



## Clinical trial results:

### Achieving appropriate exposure to RIBAvirin after a dose advise based on an abbreviated AUC of a first dose of ribavirin (ARRIBA)

#### Summary

EudraCT number	2010-020371-22
Trial protocol	NL DE
Global end of trial date	08 January 2014

#### Results information

Result version number	v1 (current)
This version publication date	21 September 2019
First version publication date	21 September 2019
Summary attachment (see zip file)	ARRIBA paper (deKanter_ARRIBA_paper_AVT.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	UMCN-AKF 10.04
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Radboudumc
Sponsor organisation address	Geert Grooteplein Zuid 10, Nijmegen, Netherlands,
Public contact	Prof. David Burger, Radboudumc, david.burger@radboudumc.nl
Scientific contact	Prof. David Burger, Radboudumc, david.burger@radboudumc.nl

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?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 January 2014
Global end of trial reached?	Yes
Global end of trial date	08 January 2014
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

To evaluate if adequate exposure to ribavirin can be achieved after a dose adjustment based on the AUC0-4h from a first dose of ribavirin.

Protection of trial subjects:

We included patients who had been treated with RBV (and PEG-IFN) before. These patients had already been exposed to RBV during several weeks or months as part of their HCV treatment. In this study they would receive two extra doses of RBV which is negligible when compared to the number of doses they have received before, and thus, no additional harm was expected. We included only patients who had received at least 4 weeks of RBV which was equal to at least 56 doses, and they received 2 additional doses.

Still we can evaluate the effectiveness of our intervention as these patients do not need chronic treatment with RBV and two single doses can be given.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2010
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	Netherlands: 19
Country: Number of subjects enrolled	Germany: 10
Worldwide total number of subjects	29
EEA total number of subjects	29

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)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	26
From 65 to 84 years	3
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruited at: Radboud university medical center, Nijmegen, and Erasmus University Medical Center, Rotterdam, both in the Netherlands, and at University Hospital Bonn, Bonn, Germany.

### Pre-assignment

Screening details:

HCV-treatment experienced patients were selected who were at least 18 years at screening, had tolerated ribavirin in the past and who were either cured or not yet eligible for subsequent HCV treatment.

### Pre-assignment period milestones

Number of subjects started	29
Number of subjects completed	26

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 3
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### Period 1

Period 1 title	treatment
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	RBV dose 1
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Ribavirine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

On day 1 of the study, participants received a single dose of ribavirin based on their body weight: <75kg: 400mg ribavirin (2 tablets of 200mg Copegus®, Roche, the Netherlands), ≥75kg: 600mg ribavirin (3 tablets of 200mg Copegus®, Roche, the Netherlands). Medication was taken at the study centre with a standardized breakfast (2 pieces of brown bread, one slice of cheese and one slice of meat, one cup of custard, and one cup of water (200mL)).

<b>Number of subjects in period 1<sup>[1]</sup></b>	RBV dose 1
Started	26
Completed	26

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline period was done after screening period, therefore screening failures were not included in the baseline period.

## Period 2

Period 2 title	RBV dose 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

<b>Arm title</b>	RBV dose 2
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Ribavirine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

IF ribavirin AUC0-4h on day 1 was adequate, i.e.  $\geq 1.755\text{mg.h/L}$ , subjects received the same dose on day 29. If exposure to ribavirin was too low, i.e. an AUC0-4h  $< 1.755\text{mg.h/L}$ , an adjusted dose of ribavirin was administered on day 29, based on a predefined algorithm.

<b>Number of subjects in period 2</b>	RBV dose 2
Started	26
Completed	26

## Baseline characteristics

### Reporting groups

Reporting group title	treatment
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Reporting group description: -

Reporting group values	treatment	Total	
Number of subjects	26	26	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
median	50		
full range (min-max)	20 to 70	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	17	17	

### Subject analysis sets

Subject analysis set title	ARRIBA
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Subject analysis set type	Per protocol
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Subject analysis set description:

All subjects eligible for inclusion

Reporting group values	ARRIBA		
Number of subjects	26		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			

From 65-84 years			
85 years and over			

Age continuous			
Units: years			
median	50		
full range (min-max)	20 to 70		
Gender categorical			
Units: Subjects			
Female	9		
Male	17		

## End points

### End points reporting groups

Reporting group title	RBV dose 1
Reporting group description: -	
Reporting group title	RBV dose 2
Reporting group description: -	
Subject analysis set title	ARRIBA
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects eligible for inclusion	

### Primary: adequate exposure

End point title	adequate exposure <sup>[1]</sup>
End point description:	
End point type	Primary
End point timeframe:	
Entire study	

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 formal statistical analyses were done

<b>End point values</b>	ARRIBA			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: %				
% of patients achieved adequate AUC0-4	62			

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Entire study

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	no
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Dictionary version	1
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### Reporting groups

Reporting group title	ARRIBA group
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Reporting group description: -

Serious adverse events	ARRIBA group		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	ARRIBA group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 26 (23.08%)		
Nervous system disorders			
headache			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	4		
Infections and infestations			
common cold			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2011	amendment 1
27 March 2013	amendment 2

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 January 2014	<p>After 50% of the patients to be included an interim analysis was done according to the protocol. Based on the stopping criteria as defined in the study protocol the results of the interim analysis propose to continue with the study. However, for a number of reasons were of the opinion that it was better not to continue with ARRIBA</p> <p>These reasons are:</p> <ul style="list-style-type: none"><li>-the target AUC0-4h was based on dual combination therapy of RBV + PegIFN;this no longer applied in 2014</li><li>- although the intervention in ARRIBA was effective in some patients, the increase in RBV exposure was not linear, so probably the dosing algorithm is not optimal</li><li>- there is a higher need to evaluate the role of RBV PK as part of DAA combinations, and possibly another target for AUC0-4h is needed, for instance when combined with Sofosbuvir in GT 3.</li></ul>	-

Notes:

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25599333>