Clinical trial results:
A Phase II, Open Label, Single Arm Trial to Evaluate the Pharmacokinetics, Safety, Tolerability, and Antiviral Activity of Rilpivirine (TMC278) in Antiretroviral-naïve HIV-1 Infected Adolescents and Children Aged >=6 to <18 Years

Summary

EudraCT number	2008-001696-30
Trial protocol	ES Outside EU/EEA
Global end of trial date	16 August 2022

Results information

Result version number	v1 (current)
This version publication date	04 March 2023
First version publication date	04 March 2023

Trial information

Trial identification

Sponsor protocol code	CR002677

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development LLC
Sponsor organisation address	920, US Highway, Route 202, South Raritan New Jersey, United States, 08869
Public contact	Clinical Registry Group, Janssen Research & Development LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development LLC, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000317-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the steady-state pharmacokinetics (based on intensive pharmacokinetic analysis) of Rilpivirine 25 milligrams (mg) once daily (QD.) or adjusted dose of Rilpivirine QD in subjects aged greater than or equal to (>=) 12 to less than (<) 18 years and >=6 to <12 years and to evaluate safety and tolerability of Rilpivirine.

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 and applicable regulatory requirements.

Background therapy:

Subjects received investigator-selected background regimen containing 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) (zidovudine [AZT], abacavir [ABC] or tenofovir disoproxil fumarate [TDF] in combination with lamivudine [3TC] or emtricitabine [FTC], in Cohort 1 (adolescents aged >=12 to <18 years) up to 240 weeks and in cohort 2 (children aged >=6 to <12 years) up to 48 Weeks.

Evidence for comparator: -

Actual start date of recruitment	07 January 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	56 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	India: 3
Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	Uganda: 20
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	South Africa: 27
Worldwide total number of subjects	54
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	18
Adolescents (12-17 years)	36
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 54 antiretroviral-naïve human Immunodeficiency Virus-1 (HIV-1) infected adolescents and children participants were enrolled and treated.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Cohort 1 and 2: Rilpivirine: All Subjects

Arm description:

Cohort 1 (adolescents aged greater than or equal to [>=] 12 to less than [<] 18 years), subjects received rilpivirine tablet 25 milligrams (mg) or adjusted dose orally once daily (QD) up to 240 weeks. In Cohort 2 (children aged >=6 to <12 years), received rilpivirine body weight adjusted dose (body weight <20 kilograms [kg]: 12.5 mg; between 20 kg to <25kg: 15 mg; >=25 kg: 25 mg) orally QD up to 48 weeks. In both the cohorts, rilpivirine was administered in combination with an investigator-selected background regimen containing 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs): zidovudine (AZT), abacavir (ABC), or tenofovir disoproxil fumarate (TDF) in combination with lamivudine (3TC) oremtricitabine (FTC).

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:

Cohort 1: Rilpivirine 25 mg QD for 240 weeks and Cohort 2: weight adjusted dose (<20 kg: 12.5 mg; 20 kg to <25 kg: 15 mg; >=25 kg: 25 mg) QD for 48 weeks.

Number of subjects in period 1	Cohort 1 and 2: Rilpivirine: All Subjects
Started	54
Completed	38
Not completed	16
Adverse Event	1
Unspecified	2
Subject reached a virologic endpoint	13

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 and 2: Rilpivirine: All Subjects

Reporting group description:

Cohort 1 (adolescents aged greater than or equal to [>=] 12 to less than [<] 18 years), subjects received rilpivirine tablet 25 milligrams (mg) or adjusted dose orally once daily (QD) up to 240 weeks. In Cohort 2 (children aged >=6 to <12 years), received rilpivirine body weight adjusted dose (body weight <20 kilograms [kg]: 12.5 mg; between 20 kg to <25kg: 15 mg; >=25 kg: 25 mg) orally QD up to 48 weeks. In both the cohorts, rilpivirine was administered in combination with an investigator-selected background regimen containing 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs): zidovudine (AZT), abacavir (ABC), or tenofovir disoproxil fumarate (TDF) in combination with lamivudine (3TC) oremtricitabine (FTC).

Reporting group values	Cohort 1 and 2: Rilpivirine: All Subjects	Total	
Number of subjects	54	54	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	18	18	
Adolescents (12-17 years)	36	36	
Adults (18-64 years)	0	0	
From 65 to 84 years	0	0	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	12.6		
standard deviation	± 3.29	-	
Title for Gender Units: subjects			
Female	27	27	
Male	27	27	

End points

End points reporting groups

Reporting group title	Cohort 1 and 2: Rilpivirine: All Subjects

Reporting group description:

Cohort 1 (adolescents aged greater than or equal to [>=] 12 to less than [<] 18 years), subjects received rilpivirine tablet 25 milligrams (mg) or adjusted dose orally once daily (QD) up to 240 weeks. In Cohort 2 (children aged >=6 to <12 years), received rilpivirine body weight adjusted dose (body weight <20 kilograms [kg]: 12.5 mg; between 20 kg to <25kg: 15 mg; >=25 kg: 25 mg) orally QD up to 48 weeks. In both the cohorts, rilpivirine was administered in combination with an investigator-selected background regimen containing 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs): zidovudine (AZT), abacavir (ABC), or tenofovir disoproxil fumarate (TDF) in combination with lamivudine (3TC) oremtricitabine (FTC).

Subject analysis set title	Cohort 1 (>=12 to <18 Years): Rilpivirine
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects received rilpivirine tablet 25 mg or adjusted dose orally QD up to 240 weeks in combination with an investigator-selected background regimen containing 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs): zidovudine (AZT), abacavir (ABC), or tenofovir disoproxil fumarate (TDF) in combination with lamivudine (3TC) oremtricitabine (FTC).

Subject analysis set title	Cohort 2 (>=6 to <12 Years): Rilpivirine
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects received rilpivirine tablet 25 mg or adjusted dose orally QD up to 240 weeks up to protocol amendment 9, up to 48 weeks from protocol amendment 10, in combination with an investigator-selected background regimen containing 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs): zidovudine (AZT), abacavir (ABC), or tenofovir disoproxil fumarate (TDF) in combination with lamivudine (3TC) or emtricitabine (FTC).

Subject analysis set title	Cohort 2 (>=10 to <20 kg): Rilpivirine 12.5 mg QD
Subject analysis set type	Per protocol

Subject analysis set description:

In Cohort 2 (children aged >=6 to <12 years), subjects received body weight adjusted dose of Rilpivirine 12.5 mg orally QD (for subjects with body weight >=10 to <20 kg) up to 48 weeks. In both the cohorts, rilpivirine was administered in combination with an investigator-selected background regimen containing 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs): zidovudine (AZT), abacavir (ABC), or tenofovir disoproxil fumarate (TDF) in combination with lamivudine (3TC) or emtricitabine (FTC).

Subject analysis set title	Cohort 2 (>=20 to <25 kg): Rilpivirine 15 mg
Subject analysis set type	Per protocol

Subject analysis set description:

In Cohort 2 (children aged >=6 to <12 years), subjects received body weight adjusted dose of Rilpivirine 15 mg orally QD (for subjects with body weight >=20 to <25 kg) up to 48 weeks. In both the cohorts, rilpivirine was administered in combination with an investigator-selected background regimen containing 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs): zidovudine (AZT), abacavir (ABC), or tenofovir disoproxil fumarate (TDF) in combination with lamivudine (3TC) or emtricitabine (FTC).

Subject analysis set title	Cohort 2 (>=20 to <25 kg): Rilpivirine 25 mg
Subject analysis set type	Per protocol

Subject analysis set description:

In Cohort 2 (children aged >=6 to <12 years), subjects received body weight adjusted dose of Rilpivirine 25 mg orally QD (for subjects with body weight >=20 to <25 kg) up to 48 weeks. In both the cohorts, rilpivirine was administered in combination with an investigator-selected background regimen containing 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs): zidovudine (AZT), abacavir (ABC), or tenofovir disoproxil fumarate (TDF) in combination with lamivudine (3TC) or emtricitabine (FTC).

Subject analysis set title	Cohort 2 (>=25 kg): Rilpivirine 25 mg
Subject analysis set type	Per protocol

Subject analysis set description:

In Cohort 2 (children aged >=6 to <12 years), subjects received body weight adjusted dose of Rilpivirine 25 mg orally QD (for subjects with body weight >=25 kg) up to 48 weeks. In both the cohorts, rilpivirine was administered in combination with an investigator-selected background regimen

containing 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs): zidovudine (AZT), abacavir (ABC), or tenofovir disoproxil fumarate (TDF) in combination with lamivudine (3TC) or emtricitabine (FTC).

Primary: Pharmacokinetics (PK) of Rilpivirine (TMC278) as Measured by Maximum Plasma Concentration (Cmax)

End point title	Pharmacokinetics (PK) of Rilpivirine (TMC278) as Measured by Maximum Plasma Concentration (Cmax)[1]

End point description:

Cmax is the maximum plasma concentration. Analysis population included all subjects who had taken at least 1 dose of rilpivirine, regardless of their compliance with the protocol and adherence to the dosing regimen. Here, N (number of subjects analysed) signifies subjects evaluated for this endpoint. "99999" indicated that mean and SD could not be calculated because number analysed was <3.

End point type	Primary

End point timeframe:

Up to Week 4

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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Cohort 1 (>=12 to <18 Years): Rilpivirine	Cohort 2 (>=10 to <20 kg): Rilpivirine 12.5 mg QD	Cohort 2 (>=20 to <25 kg): Rilpivirine 15 mg	Cohort 2 (>=20 to <25 kg): Rilpivirine 25 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	2	2	4
Units: nanogram per millilitre (ng/mL)				
arithmetic mean (standard deviation)	109 (± 38.0)	99999 (± 99999)	99999 (± 99999)	238 (± 160)

End point values	Cohort 2 (>=25 kg): Rilpivirine 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: nanogram per millilitre (ng/mL)				
arithmetic mean (standard deviation)	154 (± 52.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics of Rilpivirine as Measured by Area Under the Plasma Concentration Curve (AUC24)

End point title	Pharmacokinetics of Rilpivirine as Measured by Area Under the Plasma Concentration Curve (AUC24)[2]

End point description:

AUC24 was defined area under the plasma concentration versus time curve from time 0 to 24 hours post dosing of rilpivirine. Analysis population included all subjects who had taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen. Here, N (number of subjects analysed) signifies subjects evaluated for this endpoint. "99999" indicated that mean and SD

could not be calculated because number analysed was <3.

End point type	Primary

End point timeframe:

Up to Week 4

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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Cohort 1 (>=12 to <18 Years): Rilpivirine	Cohort 2 (>=10 to <20 kg): Rilpivirine 12.5 mg QD	Cohort 2 (>=20 to <25 kg): Rilpivirine 15 mg	Cohort 2 (>=20 to <25 kg): Rilpivirine 25 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	2	2	4
Units: nanogram*hour per milliliter (ng*hr/mL)				
arithmetic mean (standard deviation)	1872 (± 717)	99999 (± 99999)	99999 (± 99999)	3339 (± 2233)

End point values	Cohort 2 (>=25 kg): Rilpivirine 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: nanogram*hour per milliliter (ng*hr/mL)				
arithmetic mean (standard deviation)	2610 (± 776)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Plasma Human Immunodeficiency Virus -1 (HIV-1) Ribonucleic Acid (RNA) level Less Than (<) 50 Copies/mL

End point title	Percentage of Subjects With Plasma Human Immunodeficiency Virus -1 (HIV-1) Ribonucleic Acid (RNA) level Less Than (<) 50 Copies/mL

End point description:

Time to loss of virologic response algorithm (TLOVR) requires sustainedHIV-1 RNA < 50 copies/mL; confirmed HIV-1 RNA more than or equal to (>=) 50 copies/mL is considered as non-response (rebound); subject was considered non-responder after permanent discontinuation. Responder is defined as the subject with confirmed plasma viral load <50 copies/mL. Analysis population included all subjects who had taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen. "99999" indicated that data was not collected at Week 240 for Cohort 2. "9999" indicated that data was not collected at Week 48 for Cohort 2 as planned. Here, 'n' (number analysed) signifies number of subjects with available data at each specified timepoint.

End point type	Secondary

End point timeframe:

Weeks 48 and 240

End point values	Cohort 1 (>=12 to <18 Years): Rilpivirine	Cohort 2 (>=6 to <12 Years): Rilpivirine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	18		
Units: Percentage of subjects				
number (not applicable)				
Week 48 (n=36, 0)	72.2	99999		
Week 240 (n=32, 0)	43.8	99999		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events (AEs)

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

End point description:

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product and did not necessarily have a causal relationship with the treatment. Analysis population included all subjects who had taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen. This endpoint was planned to be reported for Cohort 1 only.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to Week 48 for Cohort 2 and up to Week 240 for Cohort 1

End point values	Cohort 1 (>=12 to <18 Years): Rilpivirine	Cohort 2 (>=6 to <12 Years): Rilpivirine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	18		
Units: Subjects	35	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Post Baseline Genotype Data

End point title	Number of Subjects With Post Baseline Genotype Data

End point description:

Number of subjects with post baseline genotype (nucleoside analogue reverse transcriptase inhibitors

[NRTI] and non-nucleoside reverse transcriptase inhibitors [NNRTI] resistance) data were reported. Analysis population included all subjects who had taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen. Here, N (Number of subjects analysed) signifies subjects evaluated for this endpoint.

End point type	Secondary

End point timeframe:

Cohort 2: up to 48 weeks and Cohort 1: up to 240 weeks

End point values	Cohort 1 (>=12 to <18 Years): Rilpivirine	Cohort 2 (>=6 to <12 Years): Rilpivirine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	6		
Units: Subjects				
number (not applicable)				
NNRTI	9	5		
NRTI	7	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Plasma HIV-1 RNA <50 Copies/mL by Food and Drug Administration (FDA) Snapshot Approach

End point title	Percentage of Subjects with Plasma HIV-1 RNA <50 Copies/mL by Food and Drug Administration (FDA) Snapshot Approach

End point description:

Percentage of subjects with a HIV-1 RNA <50 copies per mL were assessed using FDA snapshot approach which defines a participant's virologic response status using only the viral load at the predefined time point within a window of time, along with study drug discontinuation status. If HIV-1 RNA level is < 50 copies per mL, it is considered as virologic success as per the snapshot approach. Analysis population included all subjects who had taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen. Here, 'n' (number analysed) signifies number of subjects with available data at each specified timepoint. "99999" indicated that data was not collected at Week 240 for Cohort 2 arm because Cohort 2 duration was up to Week 48 only.

End point type	Secondary

End point timeframe:

At Week 48 (for Cohorts 1 and 2) and at Week 240 (for Cohort 1 only)

End point values	Cohort 1 (>=12 to <18 Years): Rilpivirine	Cohort 2 (>=6 to <12 Years): Rilpivirine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	18		
Units: Percentage of subjects				
number (not applicable)				

Week 48 (n= 36, 18)	72.2	72.2		
Week 240 (n= 32, 0)	53.1	99999		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cluster of Differentiation (CD4+) Cells

End point title	Change From Baseline in Cluster of Differentiation (CD4+) Cells

End point description:

The immunologic change was determined by changes in Cluster of CD4+ cell count using non-completer =failure imputation, that is discontinuation were imputed with baseline value resulting in change=0, other missing data using last observation carried forward (LOCF). Change from baseline in CD4+ cell count at Week 48 for Cohort 1 and 2 and Week 240 for Cohort 1 only were assessed. Analysis population included all subjects who had taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen. Here, 'n' (number analysed) signifies number of subjects with available data at each specified timepoint. 99999 indicated that data was not collected at Week 240 for Cohort 1 arm as analysis was not planned to be collected at Week 240 for this arm.

End point type	Secondary

End point timeframe:

Baseline and Week 48 for Cohort 1 and 2; Week 240 for Cohort 1 only

End point values	Cohort 1 (>=12 to <18 Years): Rilpivirine	Cohort 2 (>=6 to <12 Years): Rilpivirine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	18		
Units: Cells per microlitre				
arithmetic mean (standard error)				
Week 48 (n= 36, 18)	201.2 (± 32.87)	215.9 (± 62.42)		
Week 240 (n= 32, 0)	113.6 (± 26.72)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment Adherence >95% Based on Drug Accountability

End point title	Percentage of Subjects With Treatment Adherence >95% Based on Drug Accountability

End point description:

Percentage of subjects with treatment adherence >95% based on drug accountability up to 48 Weeks for Cohort 2 and up to 240 Weeks Cohort 1 were reported. Treatment adherence was defined as having a treatment adherence of greater than (>) 95 percent (%) by pill count. Analysis population included all

subjects who had 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 48 Weeks for Cohort 2 and up to 240 Weeks Cohort 1

End point values	Cohort 1 (>=12 to <18 Years): Rilpivirine	Cohort 2 (>=6 to <12 Years): Rilpivirine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	18		
Units: Percentage of subjects				
number (not applicable)				
Up to 48 weeks	80.6	77.8		
Up to 240 weeks	77.8	77.8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline (Day 1) up to 48 weeks for Cohort 2; From Baseline (Day 1) up to 240 weeks for Cohort 1

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Cohort 1 and 2: Rilpivirine: All Subjects

Reporting group description:

Cohort 1 (adolescents aged greater than or equal to [>=] 12 to less than [<] 18 years), subjects received rilpivirine tablet 25 milligrams (mg) or adjusted dose orally once daily (QD) up to 240 weeks. In Cohort 2 (children aged >=6 to <12 years), received rilpivirine body weight adjusted dose (body weight <20 kilograms [kg]: 12.5 mg; between 20 kg to <25kg: 15 mg; >=25 kg: 25 mg) orally QD up to 48 weeks. In both the cohorts, rilpivirine was administered in combination with an investigator-selected background regimen containing 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs): zidovudine (AZT), abacavir (ABC), or tenofovir disoproxil fumarate (TDF) in combination with lamivudine (3TC) oremtricitabine (FTC).

Serious adverse events	Cohort 1 and 2: Rilpivirine: All Subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort 1 and 2: Rilpivirine: All Subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 54 (24.07%)		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Infections and infestations			
Upper Respiratory Tract Infection			

subjects affected / exposed occurrences (all)	12 / 54 (22.22%) 42		
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	 3 / 54 (5.56%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2009	The overall reasons for the amendment were the addition of an optional post-Week 48 treatment extension period of 4 years, changes in withdrawal, in- and exclusion criteria and additional assessments of several hormones and CD4+ cell count.
20 May 2010	The overall reason for the amendment was to allow subjects to switch to a weight-adjusted dose, if needed, and to allow TDF and FTC as investigator-selected background regimen.
29 June 2011	The overall reasons for the amendment was the addition of Part 1b before starting Part 2 of the study and the provision of the post-Week 48 treatment extension period of 4 years through the trial and not via a specific roll-over trial.
08 October 2015	The overall reason for the amendment was to also include children of >=6 to <12 years of age.
18 December 2015	The overall reason for the amendment was the update of inclusion criterion 3 to remove the requirement that children enrolled in the study were aware of their human immunodeficiency virus (HIV) status, so that children that are unaware of their HIV status, but comply with all other inclusion and exclusion criteria were allowed to participate in the study.
01 December 2016	The overall reason for the amendment were adjustments made to allow the prescription of World Health Organization (WHO) prequalified drugs, based on local practice and availability of anti-retrovirals (ARV)s. If not available, the use of generic drugs approved by the local Health Authorities or drugs prescribed by the United Nations international organizations can be acceptable as N(t)RTI background medication. Additionally, the criterion for withdrawal after a total cumulative duration of treatment interruptions for suspected toxicities was further clarified per study period instead of over the entire study duration.
20 March 2018	The overall reason for the amendment was to update the inclusion and exclusion criteria to facilitate subject recruitment since the study target population had become scarce. Through this amendment, enrollment of subjects >=6 to <12 years of age who had a history of receiving a single dose nevirapine for prevention of prevention of mother-to-child transmission (PMTCT) in Cohort 2 of the study was allowed. The evolution of proviral genotype was assessed at screening and Week 48 and virologic response was closely monitored during the treatment period.
03 February 2020	The overall reason for the amendment was to include Rilpivirine dose recommendations for subjects in Cohort 2 with a body weight >=25 kg (25 mg QD) and <25 kg (15 mg QD). Based on accumulating data the new dose of 15 mg QD had been selected for the subgroup of participants with a body weight <25 kg. Since for subjects with body weight >=25 kg, sufficient intensive pharmacokinetic (PK) data had been gathered, this amendment also included intensive PK evaluation in newly enrolled subjects with a body weight <25 kg to further evaluate and confirm the Rilpivirine dose for participants with this lower body weight.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported