

**Clinical trial results:**

**A Phase II, Open Label Trial, to Evaluate Pharmacokinetics, Safety, Tolerability and Antiviral Activity of DRV in Combination With Low-Dose Ritonavir (DRV/Rtv) in Treatment-Experienced HIV-1 Infected Children From 3 Years to Below 6 Years of Age. Week-48 analysis. This trial is referred to as ARIEL.**

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

**Summary**

EudraCT number	2008-004630-25
Trial protocol	Outside EU/EEA
Global end of trial date	28 February 2011

**Results information**

Result version number	v2 (current)
This version publication date	23 June 2016
First version publication date	01 August 2015
Version creation reason	• Correction of full data set Review of data

**Trial information****Trial identification**

Sponsor protocol code	TMC114-TiDP29-C228
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00919854
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Tibotec Pharmaceuticals
Sponsor organisation address	Eastgate Village, Eastgate, Little Island, Cork, Ireland,
Public contact	Janssen Biologics BV, Janssen-Cilag International NV - Clinical Registry Group, +31 (0)71524 2166, ClinicalTrialsEU@its.jnj.com
Scientific contact	Janssen Biologics BV, Janssen-Cilag International NV - Clinical Registry Group, +31 (0)71524 2166, 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)	EMA-000038-PIP07-03
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	28 February 2011
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 February 2011
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of this study were to evaluate the pharmacokinetic (PK) profile of darunavir (DRV) in combination with low-dose ritonavir (RTV) administered twice daily at steady-state in children aged from 3 to less than (<) 6 years and weighing between 10 and < 20 kilogram (kg) and to support dose recommendation of DRV/rtv to be used in this population by comparing the DRV exposure achieved in these treatment-experienced HIV-1 infected children to that in HIV-1 infected adults and older children weighing more than (>)20 kg. This study also evaluated short-term safety, tolerability, and antiviral activity of DRV/RTV administered twice daily and other ARVs in treatment-experienced children aged from 3 to < 6 years over a 2-week treatment period. In addition, the study also evaluated safety, tolerability and efficacy of DRV/rtv administered b.i.d. and other ARV agents over a 24-week treatment period at the recommended dose for HIV-1 infected children aged from 3 years to < 6 year

Protection of trial subjects:

Safety was monitored by means of Data and Safety Monitoring Board (DSMB) analysis. Safety evaluations for this study included the monitoring of adverse events, vital sign measurements, electrocardiogram (ECGs), physical examination, neurological examination and clinical laboratory tests (included biochemistry parameters).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 September 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	Argentina: 4
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	South Africa: 10
Worldwide total number of subjects	21
EEA total number of subjects	0

Notes:

<b>Subjects enrolled per age group</b>	
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)	21
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: -

### Pre-assignment

Screening details:

27 subjects were recruited and treated in this study; as Good Clinical Practice (GCP) requirements were not consistently adhered to at one site (involving 6 subjects), analyses were performed excluding the subjects from this site, resulting in 21 subjects used for analyses.

### 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	DRV/rtv
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Arm description:

Combination of darunavir and low dose ritonavir administered twice daily.

Arm type	Experimental
Investigational medicinal product name	Darunavir
Investigational medicinal product code	
Other name	TMC114
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Combination of darunavir and low dose ritonavir administered twice daily.

Investigational medicinal product name	Ritonavir
Investigational medicinal product code	
Other name	RTV
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Combination of darunavir and low dose ritonavir administered twice daily.

Number of subjects in period 1	DRV/rtv
Started	21
Completed	20
Not completed	1
Adverse event, non-fatal	1

## Baseline characteristics

### Reporting groups

Reporting group title	DRV/rtv
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Reporting group description:

Combination of darunavir and low dose ritonavir administered twice daily.

Reporting group values	DRV/rtv	Total	
Number of subjects	21	21	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	21	21	
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	4.5		
standard deviation	± 0.92	-	
Title for Gender Units: subjects			
Female	11	11	
Male	10	10	

## End points

### End points reporting groups

Reporting group title	DRV/rtv
Reporting group description:	
Combination of darunavir and low dose ritonavir administered twice daily.	

### Primary: Number of Subjects With Virological Response (Viral Load Less Than 50 Copies/mL) at Week 24 - Time to Loss of Virologic Response (TLOVR)

End point title	Number of Subjects With Virological Response (Viral Load Less Than 50 Copies/mL) at Week 24 - Time to Loss of Virologic Response (TLOVR) <sup>[1]</sup>
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#### End point description:

The TLOVR algorithm was used to derive response, i.e., response and loss of response needed to be confirmed at 2 consecutive visits and subjects who permanently discontinued were considered non-responders after discontinuation. Subjects with intermittent missing viral load values were considered responders if the preceding and succeeding visits indicated response. In all other cases, intermittent values were imputed with nonresponse. Resuppression after confirmed virologic failure was considered as failure in this algorithm. Efficacy population included all subjects who received at least 1 dose of study medication.

End point type	Primary
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#### 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			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects	12			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Virological Response (Viral Load Less Than 50 Copies/mL) at Week 48 - Time to Loss of Virologic Response (TLOVR)

End point title	Number of Subjects With Virological Response (Viral Load Less Than 50 Copies/mL) at Week 48 - Time to Loss of Virologic Response (TLOVR)
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#### End point description:

The TLOVR algorithm was used to derive response, i.e., response and loss of response needed to be confirmed at 2 consecutive visits and subjects who permanently discontinued were considered non-responders after discontinuation. Subjects with intermittent missing viral load values were considered responders if the preceding and succeeding visits indicated response. In all other cases, intermittent values were imputed with nonresponse. Resuppression after confirmed virologic failure was considered as failure in this algorithm. Efficacy population included all subjects who received at least 1 dose of study medication.

End point type	Secondary
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End point timeframe:

Week 48

End point values	DRV/rtv			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects	17			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Virological Response (Viral Load Less Than 400 Copies/mL) at Week 24 and Week 48

End point title	Number of Subjects With Virological Response (Viral Load Less Than 400 Copies/mL) at Week 24 and Week 48
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End point description:

The TLOVR algorithm was used to derive response, ie, response and loss of response needed to be confirmed at 2 consecutive visits and subjects who permanently discontinued were considered non-responders after discontinuation. Subjects with intermittent missing viral load values were considered responders if the preceding and succeeding visits indicated response. In all other cases, intermittent values were imputed with nonresponse. Resuppression after confirmed virologic failure was considered as failure in this algorithm. Efficacy population included all subjects who received at least 1 dose of study medication.

In addition to the TLOVR analyses, the same sensitivity analyses as for the primary virologic response parameter were performed for plasma viral load < 400 copies/mL: 1) observed case analysis, 2) NC = F analysis, and 3) TLOVR non-VF-censored analysis.

End point type	Secondary
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End point timeframe:

Week 24 and Week 48

End point values	DRV/rtv			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects				
Week 24	17			
Week 48	18			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Less Than or Equal to 1 log10 Decrease in

## Plasma Viral Load at Week 24 and Week 48

End point title	Number of Subjects With Less Than or Equal to 1 log <sub>10</sub> Decrease in Plasma Viral Load at Week 24 and Week 48
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### End point description:

The TLOVR algorithm was used to derive response, i.e., response and loss of response needed to be confirmed at 2 consecutive visits and subjects who permanently discontinued were considered non-responders after discontinuation. Subjects with intermittent missing viral load values were considered responders if the preceding and succeeding visits indicated response. In all other cases, intermittent values were imputed with nonresponse. Resuppression after confirmed virologic failure was considered as failure in this algorithm. Efficacy population included all subjects who received at least 1 dose of study medication.

In addition to the TLOVR analyses, the same sensitivity analyses as for the primary virologic response parameter were performed for  $\geq 1$  log<sub>10</sub> decrease in plasma viral load versus baseline: 1) observed case analysis, 2) NC = F analysis, and 3) TLOVR non-VF-censored analysis.

End point type	Secondary
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### End point timeframe:

Week 24 and Week 48

End point values	DRV/rtv			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects				
Week 24	17			
Week 48	19			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Change From Baseline to Week 24 and Week 48 in Plasma log<sub>10</sub> Viral Load

End point title	Mean Change From Baseline to Week 24 and Week 48 in Plasma log <sub>10</sub> Viral Load
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### End point description:

The change in plasma log<sub>10</sub> viral load from baseline was calculated using the NC = F algorithm.

End point type	Secondary
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### End point timeframe:

Baseline, Week 24 and Week 48

End point values	DRV/rtv			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: log <sub>10</sub> copies/milliliters (mL)				
arithmetic mean (standard error)				
Week 24	-2.04 (± 0.244)			



Week 48	-2.14 ( $\pm$ 0.257)			
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Change From Baseline to Week 24 and Week 48 in CD4+ Percentage

End point title	Mean Change From Baseline to Week 24 and Week 48 in CD4+ Percentage
End point description: CD4+ cell count was calculated using NC = F algorithm	
End point type	Secondary
End point timeframe: Baseline, Week 24 and Week 48	

End point values	DRV/rtv			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of lymphocytes				
arithmetic mean (standard error)				
Week 24	4 ( $\pm$ 0.9)			
Week 48	4 ( $\pm$ 1.3)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

48 weeks

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	' 12.1'
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### Reporting groups

Reporting group title	DRV/rtv
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Reporting group description:

Combination of darunavir and low dose ritonavir administered twice daily.

Serious adverse events	DRV/rtv		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 21 (9.52%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Asthmatic Crisis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Trigger Finger			
subjects affected / exposed	1 / 21 (4.76%)		
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		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 21 (95.24%)		
Vascular disorders			

Haematoma subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 5		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Asthmatic Crisis subjects affected / exposed occurrences (all)  Oropharyngeal Pain subjects affected / exposed occurrences (all)  Nasal Congestion subjects affected / exposed occurrences (all)  Rhinorrhoea subjects affected / exposed occurrences (all)  Sneezing subjects affected / exposed occurrences (all)	5 / 21 (23.81%) 12  1 / 21 (4.76%) 3  1 / 21 (4.76%) 1  3 / 21 (14.29%) 3  3 / 21 (14.29%) 3  1 / 21 (4.76%) 1		
Investigations Breath Sounds Abnormal subjects affected / exposed occurrences (all)  Electrocardiogram QT Prolonged subjects affected / exposed occurrences (all)  QRS Axis Abnormal subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 2  1 / 21 (4.76%) 1  1 / 21 (4.76%) 1		

Weight Decreased subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Injury, poisoning and procedural complications Arthropod Bite subjects affected / exposed occurrences (all)  Animal Bite subjects affected / exposed occurrences (all)  Limb Injury subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1  1 / 21 (4.76%) 1  1 / 21 (4.76%) 1		
Nervous system disorders Psychomotor Hyperactivity subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)  Neutropenia subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1  1 / 21 (4.76%) 1		
Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all)  Otorrhoea subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2  1 / 21 (4.76%) 1		
Eye disorders Conjunctivitis Allergic subjects affected / exposed occurrences (all)  Conjunctivitis	1 / 21 (4.76%) 1		

subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	7		
Dental Caries			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Lip Ulceration			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Mouth Ulceration			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	6		
Hepatobiliary disorders			
Hepatosplenomegaly			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Pityriasis Alba			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	4		
Skin Ulcer			

subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Finger Deformity			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Cellulitis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Impetigo			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	7		
Gastroenteritis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Lower Respiratory Tract Infection			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Lice Infestation			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	2		
Mumps			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	6		
Otitis Media Acute			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Oral Herpes			

subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Pharyngotonsillitis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	4		
Otitis Media Chronic			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	6		
Tinea Capitis			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	5		
Tinea Faciei			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Tonsillitis			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Urinary Tract Infection			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Upper Respiratory Tract Infection			
subjects affected / exposed	6 / 21 (28.57%)		
occurrences (all)	9		
Varicella			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		

Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2009	The first amendment included the following changes: 1) updated the protocol text to explain the concept of drug induced liver injury (DILI) and to apply specific toxicity management rules in the presence of DILI; 2) Provided guidance for the testing of hepatitis serology for subjects without documented hepatitis B vaccination; 3) management in case of change in body weight; 4) updated text on storage conditions to ensure consistency with the label text and changes to the protocol text were made with regards to pancreatitis; 5) In addition, changes to the protocol introduction was made as a result of the most recent Investigator Brochure update (Version 10, March 2009). Changes to the protocol text were made regarding management in case of increased lipase/amylase in certain clinical situations; 6) Guidance regarding the backbone is also provided.
23 November 2009	The second amendment included a pharmacokinetic sub-study performed in children participating in trial TMC114-C228.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported