



Clinical trial results:

A phase I/II study of Invirase® boosted with Ritonavir in HIV infected infants and children 4 months to less than 6 years old

Summary

EudraCT number	2007-004617-34
Trial protocol	GB
Global end of trial date	11 March 2010

Results information

Result version number	v1 (current)
This version publication date	04 March 2016
First version publication date	04 March 2016

Trial information

Trial identification

Sponsor protocol code	NV20911
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00623597
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche Ltd
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 April 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 March 2010
Global end of trial reached?	Yes
Global end of trial date	11 March 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the pharmacokinetics of saquinavir that, when boosted with ritonavir, provides a systemic exposure in human immunodeficiency virus (HIV)-1 infected infants and children 4 months to < 6 years similar to that which has been shown to be safe and effective in older children and adults.
- To determine the safety and tolerability of saquinavir when boosted with ritonavir in HIV-1 infected infants and children 4 months to < 6 years of age.

Protection of trial subjects:

The investigators ensured that this study was conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong and South Africa) or with the laws and regulations of the country in which the research was conducted, whichever afforded greater protection to the individual. The study adhered fully to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the participant. In countries where a "Guideline for Good Clinical Practice" existed, Roche and the investigators were to strictly ensure adherence to the stated provisions.

Background therapy:

The participants in the study were allowed to take ≥ 2 background antiretroviral (ARV) regimen. Background ARVs included nucleosides (nucleoside reverse transcriptase inhibitor) and could also include ritonavir boosted lopinavir (LPV/r), as deemed appropriate by the investigator, considering the participant's prior history as well as the participant's viral resistance assessed at screening. If LPV/r was used, the total dose of ritonavir (including ritonavir that was co-formulated with lopinavir) was specified. The background ARVs was revised when initiating saquinavir and ritonavir, or remained unchanged from prestudy, as per the judgment of the investigator. Background ARVs were changed during the course of the study as needed for toxicity management or if the participant's virological or immunological response was insufficient.

Evidence for comparator:

Nil

Actual start date of recruitment	20 May 2008
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	Argentina: 7
Country: Number of subjects enrolled	Thailand: 10
Worldwide total number of subjects	18
EEA total number of subjects	1

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)	5
Children (2-11 years)	13
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 18 participants were recruited from 8 centers in Argentina (3 centers), Spain (1 center) and Thailand (4 centers). This study was conducted between May 20, 2008 and March 11, 2010.

Pre-assignment

Screening details:

Participants were HIV infected infants and young children who met the eligibility criteria were stratified into 2 groups - low age group (≥ 4 months to <2 years) and high age group (≥ 2 years to <6 years). Participants commenced treatment with saquinavir and ritonavir along with background antiretroviral (ARV) regimen.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

Participants (infants ≥ 4 months to <2 years old) received saquinavir at a dose of 50 milligram per kilogram (mg/Kg) twice a day (BID) and ritonavir at a dose of 3 mg/kg BID for body weight from 5 to <15 kg, 2.5 mg/kg BID for body weight from 15 to 40 kg and 100 mg BID for body weight >40 kg plus ≥ 2 background ARVs. After 14 days of treatment (or Day 28 for participants switching from an NNRTI containing regimen), saquinavir and ritonavir dose adjustments were made within the age group or for individual participants as deemed appropriate. The highest dose for saquinavir/ritonavir that was to be administered was not to exceed 1000 mg/100 mg BID. Participants received treatment for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Saquinavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received saquinavir mesylate (Invirase® 200 mg hard capsules [HC] and/or 500 mg film coated tablet [FCT]) up to 48 weeks. For participants who could not swallow Invirase capsules, the 200 mg capsule(s) were opened and the contents of the capsule administered in a vehicle [sugar syrup (sorbitol syrup for children with diabetes mellitus or glucose intolerance), jam or baby formula] along with ritonavir oral solution. At home saquinavir and ritonavir was to be taken concomitantly with food. On days of sampling blood for pharmacokinetic study, dosing was approximately 30 minutes after the start of breakfast. For participants who could swallow capsules and or tablets no vehicle was required. The saquinavir mesylate 500 mg FCT was not to be crushed prior to administration.

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

Dosage and administration details:

Participants received ritonavir (Norvir® 80 mg/mL oral solution) 3 mg/kg BID for body weight from 5 to <15 kg for up to 48 weeks. If a participant was prescribed Kaletra® (lopinavir/ritonavir) as part of the background ARV regimen, the ritonavir dose specified in the protocol for a child of a given weight was the total dose of ritonavir, including the ritonavir that was co-formulated in Kaletra. Thus, for participants taking Invirase plus Kaletra, the ritonavir included in the Kaletra was sufficient for boosting of both the Invirase and the lopinavir, and no additional ritonavir was to be given. At home ritonavir was

to be taken concomitantly with food. On days of sampling blood for pharmacokinetic study, dosing was approximately 30 minutes after the start of breakfast.

Arm title	Group B
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Arm description:

Participants (children ≥ 2 years to <6 years old) received saquinavir at a dose of 50 mg/Kg BID and ritonavir at a dose of 3 mg/kg BID for body weight from 5 to < 15 kg, 2.5 mg/kg BID for body weight from 15 to 40 kg and 100 mg BID for body weight > 40 kg plus ≥ 2 background ARVs. After 14 days of treatment (or Day 28 for participants switching from an NNRTI containing regimen), saquinavir and ritonavir dose adjustments were made within the age group or for individual participants as deemed appropriate. The highest dose for saquinavir/ritonavir that was to be administered was not to exceed 1000 mg/100 mg BID. Participants received treatment for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Saquinavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received saquinavir mesylate (Invirase® 200 mg HC and/or 500 mg FCT) up to 48 weeks. For participants who could not swallow Invirase capsules, the 200 mg capsule(s) were opened and the contents of the capsule administered in a vehicle [sugar syrup (sorbitol syrup for children with diabetes mellitus or glucose intolerance), jam or baby formula] and ritonavir oral solution. At home saquinavir and ritonavir was to be taken concomitantly with food. On days of sampling blood for pharmacokinetic study, dosing was approximately 30 minutes after the start of breakfast. For participants who could swallow capsules and or tablets no vehicle was required. The saquinavir mesylate 500 mg FCT was not to be crushed prior to administration.

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

Dosage and administration details:

Participants received ritonavir (Norvir® 80 mg/mL oral solution) 3 mg/kg BID for body weight from 5 to <15 kg, 2.5 mg/kg BID for body weight from 15 to 40 kg and 100 mg BID for body weight >40 kg for up to 48 weeks. If a participant was prescribed Kaletra® (lopinavir/ritonavir) as part of the background ARV regimen, the ritonavir dose specified in the protocol for a child of a given weight was the total dose of ritonavir, including the ritonavir that was co-formulated in Kaletra. Thus, for participants taking Invirase plus Kaletra, the ritonavir included in the Kaletra was sufficient for boosting of both the Invirase and the lopinavir, and no additional ritonavir was to be given. At home ritonavir was to be taken concomitantly with food. On days of sampling blood for pharmacokinetic study, dosing was approximately 30 minutes after the start of breakfast.

Number of subjects in period 1	Group A	Group B
Started	5	13
Completed	4	13
Not completed	1	0
Failed to return	1	-

Baseline characteristics

Reporting groups

Reporting group title	Group A
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Reporting group description:

Participants (infants ≥ 4 months to <2 years old) received saquinavir at a dose of 50 milligram per kilogram (mg/Kg) twice a day (BID) and ritonavir at a dose of 3 mg/kg BID for body weight from 5 to < 15 kg, 2.5 mg/kg BID for body weight from 15 to 40 kg and 100 mg BID for body weight > 40 kg plus ≥ 2 background ARVs. After 14 days of treatment (or Day 28 for participants switching from an NNRTI containing regimen), saquinavir and ritonavir dose adjustments were made within the age group or for individual participants as deemed appropriate. The highest dose for saquinavir/ritonavir that was to be administered was not to exceed 1000 mg/100 mg BID. Participants received treatment for 48 weeks.

Reporting group title	Group B
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Reporting group description:

Participants (children ≥ 2 years to <6 years old) received saquinavir at a dose of 50 mg/Kg BID and ritonavir at a dose of 3 mg/kg BID for body weight from 5 to < 15 kg, 2.5 mg/kg BID for body weight from 15 to 40 kg and 100 mg BID for body weight > 40 kg plus ≥ 2 background ARVs. After 14 days of treatment (or Day 28 for participants switching from an NNRTI containing regimen), saquinavir and ritonavir dose adjustments were made within the age group or for individual participants as deemed appropriate. The highest dose for saquinavir/ritonavir that was to be administered was not to exceed 1000 mg/100 mg BID. Participants received treatment for 48 weeks.

Reporting group values	Group A	Group B	Total
Number of subjects	5	13	18
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	5	0	5
Children (2-11 years)	0	13	13
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	0.8	4	
standard deviation	± 0.45	± 1.08	-
Gender categorical			
Units: Subjects			
Female	3	8	11
Male	2	5	7

End points

End points reporting groups

Reporting group title	Group A
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Reporting group description:

Participants (infants \geq 4 months to $<$ 2 years old) received saquinavir at a dose of 50 milligram per kilogram (mg/Kg) twice a day (BID) and ritonavir at a dose of 3 mg/kg BID for body weight from 5 to $<$ 15 kg, 2.5 mg/kg BID for body weight from 15 to 40 kg and 100 mg BID for body weight $>$ 40 kg plus \geq 2 background ARVs. After 14 days of treatment (or Day 28 for participants switching from an NNRTI containing regimen), saquinavir and ritonavir dose adjustments were made within the age group or for individual participants as deemed appropriate. The highest dose for saquinavir/ritonavir that was to be administered was not to exceed 1000 mg/100 mg BID. Participants received treatment for 48 weeks.

Reporting group title	Group B
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Reporting group description:

Participants (children \geq 2 years to $<$ 6 years old) received saquinavir at a dose of 50 mg/Kg BID and ritonavir at a dose of 3 mg/kg BID for body weight from 5 to $<$ 15 kg, 2.5 mg/kg BID for body weight from 15 to 40 kg and 100 mg BID for body weight $>$ 40 kg plus \geq 2 background ARVs. After 14 days of treatment (or Day 28 for participants switching from an NNRTI containing regimen), saquinavir and ritonavir dose adjustments were made within the age group or for individual participants as deemed appropriate. The highest dose for saquinavir/ritonavir that was to be administered was not to exceed 1000 mg/100 mg BID. Participants received treatment for 48 weeks.

Subject analysis set title	All Patient Population
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Subject analysis set type	Full analysis
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Subject analysis set description:

The All Patient Population (APP) comprised all participants who were enrolled in the study, regardless of whether they received any study drug.

Subject analysis set title	PK Analysis Population
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

The pharmacokinetics Analysis Population (PKP) comprised all the participants from whom blood samples for pharmacokinetic analysis were collected. Participants could be excluded from the PKP if no reliable PK parameters could be determined. Moreover, participants could be excluded from the PK analysis population if justified by circumstances (e.g. vomiting after drug administration) and in agreement with the sponsor.

Subject analysis set title	Safety Analysis Population
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The Safety Analysis Population (SAP) comprised all participants who received at least one dose of study medication. The SAP was used for all efficacy and safety analyses.

Primary: Plasma Trough Concentrations for Saquinavir

End point title	Plasma Trough Concentrations for Saquinavir ^[1]
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End point description:

Plasma trough concentration (C_{trough}) is the average steady state concentration prior to morning and evening dose. C_{trough} of Saquinavir was normalized to a dose of 50 mg/kg. The PKP was used for this endpoint analysis.

End point type	Primary
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End point timeframe:

Pre-dose at Weeks 8, 12, and 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: No statistical analyses were done for this end point.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: nanogram per millilitre (ng/mL)				
arithmetic mean (standard deviation)	645 (± 536)	1860 (± 1060)		

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-time Curve Over the Time Interval From Zero to Twelve Hours for Saquinavir

End point title	Area Under the Plasma Concentration-time Curve Over the Time Interval From Zero to Twelve Hours for Saquinavir ^[2]
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End point description:

The area under the plasma concentration-time curve from time zero to twelve hours (AUC_{0-12h}) is area under the plasma concentration-time curve from time zero through actual tlast. The area under the plasma concentration-time curve from time zero to twelve hours of saquinavir was normalized to a dose of 50 mg/kg.

The PKP was used for this endpoint analysis.

End point type	Primary
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End point timeframe:

Pre-dose and 3, 4, 8, 12 hours (post-dose) on Day 14 (± 2 days), or Day 28(+ 2 days) for patients switching from an Non-nucleoside reverse transcriptase inhibitor [NNRTI] containing regimen).

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: No statistical analyses were done for this end point.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: hour* microgram per millilitre (h*ug/mL)				
arithmetic mean (standard deviation)	18.7 (± 20)	38 (± 18.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Change In Hemoglobin, Total Protein And Total Albumin From Baseline at Week 24 and Week 48

End point title	Change In Hemoglobin, Total Protein And Total Albumin From Baseline at Week 24 and Week 48 ^[3]
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End point description:

Change in Hemoglobin, Total Protein and Total Albumin from baseline (BL) was calculated as the post-baseline value minus the baseline value. Week=Wk. The SAP was used for analysis of this endpoint.

End point type	Primary
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End point timeframe:

Baseline (Day 1), Week 24 and 48

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: No statistical analyses were done for this end point.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: gram per litre (g/L)				
arithmetic mean (standard deviation)				
Hemoglobin-Change from BL at Wk 24 (n=4, 13)	0 (± 3.3)	1 (± 12.1)		
Hemoglobin-Change from BL at Wk 48 (n=4, 13)	6 (± 11.8)	0 (± 14.4)		
Total Protein-Change from BL at Wk 24 (n=4, 13)	-4 (± 6)	2 (± 12.6)		
Total Protein-Change from BL at Wk 48 (n=4, 13)	-5 (± 5.7)	0 (± 14.3)		
Total Albumin-Change from BL at Wk 24 (n=4, 13)	0.5 (± 5.41)	5 (± 7.68)		
Total Albumin-Change from BL at Wk 48 (n=4, 13)	1.3 (± 2.29)	4 (± 8.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Change In Hematocrit From Baseline at Week 24 and Week 48

End point title	Change In Hematocrit From Baseline at Week 24 and Week
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End point description:

Change from baseline was calculated as the post-baseline value minus the baseline value. The SAP was used for analysis of this endpoint.

End point type	Primary
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End point timeframe:

Baseline (Day 1), Week 24 and 48

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: No statistical analyses were done for this end point.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: fraction				
arithmetic mean (standard deviation)				
Change from Baseline at Week 24 (n=4, 13)	0.01 (± 0.011)	0 (± 0.03)		
Change from Baseline at Week 48 (n=4, 13)	0.03 (± 0.037)	-0.01 (± 0.044)		

Statistical analyses

No statistical analyses for this end point

Primary: Change In White Blood Cell, Platelet, Basophil, Lymphocyte, Monocyte, Neutrophil And Eosinophil Cell Counts From Baseline at Week 24 and Week 48

End point title	Change In White Blood Cell, Platelet, Basophil, Lymphocyte, Monocyte, Neutrophil And Eosinophil Cell Counts From Baseline at Week 24 and Week 48 ^[5]
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End point description:

Change from Baseline in White Blood Cell, Platelet, Basophil, Lymphocyte, Monocyte, Neutrophil and Eosinophil Cell Counts was calculated as the post-baseline value minus the baseline value. The SAP was used for analysis of this endpoint.

End point type	Primary
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End point timeframe:

Baseline (Day 1), Week 24 and Week 48

Notes:

[5] - 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: No statistical analyses were done for this end point.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: 10 ⁹ /L				
arithmetic mean (standard deviation)				
White Blood Cell-Change from BL at Wk 24 (n=4,13)	-3 (± 2.31)	-1 (± 4.35)		
White Blood Cell-Change from BL at Wk 48 (n=4,13)	-2.1 (± 1.72)	-0.9 (± 4.38)		
Platelet-Change from BL at Wk 24 (n=4,13)	-119 (± 93.4)	24 (± 148.9)		
Platelet-Change from BL at Wk 48 (n=4,13)	-50 (± 130.4)	-2 (± 118.9)		
Basophil-Change from BL at Wk 24 (n=4,13)	-0.02 (± 0.028)	0 (± 0.031)		
Basophil-Change from BL at Wk 48 (n=4,13)	0 (± 0.03)	-0.01 (± 0.029)		
Lymphocyte-Change from BL at Wk 24 (n=2,2)	-0.9 (± 0.3)	-1.1 (± 1.2)		
Lymphocyte-Change from BL at Wk 48 (n=2,2)	-1.5 (± 0.29)	-0.7 (± 1.05)		
Monocyte-Change from BL at Wk 24 (n=4,13)	-0.41 (± 0.295)	-0.01 (± 0.361)		
Monocyte-Change from BL at Wk 48 (n=4,13)	-0.21 (± 0.179)	-0.05 (± 0.384)		
Neutrophil-Change from BL at Wk 24 (n=2,2)	-1.4 (± 0.33)	-2.8 (± 1.87)		
Neutrophil-Change from BL at Wk 48 (n=2,2)	-1.7 (± 1.15)	-1.6 (± 2.55)		

Eosinophil-Change from BL at Wk 24 (n=2,2)	0 (\pm 0.2)	0 (\pm 0.1)		
Eosinophil-Change from BL at Wk 48 (n=2,2)	0 (\pm 0.2)	0 (\pm 1.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Change In Red Blood Cell Counts From Baseline at Week 24 and Week 48

End point title	Change In Red Blood Cell Counts From Baseline at Week 24 and Week 48 ^[6]
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End point description:

Change from baseline in Red Blood Cell (RBC) counts was calculated as the post-baseline value minus the baseline value. The SAP was used for analysis of this endpoint.

End point type	Primary
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End point timeframe:

Baseline (Day 1), Week 24 and Week 48

Notes:

[6] - 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: No statistical analyses were done for this end point.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: 10*12/L				
arithmetic mean (standard deviation)				
RBC Count-Change from BL at Wk24 (n=4,13)	-0.18 (\pm 0.227)	-0.07 (\pm 0.673)		
RBC Count-Change from BL at Wk48 (n=4,13)	0.02 (\pm 0.125)	-0.16 (\pm 0.74)		

Statistical analyses

No statistical analyses for this end point

Primary: Change In Creatine Kinase, Serum Glutamic Oxaloacetic Transaminase, Alkaline Phosphatase, Serum Glutamic-Pyruvic Transaminase, Gamma-Glutamyl Transferase Counts From Baseline at Week 24 and Week 48

End point title	Change In Creatine Kinase, Serum Glutamic Oxaloacetic Transaminase, Alkaline Phosphatase, Serum Glutamic-Pyruvic Transaminase, Gamma-Glutamyl Transferase Counts From Baseline at Week 24 and Week 48 ^[7]
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End point description:

Change from baseline in Creatine Kinase (CK), Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic-Pyruvic Transaminase (SGPT), Gamma-Glutamyl Transferase (GGT), Alkaline Phosphatase (AP) was calculated as the post-baseline value minus the baseline value. The SAP was used for this endpoint analysis.

End point type	Primary
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End point timeframe:

Baseline (Day 1), Week 24 and Week 48

Notes:

[7] - 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: No statistical analyses were done for this end point.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: units per litre (U/L)				
arithmetic mean (standard deviation)				
CK, Change from Baseline at Week 24 (n= 3, 3)	112 (± 112)	-12 (± 115.9)		
CK, Change from Baseline at Week 48 (n= 3, 3)	257 (± 244.8)	-7 (± 84)		
SGOT, Change from Baseline at Week 24 (n= 4,13)	0 (± 1.5)	0 (± 8.2)		
SGOT, Change from Baseline at Week 48 (n= 4,13)	-1 (± 7.8)	0 (± 6.9)		
ALP, Change from Baseline at Week 24 (n=4, 12)	10 (± 29.8)	26 (± 23.2)		
ALP, Change from Baseline at Week 48 (n=4, 12)	47 (± 87.6)	36 (± 26.5)		
SGPT, Change from Baseline at Week 24 (n=4,13)	-9 (± 15.3)	-2 (± 13.6)		
SGPT, Change from Baseline at Week 48 (n=4,13)	-2 (± 13.4)	-3 (± 12.1)		
GGT, Change from Baseline at Week 24 (n=4, 13)	5 (± 4.7)	-7 (± 18.7)		
GGT, Change from Baseline at Week 48 (n=4, 13)	5 (± 2.1)	-5 (± 18.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Change In Total Bilirubin, Creatinine, Uric Acid From Baseline at Week 24 and Week 48

End point title	Change In Total Bilirubin, Creatinine, Uric Acid From Baseline at Week 24 and Week 48 ^[8]
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End point description:

Change from baseline in Total Bilirubin, Creatinine, Uric Acid was calculated as the post-baseline value minus the baseline value.

The SAP was used for this endpoint analysis.

End point type	Primary
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End point timeframe:

Baseline (Day 1), Week 24 and Week 48

Notes:

[8] - 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: No statistical analyses were done for this end point.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: micromolar per litre (umol/L)				
arithmetic mean (standard deviation)				
Total Bilirubin-Change from BL at Wk 24(n=4,12)	2 (± 2.8)	2 (± 5.5)		
Total Bilirubin-Change from BL at Wk 48(n=4,12)	1 (± 1.1)	2 (± 6.9)		
Cretainine- Change from BL at Wk 24 (n=4, 13)	-2 (± 6.7)	3 (± 10)		
Cretainine- Change from BL at Wk 48 (n=4, 13)	3 (± 10.7)	5 (± 9.2)		
Uric acid- Change from BL at Wk 24 (n=4, 13)	-27 (± 54.3)	68 (± 55.1)		
Uric acid- Change from BL at Wk 48 (n=3,13)	-42 (± 108.4)	61 (± 63.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Change In Blood Urea Nitrogen, Low Density Lipoprotein Cholesterol, High Density Lipoprotein Cholesterol, Triglycerides, Calcium, Potassium, Sodium, Chloride, Phosphate, Fasting Glucose From Baseline at Week 24 and Week 48

End point title	Change In Blood Urea Nitrogen, Low Density Lipoprotein Cholesterol, High Density Lipoprotein Cholesterol, Triglycerides, Calcium, Potassium, Sodium, Chloride, Phosphate, Fasting Glucose From Baseline at Week 24 and Week 48 ^[9]
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End point description:

Change from baseline in Blood Urea Nitrogen (BUN), Low Density Lipoprotein (LDL) Cholesterol, High Density Lipoprotein (HDL) Cholesterol, Triglycerides, Calcium, Potassium, Sodium, Chloride, Phosphate, Fasting Glucose was calculated as the post-baseline value minus the baseline value. The SAP was used for this endpoint analysis.

End point type	Primary
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End point timeframe:

Baseline (Day 1), Week 24 and Week 48

Notes:

[9] - 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: No statistical analyses were done for this end point.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: millimole per litre (mmol/L)				
arithmetic mean (standard deviation)				
BUN,Change from Baseline at Week 24 (n= 3, 13)	-1.5 (± 2.78)	1 (± 2.2)		
BUN,Change from Baseline at Week 48 (n= 3, 13)	0.4 (± 0.66)	1.1 (± 2)		
LDL,Change from Baseline at Week 24 (n= 3, 13)	0.21 (± 0.237)	0.21 (± 1.389)		

LDL,Change from Baseline at Week 48 (n= 3, 13)	0.23 (± 0.596)	-0.11 (± 1.038)		
HDL,Change from Baseline at Week 24 (n= 3, 13)	0.21 (± 0.202)	0.13 (± 0.369)		
HDL,Change from Baseline at Week 48 (n= 3, 13)	0.41 (± 0.233)	0.17 (± 0.387)		
Triglyceride,Change from BL at Wk 24 (n=4,13)	-0.28 (± 0.597)	-0.19 (± 1.376)		
Triglyceride,Change from BL at Wk 48 (n=4,13)	-0.19 (± 0.496)	-0.15 (± 1.558)		
Calcium,Change from BL at Wk 24 (n=2, 12)	-0.15 (± 0.04)	0.15 (± 0.17)		
Calcium,Change from BL at Wk 48 (n=2, 12)	-0.16 (± 0.09)	0.09 (± 0.17)		
Potassium,Change from BL at Wk 24 (n=4,13)	-0.1 (± 0.16)	-0.3 (± 0.63)		
Potassium,Change from BL at Wk 48 (n=4,13)	0.2 (± 0.59)	-0.2 (± 0.54)		
Sodium,Change from BL at Wk 24 (n=4,13)	2 (± 1.3)	-1 (± 2.3)		
Sodium,Change from BL at Wk 48 (n=4,13)	1 (± 2.2)	-1 (± 3.8)		
Chloride,Change from BL at Wk 24 (n=4,13)	-1 (± 2.8)	-2 (± 4.2)		
Chloride,Change from BL at Wk 48 (n=4,13)	1 (± 1.3)	-2 (± 3.6)		
Phosphate,Change from BL at Wk 24 (n=2, 12)	-0.02 (± 0.114)	0.17 (± 0.188)		
Phosphate,Change from BL at Wk 48 (n=2, 13)	-0.26 (± 0)	0.12 (± 0.212)		
Fasting Glucose,Change from BL at Wk 24 (n=4,13)	-0.26 (± 0.963)	0.02 (± 1.253)		
Fasting Glucose,Change from BL at Wk 48 (n=4,13)	-0.07 (± 0.857)	0.14 (± 1.537)		

Statistical analyses

No statistical analyses for this end point

Primary: Change In Hematuria, Glycosuria And Proteinuria From Baseline at Week 24 and Week 48

End point title	Change In Hematuria, Glycosuria And Proteinuria From Baseline at Week 24 and Week 48 ^[10]
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End point description:

Change from baseline in Hematuria, Glycosuria And Proteinuria was calculated as the post-baseline value minus the baseline value. The SAP was used for analysis of this endpoint.

End point type	Primary
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End point timeframe:

Baseline (Day 1), Week 24 and Week 48

Notes:

[10] - 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: No statistical analyses were done for this end point.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: [0 to 4+]				
arithmetic mean (standard deviation)				
Hematuria-Change from BL at Wk 24 (n= 1, 2)	0 (± 0)	0 (± 0)		
Hematuria-Change from BL at Wk 48 (n= 1, 2)	0 (± 0)	0 (± 0)		
Glycosuria-Change from BL at Wk 24 (n= 1, 2)	0 (± 0)	0 (± 0)		
Glycosuria-Change from BL at Wk 48 (n= 1, 2)	0 (± 0)	0 (± 0)		
Proteinuria-Change from BL at Wk 24 (n= 1, 2)	0 (± 0)	0 (± 0)		
Proteinuria-Change from BL at Wk 48 (n= 1, 2)	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Adverse Events and Serious Adverse Events

End point title	Incidence of Adverse Events and Serious Adverse Events ^[11]
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End point description:

An adverse event (AE) is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is a significant medical event in the investigator's judgment or requires intervention to prevent one or other of these outcomes. The SAP was used for this endpoint analysis.

End point type	Primary
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End point timeframe:

Up to 52 weeks

Notes:

[11] - 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: No statistical analyses were done for this end point.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: Number				
Subjects with serious adverse events	1	2		
Subjects with non-serious adverse events	5	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Trough Concentrations for Ritonavir

End point title	Plasma Trough Concentrations for Ritonavir
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End point description:

Plasma trough concentration is the average steady state concentration prior to morning and evening dose. Ctrough of Ritonavir was normalized to a dose of 100 mg/kg.
The PKP was used for analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Pre-dose at Weeks 8, 12, 24

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: ng/mL				
arithmetic mean (standard deviation)	577 (± 366)	995 (± 548)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration for Saquinavir and Ritonavir

End point title	Maximum Observed Concentration for Saquinavir and Ritonavir
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End point description:

The Plasma Concentration (C_{max}) is defined as maximum observed analyte concentration. C_{max} was normalized to a dose of 50 mg/kg for Saquinavir and 100 mg/kg for Ritonavir.
The PKP was used for analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Pre-dose and 3, 4, 8, 12 hours (post-dose) on Day 14 (± 2 days), or Day 28(+ 2 days) for patients switching from an NNRTI containing regimen and at Week 24.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: ng/mL				
arithmetic mean (standard deviation)				
Saquinavir	2910 (± 3110)	5570 (± 2780)		
Ritonavir	2050 (± 1270)	3370 (± 2020)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve Over the Time Interval From Zero to Twelve Hours for Ritonavir

End point title	Area Under the Plasma Concentration-time Curve Over the Time Interval From Zero to Twelve Hours for Ritonavir
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End point description:

The area under the plasma concentration-time curve from time zero to twelve hours (AUC_{0-12h}) is area under the plasma concentration-time curve from time zero through actual tlast. The area under the plasma concentration-time curve from time zero to twelve hours of ritonavir was normalized to a dose of 100 mg/kg.

The PKP was used for analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Pre-dose and 3, 4, 8, 12 hours (post-dose) on Day 14 (\pm 2 days), or Day 28(\pm 2 days) for patients switching from an NNRTI containing regimen

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: h*ug/ml				
arithmetic mean (standard deviation)	13.6 (\pm 8.18)	21.8 (\pm 11.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Human Immunodeficiency Virus Viral Load

End point title	Change From Baseline in Mean Human Immunodeficiency Virus Viral Load
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End point description:

Change from baseline in plasma HIV-1 RNA was derived as Change from baseline = Log₁₀ (HIV-1 RNA at week x) – Log₁₀ (HIV-1 RNA at baseline). A baseline collection was made if there was not already a value available taken within the previous 4 weeks. The SAP was used for analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline (Day 1), Weeks 8, 12, 24, 36, and 48 or upon premature discontinuation.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: log10 copies/mL				
arithmetic mean (standard deviation)				
Change from Baseline at Week 24 (n= 3, 13)	-0.75 (± 1.48)	-1.81 (± 1.57)		
Change from Baseline at Week 48 (n= 3, 13)	-1.27 (± 1.01)	-1.39 (± 1.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Human Immunodeficiency Virus –Ribonucleic acid <400 copies/mL

End point title	Number of Participants with Human Immunodeficiency Virus –Ribonucleic acid <400 copies/mL
End point description: The number of participants with HIV-1 RNA results <400 copies/mL were reported. A baseline collection was made if there was not already a value available taken within the previous 4 weeks. The SAP was used for analysis of this endpoint.	
End point type	Secondary
End point timeframe: Baseline (Day 1), Weeks 8, 12, 24, 36, and 48 or upon premature discontinuation	

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: Number				
Baseline (n= 5, 13)	1	5		
Week 24 (n= 3, 13)	2	13		
Week 48 (n= 3, 13)	2	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Human Immunodeficiency Virus –Ribonucleic acid <50 copies/mL

End point title	Number of Participants with Human Immunodeficiency Virus –Ribonucleic acid <50 copies/mL
End point description: The number of participants with Human Immunodeficiency Virus (HIV)-1 Ribonucleic acid (RNA) results <50 copies/mL were reported. A baseline collection was made if there was not already a value available taken within the previous 4 weeks. The SAP was used for analysis of this endpoint.	

End point type	Secondary
End point timeframe:	
Baseline (Day 1), Weeks 8, 12, 24, 36, and 48 or upon premature discontinuation	

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: Number				
Baseline (n= 5, 13, 18)	0	4		
Week 24 (n= 3, 13, 16)	2	11		
Week 48 (n= 3, 13, 16)	2	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with >1 log Decrease from Baseline in Human Immunodeficiency Virus–Ribonucleic acid

End point title	Number of Participants with >1 log Decrease from Baseline in Human Immunodeficiency Virus–Ribonucleic acid
End point description:	
The number of participants experiencing a greater than 1 log drop from baseline (day 1) (log 10 transformed) were reported.	
The SAP was used for analysis of this endpoint.	
End point type	Secondary
End point timeframe:	
From Week 8, 24 and 48	

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: Number				
Week 8 (n= 4, 12)	1	7		
Week 24 (n= 3, 13)	1	8		
Week 48 (n= 3, 13)	1	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Virological Failure

End point title	Number of participants with Virological Failure
End point description:	
Virological failure was defined as: viral load ≥ 400 copies/mL on two consecutive occasions (missing visits was assumed to be above 400 copies/mL). The number of participants classified as virological failure by age group and viral load ($\leq 10,000$ copies, $>10,000$ copies) were presented. Week=Wk, Virological failure =VF, Baseline= BL, copies per microlitre=c/mL. The SAP was used for analysis of this endpoint.	
End point type	Secondary
End point timeframe:	
From Week 12 till Week 48	

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: Number				
VF at Week 12 (n= 5, 13)	2	1		
VF at Week 24 (n= 5, 13)	2	0		
VF at Week 48 (n= 5, 13)	3	1		
HIV-RNA $\leq 10,000$ copies/mL at Wk 12 (n= 3, 6)	1	0		
HIV-RNA $\leq 10,000$ copies/mL at Wk 24 (n= 3, 6)	1	0		
HIV-RNA $\leq 10,000$ copies/mL at Wk 48 (n= 3, 6)	2	0		
HIV-RNA $>10,000$ copies/mL at Week 12 (n= 2, 7)	1	1		
HIV-RNA $>10,000$ copies/mL at Week 24 (n= 2, 7)	1	0		
HIV-RNA $>10,000$ copies/mL at Week 48 (n= 2, 7)	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cluster Differentiation Antigen 4 Lymphocyte Count

End point title	Change From Baseline in Cluster Differentiation Antigen 4 Lymphocyte Count
End point description:	
Change from Baseline in Cluster Differentiation Antigen 4 (CD4+) lymphocyte count at 24 weeks and 48 weeks were presented by age group. Change from baseline in CD4+ lymphocyte count was derived as follows: Change from baseline = (CD4+ count at week 24/48) – (CD4+ count at baseline). A baseline collection was made if there was not already a value available taken within the previous 4 weeks. Baseline was on Day 1. The SAP was used for analysis of this endpoint.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1), Weeks 8, 12, 24, 36, and 48 or upon premature discontinuation	

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: counts per microlitre (c/μL)				
arithmetic mean (standard deviation)				
Change from Baseline at Week 24 (n=3, 12)	94.9 (± 643.28)	-34.53 (± 821.31)		
Change from Baseline at Week 48 (n=3, 12)	-50.07 (± 1013.23)	126.11 (± 528.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cluster Differentiation Antigen 8 Lymphocyte Count

End point title	Change From Baseline in Cluster Differentiation Antigen 8 Lymphocyte Count
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End point description:

Change from baseline in Cluster Differentiation Antigen 8 (CD8+) lymphocyte count at 24 weeks and 48 weeks were presented by age group. Change from baseline in CD8+ lymphocyte count was derived as follows: Change from baseline = (CD8+ count at week 24/48) – (CD8+ count at baseline). A baseline collection was made if there was not already a value available taken within the previous 4 weeks.

Baseline was on Day 1.

The SAP was used for analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Baseline (Day 1), Weeks 8, 12, 24, 36, and 48 or upon premature discontinuation

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	13		
Units: counts per microlitre (c/μl)				
arithmetic mean (standard deviation)				
Change from Baseline at Week 24 (n=3, 12)	-200.49 (± 161.05)	-3.5 (± 790.86)		
Change from Baseline at Week 48 (n=3, 12)	-92.07 (± 455.23)	40.52 (± 641.27)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 56 weeks

Adverse event reporting additional description:

Serious adverse events and non-serious adverse events are reported in Safety Population Set. The Safety Analysis Population (SAP) comprised all participants who received at least one dose of study medication. The SAP was used for all efficacy and safety analyses.

Assessment type	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	Group A
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Reporting group description: -

Reporting group title	Group B
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Reporting group description: -

Reporting group title	Total
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Reporting group description:

Participants received saquinavir at a dose of 50 mg/Kg BID and ritonavir at a dose of 3 mg/kg BID for body weight from 5 to < 15 kg, 2.5 mg/kg BID for body weight from 15 to 40 kg and 100 mg BID for body weight > 40 kg plus >= 2 background ARVs. After 14 days of treatment (or Day 28 for participants switching from an NNRTI containing regimen), saquinavir and ritonavir dose adjustments were made within the age group or for individual participants as deemed appropriate. The highest dose for saquinavir/ritonavir that was to be administered was not to exceed 1000 mg/100 mg BID. Participants received treatment for 48 weeks.

Serious adverse events	Group A	Group B	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	2 / 13 (15.38%)	3 / 18 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 13 (7.69%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Group A	Group B	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	9 / 13 (69.23%)	14 / 18 (77.78%)
Investigations			
Weight Decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Gait Disturbance			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)	2 / 13 (15.38%)	3 / 18 (16.67%)
occurrences (all)	1	13	14
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	3 / 13 (23.08%)	3 / 18 (16.67%)
occurrences (all)	0	4	4
Dental Caries			
subjects affected / exposed	1 / 5 (20.00%)	2 / 13 (15.38%)	3 / 18 (16.67%)
occurrences (all)	1	2	3
Constipation			
subjects affected / exposed	2 / 5 (40.00%)	0 / 13 (0.00%)	2 / 18 (11.11%)
occurrences (all)	2	0	2
Abdominal Pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Abdominal Pain Lower			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Gingivitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 13 (7.69%) 1	1 / 18 (5.56%) 1
Epistaxis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 13 (7.69%) 1	1 / 18 (5.56%) 1
Skin and subcutaneous tissue disorders			
Dermatitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 13 (7.69%) 1	1 / 18 (5.56%) 1
Intertrigo subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 13 (7.69%) 1	1 / 18 (5.56%) 1
Renal and urinary disorders			
Enuresis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 13 (7.69%) 1	1 / 18 (5.56%) 1
Musculoskeletal and connective tissue disorders			
Synovitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 13 (7.69%) 1	1 / 18 (5.56%) 1
Infections and infestations			
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 13 (7.69%) 2	2 / 18 (11.11%) 3
Bronchitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 13 (15.38%) 2	2 / 18 (11.11%) 2
Impetigo subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 13 (7.69%) 2	1 / 18 (5.56%) 2
Otitis Media subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 13 (7.69%) 2	1 / 18 (5.56%) 2
Cellulitis			

subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Cystitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Giardiasis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Herpangina			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Otitis Media Acute			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Pyoderma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Rhinitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Toxocariasis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Urinary Tract Infection			

subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	1 / 18 (5.56%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2008	The protocol was amended to clarify -units for AUC, inclusion and exclusion criteria, information added on funding of ARV medication, criteria for premature withdrawal, genotypic resistance testing in screening examination and HIV-RNA viral load assessment, instruction for ritonavir dosing, footnotes and correction of units and typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported