Clinical trial results:
A Phase I/II, Randomized, Observer-Blind, Multicenter Study to Evaluate Immunogenicity and Safety of Four Influenza Vaccines in Healthy Pediatric Subjects 6 to < 48 Months of Age.

Summary

EudraCT number	2013-002081-39
Trial protocol	FI
Global end of trial date	24 February 2015

Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	15 March 2016

Trial information

Trial identification

Sponsor protocol code	V58P16

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02035696
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines & Diagnostics AG
Sponsor organisation address	CH, Basel, Switzerland, 4002
Public contact	Posting Director, Novartis Vaccines & Diagnostics, RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines & Diagnostics, RegistryContactVaccinesUS@novartis.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	30 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 June 2014
Global end of trial reached?	Yes
Global end of trial date	24 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Immunogenicity Objective
To select an optimal dose of TIVc for pediatric subjects 6 to < 48 months of age by desirability index score (The overall desirability index is based on comparison of post-vaccination haemagglutination inhibition (HI) assay results and specific solicited adverse events following any vaccination)

Protection of trial subjects:

Ongoing review of blinded safety data will be performed by an independent Data Monitoring Committee (DMC). Safety data will be reviewed on a regular basis as governed by the DMC Charter. If safety signals of concern are observed by the DMC, the DMC may recommend that study vaccination be halted until the DMC determines if it is appropriate to proceed with vaccination as specified in the Charter.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	7 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 34
Country: Number of subjects enrolled	Thailand: 291
Country: Number of subjects enrolled	Philippines: 345
Country: Number of subjects enrolled	Finland: 1
Worldwide total number of subjects	671
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)	336

Children (2-11 years)	335
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:

6 centers in the United States, 1 center in Finland, 2 centers in Thailand, 2 centers in Philippines

Pre-assignment

Screening details:

All enrolled Subjects were included in the trial

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	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

This study was conducted in an observer-blind fashion. To maintain the observer-blind design of study, the roles and responsibilities of the “blinded” and “unblinded” team members were defined and maintained. Safety assessments and study-related procedures (except for vaccine administration done by unblinded staff) and monitoring thereof were to be performed by “blinded” team members.
The database doesnt provide the option as observer blind that is the reason "Double blind" has been selected.

Arms

Are arms mutually exclusive?	No
Arm title	TIVc-High Dose

Arm description:

Subjects (6 to <48 months old) received two doses of 0.75 mL of TIVc vaccine.

Arm type	Experimental
Investigational medicinal product name	Mammalian cell culture-derived trivalent influenza vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

IM/0.75mL

Arm title	TIVc-Full Dose

Arm description:

Subjects (6 to <48 months old) received two doses of 0.50 mL of TIVc vaccine.

Arm type	Experimental
Investigational medicinal product name	Mammalian cell culture-derived trivalent influenza vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

IM/0.50 mL

Arm title	TIVc- Half Dose

Arm description:

Subjects (6 to <48 months old) received two doses of 0.25 mL of TIVc vaccine.

Arm type	Experimental

Investigational medicinal product name	Mammalian cell culture-derived trivalent influenza vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

IM/0.25 mL

Arm title	TIVe

Arm description:

Subjects aged 6 to <36 months were administered two doses of 0.25 mL TIVe and subjects aged 36 to <48 months were administered two doses 0.50 mL of TIVe vaccine.

Arm type	Active comparator
Investigational medicinal product name	Egg Derived Trivalent Influenza Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

IM/0.25 mL- Subjects aged 6 to <36 months
IM/0.50 mL- Subjects aged 36 to <48 months

Number of subjects in period 1	TIVc-High Dose	TIVc-Full Dose	TIVc- Half Dose
Started	174	166	167
Completed	171	163	164
Not completed	3	3	3
Consent withdrawn by subject	3	-	2
Lost to follow-up	-	3	1

Number of subjects in period 1	TIVe
Started	164
Completed	161
Not completed	3
Consent withdrawn by subject	1
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	TIVc-High Dose
Reporting group description:	
Subjects (6 to <48 months old) received two doses of 0.75 mL of TIVc vaccine.	
Reporting group title	TIVc-Full Dose
Reporting group description:	
Subjects (6 to <48 months old) received two doses of 0.50 mL of TIVc vaccine.	
Reporting group title	TIVc- Half Dose
Reporting group description:	
Subjects (6 to <48 months old) received two doses of 0.25 mL of TIVc vaccine.	
Reporting group title	TIVe
Reporting group description:	
Subjects aged 6 to <36 months were administered two doses of 0.25 mL TIVe and subjects aged 36 to <48 months were administered two doses 0.50 mL of TIVe vaccine.	

Reporting group values	TIVc-High Dose	TIVc-Full Dose	TIVc- Half Dose
Number of subjects	174	166	167
Age categorical			
Units: Subjects			
Infants and toddlers (28 days - 23 months)	88	83	83
Children (2-11 years)	86	83	84
Age continuous			
Units: months			
arithmetic mean	25.3	25	25.6
standard deviation	± 11.5	± 11.5	± 11.5
Gender categorical			
Units: Subjects			
Female	84	82	77
Male	90	84	90

Reporting group values	TIVe	Total	
Number of subjects	164	671	
Age categorical			
Units: Subjects			
Infants and toddlers (28 days - 23 months)	82	336	
Children (2-11 years)	82	335	
Age continuous			
Units: months			
arithmetic mean	25.3		
standard deviation	± 11.9	-	
Gender categorical			
Units: Subjects			
Female	87	330	
Male	77	341	

End points

End points reporting groups

Reporting group title	TIVc-High Dose
Reporting group description:	
Subjects (6 to <48 months old) received two doses of 0.75 mL of TIVc vaccine.	
Reporting group title	TIVc-Full Dose
Reporting group description:	
Subjects (6 to <48 months old) received two doses of 0.50 mL of TIVc vaccine.	
Reporting group title	TIVc- Half Dose
Reporting group description:	
Subjects (6 to <48 months old) received two doses of 0.25 mL of TIVc vaccine.	
Reporting group title	TIVe
Reporting group description:	
Subjects aged 6 to <36 months were administered two doses of 0.25 mL TIVe and subjects aged 36 to <48 months were administered two doses 0.50 mL of TIVe vaccine.	
Subject analysis set title	All Enrolled Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All screened subjects who provided informed consent and provided demographic and/or other baseline screening measurements, regardless of the subject's randomization and vaccination status in the trial and received a subject ID.	
Subject analysis set title	Full Analysis Set (FAS), Immunogenicity Desirability – FASd
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects in the All Enrolled Set who are randomized and: • Receive at least one study vaccination at day 1 and/or day 29, and • Provide immunogenicity data pre- (day 1) and postvaccination (day 50), and • Provide postvaccination solicited adverse event data from day 1 (6 hours) until day 3	
Subject analysis set title	Full Analysis Set (FAS), FASc1
Subject analysis set type	Full analysis
Subject analysis set description:	
Receive at least one study vaccination and provide immunogenicity data at day 50 (HI antibody titer ≥ 1:40).	
Subject analysis set title	FASc2
Subject analysis set type	Full analysis
Subject analysis set description:	
Receive at least one study vaccination and provide immunogenicity data at baseline (day 1) and day 50 (seroconversion of HI titer, seroprotection of MN titer, GMTs and ratio of GMTs).	
Subject analysis set title	PPSd
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects in the FASd who: • Correctly received the vaccines (i.e., received the vaccines to which the subjects were randomized and at the scheduled time points). • Provided immunogenicity data pre- (day 1) and post vaccination (day 50). • Provided post vaccination solicited adverse event data (from day 1 (6 hours) until day 3 for at least one local reaction and at least one systemic reaction). • Had no reportable protocol deviations leading to exclusion as defined prior to unblinding/analysis. • Were not excluded due to other reasons defined prior to unblinding or analysis.	
Subject analysis set title	PPSc1
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects in the FASc1 who: • Correctly received the vaccines (i.e., received the vaccines to which the subjects were randomized and	

at the scheduled time points).
• Received at least one study vaccination and provide immunogenicity data at day 50 (HI antibody titer ≥ 1:40).
• Had no reportable protocol deviations leading to exclusion as defined prior to unblinding/analysis.
• Were not excluded due to other reasons defined prior to unblinding or analysis.

Subject analysis set title	PPSc2
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects in the FASc2 who:
• Correctly receive the vaccine (i.e., receive the vaccine to which the subjects is randomized and at the scheduled time points).
• Receive at least one study vaccination and provide immunogenicity data at baseline (day 1) and day 50 (seroconversion of HI titer, seroprotection of MN titer, GMTs and ratio of GMTs)
• Have no reportable protocol deviations leading to exclusion (see section 6.2 of Statistical Analysis Plan version 2 issued on 03 Dec 2014) as defined prior to unblinding/analysis.
• Are not excluded due to other reasons defined prior to unblinding or analysis (see section 6.2 of Statistical Analysis Plan version 2 issued on 03 Dec 2014).

Subject analysis set title	Solicited Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects in the Exposed Set with any solicited adverse event data and/or indicators of solicited adverse events.

Subject analysis set title	Unsolicited Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects in the Exposed Set with unsolicited adverse event data.

Subject analysis set title	Ratio of GMTs
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Ratio of different doses (ie. High dose TIVc : TIVe, Full dose TIVc : TIVe, Half dose TIVc: TIVe) are compared on day 1 and day 50.

Primary: Ratios of Geometric Mean Titer (GMT) in subjects (6 to <48 months old) after receiving two doses of either TIVc or TIVe vaccine

End point title	Ratios of Geometric Mean Titer (GMT) in subjects (6 to <48 months old) after receiving two doses of either TIVc or TIVe vaccine

End point description:

Immunogenicity was assessed in terms of ratios of GMTs in subjects (6 to <48 months old), measured by HI assay, day 1 to day 50 after vaccination with two doses of either TIVc or TIVe vaccine.
Analysis was done on Per Protocol (PP) population i.e. all subjects in the FAS Efficacy/Immunogenicity Set who are not excluded due to reasons defined prior to unblinding or analysis.

End point type	Primary

End point timeframe:

Day 50/Day 1

End point values	TIVc-High Dose	TIVc-Full Dose	TIVc- Half Dose	TIVe
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	145	142	149
Units: Ratios				
geometric mean (confidence interval 95%)				

A/H1N1	11 (6.18 to 20)	8.25 (4.48 to 15)	8.62 (4.68 to 16)	5.27 (2.9 to 9.59)
A/H3N2	15 (8.79 to 24)	15 (8.92 to 26)	9.49 (5.61 to 16)	17 (10 to 29)
B strains	5.7 (3.74 to 8.69)	4.85 (3.13 to 7.54)	4.45 (2.87 to 6.91)	7.21 (4.69 to 11)

Statistical analyses

Statistical analysis title	TIVc-High Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc-High Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain A/H1N1 at Day 1.

Comparison groups	TIVc-High Dose v TIVe
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Vaccine Group Ratios
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.52

Notes:

[1] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc-High Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc-High Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain A/H1N1 at Day 50.

Comparison groups	TIVc-High Dose v TIVe
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Vaccine Group Ratios
Point estimate	2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.33
upper limit	3.26

Notes:

[2] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc-High Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc-High Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain A/H3N2 at Day 1.

Comparison groups	TIVc-High Dose v TIVe

Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Vaccine Group Ratios
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.12

Notes:

[3] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc-High Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc-High Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain A/H3N2 at Day 50.

Comparison groups	TIVc-High Dose v TIVe
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Vaccine Group Ratios
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.8

Notes:

[4] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc-High Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc-High Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain B at Day 1.

Comparison groups	TIVc-High Dose v TIVe
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Vaccine Group Ratios
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.08

Notes:

[5] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc-High Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc-High Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain B at Day 50.

Comparison groups	TIVc-High Dose v TIVe
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Vaccine Group Ratios
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.03

Notes:

[6] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc-Full Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc-Full Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain A/H1N1 at Day 1.

Comparison groups	TIVe v TIVc-Full Dose
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	Vaccine Group Ratios
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.97

Notes:

[7] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc-Full Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc-Full Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain A/H1N1 at Day 50.

Comparison groups	TIVe v TIVc-Full Dose
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	Vaccine Group Ratios
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.27
upper limit	3.15

Notes:

[8] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc-Full Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc-Full Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain A/H3N2 at Day 1.

Comparison groups	TIVe v TIVc-Full Dose
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	Vaccine Group Ratios
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.88

Notes:

[9] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc-Full Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc-Full Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain A/H3N2 at Day 50.

Comparison groups	TIVe v TIVc-Full Dose
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	Vaccine Group Ratios
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.66

Notes:

[10] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc-Full Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc-Full Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain B at Day 1.

Comparison groups	TIVe v TIVc-Full Dose
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Parameter estimate	Vaccine Group Ratios
Point estimate	0.95

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.03

Notes:

[11] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc-Full Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc-Full Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain B at Day 50.

Comparison groups	TIVe v TIVc-Full Dose
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
Parameter estimate	Vaccine Group Ratios
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.84

Notes:

[12] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc- Half Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc- Half Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain A/H1N1 at Day 1.

Comparison groups	TIVe v TIVc- Half Dose
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
Parameter estimate	Vaccine Group Ratios
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.61

Notes:

[13] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc- Half Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc- Half Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain A/H1N1 at Day 50.

Comparison groups	TIVe v TIVc- Half Dose

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
Parameter estimate	Vaccine Group Ratios
Point estimate	1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	2.7

Notes:

[14] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc- Half Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc- Half Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain A/H3N2 at Day 1.

Comparison groups	TIVe v TIVc- Half Dose
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
Parameter estimate	Vaccine Group Ratios
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.2

Notes:

[15] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc- Half Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc- Half Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain A/H3N2 at Day 50.

Comparison groups	TIVe v TIVc- Half Dose
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	non-inferiority[16]
Parameter estimate	Vaccine Group Ratios
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.56

Notes:

[16] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc- Half Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc- Half Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain B at Day 1.

Comparison groups	TIVe v TIVc- Half Dose
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
Parameter estimate	Vaccine Group Ratios
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.02

Notes:

[17] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Statistical analysis title	TIVc- Half Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of a TIVc- Half Dose to TIVe, assessed in terms of vaccine group GMT ratios against influenza strain B at Day 50.

Comparison groups	TIVe v TIVc- Half Dose
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	non-inferiority[18]
Parameter estimate	Vaccine Group Ratios
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.76

Notes:

[18] - Non-inferiority was established if the Lower limit of the 2- sided 95% CI of the vaccine group GMT ratio ≥ 0.67.

Primary: Percentages of Subjects (6 to <48 months old) achieving seroconversion or significant increase after receiving two doses of either TIVc or TIVe vaccine.

End point title	Percentages of Subjects (6 to <48 months old) achieving seroconversion or significant increase after receiving two doses of either TIVc or TIVe vaccine.

End point description:

Immunogenicity was assessed in terms number (%) of subjects (6 to <48 months old) achieving seroconversion as measured by HI antibody titer, day 50 after vaccination with two doses of either TIVc or TIVe vaccine.
Seroconversion was defined as subjects with either a pre-vaccination (baseline) HI titer < 1:10 and post-vaccination HI titer ≥ 1:40 or with a pre-vaccination HI titer ≥ 1:10 and a ≥ 4-fold increase in post-vaccination HI antibody titer.
Analysis was done on PP population.

End point type	Primary

End point timeframe:

Day 50 post vaccination.

End point values	TIVc-High Dose	TIVc-Full Dose	TIVc- Half Dose	TIVe
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	145	142	149
Units: Percentages of Subjects				
number (confidence interval 95%)				
A/H1N1_Day 50	83 (77 to 89)	82 (75 to 88)	80 (72 to 86)	74 (66 to 81)
A/H3N2_Day 50	94 (89 to 97)	90 (84 to 95)	87 (81 to 92)	93 (87 to 96)
B_Day 50	69 (61 to 76)	70 (61 to 77)	63 (54 to 71)	80 (73 to 86)

Statistical analyses

Statistical analysis title	TIVc-High Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of TIVc-High Dose to TIVe, assessed in terms of Vaccine Group Differences with seroconversion against influenza strain A/H1N1.

Comparison groups	TIVc-High Dose v TIVe
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	non-inferiority[19]
Parameter estimate	Vaccine Group Differences]
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	18.8

Notes:

[19] - Non-inferiority was established if the Lower limit of the 2-sided 95% CI on the difference between seroconversion rates ≥ -10%.

Statistical analysis title	TIVc-High Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of TIVc-High Dose to TIVe, assessed in terms of Vaccine Group Differences with seroconversion against influenza strain A/H3N2.

Comparison groups	TIVc-High Dose v TIVe
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	non-inferiority[20]
Parameter estimate	Vaccine Group Differences
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	7.7

Notes:

[20] - Non-inferiority was established if the Lower limit of the 2-sided 95% CI on the difference between seroconversion rates ≥ -10%.

Statistical analysis title	TIVc-High Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of TIVc-High Dose to TIVe, assessed in terms of Vaccine Group Differences with seroconversion against influenza strain B.

Comparison groups	TIVc-High Dose v TIVe
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
Parameter estimate	Vaccine Group Differences
Point estimate	-11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.9
upper limit	-1.4

Notes:

[21] - Non-inferiority was established if the Lower limit of the 2-sided 95% CI on the difference between seroconversion rates ≥ -10%.

Statistical analysis title	TIVc-Full Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of TIVc-Full Dose to TIVe, assessed in terms of Vaccine Group Differences with seroconversion against influenza strain A/H1N1.

Comparison groups	TIVe v TIVc-Full Dose
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	non-inferiority[22]
Parameter estimate	Vaccine Group Differences
Point estimate	8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	17.7

Notes:

[22] - Non-inferiority was established if the Lower limit of the 2-sided 95% CI on the difference between seroconversion rates ≥ -10%.

Statistical analysis title	TIVc-Full Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of TIVc-Full Dose to TIVe, assessed in terms of Vaccine Group Differences with seroconversion against influenza strain A/H3N2.

Comparison groups	TIVe v TIVc-Full Dose
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	non-inferiority[23]
Parameter estimate	Vaccine Group Differences
Point estimate	-2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.1
upper limit	4.3

Notes:

[23] - Non-inferiority was established if the Lower limit of the 2-sided 95% CI on the difference between seroconversion rates ≥ -10%.

Statistical analysis title	TIVc-Full Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of TIVc-Full Dose to TIVe, assessed in terms of Vaccine Group Differences with seroconversion against influenza strain B.

Comparison groups	TIVe v TIVc-Full Dose
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	non-inferiority[24]
Parameter estimate	Vaccine Group Differences
Point estimate	-10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.1
upper limit	0

Notes:

[24] - Non-inferiority was established if the Lower limit of the 2-sided 95% CI on the difference between seroconversion rates ≥ -10%.

Statistical analysis title	TIVc- Half Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of TIVc- Half Dose to TIVe, assessed in terms of Vaccine Group Differences with seroconversion against influenza strain A/H1N1.

Comparison groups	TIVe v TIVc- Half Dose
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	non-inferiority[25]
Parameter estimate	Vaccine Group Differences
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	15.4

Notes:

[25] - Non-inferiority was established if the Lower limit of the 2-sided 95% CI on the difference between seroconversion rates ≥ -10%.

Statistical analysis title	TIVc- Half Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of TIVc- Half Dose to TIVe, assessed in terms of Vaccine Group Differences with seroconversion against influenza strain A/H3N2.

Comparison groups	TIVe v TIVc- Half Dose

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	non-inferiority[26]
Parameter estimate	Vaccine Group Differences
Point estimate	-5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.6
upper limit	1.7

Notes:

[26] - Non-inferiority was established if the Lower limit of the 2-sided 95% CI on the difference between seroconversion rates ≥ -10%.

Statistical analysis title	TIVc- Half Dose, TIVe

Statistical analysis description:

Non-inferiority of immune responses of TIVc- Half Dose to TIVe, assessed in terms of Vaccine Group Differences with seroconversion against influenza strain B.

Comparison groups	TIVe v TIVc- Half Dose
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	non-inferiority[27]
Parameter estimate	Vaccine Group Differences
Point estimate	-17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.3
upper limit	-6.8

Notes:

[27] - Non-inferiority was established if the Lower limit of the 2-sided 95% CI on the difference between seroconversion rates ≥ -10%.

Primary: Differences in Number of subjects (6 to <48 months old) reporting severe solicited local and systemic reactions after vaccination with either TIVc or TIVe vaccine

End point title	Differences in Number of subjects (6 to <48 months old) reporting severe solicited local and systemic reactions after vaccination with either TIVc or TIVe vaccine[28][29]

End point description:

Safety was assessed in terms of number of subjects (6 to <48 months old) reporting severe local solicited AEs and severe local systemic AEs, 3 days after vaccination with either TIVc or TIVe vaccine. Analysis was done on solicited safety data set i.e. all subjects in the exposed set who provide post-vaccination solicited adverse event data.

End point type	Primary

End point timeframe:

Day 1 to Day 3

Notes:

[28] - 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 analysis was reported for this outcome measure.

[29] - 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: No statistical analysis was reported for this outcome measure.

End point values	TIVc-High Dose	TIVc-Full Dose	TIVc- Half Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	145	142	
Units: Desirability Index				
number (not applicable)				
Differences in % severe solicited local AEs	0	0	0	
Differences in % severe solicited systemic AEs	0.04	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Subjects (6 to <48 months old) achieving seroconversion or significant increase after receiving two doses of either TIVc or TIVe vaccine.

End point title	Percentages of Subjects (6 to <48 months old) achieving seroconversion or significant increase after receiving two doses of either TIVc or TIVe vaccine.

End point description:

Immunogenicity was assessed in terms number (%) of subjects (6 to <48 months old) achieving seroconversion as measured by HI assay, day 50 after vaccination with two doses of either TIVc or TIVe vaccine.
Seroconversion was defined as subjects with either a pre-vaccination (baseline) HI titer < 1:10 and post-vaccination HI titer ≥ 1:40 or with a pre-vaccination HI titer ≥ 1:10 and a ≥ 4-fold increase in post-vaccination HI antibody titer.
The Center for Biologics Evaluation, Research, and Review (CBER) criterion for pediatric population is that the lower bound of the two-sided 95% confidence interval (CI) for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 40%.
Analysis was done on Full analysis set.

End point type	Secondary

End point timeframe:

Day 50 post vaccination

End point values	TIVc-High Dose	TIVc-Full Dose	TIVc- Half Dose	TIVe
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	170	164	161	159
Units: Percentages of Subjects				
number (confidence interval 95%)				
A/H1N1	84 (77 to 89)	80 (74 to 86)	82 (75 to 88)	73 (65 to 80)
A/H3N2	94 (89 to 97)	91 (85 to 95)	88 (81 to 92)	93 (88 to 96)
B strain	68 (61 to 75)	70 (62 to 76)	63 (55 to 70)	79 (72 to 85)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Subjects (6 to <48 months old) achieving HI titer ≥ 1:40 after receiving two doses of either TIVc or TIVe vaccine.

End point title	Percentages of Subjects (6 to <48 months old) achieving HI titer ≥ 1:40 after receiving two doses of either TIVc or TIVe vaccine.

End point description:

Immunogenicity was assessed in terms of number (%) of subjects (6 to <48 months old) achieving HI titer ≥1:40 as measured by HI assay, day 50 after vaccination with two doses of either TIVc or TIVe vaccine.
The CBER criterion for pediatric population is that the lower bound of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 should meet or exceed 70% The CHMP criterion for pediatric population is that the percentage of subjects achieving HI antibody titers ≥1:40 should be >70%.
Analysis was done on FAS.

End point type	Secondary

End point timeframe:

Day 1, Day 50 post vaccination

End point values	TIVc-High Dose	TIVc-Full Dose	TIVc- Half Dose	TIVe
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	170	164	161	159
Units: Percentages of Subjects				
number (confidence interval 95%)				
A/H1N1: Day 1	28 (21 to 36)	34 (27 to 43)	28 (21 to 36)	28 (21 to 35)
A/H1N1: Day 50	86 (79 to 91)	87 (80 to 92)	84 (77 to 89)	78 (70 to 84)
A/H3N2: Day 1	45 (37 to 53)	41 (33 to 50)	47 (39 to 56)	51 (43 to 59)
A/H3N2: Day 50	98 (94 to 100)	98 (94 to 100)	96 (92 to 99)	99 (96 to 100)
B: Day 1	2 (0 to 6)	0 (0 to 3)	1 (0.016 to 3)	3 (1 to 8)
B: Day 50	69 (61 to 76)	70 (61 to 77)	63 (54 to 71)	81 (73 to 87)

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Ratios (GMR) in subjects (6 to <48 months old) after receiving two doses of either TIVc or TIVe vaccine.

End point title	Geometric Mean Ratios (GMR) in subjects (6 to <48 months old) after receiving two doses of either TIVc or TIVe vaccine.

End point description:

Immunogenicity was assessed in terms of GMR in subjects (6 to <48 months old) as measured by HI assay, day 50 after vaccination with two doses of either TIVc or TIVe vaccine. The CHMP criterion is mean geometric ratio (GMR) >2.5.
Analysis was done on FAS.

End point type	Secondary

End point timeframe:

Day 50 post vaccination over day 1.

End point values	TIVc-High Dose	TIVc-Full Dose	TIVc- Half Dose	TIVe
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	170	164	161	159
Units: Ratio				
number (confidence interval 95%)				
A/H1N1	12 (7.05 to 19)	8.58 (5.08 to 14)	8.94 (5.28 to 15)	5.14 (3.04 to 8.68)
A/H3N2	12 (7.83 to 19)	13 (8.05 to 20)	7.68 (4.91 to 12)	14 (8.83 to 22)
B.	6.14 (4.27 to 8.84)	5.29 (3.64 to 7.7)	4.72 (3.24 to 6.88)	7.57 (5.21 to 11)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Subjects (6 to <48 months old) with high post vaccination HI titers (i.e. HI titers ≥1:110, ≥1:150, ≥1:330 and ≥1:629) after receiving two doses of either TIVc or TIVe vaccine.

End point title	Percentages of Subjects (6 to <48 months old) with high post vaccination HI titers (i.e. HI titers ≥1:110, ≥1:150, ≥1:330 and ≥1:629) after receiving two doses of either TIVc or TIVe vaccine.

End point description:

Immunogenicity was assessed in terms of number (%) of subjects (6 to <48 months old) achieving post vaccination HI titers (i.e. HI titers ≥1:110, ≥1:150, ≥1:330 and ≥1:629) as measured by HI assay, day 50 after vaccination with two doses of either TIVc or TIVe vaccine.
Analysis was done on PPS.

End point type	Secondary

End point timeframe:

Day 1 and Day 50 post vaccination.

End point values	TIVc-High Dose	TIVc-Full Dose	TIVc- Half Dose	TIVe
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	145	142	149
Units: Percentages of Subjects				
number (confidence interval 95%)				
A/H1N1: Day 1: HI titers ≥1:110	26 (19 to 33)	31 (24 to 39)	26 (19 to 34)	26 (19 to 34)
A/H1N1: Day 50: HI titers ≥1:110	78 (70 to 84)	81 (73 to 87)	72 (64 to 79)	60 (51 to 68)
A/H3N2: Day 1: HI titers ≥1:110	40 (33 to 49)	38 (30 to 46)	42 (34 to 51)	47 (39 to 55)
A/H3N2: Day 50: HI titers ≥1:110	88 (82 to 93)	87 (80 to 92)	82 (74 to 88)	97 (93 to 99)
B: Day 1: HI titers ≥1:110	1 (0.016 to 4)	0 (0 to 3)	0 (0 to 3)	0 (0 to 2)
B: Day 50: HI titers ≥1:110	40 (32 to 48)	30 (23 to 39)	25 (18 to 33)	38 (30 to 47)
A/H1N1: Day 1: HI titers ≥1:151	25 (18 to 33)	30 (23 to 39)	26 (19 to 34)	26 (19 to 33)
A/H1N1: Day 50: HI titers ≥1:151	76 (69 to 83)	77 (70 to 84)	71 (63 to 78)	58 (50 to 66)
A/H3N2: Day 1: HI titers ≥1:151	40 (33 to 49)	38 (30 to 46)	42 (34 to 51)	47 (39 to 55)
A/H3N2: Day 50: HI titers ≥1:151	88 (82 to 93)	87 (80 to 92)	81 (74 to 87)	97 (93 to 99)
B: Day 1: HI titers ≥1:151	0 (0 to 2)	0 (0 to 3)	0 (0 to 3)	0 (0 to 2)
B: Day 50: HI titers ≥1:151	39 (31 to 47)	30 (23 to 39)	25 (18 to 33)	38 (30 to 47)

A/H1N1: Day 1: HI titers ≥1:330	12 (7 to 18)	14 (9 to 21)	26 (19 to 34)	11 (6 to 17)
A/H1N1: Day 50: HI titers ≥1:330	51 (43 to 59)	52 (43 to 60)	71 (63 to 78)	35 (27 to 43)
A/H3N2: Day 1: HI titers ≥1:330	16 (11 to 23)	12 (7 to 18)	42 (34 to 51)	21 (15 to 28)
A/H3N2: Day 50: HI titers ≥1:330	62 (53 to 69)	57 (49 to 65)	81 (74 to 87)	68 (60 to 76)
B: Day 1: HI titers ≥1:330	0 (0 to 2)	0 (0 to 3)	0 (0 to 3)	0 (0 to 2)
B: Day 50: HI titers ≥1:330	4 (1 to 8)	5 (2 to 10)	24 (17 to 32)	7 (4 to 13)
A/H1N1: Day 1: HI titers ≥1:629	9 (5 to 15)	12 (7 to 18)	12 (7 to 18)	8 (4 to 14)
A/H1N1: Day 50: HI titers ≥1:629	48 (40 to 56)	48 (40 to 57)	44 (35 to 52)	34 (26 to 42)
A/H3N2: Day 1: HI titers ≥1:629	16 (11 to 23)	12 (7 to 18)	13 (8 to 19)	21 (15 to 28)
A/H3N2: Day 50: HI titers ≥1:629	62 (53 to 69)	57 (48 to 65)	52 (44 to 61)	68 (60 to 76)
B: Day 1: HI titers ≥1:629	0 (0 to 2)	0 (0 to 3)	0 (0 to 3)	0 (0 to 2)
B: Day 50: HI titers ≥1:629	4 (1 to 8)	4 (2 to 9)	4 (1 to 8)	7 (3 to 12)

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Ratios (GMR) in subjects (6 to <48 months old) after receiving two doses of either TIVc or TIVe vaccine

End point title	Geometric Mean Ratios (GMR) in subjects (6 to <48 months old) after receiving two doses of either TIVc or TIVe vaccine

End point description:

Immunogenicity was assessed in terms of GMR in subjects (6 to <48 months old) as measured by MN assay, day 50 after vaccination with two doses of either TIVc or TIVe vaccine.
Analysis was done on PPS.

End point type	Secondary

End point timeframe:

Day 50 post vaccination over day 1.

End point values	TIVc-High Dose	TIVc-Full Dose	TIVc- Half Dose	TIVe
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	145	142	149
Units: Ratio				
number (confidence interval 95%)				
A/H1N1	11 (6.18 to 20)	8.25 (4.48 to 15)	8.62 (4.68 to 16)	5.27 (2.9 to 9.59)
A/H3N2	15 (8.79 to 24)	15 (8.92 to 26)	9.49 (5.61 to 16)	17 (10 to 29)
B.	5.7 (3.74 to 8.69)	4.85 (3.13 to 7.54)	4.45 (2.87 to 6.91)	7.21 (4.69 to 11)

Statistical analyses

No statistical analyses for this end point

Secondary: Ratios of Geometric Mean Titer (GMT) in subjects (6 to <48 months old) after receiving two doses of either TIVc or TIVe vaccine as measured by HI assay.

End point title	Ratios of Geometric Mean Titer (GMT) in subjects (6 to <48 months old) after receiving two doses of either TIVc or TIVe vaccine as measured by HI assay.

End point description:

Immunogenicity was assessed in terms of ratios of GMTs in subjects (6 to <48 months old), measured by HI assay, day 1 to day 50 after vaccination with two doses of either TIVc or TIVe vaccine.
Analysis was done on PPS population.

End point type	Secondary

End point timeframe:

Day 50 /Day 1

End point values	Ratio of GMTs			
Subject group type	Subject analysis set			
Number of subjects analysed	156			
Units: Ratios				
number (confidence interval 95%)				
A/H1N1 (High dose TIVc:TIVe, Day 1)	0.99 (0.65 to 1.52)			
A/H1N1 (Full dose TIVc:TIVe, Day 1)	1.28 (0.83 to 1.97)			
A/H1N1 (Half dose TIVc:TIVe, Day 1)	1.05 (0.68 to 1.61)			
A/H1N1 (High dose TIVc:TIVe, Day 50)	2.09 (1.33 to 3.26)			
A/H1N1 (Full dose TIVc:TIVe, Day 50)	2 (1.27 to 3.15)			
A/H1N1 (Half dose TIVc:TIVe, Day 50)	1.71 (1.09 to 2.7)			
A/H3N2 (High dose TIVc:TIVe, Day 1)	0.72 (0.46 to 1.12)			
A/H3N2 (Full dose TIVc:TIVe, Day 1)	0.56 (0.36 to 0.88)			
A/H3N2 (Half dose TIVc:TIVe, Day 1)	0.76 (0.48 to 1.2)			
A/H3N2 (High dose TIVc:TIVe, Day 50)	0.6 (0.45 to 0.8)			
A/H3N2 (Full dose TIVc:TIVe, Day 50)	0.49 (0.37 to 0.66)			
A/H3N2 (Half dose TIVc:TIVe, Day 50)	0.42 (0.31 to 0.56)			
B (High dose TIVc:TIVe, Day 1)	0.99 (0.91 to 1.08)			
B (Full dose TIVc:TIVe, Day 1)	0.95 (0.88 to 1.03)			
B (Half dose TIVc:TIVe, Day 1)	0.94 (0.86 to 1.02)			
B (High dose TIVc:TIVe, Day 50)	0.79 (0.6 to 1.03)			
B (Full dose TIVc:TIVe, Day 50)	0.64 (0.49 to 0.84)			
B (Half dose TIVc:TIVe, Day 50)	0.58 (0.44 to 0.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects (6 to <48 months old) reporting solicited local (Grading Type I)and systemic adverse events (AEs) after two doses of either TIVc or TIVe vaccine.

End point title	Number of subjects (6 to <48 months old) reporting solicited local (Grading Type I)and systemic adverse events (AEs) after two doses of either TIVc or TIVe vaccine.

End point description:

Safety was assessed in terms of number of subjects (6 to <48 months old) reporting solicited local and systemic reactions, day 1 to day 7 after vaccination with two doses of either TIVc or TIVe vaccine (By Any Vaccination).
Analyses was done on solicited safety data set.

End point type	Secondary

End point timeframe:

Day 1 to Day 7

End point values	TIVc-High Dose	TIVc-Full Dose	TIVc- Half Dose	TIVe
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	174	165	167	161
Units: Subjects				
Any local	64	58	60	54
Injection-site erythema	19	24	24	17
Injection-site induration	13	14	9	8
Injection-site ecchymosis	9	9	7	7
Injection-site tenderness	50	43	42	45
Any systemic	78	72	69	66
Change in eating habits	29	35	28	29
Sleepiness	30	28	21	24
Irritability	30	31	29	27
Vomiting	21	20	22	14
Diarrhea	31	31	29	34
Chills	7	5	5	9
Fever (≥ 38°C)	15	20	21	21
Prophylactic use of antipyretics/analgesics	9	21	25	13
Therapeutic use of antipyretics/analgesics	17	21	24	22

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects (6 to <48 months old) reporting unsolicited adverse events (AEs) after two doses of either TIVc or TIVe vaccine.

End point title	Number of subjects (6 to <48 months old) reporting unsolicited adverse events (AEs) after two doses of either TIVc or TIVe vaccine.

End point description:

Safety was assessed in terms of number of subjects (6 to <48 months old) reporting unsolicited reactions after Each /any Vaccination from Day 1 [Post Vaccination] to Day 29 [Pre Clinic Visit] and Day 29 [Post Vaccination] to Day 50 [Pre Clinic Visit] , Serious Adverse Events (SAEs), AEs leading to New Onset of Chronic Diseases (NOCD), AEs leading to withdrawal from the study and concomitant medications (day 1 to day 209) after vaccination with two doses of either TIVc or TIVe vaccine (By Any Vaccination).
Analyses was done on unsolicited safety data set i.e. all subjects in the exposed set who have post-vaccination unsolicited AE data.

End point type	Secondary

End point timeframe:

Unsolicited AEs after Each/any Vaccination from Day 1 to Day 29 and Day 29 to Day 50 , Day 1 to Day 209.

End point values	TIVc-High Dose	TIVc-Full Dose	TIVc- Half Dose	TIVe
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	174	166	167	164
Units: Subjects				
Any AEs(after any vaccination)	102	107	91	94
Possibly/probably related AEs (after any vacc.)	38	43	43	35
Any AEs(after each vaccination)	79	84	69	76
Possibly/probably related AEs (after each vacc.)	56	64	50	48
AEs leading to NOCDs	30	33	31	31
AEs leading to withdrawal from the study	111	20	18	14
SAEs	4	8	10	6
Possibly/probably related SAEs	0	0	0	0
Medically attended AEs	0	0	0	0
New onset of chronic diseases	0	1	1	1
Death	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited AEs were collected from day 1 to day 7 post vaccination, unsolicited AEs were collected from day 1 to day 50 post vaccination and SAEs were collected from day 1 to day 209 post vaccination.

Adverse event reporting additional description:

Solicited AEs were collected from day 1 to day 7 post vaccination, unsolicited AEs were collected from day 1 to day 50 post vaccination.
A systematic adverse event is equivalent to an event that was solicited by the diary card, whereas a non-systematic event is an unsolicited adverse event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	TIVc-High Dose

Reporting group description:

Subjects (6 to <48 months old) received two doses of 0.75 mL of TIVc vaccine

Reporting group title	TIVc-Full Dose

Reporting group description:

Subjects(6 to <48 months old) received two doses of 0.50 mL of TIVc vaccine

Reporting group title	TIVc- Half Dose

Reporting group description:

Subjects (6 to <48 months old)received two doses of 0.25 mL of TIVc vaccine

Reporting group title	TIVe

Reporting group description:

Subjects (6 to <48 months old) received two doses of TIVe vaccine

Serious adverse events	TIVc-High Dose	TIVc-Full Dose	TIVc- Half Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 174 (2.30%)	8 / 166 (4.82%)	10 / 167 (5.99%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 174 (0.57%)	2 / 166 (1.20%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Febrile convulsion			

subjects affected / exposed	1 / 174 (0.57%)	2 / 166 (1.20%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 174 (0.00%)	0 / 166 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 166 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal Hernia			
subjects affected / exposed	0 / 174 (0.00%)	0 / 166 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 174 (0.00%)	2 / 166 (1.20%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 174 (0.57%)	0 / 166 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 174 (0.00%)	0 / 166 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amoebiasis			

subjects affected / exposed	0 / 174 (0.00%)	0 / 166 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 174 (0.00%)	2 / 166 (1.20%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 174 (1.15%)	0 / 166 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand-Foot-And-Mouth Disease			
subjects affected / exposed	0 / 174 (0.00%)	0 / 166 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital Cellulitis			
subjects affected / exposed	0 / 174 (0.00%)	1 / 166 (0.60%)	0 / 167 (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
Pharyngitis			
subjects affected / exposed	0 / 174 (0.00%)	0 / 166 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngotonsillitis			
subjects affected / exposed	0 / 174 (0.00%)	0 / 166 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 174 (0.00%)	2 / 166 (1.20%)	2 / 167 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal sepsis			

subjects affected / exposed	0 / 174 (0.00%)	0 / 166 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 174 (0.00%)	0 / 166 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 174 (0.00%)	0 / 166 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 174 (0.00%)	0 / 166 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 174 (0.00%)	0 / 166 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	TIVe		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 164 (3.66%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 164 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Febrile convulsion			

subjects affected / exposed	3 / 164 (1.83%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 164 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 164 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal Hernia			
subjects affected / exposed	0 / 164 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 164 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 164 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 164 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Amoebiasis			

subjects affected / exposed	1 / 164 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 164 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 164 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hand-Foot-And-Mouth Disease				
subjects affected / exposed	1 / 164 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Periorbital Cellulitis				
subjects affected / exposed	0 / 164 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	0 / 164 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngotonsillitis				
subjects affected / exposed	0 / 164 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 164 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pseudomonal sepsis				

subjects affected / exposed	1 / 164 (0.61%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subcutaneous abscess			
subjects affected / exposed	0 / 164 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 164 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Varicella			
subjects affected / exposed	1 / 164 (0.61%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 164 (0.61%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	TIVc-High Dose	TIVc-Full Dose	TIVc- Half Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	135 / 174 (77.59%)	123 / 166 (74.10%)	132 / 167 (79.04%)
Nervous system disorders			
Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed	30 / 174 (17.24%)	28 / 166 (16.87%)	21 / 167 (12.57%)
occurrences (all)	38	34	29
General disorders and administration site conditions			
Chills			
subjects affected / exposed	7 / 174 (4.02%)	5 / 166 (3.01%)	7 / 167 (4.19%)
occurrences (all)	7	7	8

Influenza like illness			
subjects affected / exposed	20 / 174 (11.49%)	38 / 166 (22.89%)	35 / 167 (20.96%)
occurrences (all)	22	44	40
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	30 / 174 (17.24%)	36 / 166 (21.69%)	32 / 167 (19.16%)
occurrences (all)	40	47	42
Injection site haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	9 / 174 (5.17%)	10 / 166 (6.02%)	8 / 167 (4.79%)
occurrences (all)	12	13	8
Injection site induration			
alternative assessment type: Systematic			
subjects affected / exposed	13 / 174 (7.47%)	16 / 166 (9.64%)	12 / 167 (7.19%)
occurrences (all)	17	18	13
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	56 / 174 (32.18%)	48 / 166 (28.92%)	47 / 167 (28.14%)
occurrences (all)	84	65	66
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	22 / 174 (12.64%)	28 / 166 (16.87%)	32 / 167 (19.16%)
occurrences (all)	27	35	34
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	32 / 174 (18.39%)	32 / 166 (19.28%)	30 / 167 (17.96%)
occurrences (all)	47	41	38
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	21 / 174 (12.07%)	20 / 166 (12.05%)	22 / 167 (13.17%)
occurrences (all)	26	24	30
Psychiatric disorders			
Eating disorder			
alternative assessment type: Systematic			

subjects affected / exposed	29 / 174 (16.67%)	35 / 166 (21.08%)	28 / 167 (16.77%)
occurrences (all)	35	43	39
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	34 / 174 (19.54%)	37 / 166 (22.29%)	34 / 167 (20.36%)
occurrences (all)	48	52	41
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 174 (3.45%)	11 / 166 (6.63%)	12 / 167 (7.19%)
occurrences (all)	8	14	14
Gastroenteritis			
subjects affected / exposed	17 / 174 (9.77%)	17 / 166 (10.24%)	15 / 167 (8.98%)
occurrences (all)	19	19	16
Impetigo			
subjects affected / exposed	6 / 174 (3.45%)	8 / 166 (4.82%)	10 / 167 (5.99%)
occurrences (all)	7	8	13
Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	19 / 174 (10.92%)	17 / 166 (10.24%)	22 / 167 (13.17%)
occurrences (all)	24	22	29
Rhinitis			
alternative assessment type: Systematic			
subjects affected / exposed	22 / 174 (12.64%)	30 / 166 (18.07%)	19 / 167 (11.38%)
occurrences (all)	31	41	23
Upper respiratory tract infection			
subjects affected / exposed	48 / 174 (27.59%)	44 / 166 (26.51%)	53 / 167 (31.74%)
occurrences (all)	79	62	68

Non-serious adverse events	TIVe		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	118 / 164 (71.95%)		
Nervous system disorders			
Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed	24 / 164 (14.63%)		
occurrences (all)	30		

General disorders and administration site conditions			
Chills			
subjects affected / exposed	9 / 164 (5.49%)		
occurrences (all)	11		
Influenza like illness			
subjects affected / exposed	37 / 164 (22.56%)		
occurrences (all)	46		
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	29 / 164 (17.68%)		
occurrences (all)	40		
Injection site haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 164 (4.27%)		
occurrences (all)	7		
Injection site induration			
alternative assessment type: Systematic			
subjects affected / exposed	10 / 164 (6.10%)		
occurrences (all)	11		
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	47 / 164 (28.66%)		
occurrences (all)	66		
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	22 / 164 (13.41%)		
occurrences (all)	30		
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	36 / 164 (21.95%)		
occurrences (all)	46		
Vomiting			
alternative assessment type: Systematic			

subjects affected / exposed	14 / 164 (8.54%)		
occurrences (all)	17		
Psychiatric disorders			
Eating disorder			
alternative assessment type: Systematic			
subjects affected / exposed	29 / 164 (17.68%)		
occurrences (all)	36		
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	29 / 164 (17.68%)		
occurrences (all)	34		
Infections and infestations			
Bronchitis			
subjects affected / exposed	12 / 164 (7.32%)		
occurrences (all)	13		
Gastroenteritis			
subjects affected / exposed	15 / 164 (9.15%)		
occurrences (all)	19		
Impetigo			
subjects affected / exposed	6 / 164 (3.66%)		
occurrences (all)	6		
Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	25 / 164 (15.24%)		
occurrences (all)	33		
Rhinitis			
alternative assessment type: Systematic			
subjects affected / exposed	26 / 164 (15.85%)		
occurrences (all)	33		
Upper respiratory tract infection			
subjects affected / exposed	41 / 164 (25.00%)		
occurrences (all)	82		

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: