Clinical trial results:
A phase II, open-label trial, to evaluate pharmacokinetics, safety, tolerability and antiviral activity of DRV/rtv once daily in treatment-naïve HIV-1 infected adolescents aged between 12 and < 18 years. Week-48 Final analysis. This trial is referred to as DIONE.

Summary

EudraCT number	2008-004631-37
Trial protocol	IE GB FR ES IT Outside EU/EEA
Global end of trial date	31 March 2011

Results information

Result version number	v2 (current)
This version publication date	23 June 2016
First version publication date	29 July 2015
Version creation reason	• Correction of full data set Review of data

Trial information

Trial identification

Sponsor protocol code	TMC114-TiDP29-C230

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00915655
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Tibotec Pharmaceuticals
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, 2340
Public contact	Clinical Registry Group, Tibotec Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Tibotec Pharmaceuticals Ltd, 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-000038-PIP01-07
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	31 March 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the pharmacokinetics, safety, tolerability, and efficacy of darunavir with low-dose ritonavir (DRV/rtv) administered at 800/100 mg once daily (q.d.) in combination with an investigator-selected background regimen, consisting of either zidovudine (AZT)/lamivudine (3TC) or abacavir (ABC)/3TC, over a 24-week treatment period in antiretroviral (ARV) treatment-naïve HIV-1 infected adolescents aged between 12 and < 18 years and weighing ≥ 40 kg.

Protection of trial subjects:

Safety and tolerability of subjects were evaluated by monitoring of the incidence and type of adverse events (AEs)/ HIV-Related Events, performing Clinical Laboratory Tests (Hematology and Coagulation, Biochemistry, Urinalysis, Hepatitis Serology/Viremia) , Cardiovascular Safety tests (Electrocardiogram, Vital Signs) and other safety evaluations including Physical examination and Pubertal Development - Tanner Stage throughout the study.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	21 August 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Ukraine: 6
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	12
EEA total number of subjects	4

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

Subject disposition

Recruitment

Recruitment details:

The study was conducted from 21-Aug-2009 to 31-March-2011 and subjects from 6 countries were enrolled.

Pre-assignment

Screening details:

In total 12 subjects were screened, and all 12 subjects were treated and completed the entire 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	DRV/rtv 800/100 mg q.d.

Arm description:

Subjects were administered with Darunavir in combination with low-dose of ritonavir (DRV/rtv) at 800/100 mg once daily (q.d.) in combination with an investigator-selected background regimen, consisting of either zidovudine (AZT)/lamivudine (3TC) or abacavir (ABC)/3TC.

Arm type	Experimental
Investigational medicinal product name	Darunavir
Investigational medicinal product code	TMC114
Other name	Prezista
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered with two Darunavir 400 milligrams (mg) film coated tablets (2x400mg=800mg) orally once in a day.

Investigational medicinal product name	Ritonavir
Investigational medicinal product code	RTV
Other name	Norvir
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered with Ritonavir 100 milligrams (mg) capsule orally once in a day.

Number of subjects in period 1	DRV/rtv 800/100 mg q.d.
Started	12
Completed	12

Baseline characteristics

Reporting groups	
Reporting group title	DRV/rtv 800/100 mg q.d.

Reporting group description:

Subjects were administered with Darunavir in combination with low-dose of ritonavir (DRV/rtv) at 800/100 mg once daily (q.d.) in combination with an investigator-selected background regimen, consisting of either zidovudine (AZT)/lamivudine (3TC) or abacavir (ABC)/3TC.

Reporting group values	DRV/rtv 800/100 mg q.d.	Total	
Number of subjects	12	12	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	12	12	
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	14.6		
standard deviation	± 1.69	-	
Title for Gender Units: subjects			
Female	8	8	
Male	4	4	

End points

End points reporting groups

Reporting group title	DRV/rtv 800/100 mg q.d.

Reporting group description:

Subjects were administered with Darunavir in combination with low-dose of ritonavir (DRV/rtv) at 800/100 mg once daily (q.d.) in combination with an investigator-selected background regimen, consisting of either zidovudine (AZT)/lamivudine (3TC) or abacavir (ABC)/3TC.

Primary: Virological Response[Viral Load <50 Copies/mL, (Time to Loss of Virologic Response) TLOVR]

End point title	Virological Response[Viral Load <50 Copies/mL, (Time to Loss of Virologic Response) TLOVR][1]

End point description:

The analysis is based on virologic response defined as percentage of patients with confirmed plasma viral load less than (<) 50 HIV-1 RNA copies/mL at Week 24 calculated according to the Food and Drug Administration (FDA) Time to Loss of Virologic Response (TLOVR) algorithm.

End point type	Primary

End point timeframe:

Week 24

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	DRV/rtv 800/100 mg q.d.			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects				
Yes	11			
No	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Virological Response [Viral Load <50 Copies/mL, FDA-SNAPSHOT]

End point title	Virological Response [Viral Load <50 Copies/mL, FDA-SNAPSHOT]

End point description:

The analysis is based on the last observed viral load (VL) data within the Week 24 window. Virologic response is defined as a VL less than (<) 50 copies/mL (observed case). Virologic Failure includes a) patients who had greater than or equal to (>=) 50 copies/millilitre (mL) in the Week 24 window, b) patients who discontinued prior to Week 24 for lack or loss of efficacy, c) patients who had a switch in their background regimen that was not permitted by the protocol, and d) patients who discontinued for reasons other than adverse events (AEs)/death, and lack or loss of efficacy (provided their last available viral load was detectable).

End point type	Secondary

End point timeframe:

Week 24

End point values	DRV/rtv 800/100 mg q.d.			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Virologic response-Other parameters

End point title	Virologic response-Other parameters

End point description:

Virologic response defined as the percentage of subjects with (1) a confirmed plasma viral load <400 copies/mL, and (2) a confirmed ≥ 1 log10 decrease in plasma viral load versus baseline, calculated according to the TLOVR algorithm

End point type	Secondary

End point timeframe:

Week 2 to Week 48

End point values	DRV/rtv 800/100 mg q.d.			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in plasma viral load versus baseline

End point title	Change in plasma viral load versus baseline

End point description:

The change in plasma log10 viral load from baseline was calculated using the NC = F algorithm.

End point type	Secondary

End point timeframe:

Upto Week 48

End point values	DRV/rtv 800/100 mg q.d.			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first virologic response

End point title	Time to first virologic response

End point description:

The time to first virologic response (defined as plasma viral load < 50 copies/mL, < 400 copies/mL, and ≥ 1 log10 decrease in plasma viral load versus baseline) was calculated according to the TLOVR algorithm. In this algorithm, subjects who never achieved virologic response were censored at their last available assessment time point during the treatment period.

End point type	Secondary

End point timeframe:

Up to Week 48

End point values	DRV/rtv 800/100 mg q.d.			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Immunologic response

End point title	Immunologic response

End point description:

CD4+ cell count was calculated using the NC = F algorithm.

End point type	Secondary

End point timeframe:

Up to Week 48

End point values	DRV/rtv 800/100 mg q.d.			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects	12			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline upto week 52.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups	
Reporting group title	DRV/rtv 800/100 mg q.d.

Reporting group description:

darunavir with low-dose ritonavir (DRV/rtv) administered at 800/100 mg once daily (q.d.) in combination with an investigator-selected background regimen, consisting of either zidovudine (AZT)/lamivudine (3TC) or abacavir (ABC)/3TC

Serious adverse events	DRV/rtv 800/100 mg q.d.		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Traumatic Brain Injury			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Cervical Dysplasia			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	DRV/rtv 800/100 mg q.d.		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Reproductive system and breast disorders			
Uterine Cervical Erosion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Rhinitis Allergic			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Psychiatric disorders			

Attention Deficit/Hyperactivity Disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Limb Injury			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nail Injury			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Neutropenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	3		
Leukopenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	4		
Eye disorders			
Conjunctival Hyperaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Keratitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Conjunctivitis Allergic			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vision Blurred			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Abdominal Pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	7		
Nausea			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infections and infestations			
Asymptomatic Bacteriuria			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Herpes Simplex			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Furuncle			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Herpes Zoster			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Otitis Media Acute			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory Tract Infection Viral			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tooth Abscess			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported