Clinical trial results:
A Phase I/II, Open-label Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of Etravirine (ETR) in Antiretroviral (ARV) Treatment-experienced HIV-1 Infected Infants and Children, Aged >= 2 Months to <6 Years

Summary

EudraCT number	2012-002630-36
Trial protocol	Outside EU/EEA
Global end of trial date	26 August 2020

Results information

Result version number	v1 (current)
This version publication date	31 March 2021
First version publication date	31 March 2021

Trial information

Trial identification

Sponsor protocol code	TMC125-TIDP35-C234

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01504841
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Division of the National Institute of Allergy and Infectious Diseases (DAIDS)
Sponsor organisation address	5601 Fishers Lane, Rockville, United States,
Public contact	Clinical Registry Group, Janssen Research and Development, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research and Development, 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-000222-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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 August 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 August 2020
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 (PK), safety and tolerability and appropriate dose of etravirine (ETR) in combination with an optimized background regimen (OBR) for human immunodeficiency virus (HIV)-1 infected children aged greater than or equal to (>=) 2 years to less than (<) 6 years.

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 Practices and applicable regulatory requirements. Safety evaluations were based upon adverse events (AEs) reported throughout the study, clinical laboratory test results, changes in physical examination including vital signs and electrocardiogram (ECGs) results.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	South Africa: 13
Worldwide total number of subjects	26
EEA total number of subjects	0

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)	6

Children (2-11 years)	20
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 26 subjects were enrolled in the study and received at least 1 dose of etravirine (ETR). Out of those 26, 17 subjects completed the study.

Pre-assignment

Screening details:

3 sequential age cohorts were planned with 20 subjects in cohort 1, 6 subjects in cohort 2 and no enrollments occurred in cohort 3 during the study.

Period 1

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

Arms

Arm title	Etravirine

Arm description:

Subjects were divided into 2 age-based cohorts: Cohort 1 (greater than or equal to [>=] 2 years to less than [<] 6 years age) and Cohort 2 (>= 1 year to <2 years age). Subjects received etravirine (ETR) together with an optimized background regimen (OBR) consisting of one active boosted protease inhibitor (PI) and at least one other active antiretroviral (ARV) drug. ETR was administered as 25 milligrams (mg) scored tablets and/or 100 mg tablets twice daily, swallowed whole or dispersed in an appropriate liquid vehicle 30 minutes following a meal. Dose was decided according to dosing tables in protocol.

Arm type	Experimental
Investigational medicinal product name	Etravirine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

ETR 25mg and/or 100mg was administered orally twice daily either swallowed as a whole tablet or dispersed in an appropriate liquid.

Number of subjects in period 1	Etravirine
Started	26
Completed	17
Not completed	9
Consent withdrawn by subject	2
Completion of protocol	7

Baseline characteristics

Reporting groups	
Reporting group title	Etravirine

Reporting group description:

Subjects were divided into 2 age-based cohorts: Cohort 1 (greater than or equal to [>=] 2 years to less than [<] 6 years age) and Cohort 2 (>= 1 year to <2 years age). Subjects received etravirine (ETR) together with an optimized background regimen (OBR) consisting of one active boosted protease inhibitor (PI) and at least one other active antiretroviral (ARV) drug. ETR was administered as 25 milligrams (mg) scored tablets and/or 100 mg tablets twice daily, swallowed whole or dispersed in an appropriate liquid vehicle 30 minutes following a meal. Dose was decided according to dosing tables in protocol.

Reporting group values	Etravirine	Total	
Number of subjects	26	26	
Title for AgeCategorical Units: subjects			
infants and toddlers(28 days-23 months)	6	6	
Children (2-11 years)	20	20	
Adolescents (12-17 years)	0	0	
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	3.2		
standard deviation	± 1.52	-	
Title for Gender Units: subjects			
Female	12	12	
Male	14	14	
Ethnicity Units: Subjects			
Hispanic or Latino	10	10	
Not Hispanic or Latino	5	5	
Unknown or Not Reported	11	11	
Race Units: Subjects			
Black or African American	13	13	
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Multiple	4	4	
Other	2	2	
Missing	5	5	
Unknown	1	1	
Not Reported	1	1	
Region of Enrollment Units: Subjects			

Brazil	9	9	
South Africa	13	13	
United States	4	4	
CD4 Count Units: Subjects			
<200 cells/µL	1	1	
>=200 - <500 cells/µL	4	4	
>=500 - <1000 cells/µL	11	11	
>=1000 cells/µL	10	10	
CD4 Percent Units: Subjects			
<25%	12	12	
>=25%	14	14	

End points

End points reporting groups

Reporting group title	Etravirine

Reporting group description:

Subjects were divided into 2 age-based cohorts: Cohort 1 (greater than or equal to [>=] 2 years to less than [<] 6 years age) and Cohort 2 (>= 1 year to <2 years age). Subjects received etravirine (ETR) together with an optimized background regimen (OBR) consisting of one active boosted protease inhibitor (PI) and at least one other active antiretroviral (ARV) drug. ETR was administered as 25 milligrams (mg) scored tablets and/or 100 mg tablets twice daily, swallowed whole or dispersed in an appropriate liquid vehicle 30 minutes following a meal. Dose was decided according to dosing tables in protocol.

Subject analysis set title	Cohort 1: >=2 to <6 years age
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received ETR together with an OBR consisting of one active boosted PI and at least one other active ARV drug. ETR was administered as 25 mg scored tablets and/or 100 mg tablets twice daily, swallowed whole or dispersed in an appropriate liquid vehicle 30 minutes following a meal. Dose was decided according to dosing tables in protocol.

Subject analysis set title	Cohort 2: >=1 to <2 years age
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received ETR together with an OBR consisting of one active boosted PI and at least one other active ARV drug. ETR was administered as 25 mg scored tablets and/or 100 mg tablets twice daily, swallowed whole or dispersed in an appropriate liquid vehicle 30 minutes following a meal. Dose was decided according to dosing tables in protocol.

Primary: Termination From Treatment due to a Suspected Adverse Drug Reaction (SADR)

End point title	Termination From Treatment due to a Suspected Adverse Drug Reaction (SADR)[1]

End point description:

An event judged to be at least possibly related to the study treatment was considered to be a SADR. Number of subjects who discontinued treatment due to a SADR by Cohort were reported. Intent to treat (ITT) population consisted of all subjects who had taken at least one dose of etravirine (ETR).

End point type	Primary

End point timeframe:

Up to 5.77 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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Cohort 1: >=2 to <6 years age	Cohort 2: >=1 to <2 years age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	6		
Units: subjects	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Adverse Events of Grade 3 or Higher Severity

End point title	Number of Subjects With Adverse Events of Grade 3 or Higher Severity[2]

End point description:

An AE is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. Number of subjects with grade 3 or higher severity adverse events were reported. ITT population consisted of all subjects who had taken at least one dose of ETR.

End point type	Primary

End point timeframe:

Up to 5.77 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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Cohort 1: >=2 to <6 years age	Cohort 2: >=1 to <2 years age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	6		
Units: subjects	10	5		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Deaths

End point title	Number of Deaths[3]

End point description:

Number of deaths on study, by cohort were reported. ITT population consisted of all subjects who had taken at least one dose of ETR.

End point type	Primary

End point timeframe:

Up to 5.77 years

Notes:

[3] - 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: >=2 to <6 years age	Cohort 2: >=1 to <2 years age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	6		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-Time Curve Over 12 Hours of ETR

End point title	Area Under the Plasma Concentration-Time Curve Over 12 Hours of ETR[4]

End point description:

AUC12h was defined as area under curve from time of administration of ETR to 12 hours post dosing. AUC12h was determined at initial dose and recommended dose of ETR. ITT population consisted of all subjects who had taken at least one dose of ETR.

End point type	Primary

End point timeframe:

Pre-dose, 1, 2, 4, 6, 9, and 12 hours post-dose measured at intensive PK visit (within 7-10 days after last dose of study drug administration)

Notes:

[4] - 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: >=2 to <6 years age	Cohort 2: >=1 to <2 years age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	4		
Units: nanogram*hour per mililiter				
geometric mean (standard deviation)	5512.85 (± 3615.36)	4821.76 (± 3167.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events of Grade 3 or Higher Severity Judged to be at Least Possibly Attributable to the Study Medications

End point title	Number of Subjects With Adverse Events of Grade 3 or Higher Severity Judged to be at Least Possibly Attributable to the Study Medications

End point description:

An AE is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. Number of subjects with grade 3 or higher severity adverse events possibly related to study treatment were reported by cohort. ITT population consisted of all subjects who had taken at least one dose of ETR.

End point type	Secondary

End point timeframe:

Up to 5.77 years

End point values	Cohort 1: >=2 to <6 years age	Cohort 2: >=1 to <2 years age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	6		
Units: subjects	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Confirmed Virologic Failure at Weeks 24 and 48

End point title	Number of Subjects With Confirmed Virologic Failure at Weeks 24 and 48

End point description:

Number of subjects with confirmed Virologic Failure, defined as: failure to suppress plasma human immunodeficiency virus (HIV)-1 ribosenucleic acid (RNA) to fewer than 400 copies per milliliter (copies/mL) and failure to achieve at least a 2-log10 reduction (from baseline) in HIV-1 RNA at Weeks 24 or 48, by Cohort, with Clopper-Pearson confidence intervals. The initial HIV-1 RNA results that met the Virologic Failure definition were each confirmed by a second result obtained within 1 to 4 weeks of the initial result obtained at Week 24 and/or 48. ITT population consisted of all subjects who had taken at least one dose of ETR.

End point type	Secondary

End point timeframe:

Weeks 24 and 48

End point values	Cohort 1: >=2 to <6 years age	Cohort 2: >=1 to <2 years age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	4		
Units: subjects				
Week 24	2	1		
Week 48	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Discontinued due to Toxicity or Virologic Failure

End point title	Treatment Discontinued due to Toxicity or Virologic Failure

End point description:

Number of subjects who discontinued study treatment (ETR) due to a toxicity or Virologic Failure (VF), by cohort were reported. ITT population consisted of all subjects who had taken at least one dose of ETR.

End point type	Secondary

End point timeframe:

From baseline to occurrence of event, up to Week 48

End point values	Cohort 1: >=2 to <6 years age	Cohort 2: >=1 to <2 years age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	6		
Units: subjects	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Optimized Background Regimen Due to Virologic Failure

End point title	Change in Optimized Background Regimen Due to Virologic Failure

End point description:

Number of subjects who initiated a change in their optimized background regimen (OBR) due to virologic failure, by Cohort were reported. ITT population consisted of all subjects who had taken at least one dose of ETR.

End point type	Secondary

End point timeframe:

Measured at entry and at Weeks 8, 12, 24, and 48

End point values	Cohort 1: >=2 to <6 years age	Cohort 2: >=1 to <2 years age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	4		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: New Onset Opportunistic Infection (OI) or AIDS Diagnosis

End point title	New Onset Opportunistic Infection (OI) or AIDS Diagnosis

End point description:

Number of subjects with a new onset opportunistic infection (OI) or Acquired immunodeficiency syndrome (AIDS) diagnosis, by Cohort were reported. ITT population consisted of all subjects who had taken at least one dose of ETR.

End point type	Secondary

End point timeframe:

From baseline to occurrence of event, up to Week 48

End point values	Cohort 1: >=2 to <6 years age	Cohort 2: >=1 to <2 years age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	4		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CD4+ and CD8+ Cell Count

End point title	Change from Baseline in CD4+ and CD8+ Cell Count

End point description:

Change from baseline in cluster of differentiation (CD)4 and CD8 cell counts was reported to assess the immunologic change. ITT population consisted of all subjects who had taken at least one dose of ETR.

End point type	Secondary

End point timeframe:

Every 12 Weeks from Baseline, up to 5.77 years or early discontinuation

End point values	Cohort 1: >=2 to <6 years age	Cohort 2: >=1 to <2 years age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	6		
Units: cells per microliter				
arithmetic mean (standard error)				
CD4 count	82.6 (± 111.01)	-36.2 (± 262.50)		
CD8 count	-571.7 (± 165.82)	-591.2 (± 224.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CD4+ and CD8+ Cell Percentage

End point title	Change from Baseline in CD4+ and CD8+ Cell Percentage

End point description:

Change from baseline in CD4 and CD8 cell percentage was reported to assess the immunologic change.

ITT population consisted of all subjects who had taken at least one dose of ETR.

End point type	Secondary

End point timeframe:

Every 12 Weeks from Baseline, up to 5.77 years or early discontinuation

End point values	Cohort 1: >=2 to <6 years age	Cohort 2: >=1 to <2 years age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	6		
Units: percentage				
arithmetic mean (standard error)				
CD4 percentage	9.52 (± 1.857)	4.27 (± 3.816)		
CD8 percentage	-10.44 (± 2.137)	-3.22 (± 2.806)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CD4/CD8 Ratio

End point title	Change from Baseline in CD4/CD8 Ratio

End point description:

Change from baseline in CD4/CD8 count ratio was reported to assess the immunologic change. ITT population consisted of all subjects who had taken at least one dose of ETR.

End point type	Secondary

End point timeframe:

Every 12 Weeks from Baseline, up to 5.77 years or early discontinuation

End point values	Cohort 1: >=2 to <6 years age	Cohort 2: >=1 to <2 years age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	6		
Units: ratio				
arithmetic mean (standard error)	0.5171 (± 0.10223)	0.1323 (± 0.12798)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 5.77 years

Adverse event reporting additional description:

Safety set included all subjects who have taken at least 1 dose of etravirine (ETR), regardless of their compliance with the protocol and adherence to the dosing regimen.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Etravirine

Reporting group description:

Subjects were divided into 2 age-based cohorts: Cohort 1 (greater than or equal to [>=] 2 years to less than [<] 6 years age) and Cohort 2 (>= 1 year to <2 years age). Subjects received etravirine (ETR) together with an optimized background regimen (OBR) consisting of one active boosted protease inhibitor (PI) and at least one other active antiretroviral (ARV) drug. ETR was administered as 25 milligrams (mg) scored tablets and/or 100 mg tablets twice daily, swallowed whole or dispersed in an appropriate liquid vehicle 30 minutes following a meal. Dose was decided according to dosing tables in protocol.

Serious adverse events	Etravirine		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 26 (30.77%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Lipase Increased			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Neutrophil Count Decreased			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Platelet Count Decreased			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Forearm Fracture			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ligament Sprain			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Etravirine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Papilloma			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	14 / 26 (53.85%)		
occurrences (all)	32		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Bronchospasm			

subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	5		
Childhood Asthma			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	19 / 26 (73.08%)		
occurrences (all)	73		
Dyspnoea			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Oropharyngeal Pain			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	8		
Nasal Congestion			
subjects affected / exposed	20 / 26 (76.92%)		
occurrences (all)	47		
Pharyngeal Erythema			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Pharyngeal Inflammation			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Rales			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	10		
Rhinorrhoea			
subjects affected / exposed	15 / 26 (57.69%)		
occurrences (all)	34		
Sneezing			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Wheezing			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	4		
Investigations			

Blood Pressure Diastolic Increased subjects affected / exposed occurrences (all) Blood Pressure Systolic Increased subjects affected / exposed occurrences (all) Weight Decreased subjects affected / exposed occurrences (all)	7 / 26 (26.92%) 21 5 / 26 (19.23%) 11 4 / 26 (15.38%) 5		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 3		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 8 3 / 26 (11.54%) 3		
Blood and lymphatic system disorders Iron Deficiency Anaemia subjects affected / exposed occurrences (all) Lymphadenopathy subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 6 10 / 26 (38.46%) 16		
Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all) Otorrhoea subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 4 7 / 26 (26.92%) 7		
Eye disorders			

Eye Discharge			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	5		
Anal Pruritus			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	11 / 26 (42.31%)		
occurrences (all)	16		
Mouth Ulceration			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Oral Disorder			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	5 / 26 (19.23%)		
occurrences (all)	12		
Skin and subcutaneous tissue disorders			
Dermatitis Allergic			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Dry Skin			
subjects affected / exposed	5 / 26 (19.23%)		
occurrences (all)	8		
Eczema			
subjects affected / exposed	5 / 26 (19.23%)		
occurrences (all)	7		
Macule			

subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Papule			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	4		
Rash Papular			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	13 / 26 (50.00%)		
occurrences (all)	34		
Rash Pruritic			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Infections and infestations			
Abscess Limb			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Acarodermatitis			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	4		
Acute Sinusitis			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	5		
Body Tinea			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	4		
Impetigo			
subjects affected / exposed	7 / 26 (26.92%)		
occurrences (all)	8		

Lice Infestation				
subjects affected / exposed	3 / 26 (11.54%)			
occurrences (all)	3			
Molluscum Contagiosum				
subjects affected / exposed	3 / 26 (11.54%)			
occurrences (all)	3			
Nasopharyngitis				
subjects affected / exposed	2 / 26 (7.69%)			
occurrences (all)	2			
Oral Candidiasis				
subjects affected / exposed	2 / 26 (7.69%)			
occurrences (all)	2			
Otitis Media Acute				
subjects affected / exposed	6 / 26 (23.08%)			
occurrences (all)	7			
Parotitis				
subjects affected / exposed	2 / 26 (7.69%)			
occurrences (all)	2			
Pharyngitis				
subjects affected / exposed	8 / 26 (30.77%)			
occurrences (all)	10			
Pneumonia Bacterial				
subjects affected / exposed	2 / 26 (7.69%)			
occurrences (all)	2			
Rhinitis				
subjects affected / exposed	2 / 26 (7.69%)			
occurrences (all)	2			
Tinea Capitis				
subjects affected / exposed	7 / 26 (26.92%)			
occurrences (all)	9			
Tinea Faciei				
subjects affected / exposed	2 / 26 (7.69%)			
occurrences (all)	2			
Tonsillitis				
subjects affected / exposed	4 / 26 (15.38%)			
occurrences (all)	4			

Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) Urinary Tract Infection subjects affected / exposed occurrences (all) Varicella subjects affected / exposed occurrences (all)	 3 / 26 (11.54%) 7 2 / 26 (7.69%) 2 2 / 26 (7.69%) 2		
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all) Failure to Thrive subjects affected / exposed occurrences (all)	 6 / 26 (23.08%) 12 4 / 26 (15.38%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2012	The first amendment was issued to remove Cohorts IIB and IIIB (greater than or equal to [>=] 2-month to less than [<] 2-year old treatment-naive children, with or without exposure to antiretrovirals (ARVs) as part of a regimen to prevent mother-to-child transmission). Consequently, the number of cohorts was changed from 5 to 3, the sample size was updated from 80 to 50 subjects, and stratification by ARV exposure was deleted. All sections throughout the protocol were updated accordingly, including the protocol title and study objectives.
04 October 2013	The second amendment was issued to revise the criteria for individual and cohort dose evaluations and adjustments. Intensive pharmacokinetic (PK) sampling was to be performed on Day 14 (plus minus [+-] 4 days) of the study to allow etravirine (ETR) plasma concentrations to reach steady-state. In order to meet the PK criteria, at least 10 of 12 subjects per cohort were to have an area under plasma concentration-time curve over 12 hours of ETR (AUC12h) greater than (>) 2,350 nanograms * hour per milliliter (ng*h/mL) (>10th percentile of the adult AUC12h in the DUET studies) and a geometric mean AUC12h in the cohort to fall within 80 percent (%) to 130% of the geometric mean AUC12h in adults (that is, between 3,618 and 5,879 ng*h/mL). For individual PK-determined dose adjustments, a stepwise approach was introduced aimed at obtaining an ETR AUC12h around the 20th percentile of the adult AUC12h (instead of the median adult AUC12h) and with a first dose adjustment capped at 200 milligrams (mg) twice daily (bid).
05 December 2014	The third amendment was issued to incorporate revisions related to a change in the starting ETR dose (as per the new weight-banded ETR dosing table) for the study cohorts and a change in the overall PK criteria for evaluation of the (mini-)cohorts. Based on the high interindividual variability for apparent ETR clearance in the population PK model (62%), the target range for the geometric mean ETR AUC12h ratio (pediatric/adults) per age cohort was revised to be between 60% and 150% (instead of between 80% and 130%) of the geometric mean AUC12h in adults in the DUET studies (between 2,713 and 6,783 ng*h/mL). Since 2 subjects of the original mini-cohort already passed PK and safety criteria on the dose per amendment #2, and based on their body weight the same ETR dose would apply for them per amendment #3, it was agreed that these 2 subjects could be considered toward the new Cohort I minicohort under the amended protocol. Therefore, only 4 additional subjects needed to be enrolled to complete enrollment into that new mini-cohort. It was also agreed that subjects of the failed mini-cohort could be dose adjusted after an additional truncated intensive PK evaluation. The number of subjects to be enrolled was updated to account for the number of subjects needed to complete the dose-finding stage of the study and considering the number of subjects who were started on the final recommended ETR dose according to PK and safety criteria for that cohort.
10 March 2016	The fourth amendment was issued to revise the cohort management plan to allow early opening of the mini-cohort of Cohort III (while the first mini-cohort of Cohort II could still be enrolling) provided that the available Cohort II safety and PK were acceptable. Subjects <6 months of age could only be enrolled after initial safety and PK data from subjects between 6 months and 1 year of age were available. A go/no-go decision for further recruitment of study subjects was set approximately 2 years following the opening of Cohort II. At that time, an analysis was to be performed across all age cohorts (the Week-24 analysis). The accrual rate, and all relevant safety and PK data, were to be examined for determination of safety and value in continuing recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported