Clinical trial results:
Safety and immunogenicity of 3 adjuvated reduced dose inactivated poliovirus vaccines (IPV-Al SSI) and non-adjuvated full dose IPV SSI, given as a booster vaccination to adolescents with a history of IPV vaccination at 3, 5, 12 months and 5 years of age

Summary

EudraCT number	2014-000052-29
Trial protocol	DK
Global end of trial date	05 March 2015

Results information

Result version number	v1 (current)
This version publication date	10 November 2016
First version publication date	10 November 2016

Trial information

Trial identification

Sponsor protocol code	VIPV-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02280447
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Statens Serum Institut
Sponsor organisation address	Artillerivej 5, Copenhagen, Denmark, 2300
Public contact	Toxicology and Clinical Development, Statens Serum Institut, +45 32683598, btc@ssi.dk
Scientific contact	Toxicology and Clinical Development, Statens Serum Institut, +45 32683598, btc@ssi.dk

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	21 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 March 2015
Global end of trial reached?	Yes
Global end of trial date	05 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

For each of the 3 poliovirus types 1, 2 and 3 to demonstrate the non-inferiority of the booster effect (day 28 / day 0 titres) of each of the 3 adjuvated reduced dose IPV-Al formulations (1/3 dose, 1/5 dose and 1/10 dose) compared to the non-adjuvated IPV (full dose)

Protection of trial subjects:

Equipment and medication for treatment of an anaphylactic reaction were in place at all sites when administering the vaccines. After administration of the vaccine, the trial subject stayed at the trial site for 30 minutes under observation. Caution was taken in known cases of allergy to formaldehyde and aluminium. To minimise the occurrence of vasovagal syncope (i.e. fainting), the adolescents were offered to lie down during the administration of vaccine and blood drawings. To minimise the pain during administration of vaccine and blood drawings the adolescents were offered application of local anaesthetics, such as EMLA®, at the injection/sampling sites.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 November 2014
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	Denmark: 240
Worldwide total number of subjects	240
EEA total number of subjects	240

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)	71
Adolescents (12-17 years)	169
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The 10-15-years-old adolescents were recruited through advertisements in newspapers, social media, and posters at schools and institutions. All written texts in advertisements and posters etc. were approved in advance by the EC.

Pre-assignment

Screening details:

A total of 242 subjects were assessed for eligibility during the screening at Visit 1. Two subjects discontinued the trial before allocation to and receipt of the trial vaccine.

Period 1

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

Blinding implementation details:

This clinical trial was observer-blind. Only dedicated site staff and the CRA had access to vaccine dispensing, administration and accountability data where specific subject numbers were linked to the type of vaccine administered. These unblinded trial team members were not allowed to share information on the identity of the trial vaccines with other trial team members or any other person.

Arms

Are arms mutually exclusive?	Yes
Arm title	1/3 IPV-Al SSI

Arm description: -

Arm type	Experimental
Investigational medicinal product name	1/3 IPV-Al SSI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL was injected intramuscularly perpendicular to the skin in the deltoid muscle by use of a 23 Gauge, 25 mm (blue) Terumo hypodermic needle.

Arm title	1/5 IPV-Al SSI

Arm description: -

Arm type	Experimental
Investigational medicinal product name	1/5 IPV-Al SSI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL was injected intramuscularly perpendicular to the skin in the deltoid muscle by use of a 23 Gauge, 25 mm (blue) Terumo hypodermic needle.

Arm title	1/10 IPV-Al SSI

Arm description: -

Arm type	Experimental

Investigational medicinal product name	1/10 IPV-Al SSI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL was injected intramuscularly perpendicular to the skin in the deltoid muscle by use of a 23 Gauge, 25 mm (blue) Terumo hypodermic needle.

Arm title	IPV SSI

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	IPV SSI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL was injected intramuscularly perpendicular to the skin in the deltoid muscle by use of a 23 Gauge, 25 mm (blue) Terumo hypodermic needle.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: This trial was observer-blind. Only dedicated site staff and the CRA from Larix A/S had access to vaccine dispensing, administration and accountability data where specific subject numbers were linked to the type of vaccine administered. These unblinded trial team members were not allowed to share information on the identity of the trial vaccines with other trial team members or any other person.

Number of subjects in period 1	1/3 IPV-Al SSI	1/5 IPV-Al SSI	1/10 IPV-Al SSI
Started	60	61	59
Completed	60	61	59

Number of subjects in period 1	IPV SSI
Started	60
Completed	60

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	240	240	
Age categorical			
240 subjects enrolled. Mean (SD) age was 12.5 (1.6). Age groups were 10-12 (n=111) and 13-15 (n=129).			
Units: Subjects			
10-12 years of age	111	111	
13-15 years of age	129	129	
Age continuous			
Units: years			
arithmetic mean	12.5		
standard deviation	± 1.6	-	
Gender categorical			
Units: Subjects			
Female	105	105	
Male	135	135	

End points

End points reporting groups

Reporting group title	1/3 IPV-Al SSI
Reporting group description: -	
Reporting group title	1/5 IPV-Al SSI
Reporting group description: -	
Reporting group title	1/10 IPV-Al SSI
Reporting group description: -	
Reporting group title	IPV SSI
Reporting group description: -	

Primary: Immunogenicity

End point title	Immunogenicity[1][2]

End point description:

Booster effect (day 28 / day 0 titres), from individual serum titre values for antibodies against poliovirus type 1, 2 and 3 measured in pre-vaccination and post-vaccination serum samples by Vero Cell neutralising assay

End point type	Primary

End point timeframe:

Visit 1 (day 0) to Visit 2 (day 28-35)

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: Endpoint was booster effect defined as day 28/day 0 titres. On log2 scale, endpoint corresponded to difference since baseline in log2 titre analysed in an ANCOVA with treatment as factor and pre-vaccination log2 titre as covariate. 3 IPV-Al SSI formulations were compared to IPV SSI in the model including all treatment arms. Separate analyses were performed for each 3 poliovirus types. Estimated treatment differences were transformed back and presented as ratios of booster effects with 95% CI.
[2] - 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: The endpoint is a ratio between 3 investigational arms versus a 4th comparator arm. This justifies that there is only ratios for the three investigational arms.

End point values	1/3 IPV-Al SSI	1/5 IPV-Al SSI	1/10 IPV-Al SSI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	61	59	
Units: titre				
number (confidence interval 95%)				
Poliovirus Type 1	0.402 (0.263 to 0.614)	0.308 (0.202 to 0.469)	0.169 (0.11 to 0.258)	
Poliovirus Type 2	0.262 (0.174 to 0.394)	0.275 (0.183 to 0.413)	0.16 (0.106 to 0.241)	
Poliovirus Type 3	0.232 (0.152 to 0.354)	0.26 (0.17 to 0.395)	0.143 (0.094 to 0.219)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Visit 1 (day 0) to visit 2 (day 28-35)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1
Reporting groups	
Reporting group title	1/3 IPV-Al SSI
Reporting group description: -	
Reporting group title	1/5 IPV-Al SSI
Reporting group description: -	
Reporting group title	1/10 IPV-Al SSI
Reporting group description: -	
Reporting group title	IPV SSI
Reporting group description: -	

Serious adverse events	1/3 IPV-Al SSI	1/5 IPV-Al SSI	1/10 IPV-Al SSI
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	IPV SSI		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	1/3 IPV-Al SSI	1/5 IPV-Al SSI	1/10 IPV-Al SSI
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 60 (65.00%)	30 / 61 (49.18%)	36 / 59 (61.02%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Skin papilloma			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 59 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complication	Additional description: PT reported: Procedural pain and Ligament sprain		
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Nervous system disorder	Additional description: Reported PT: Headache and Presyncope		
subjects affected / exposed	9 / 60 (15.00%)	12 / 61 (19.67%)	10 / 59 (16.95%)
occurrences (all)	11	12	10
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site reaction and systemic adverse events	Additional description: Reported PTs: Injection site reactions included pain, swelling, erythema, pruritus, haematoma, and warmth; systemic adverse events included influenza like illness, axillary pain, vessel puncture site pain, fatigue, and Pyrexia		
subjects affected / exposed	31 / 60 (51.67%)	21 / 61 (34.43%)	28 / 59 (47.46%)
occurrences (all)	46	28	41
Gastrointestinal disorders			
Gastrointestional disorders	Additional description: Reported PTs: Nausea, Diarrhoea, Vomiting, Abdominal pain upper and Abdominal pain		
subjects affected / exposed	9 / 60 (15.00%)	5 / 61 (8.20%)	10 / 59 (16.95%)
occurrences (all)	11	5	14
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: Reported PTs: Oropharyngeal pain, Cough and Pharyngeal inflammation		
subjects affected / exposed	3 / 60 (5.00%)	1 / 61 (1.64%)	2 / 59 (3.39%)
occurrences (all)	4	1	2
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: Reported PTs: Rash, Erythema and Eczema		
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	3 / 59 (5.08%)
occurrences (all)	0	1	3
Musculoskeletal and connective tissue disorders			

Musculoskeletal and connective tissue disorder	Additional description: Reported PTs: Myalgia, Back pain, Muscle spasms		
subjects affected / exposed	5 / 60 (8.33%)	3 / 61 (4.92%)	4 / 59 (6.78%)
occurrences (all)	5	3	5
Infections and infestations			
Infection and infestations	Additional description: Reported PTs: Gastroenteritis, Nasopharyngitis, Influenza, Vulvovaginal mycotic infection, Skin infection, Sinusitis, Pneumonia, Otitis externa, and Oral herpes		
subjects affected / exposed	5 / 60 (8.33%)	4 / 61 (6.56%)	6 / 59 (10.17%)
occurrences (all)	6	5	6

Non-serious adverse events	IPV SSI		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 60 (61.67%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complication	Additional description: PT reported: Procedural pain and Ligament sprain		
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Nervous system disorders			
Nervous system disorder	Additional description: Reported PT: Headache and Presyncope		
subjects affected / exposed	17 / 60 (28.33%)		
occurrences (all)	18		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Injection site reaction and systemic adverse events	Additional description: Reported PTs: Injection site reactions included pain, swelling, erythema, pruritus, haematoma, and warmth; systemic adverse events included influenza like illness, axillary pain, vessel puncture site pain, fatigue, and Pyrexia		
subjects affected / exposed	25 / 60 (41.67%)		
occurrences (all)	35		
Gastrointestinal disorders			
Gastrointestional disorders	Additional description: Reported PTs: Nausea, Diarrhoea, Vomiting, Abdominal pain upper and Abdominal pain		

subjects affected / exposed	9 / 60 (15.00%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: Reported PTs: Oropharyngeal pain, Cough and Pharyngeal inflammation		
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: Reported PTs: Rash, Erythema and Eczema		
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorder	Additional description: Reported PTs: Myalgia, Back pain, Muscle spasms		
subjects affected / exposed	9 / 60 (15.00%)		
occurrences (all)	9		
Infections and infestations			
Infection and infestations	Additional description: Reported PTs: Gastroenteritis, Nasopharyngitis, Influenza, Vulvovaginal mycotic infection, Skin infection, Sinusitis, Pneumonia, Otitis externa, and Oral herpes		
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported