



## Clinical trial results:

### Randomised, Double-Blind, Placebo-Controlled, Phase IIa Study in Healthy Volunteers to Evaluate the Protective Efficacy and Safety of CR8020 in an Influenza Challenge Model

#### Summary

EudraCT number	2013-002185-39
Trial protocol	GB
Global end of trial date	22 January 2014

#### Results information

Result version number	v1
This version publication date	06 July 2016
First version publication date	03 June 2015

#### Trial information

##### Trial identification

Sponsor protocol code	CR8020FLZ2002
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01938352
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Crucell Holland B.V
Sponsor organisation address	Newtonweg 1, Leiden, Netherlands, 2333 CP
Public contact	Clinical Registry Group, Crucell Vaccine Institute, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Crucell Vaccine Institute, ClinicalTrialsEU@its.jnj.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?	No

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	22 January 2014
Is this the analysis of the primary completion data?	No

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Global end of trial reached?	Yes
Global end of trial date	22 January 2014
Was the trial ended prematurely?	No

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Notes:

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**General information about the trial**

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Main objective of the trial:

To evaluate the reduction in AUC of virus load from the nasal mucosa in the CR8020 treatment group compared to placebo, post influenza virus challenge.

Protection of trial subjects:

The safety assessments included laboratory measurements (for example hematology, urinalysis, pregnancy test on females of childbearing potential); vital sign measurements; electrocardiograms (ECGs), and physical examination. Adverse events and vital signs were monitored throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	United Kingdom: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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Notes:

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**Subjects enrolled per age group**

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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)	22
From 65 to 84 years	0

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85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 22 participants were enrolled in this study. All 22 participants were included in the safety analysis set and 19 participants were included in the efficacy analysis set during this study.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Data analyst, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	CR8020 Group

Arm description:

Participants received a single dose of 15 milligram per kilogram (mg/kg) of CR8020 administered as an intravenous infusion over 2 hours on Day -2. On Day 0, participants were intranasally inoculated with the challenge virus.

Arm type	Experimental
Investigational medicinal product name	CR8020
Investigational medicinal product code	CR8020/JNJ-54235051
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

CR8020 15 mg/kg, administered by intravenous infusion.

<b>Arm title</b>	Placebo Group
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Arm description:

Participants received a single dose of Placebo [5 percent (%) dextrose in water] administered by intravenous infusion over 2 hours on Day -2. On Day 0, participants were intranasally inoculated with the challenge virus.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo (5% dextrose in water), given as an intravenous infusion.

<b>Number of subjects in period 1</b>	CR8020 Group	Placebo Group
Started	11	11
Completed	11	10
Not completed	0	1
Lost to follow-up	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	CR8020 Group
Reporting group description: Participants received a single dose of 15 milligram per kilogram (mg/kg) of CR8020 administered as an intravenous infusion over 2 hours on Day -2. On Day 0, participants were intranasally inoculated with the challenge virus.	
Reporting group title	Placebo Group
Reporting group description: Participants received a single dose of Placebo [5 percent (%) dextrose in water] administered by intravenous infusion over 2 hours on Day -2. On Day 0, participants were intranasally inoculated with the challenge virus.	

Reporting group values	CR8020 Group	Placebo Group	Total
Number of subjects	11	11	22
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	11	22
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	27.7	24.8	
standard deviation	± 5.98	± 5.46	-
Title for Gender Units: subjects			
Female	3	3	6
Male	8	8	16

## End points

### End points reporting groups

Reporting group title	CR8020 Group
Reporting group description: Participants received a single dose of 15 milligram per kilogram (mg/kg) of CR8020 administered as an intravenous infusion over 2 hours on Day -2. On Day 0, participants were intranasally inoculated with the challenge virus.	
Reporting group title	Placebo Group
Reporting group description: Participants received a single dose of Placebo [5 percent (%) dextrose in water] administered by intravenous infusion over 2 hours on Day -2. On Day 0, participants were intranasally inoculated with the challenge virus.	
Subject analysis set title	Efficacy Analysis Set
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Efficacy analysis set (N=19) included all randomized participants inoculated with challenge virus.	
Subject analysis set title	Pharmacokinetic Analysis Set
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Pharmacokinetic analysis set included all participants (N=11) who received CR8020 and who did not have any important events or protocol deviations that would affect the integrity of the pharmacokinetic (PK) data or too few serum concentration data points to allow accurate assessment of the derived PK parameters.	

### Primary: Area under the curve (AUC) of viral load

End point title	Area under the curve (AUC) of viral load
End point description: The AUC was calculated based on quantitative polymerase chain reaction (qPCR) results for nasopharyngeal (NP) swabs collected thrice daily post-viral challenge up to the start of oseltamivir treatment on Day 6.	
End point type	Primary
End point timeframe: During the 7 days following influenza virus challenge	

End point values	CR8020 Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11 <sup>[1]</sup>	8 <sup>[2]</sup>		
Units: units on a standard curve				
arithmetic mean (standard deviation)	73112.74 (± 155588.9)	27.5 (± 78)		

Notes:

[1] - Efficacy Analysis Set

[2] - Efficacy Analysis Set

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Null hypothesis: AUC Viral Load is not greater in CR8020 group than placebo group.	

Comparison groups	CR8020 Group v Placebo Group
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority <sup>[3]</sup>
P-value	= 0.028 <sup>[4]</sup>
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - Placebo controlled

[4] - P-value was based on the 1-sided Wilcoxon Rank Sum test at 5% significance level.

## Secondary: Percentage of participants with detected and quantitative influenza infection rate

End point title	Percentage of participants with detected and quantitative influenza infection rate
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End point description:

Detected influenza infection rate was defined as greater than or equal to ( $\geq 4$ ) qPCR positive NP swabs post-viral challenge, including all samples up to discharge from the quarantine. All values above the detection limit (non-negative values) were considered positive.

Quantitative influenza infection rate was defined as  $\geq 4$  qPCR positive NP swabs post-viral challenge, including all samples up to discharge from the quarantine. All values above the quantification limit (quantitative values) were considered positive.

End point type	Secondary
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End point timeframe:

Up to 7 days following influenza virus challenge

End point values	CR8020 Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11 <sup>[5]</sup>	8 <sup>[6]</sup>		
Units: Percentage of participants				
number (not applicable)	54.5	0		

Notes:

[5] - Efficacy analysis set

[6] - Efficacy analysis set

## Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis 2
Comparison groups	CR8020 Group v Placebo Group
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority <sup>[7]</sup>
P-value	= 0.018 <sup>[8]</sup>
Method	Fisher exact
Confidence interval	
level	90 %
sides	2-sided
lower limit	16.9
upper limit	81.57

Notes:

[7] - Placebo controlled

[8] - P-value was based on the 2-sided Fisher exact test at 5% significance level.

### Secondary: AUC of influenza composite symptoms

End point title	AUC of influenza composite symptoms
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End point description:

AUC of influenza composite symptoms was calculated based on the sum of the individual scores (0 to 3) on each of the 10 pre-defined clinical influenza symptoms as recorded by the participants post viral challenge up to the start of oseltamivir treatment on Day 6.

End point type	Secondary
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End point timeframe:

Up to 7 days following influenza virus challenge

End point values	CR8020 Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11 <sup>[9]</sup>	8 <sup>[10]</sup>		
Units: units on a scale				
arithmetic mean (standard deviation)	7.03 (± 7.985)	2.25 (± 3.69)		

Notes:

[9] - Efficacy analysis set

[10] - Efficacy analysis set

### Statistical analyses

Statistical analysis title	Statistical analysis 3
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Statistical analysis description:

Null hypothesis: AUC influenza composite symptoms is not greater in CR8020 group than placebo.

Comparison groups	CR8020 Group v Placebo Group
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Number of subjects included in analysis	19
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Analysis specification	Pre-specified
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Analysis type	superiority <sup>[11]</sup>
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P-value	= 0.02 <sup>[12]</sup>
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Method	Wilcoxon (Mann-Whitney)
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Notes:

[11] - Placebo controlled

[12] - P-value was based on the 1-sided Wilcoxon Rank Sum test at 5% significance level.

### Secondary: Maximum serum concentration (Cmax) of CR8020

End point title	Maximum serum concentration (Cmax) of CR8020 <sup>[13]</sup>
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End point description:

Cmax following a single 2-hour intravenous infusion of 15 mg/kg of CR8020. This pharmacokinetic parameter was calculated in 11 participants in the CR8020 group who received a complete dose of CR8020.

End point type	Secondary
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End point timeframe:

Day -2 (pre- and post-dose), Day -1, Day 0 (pre-challenge) and on Days 1, 2, 5, 28 and 96.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This pharmacokinetic parameter was calculated in 11 participants in the CR8020 group only, who had received a complete dose of CR8020 in this study.

End point values	CR8020 Group			
Subject group type	Reporting group			
Number of subjects analysed	11 <sup>[14]</sup>			
Units: microgram per milliliter (µg/mL)				
arithmetic mean (standard deviation)	330.16 (± 63.643)			

Notes:

[14] - Pharmacokinetics Analysis Set

## Statistical analyses

No statistical analyses for this end point

## Secondary: Area under the serum concentration- time curve [AUC(0-t) and AUC(0-7d)] of CR8020

End point title	Area under the serum concentration- time curve [AUC(0-t) and AUC(0-7d)] of CR8020 <sup>[15]</sup>
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End point description:

AUC(0-t) was defined as area under the serum concentration-time curve from 0 to the time of the last measurable concentration. AUC(0-7d) was defined as area under the serum concentration-time curve from time 0 to Day 7. This pharmacokinetic parameter was calculated in 11 participants in the CR8020 group who received a complete dose of CR8020.

End point type	Secondary
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End point timeframe:

Day -2 (pre- and post-dose), Day -1, Day 0 (pre-challenge) and on Days 1, 2, 5, 28 and 96.

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This pharmacokinetic parameter was calculated in 11 participants in the CR8020 group only, who had received a complete dose of CR8020 in this study.

End point values	CR8020 Group			
Subject group type	Reporting group			
Number of subjects analysed	11 <sup>[16]</sup>			
Units: microgram day per milliliter (µg·day/mL)				
arithmetic mean (standard deviation)				
AUC(0-t)	5460.5 (± 991.37)			
AUC(0-7d)	1319.8 (± 250.04)			

Notes:

[16] - Pharmacokinetics Analysis Set

## Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Day 96

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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### Reporting groups

Reporting group title	CR8020 Group
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Reporting group description:

Participants received a single dose of 15 milligram per kilogram (mg/kg) of CR8020 administered as an intravenous infusion over 2 hours on Day -2. On Day 0, participants were intranasally inoculated with the challenge virus.

Reporting group title	Placebo Group
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Reporting group description:

Participants received a single dose of Placebo (5% dextrose in water) administered by intravenous infusion over 2 hours on Day -2. On Day 0, participants were intranasally inoculated with the challenge virus.

Serious adverse events	CR8020 Group	Placebo Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Electrocardiogram t wave inversion			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CR8020 Group	Placebo Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 11 (81.82%)	6 / 11 (54.55%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	3 / 11 (27.27%)	
occurrences (all)	0	3	

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Amylase increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Lipase increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Face injury			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Scratch			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Nervous system disorders			

Presyncope subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 11 (9.09%) 1	
Dizziness subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 11 (0.00%) 0	
General disorders and administration site conditions Catheter site bruise subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 11 (9.09%) 1	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 11 (9.09%) 3	
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)  Nasal congestion subjects affected / exposed occurrences (all)  Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0  1 / 11 (9.09%) 1  1 / 11 (9.09%) 1	1 / 11 (9.09%) 2  0 / 11 (0.00%) 0  0 / 11 (0.00%) 0	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 11 (9.09%) 1	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 11 (0.00%) 0	
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all)  Influenza	1 / 11 (9.09%) 1	0 / 11 (0.00%) 0	

subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 11 (18.18%)	1 / 11 (9.09%)	
occurrences (all)	3	1	
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported