Clinical trial results:
A Phase II, open-label trial to evaluate the safety, tolerability and antiviral activity of TMC125 in antiretroviral experienced HIV-1 infected children and adolescents

Summary

EudraCT number	2007-007086-21
Trial protocol	GB DE BE PT ES FR NL IT
Global end of trial date	30 August 2011

Results information

Result version number	v1
This version publication date	06 July 2016
First version publication date	16 May 2015

Trial information

Trial identification

Sponsor protocol code	TMC125-TiDP35-C213

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00665847
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development
Sponsor organisation address	Archimedsweg 29-2333CM, Leiden, Netherlands, B235-0
Public contact	Janssen Research & Development, Clinical Registry Group, ClinicalTrialsEU@its.jnj.com
Scientific contact	Janssen Research & Development, Clinical Registry Group, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 August 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 August 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate safety and tolerability of etravirine in combination with other antiretroviral (ARVs) over a 24-week treatment period in children and adolescents.

Protection of trial subjects:

The safety assessments included laboratory measurements (for example hematology and coagulation, biochemistry, urinalysis, hepatitis serology/Viremia), cardiovascular safety, vital sign measurements and electrocardiograms (ECGs). Adverse events and vital signs were monitored throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 August 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 15
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Puerto Rico: 1
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Thailand: 20
Country: Number of subjects enrolled	United States: 15
Country: Number of subjects enrolled	South Africa: 10
Worldwide total number of subjects	101
EEA total number of subjects	27

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)	41
Adolescents (12-17 years)	60
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 41 investigators in 13 countries enrolled participants in study TMC125-C213.

Pre-assignment

Screening details:

A total of 103 participants were documented as being enrolled in the study, however 2 participants were randomized in error. Therefore, 101 participants were enrolled and treated with etravirine (ETR) also known as TMC125 and included in the intent-to-treat (ITT) population.

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	TMC125

Arm description:

TMC125 dosed according to body weight (kilogram) from 100 milligram (mg) to 200 mg twice a day

Arm type	Experimental
Investigational medicinal product name	TMC125
Investigational medicinal product code	TMC125 (formulation F060)
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TMC125 dosed according to body weight (kilogram) from 100 milligram (mg) to 200 mg twice a day

Number of subjects in period 1	TMC125
Started	101
Completed	76
Not completed	25
Consent withdrawn by subject	2
Adverse event	8
Resistance to TMC125	1
Switch to commercial medication	1
Subject reached a virologic endpoint	4
Subject non-compliant	8
Subject ineligible to continue the trial	1

Baseline characteristics

Reporting groups	
Reporting group title	TMC125
Reporting group description:	
TMC125 dosed according to body weight (kilogram) from 100 milligram (mg) to 200 mg twice a day	

Reporting group values	TMC125	Total	
Number of subjects	101	101	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	41	41	
Adolescents (12-17 years)	60	60	
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	12.2		
standard deviation	± 2.99	-	
Title for Gender Units: subjects			
Female	64	64	
Male	37	37	

End points

End points reporting groups

Reporting group title	TMC125

Reporting group description:

TMC125 dosed according to body weight (kilogram) from 100 milligram (mg) to 200 mg twice a day

Primary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs)[1]

End point description:

A treatment-emergent adverse event (TEAE) was defined as an event that occurred in the 48-week treatment period during which it emerged (i.e. started or worsened in severity, relation, or other attribute), and not in the subsequent study periods, even if the event continued to be present. Adverse events were graded from 1 to 4 in severity using the Division of Acquired Immunodeficiency Syndrome severity scale (grade 1 being less severe and grade 4 being more severe). ETR=etravirine/TMC125; OBR=optimized background regimen

End point type	Primary

End point timeframe:

48 weeks

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 were done, no inferential statistical analyses were performed.

End point values	TMC125			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: Participants				
Any TEAE	89			
TEAEs that were fatal	0			
TEAEs that were serious	5			
TEAEs that were grade 3 or 4 in severity	14			
TEAEs leading to temporary ETR discontinuation	8			
TEAEs leading to permanent ETR discontinuation	8			
TEAEs possibly related to ETR	23			
TEAEs probably related to ETR	14			
TEAEs very likely related to ETR	3			
TEAEs at least possibly related to ETR	33			
TEAEs possibly related to OBR	27			
TEAEs probably related to OBR	12			
TEAEs very likely related to OBR	5			
TEAEs at least possibly related to OBR	36			
TEAEs of at least grade 2 in severity	21			
TEAEs of at least grade 3 in severity	3			
TEAEs of interest: Skin event	31			
TEAEs of interest: Rash	23			
TEAEs of interest: severe cutaneous reactions	7			

TEAEs of interest: angioedema	4			
TEAEs of interest: neuropsychiatric events	2			
TEAEs of interest: hepatic events	0			
TEAEs of interest: cardiac events	0			
TEAEs of interest: bleeding events	0			
TEAEs of interest: pancreatic events	1			
TEAEs of interest: lipid-related events	6			
TEAEs of interest: neoplasms	1			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs)[2]

End point description:

The percentage of participants with a treatment-emergent adverse event (TEAE) (defined as an event that occurred in the 48-week treatment period during which it emerged [i.e. started or worsened in severity, relation, or other attribute], and not in the subsequent study periods, even if the event continued to be present] are provided below. Adverse events were graded from 1 to 4 in severity using the Division of Acquired Immunodeficiency Syndrome severity scale (grade 1 being less severe and grade 4 being more severe). ETR=etravirine/TMC125; OBR=optimized background regimen.

End point type	Primary

End point timeframe:

48 weeks

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 were done, no inferential statistical analyses were performed.

End point values	TMC125			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: Percentage of Participants				
number (not applicable)				
Any TEAE	88.1			
TEAEs that were fatal	0			
TEAEs that were serious	5			
TEAEs that were grade 3 or 4 in severity	13.9			
TEAEs leading to temporary ETR discontinuation	7.9			
TEAEs leading to permanent ETR discontinuation	7.9			
TEAEs possibly related to ETR	22.8			
TEAEs probably related to ETR	13.9			
TEAEs very likely related to ETR	3			
TEAEs at least possibly related to ETR	32.7			
TEAEs possibly related to OBR	26.7			
TEAEs probably related to OBR	11.9			

TEAEs very likely related to OBR	5			
TEAEs at least possibly related to OBR	35.6			
TEAEs of at least grade 2 in severity	20.8			
TEAEs of at least grade 3 in severity	3			
TEAEs of interest: Skin event	30.7			
TEAEs of interest: Rash	22.8			
TEAEs of interest: severe cutaneous reactions	6.9			
TEAEs of interest: angioedema	4			
TEAEs of interest: neuropsychiatric events	2			
TEAEs of interest: hepatic events	0			
TEAEs of interest: cardiac events	0			
TEAEs of interest: bleeding events	0			
TEAEs of interest: pancreatic events	1			
TEAEs of interest: lipid-related events	5.9			
TEAEs of interest: neoplasms	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve Over 12 Hours at Steady-state (AUC12h) of Etravirine

End point title	Area Under the Plasma Concentration-Time Curve Over 12 Hours at Steady-state (AUC12h) of Etravirine

End point description:

The AUC12h is a Bayesian estimation based on a population pharmacokinetic model and sparse samples collected at each visit over the duration of trial. For each sparse sample taken, the time blood sample was recorded as well as the time of etravirine intake just prior to the time of blood sample.

End point type	Secondary

End point timeframe:

Weeks 4-48

End point values	TMC125			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: ng.h/mL				
arithmetic mean (standard deviation)	5216 (± 4305)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Concentration (C0h) of Etravirine

End point title	Trough Plasma Concentration (C0h) of Etravirine

End point description:

Trough plasma concentration is the plasma concentration before dosing or at the end of the dosing interval of any dose other than the first dose.

End point type	Secondary

End point timeframe:

Week 48

End point values	TMC125			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: ng/mL				
arithmetic mean (standard deviation)	346 (± 342)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Etravirine

End point title	Maximum Plasma Concentration (Cmax) of Etravirine

End point description:

Etravirine/TMC125 (ETR) Cmax was approximated for each individual using the median value of plasma ETR concentrations taken 4 hours postdose (± 1 hour), when available, on the day of the Week 4 visit.

End point type	Secondary

End point timeframe:

Week 4

End point values	TMC125			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: ng/mL				
arithmetic mean (standard deviation)	589 (± 486)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Virologic Response at Week 24

End point title	Percentage of Participants With Virologic Response at Week 24

End point description:

Virologic response was defined as the percentage of participants with plasma viral load less than (<) 50

copies/ milliliter (mL) at Week 24 calculated according to the non-completer=failure (NC=F) imputation method.

End point type	Secondary

End point timeframe:

Week 24

End point values	TMC125			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: Percentage of Participants				
number (not applicable)	52.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Human Immunodeficiency Virus – Type 1 (HIV-1) Ribonucleic Acid (RNA) in Plasma Over Time

End point title	Change From Baseline in Human Immunodeficiency Virus – Type 1 (HIV-1) Ribonucleic Acid (RNA) in Plasma Over Time

End point description:

Human Immunodeficiency Virus – Type 1 (HIV-1) Ribonucleic Acid (RNA) in Plasma were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	TMC125			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: log10 copies/mL				
arithmetic mean (standard error)	-1.53 (± 0.132)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CD4 Cell Counts Over Time

End point title	Change From Baseline in CD4 Cell Counts Over Time

End point description:

CD4 cells (a type of white blood cells) are circulating in blood and gives an idea of how strong the HIV positive person's immune system really is. The values of CD4 cell counts were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	TMC125			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: 10E6 cells/L				
arithmetic mean (standard error)	156 (± 22.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Emergence of Non-Nucleoside Reverse Transcriptase Inhibitor Resistance-Associated Mutations (NNRTI RAMs) in Participants Classified as Virologic Failures

End point title	The Emergence of Non-Nucleoside Reverse Transcriptase Inhibitor Resistance-Associated Mutations (NNRTI RAMs) in Participants Classified as Virologic Failures

End point description:

Virologic failure (lack of response) was defined as: plasma viral load decline of < 0.5 log10 from Baseline by Week 8 and/or plasma viral load decline of <1.0 log10 from Baseline by Week 12. Virologic failure (loss of response) was defined as 2 consecutive measurements of plasma viral load greater than (>) 0.5 log10 above the nadir after a minimum of 12 weeks of treatment. The table below provides data for 41 viologic failures of which 30 had mutation data available. In the table below, only the 4 most frequently emerging mutations are presented (emerging in at least 3 patients).

End point type	Secondary

End point timeframe:

Baseline and Endpoint (up to Week 48)

End point values	TMC125			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Participants				
V90I	3			
L100I	3			
E138A	3			
Y181C	8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 52

Adverse event reporting additional description:

Only participants who had at least one of the TEAEs listed in the Other (non Serious) AE table are included in the Total no. participants with Non-Serious Adverse Events.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	TMC125

Reporting group description:

TMC125 dosed according to body weight (kilogram) from 100 milligram (mg) to 200 mg twice a day

Serious adverse events	TMC125		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 101 (4.95%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Immunoglobulins			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphocyte morphology abnormal			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Weight decreased			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Drug toxicity			

subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Drug resistance			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Ulcerative keratitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Treatment noncompliance			
subjects affected / exposed	1 / 101 (0.99%)		
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	TMC125		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 101 (69.31%)		
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 101 (8.91%)		
occurrences (all)	12		
General disorders and administration site conditions			

Pyrexia subjects affected / exposed occurrences (all)	9 / 101 (8.91%) 10		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	6 / 101 (5.94%) 6		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	16 / 101 (15.84%) 18 10 / 101 (9.90%) 11 11 / 101 (10.89%) 11		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	13 / 101 (12.87%) 18 6 / 101 (5.94%) 10		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Rash maculo-papular subjects affected / exposed occurrences (all)	11 / 101 (10.89%) 12 9 / 101 (8.91%) 10		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Oral herpes	9 / 101 (8.91%) 10		

subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	8		
Pharyngitis			
subjects affected / exposed	8 / 101 (7.92%)		
occurrences (all)	11		
Rhinitis			
subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	8		
Upper respiratory tract infection			
subjects affected / exposed	27 / 101 (26.73%)		
occurrences (all)	41		
Sinusitis			
subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2008	The overall reason for the amendment was to address feedback provided by the United States Food and Drug Administration (US FDA) and modify inclusive criterion.
30 January 2009	The overall reason for the amendment was to modify inclusion criterion.
24 March 2010	The overall reason for the amendment was to adjust body weight criterion, definition Serious Adverse Events (SAE) and criterion regarding co-enrollment of participants in another study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported