Clinical trial results:
A Phase III Open, Randomized, Parallel, Multi-Center Study in Children Aged 6 - <36 Months to Compare the Immunogenicity and Safety of a Single 0.5 mL Dose of Inflexal V With a 0.25 mL 2-Dose Regimen of Inflexal V Administered According to a 0/4 Week Schedule and Followed-up for 6 Months

Summary

EudraCT number	2010-019745-25
Trial protocol	IT
Global end of trial date	29 July 2011

Results information

Result version number	v2 (current)
This version publication date	23 June 2016
First version publication date	08 July 2015
Version creation reason	• Correction of full data set Review of data

Trial information

Trial identification

Sponsor protocol code	INF-V-A005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01229397
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Crucell Switzerland AG
Sponsor organisation address	Rehhagstrasse 79, Bern, Switzerland, 3018
Public contact	Crucell Switzerland AG, Clinical Registry Group, ClinicalTrialsEU@its.jnj.com
Scientific contact	Crucell Switzerland AG, Clinical Registry Group, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 July 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the immunogenicity of a single full (0.5 milliliter [mL]) dose and a 0.25 mL 2-dose regime of Inflexal V in unprimed children aged 6 - less than (<) 36 months, using the European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) guideline for the re-registration of the seasonal influenza vaccine in adults (aged greater than or equal to [>=] 18 - less than or equal to [<=] 60 years) as reference.

Protection of trial subjects:

The participants were observed closely for at least 30 minutes after vaccination with appropriate medical treatment readily available in case of rare anaphylactic reaction Local solicited adverse events (30 min after vaccination) were evaluated by the investigator. Each participant's parents or legal guardians received a Participant Diary and were requested to record all adverse events (AEs) and body temperature on the day of vaccination and on the following 3 days. All AEs, including serious adverse events (SAEs), as well as concomitant medications were evaluated at each visit throughout the study. The parents or legal guardians were instructed to contact the investigator immediately should the participant experience any signs or symptoms they perceive as serious during the period extending from the first study-specific procedure up to and including 6 months after administration of the investigational medicinal product (IMP). The tolerability of the 2 dose regimens of the study vaccine was assessed by the participants' parents/legal guardians and by the investigator 4 weeks after completion of vaccination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 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	Italy: 205
Worldwide total number of subjects	205
EEA total number of subjects	205

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)	85
Children (2-11 years)	120
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:

Recruitment period: 05 October - 17 January 2011; Location: University of Milan

Pre-assignment

Screening details:

A total of 205 participants were enrolled and vaccinated with Inflexal and included in the all randomized population set.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Inflexal V 0.25 mL x 2

Arm description:

2 doses of Inflexal V influenza vaccine (surface antigen, inactivated, virosome) 2010/2011, 4 weeks apart, containing per 0.25 milliliter (mL) dose:
• 7.5 microgram (µg) HA antigen of A/California/7/2009 (H1N1)-like virus
• 7.5 µg HA antigen of A/Perth/16/2009 (H3N2)-like virus
• 7.5 µg HA antigen of B/Brisbane/60/2008-like virus

Arm type	Active comparator
Investigational medicinal product name	INFLEXAL V
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Inflexal V 0.25 milliliter (mL) intramuscular injection twice, 4 weeks apart

Arm title	Inflexal V 0.5 mL x 1

Arm description:

1 dose of Inflexal V influenza vaccine (surface antigen, inactivated, virosome) 2010/2011, containing per 0.5 milliliter (mL) dose:
• 15 microgram (µg) HA antigen of A/California/7/2009 (H1N1)-like virus
• 15 µg HA antigen of A/Perth/16/2009 (H3N2)-like virus
• 15 µg HA antigen of B/Brisbane/60/2008-like virus

Arm type	Experimental
Investigational medicinal product name	INFLEXAL V
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Inflexal V 0.5 milliliter (mL) intramuscular injection once only

Number of subjects in period 1	Inflexal V 0.25 mL x 2	Inflexal V 0.5 mL x 1
Started	103	102
Completed	92	93
Not completed	11	9
Consent withdrawn by subject	3	3
Migrated/moved from study area	1	-
Lost to follow-up	7	6

Baseline characteristics

Reporting groups

Reporting group title	Inflexal V 0.25 mL x 2

Reporting group description:

2 doses of Inflexal V influenza vaccine (surface antigen, inactivated, virosome) 2010/2011, 4 weeks apart, containing per 0.25 milliliter (mL) dose:
• 7.5 microgram (µg) HA antigen of A/California/7/2009 (H1N1)-like virus
• 7.5 µg HA antigen of A/Perth/16/2009 (H3N2)-like virus
• 7.5 µg HA antigen of B/Brisbane/60/2008-like virus

Reporting group title	Inflexal V 0.5 mL x 1

Reporting group description:

1 dose of Inflexal V influenza vaccine (surface antigen, inactivated, virosome) 2010/2011, containing per 0.5 milliliter (mL) dose:
• 15 microgram (µg) HA antigen of A/California/7/2009 (H1N1)-like virus
• 15 µg HA antigen of A/Perth/16/2009 (H3N2)-like virus
• 15 µg HA antigen of B/Brisbane/60/2008-like virus

Reporting group values	Inflexal V 0.25 mL x 2	Inflexal V 0.5 mL x 1	Total
Number of subjects	103	102	205
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)	43	42	85
Children (2-11 years)	60	60	120
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	1.8	1.8	
standard deviation	± 0.52	± 0.61	-
Gender categorical Units: Subjects			
Female	37	37	74
Male	66	65	131

Subject analysis sets

Subject analysis set title	Inflexal V 0.25 mL x 2 - After 1st Vaccination
Subject analysis set type	Safety analysis

Subject analysis set description:

Inflexal V influenza vaccine (surface antigen, inactivated, virosome) 2010/2011, 4 weeks apart, containing per 0.25 milliliter (mL) dose:
• 7.5 microgram (µg) HA antigen of A/California/7/2009 (H1N1)-like virus
• 7.5 µg HA antigen of A/Perth/16/2009 (H3N2)-like virus
• 7.5 µg HA antigen of B/Brisbane/60/2008-like virus

Subject analysis set title	Inflexal V 0.25 mL x 2 - After 2nd Vaccination
Subject analysis set type	Safety analysis

Subject analysis set description:

Inflexal V influenza vaccine (surface antigen, inactivated, virosome) 2010/2011, 4 weeks apart, containing per 0.25 milliliter (mL) dose:
• 7.5 microgram (µg) HA antigen of A/California/7/2009 (H1N1)-like virus
• 7.5 µg HA antigen of A/Perth/16/2009 (H3N2)-like virus
• 7.5 µg HA antigen of B/Brisbane/60/2008-like virus

Reporting group values	Inflexal V 0.25 mL x 2 - After 1st Vaccination	Inflexal V 0.25 mL x 2 - After 2nd Vaccination	
Number of subjects	102	101	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	42	42	
Children (2-11 years)	60	59	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean			
standard deviation	±	±	
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Inflexal V 0.25 mL x 2

Reporting group description:

2 doses of Inflexal V influenza vaccine (surface antigen, inactivated, virosome) 2010/2011, 4 weeks apart, containing per 0.25 milliliter (mL) dose:
• 7.5 microgram (µg) HA antigen of A/California/7/2009 (H1N1)-like virus
• 7.5 µg HA antigen of A/Perth/16/2009 (H3N2)-like virus
• 7.5 µg HA antigen of B/Brisbane/60/2008-like virus

Reporting group title	Inflexal V 0.5 mL x 1

Reporting group description:

1 dose of Inflexal V influenza vaccine (surface antigen, inactivated, virosome) 2010/2011, containing per 0.5 milliliter (mL) dose:
• 15 microgram (µg) HA antigen of A/California/7/2009 (H1N1)-like virus
• 15 µg HA antigen of A/Perth/16/2009 (H3N2)-like virus
• 15 µg HA antigen of B/Brisbane/60/2008-like virus

Subject analysis set title	Inflexal V 0.25 mL x 2 - After 1st Vaccination
Subject analysis set type	Safety analysis

Subject analysis set description:

Inflexal V influenza vaccine (surface antigen, inactivated, virosome) 2010/2011, 4 weeks apart, containing per 0.25 milliliter (mL) dose:
• 7.5 microgram (µg) HA antigen of A/California/7/2009 (H1N1)-like virus
• 7.5 µg HA antigen of A/Perth/16/2009 (H3N2)-like virus
• 7.5 µg HA antigen of B/Brisbane/60/2008-like virus

Subject analysis set title	Inflexal V 0.25 mL x 2 - After 2nd Vaccination
Subject analysis set type	Safety analysis

Subject analysis set description:

Inflexal V influenza vaccine (surface antigen, inactivated, virosome) 2010/2011, 4 weeks apart, containing per 0.25 milliliter (mL) dose:
• 7.5 microgram (µg) HA antigen of A/California/7/2009 (H1N1)-like virus
• 7.5 µg HA antigen of A/Perth/16/2009 (H3N2)-like virus
• 7.5 µg HA antigen of B/Brisbane/60/2008-like virus

Primary: Immunogenicity of a Single Full (0.5 mL) Dose and a 0.25 mL 2-dose Regimen of Inflexal V, Using the European Medicines Agency (EMA) Guideline for the Re-registration of the Seasonal Influenza Vaccine in Adults as Reference

End point title	Immunogenicity of a Single Full (0.5 mL) Dose and a 0.25 mL 2-dose Regimen of Inflexal V, Using the European Medicines Agency (EMA) Guideline for the Re-registration of the Seasonal Influenza Vaccine in Adults as Reference[1]

End point description:

Seroprotection rate.

End point type	Primary

End point timeframe:

This assesment was done for immunogenicity data collected at Day 29 after completion of designated vaccination regimen

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	Inflexal V 0.25 mL x 2	Inflexal V 0.5 mL x 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	99		
Units: Participants				
number (confidence interval 95%)				
Percentage of participants seroprotected: A/H1N1	99 (94.4 to 100)	98 (92.9 to 99.8)		
Percentage of participants seroprotected: A/H3N2	99 (94.4 to 100)	97 (91.4 to 99.4)		
Percentage of participants seroprotected: B-strain	92.9 (85.8 to 97.1)	86.9 (78.6 to 92.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Immunogenicity of a Single Full (0.5 mL) Dose and a 0.25 mL 2-dose Regimen of Inflexal V, Using the European Medicines Agency (EMA) Guideline for the Re-registration of the Seasonal Influenza Vaccine in Adults as Reference

End point title	Immunogenicity of a Single Full (0.5 mL) Dose and a 0.25 mL 2-dose Regimen of Inflexal V, Using the European Medicines Agency (EMA) Guideline for the Re-registration of the Seasonal Influenza Vaccine in Adults as Reference[2]

End point description:

Seroconversion rate.

End point type	Primary

End point timeframe:

This assesment was done for immunogenicity data collected at Day 29 after completion of designated vaccination 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Inflexal V 0.25 mL x 2	Inflexal V 0.5 mL x 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	99		
Units: Participants				
number (confidence interval 95%)				
Percentage of participants seroconverted: A/H1N1	99 (94.4 to 100)	98 (92.9 to 99.8)		
Percentage of participants seroconverted: A/H3N2	99 (94.4 to 100)	97 (91.4 to 99.4)		
Percentage of participants seroconverted: B-strain	92.9 (85.8 to 97.1)	86.9 (78.6 to 92.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Immunogenicity of a Single Full (0.5 mL) Dose and a 0.25 mL 2-dose Regimen of Inflexal V, Using the European Medicines Agency (EMA) Guideline for the Re-registration of the Seasonal Influenza Vaccine in Adults as Reference

End point title	Immunogenicity of a Single Full (0.5 mL) Dose and a 0.25 mL 2-dose Regimen of Inflexal V, Using the European Medicines Agency (EMA) Guideline for the Re-registration of the Seasonal Influenza Vaccine in Adults as Reference[3]

End point description:

GMT-fold increase - calculated as the GMT on Day 22 divided by the baseline GMT value.

End point type	Primary

End point timeframe:

This assesment was done for immunogenicity data collected at Day 29 after completion of designated vaccination regimen

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Inflexal V 0.25 mL x 2	Inflexal V 0.5 mL x 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	99		
Units: Participants				
number (confidence interval 95%)				
GMT fold increase from baseline: A/H1N1	25.5 (21.3 to 30.5)	19.6 (16.9 to 22.7)		
GMT fold increase from baseline: A/H3N2	31.6 (26.7 to 37.3)	24.6 (20.7 to 29.3)		
GMT fold increase from baseline: B-strain	12.8 (11.2 to 14.6)	14.7 (12.3 to 17.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Local and Systemic Adverse Events (AE) as a Measure of Safety and Tolerability

End point title	Percentage of Participants With Local and Systemic Adverse Events (AE) as a Measure of Safety and Tolerability[4]

End point description:

Solicited local and systemic AEs were collected from Day 1 (day of vaccination) to Day 4 inclusive using a subject diary.

End point type	Secondary

End point timeframe:

Solicited local and systemic AEs were collected from Day 1 (day of vaccination) to Day 4 inclusive using a subject diary

Notes:

[4] - 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: For this endpoint Inflexal V 0.5 mL x 1, Inflexal V 0.25mL x 2 - After 1st Vaccination, Inflexal V 0.25mL x 2 - After2nd Vaccination reporting groups were only analysed.

End point values	Inflexal V 0.5 mL x 1	Inflexal V 0.25 mL x 2 - After 1st Vaccination	Inflexal V 0.25 mL x 2 - After 2nd Vaccination	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	100	102	101	
Units: Percentage of participants				
number (not applicable)				
AEs (unsolicited and solicited)	49	50	47.5	
Unsolicited AEs	30	28.4	31.7	
Solicited local AEs	17.2	22.4	17.2	
Solicited systemic AEs	20.2	16.3	17.2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any Adverse event (AE) occurring within 1 month (minimum 28 days) following vaccine administration was recorded. Any serious adverse events (SAE) occurring from study start up to 6 months (at least 180 days) following vaccine administration was recorded.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Inflexal V 0.25 mL x 2 - After 1st Vaccination

Reporting group description:

Inflexal V influenza vaccine (surface antigen, inactivated, virosome) 2010/2011, 4 weeks apart, containing per 0.25 milliliter (mL) dose:
• 7.5 microgram (µg) HA antigen of A/California/7/2009 (H1N1)-like virus
• 7.5 µg HA antigen of A/Perth/16/2009 (H3N2)-like virus
• 7.5 µg HA antigen of B/Brisbane/60/2008-like virus

Reporting group title	Inflexal V 0.5 mL x 1

Reporting group description:

1 dose of Inflexal V influenza vaccine (surface antigen, inactivated, virosome) 2010/2011, containing per 0.5 milliliter (mL) dose:
• 15 microgram (µg) HA antigen of A/California/7/2009 (H1N1)-like virus
• 15 µg HA antigen of A/Perth/16/2009 (H3N2)-like virus
• 15 µg HA antigen of B/Brisbane/60/2008-like virus

Reporting group title	Inflexal V 0.25 mL x 2 - After 2nd Vaccination

Reporting group description:

Inflexal V influenza vaccine (surface antigen, inactivated, virosome) 2010/2011, 4 weeks apart, containing per 0.25 milliliter (mL) dose:
• 7.5 microgram (µg) HA antigen of A/California/7/2009 (H1N1)-like virus
• 7.5 µg HA antigen of A/Perth/16/2009 (H3N2)-like virus
• 7.5 µg HA antigen of B/Brisbane/60/2008-like virus

Serious adverse events	Inflexal V 0.25 mL x 2 - After 1st Vaccination	Inflexal V 0.5 mL x 1	Inflexal V 0.25 mL x 2 - After 2nd Vaccination
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 102 (0.98%)	4 / 100 (4.00%)	0 / 101 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 102 (0.98%)	1 / 100 (1.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary Disease			

subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenterisits rotavirus			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Inflexal V 0.25 mL x 2 - After 1st Vaccination	Inflexal V 0.5 mL x 1	Inflexal V 0.25 mL x 2 - After 2nd Vaccination
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 102 (50.00%)	49 / 100 (49.00%)	48 / 101 (47.52%)
General disorders and administration site conditions			
Pyrexia unsolicited			
subjects affected / exposed	11 / 102 (10.78%)	9 / 100 (9.00%)	10 / 101 (9.90%)
occurrences (all)	11	9	13
Erythema (at the injection site)			
subjects affected / exposed	15 / 102 (14.71%)	10 / 100 (10.00%)	7 / 101 (6.93%)
occurrences (all)	15	10	7
Induration (at the injection site)			
subjects affected / exposed	7 / 102 (6.86%)	6 / 100 (6.00%)	2 / 101 (1.98%)
occurrences (all)	7	6	2
Pain (at the injection site)			

subjects affected / exposed	11 / 102 (10.78%)	9 / 100 (9.00%)	10 / 101 (9.90%)
occurrences (all)	11	9	10
Haemorrhage (at the injection site)			
subjects affected / exposed	3 / 102 (2.94%)	5 / 100 (5.00%)	4 / 101 (3.96%)
occurrences (all)	3	5	4
Malaise			
subjects affected / exposed	9 / 102 (8.82%)	7 / 100 (7.00%)	8 / 101 (7.92%)
occurrences (all)	9	7	8
Pyrexia solicited			
subjects affected / exposed	8 / 102 (7.84%)	15 / 100 (15.00%)	11 / 101 (10.89%)
occurrences (all)	8	15	11
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 102 (0.00%)	3 / 100 (3.00%)	8 / 101 (7.92%)
occurrences (all)	0	3	8
Infections and infestations			
Otitis media acute			
subjects affected / exposed	4 / 102 (3.92%)	5 / 100 (5.00%)	3 / 101 (2.97%)
occurrences (all)	4	5	3
Rhinitis			
subjects affected / exposed	1 / 102 (0.98%)	2 / 100 (2.00%)	9 / 101 (8.91%)
occurrences (all)	1	2	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2010	The overall reason for the amendment was to introduced a 6 month follow-up visit for the participants enrolled in the study, at which an additional blood sample for immunogenicity evaluation was taken.
20 December 2010	The overall reason for the amendment was to change the principal investigator.
06 May 2011	The overall reason for the amendment was to establish second interim analysis after immunogenicity data for the follow-up visit at Day 212 (plus [+] or minus [-] 7 days) had become available for at least 70 participants in each study arm.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported