84%)	1 / 363 (0.28%)	
occurrences (all)	1	1	
Dengue Fever			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	1	0	
Eye Infection Toxoplasmal			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Fungal Infection			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Genital Herpes			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Hepatitis C			
subjects affected / exposed	2 / 119 (1.68%)	0 / 363 (0.00%)	
occurrences (all)	2	0	
Herpes Simplex			
subjects affected / exposed	1 / 119 (0.84%)	1 / 363 (0.28%)	
occurrences (all)	1	1	
Herpes Zoster			
subjects affected / exposed	1 / 119 (0.84%)	2 / 363 (0.55%)	
occurrences (all)	2	2	
Hordeolum			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	

Influenza			
subjects affected / exposed	0 / 119 (0.00%)	2 / 363 (0.55%)	
occurrences (all)	0	2	
Latent Tuberculosis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Lymph Node Tuberculosis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 119 (0.00%)	2 / 363 (0.55%)	
occurrences (all)	0	2	
Oral Herpes			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	1	0	
Otitis Externa			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Otitis Media			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Perineal Abscess			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	1	0	
Periorbital Cellulitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Respiratory Tract Infection Viral			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Syphilis			
subjects affected / exposed	2 / 119 (1.68%)	2 / 363 (0.55%)	
occurrences (all)	3	2	

Tonsillitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 119 (0.00%)	3 / 363 (0.83%)	
occurrences (all)	0	3	
Urinary Tract Infection			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	1	0	
Diabetes Mellitus			
subjects affected / exposed	1 / 119 (0.84%)	0 / 363 (0.00%)	
occurrences (all)	1	0	
Hypercholesterolaemia			
subjects affected / exposed	1 / 119 (0.84%)	1 / 363 (0.28%)	
occurrences (all)	3	3	
Hyperglycaemia			
subjects affected / exposed	1 / 119 (0.84%)	1 / 363 (0.28%)	
occurrences (all)	1	3	
Hyperuricaemia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	
Vitamin D Deficiency			
subjects affected / exposed	0 / 119 (0.00%)	1 / 363 (0.28%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2011	Amendment 1, issued on 5 May 2011, was considered substantial and the overall reason for the amendment was to replace the serum pregnancy test by a urine pregnancy test, add a reminder for the human leukocyte antigen (HLA)-B*5701 allele testing and viral genotype determination, switching of background nucleos(t)ide reverse transcriptase inhibitors [N(t)RTI]s from the roll-over visit onwards was allowed, effective methods of birth control for male and female subjects were updated and the withdrawal criteria were updated.
28 November 2016	Amendment 3, issued on 28 November 2016 (with country-specific amendments in South Africa and Chile [25 July 2017]), was considered substantial and the overall reason for the amendment was the simplification of the study and the reduction of study-related activities to a minimum for the limited number of subjects remaining in this study. The main component of the study remained to allow subjects who experienced and were expected to continue experiencing clinical benefit from rilpivirine (RPV) treatment to have continued access to RPV in a simplified study setting or to be switched to local (RPV-based) treatment options or local standard of care, as appropriate.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not all AEs were collected; AEs considered related to RPV, leading to discontinuations, SAEs, or grade 3/4 events of rash regardless of causality were collected; discontinuation rate was > 90 percent which makes interpretation of results difficult.

Notes: