EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2016
EMA/CHMP/456641/2016
Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Fluenz Tetra

influenza vaccine (live attenuated, nasal)

Procedure no: EMEA/H/C/002617/P46/008

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Abbreviations

AE	Adverse event
AOM	Acute otitis media
ATC	Anatomical Therapeutic Chemical
att	Attenuated
ca or CA	Cold-adapted
CDC-ILI	Influenza-like-illness per the Centers for Disease Control
cGAG	Concentrated gelatin-arginine-glutamate
CI	Confidence interval
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
eCRF	Electronic case report form
FFU	Fluorescent focus unit
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive voice response system
IWRS	Interactive web response system
LAIV	Live attenuated influenza vaccine
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
ND	Not determined
NVL	Non-vaccine like
PCR	Polymerase chain reaction
PP	Per-protocol
PT	Preferred term of MedDRA
Q/LAIV	Quadrivalent live attenuated influenza vaccine
RR	Relative risk
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
SOB	Shortness of breath
SOC	System organ class of MedDRA
SP	Sucrose phosphate
T/LAIV	Trivalent live attenuated influenza vaccine
TEAE	Treatment-emergent adverse event
TIV	trivalent inactivated influenza vaccine
ts	Temperature-sensitive
USA	United States of America
VL	Vaccine like
WBDC	Web based data capture
WHO	World health organization
wt or WT	Wild type

1. Introduction

On 24 March 2016, the MAH submitted the final study report of standalone study D2560C00006 for Fluenz Tetra, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

> Study D2560C00006 – A Phase 3 randomised, double-blind study to evaluate the efficacy and safety of MEDI3250 compared to placebo in healthy Japanese children age 7 years through 18 years.

As communicated to the Agency on 21 October 2015 (attached), the final study report submission is delayed beyond the 6 month time frame stipulated in Regulation (EC) No 1901/2006. However, the MAH stated that this final CSR has no regulatory consequences, as identified by the MAH, and does not necessitate any changes to the PI Annexes.

2. Scientific discussion

2.1. Information on the development program

This study was conducted over the 2014-2015 influenza season to support the licensure of the vaccine in Japan (October 2014 – May 2015).

2.2. Information on the pharmaceutical formulation used in the study

Subjects in the vaccine group received the recommended dosage schedule for intranasal administration was 0.2 mL (0.1 mL per nostril). For children aged 7–8 years not previously vaccinated against seasonal influenza, a second dose was given after an interval of at least 4 weeks.

Subjects in the placebo group received a placebo nasal spray.

Table 1. Identity of investigational product(s)

IP	Dosage form and strength	Manufacturer
MEDI3250 Nasal Spray 0.2 mL	0.2 mL aseptically filled into nasal sprayer (BD Accuspray device). Each dose contains $10^{7.0 \pm 0.5}$ FFU of each of 4 *ca*, *att*, *ts*, 6:2 reassortant influenza strains (A/H1N1 [A/California/7/2009], A/H3N2 [A/Texas/50/2012], B of Victoria lineage [B/Brisbane/60/2008], and B of Yamagata lineage [B/Massachusetts/2/2012])	MedImmune
MEDI3250 Nasal Spray placebo 0.2 mL	cGAG and 1× SP buffer 0.2 mL aseptically filled into nasal sprayer (BD Accuspray device).	MedImmune

att Attenuated, *ca* Cold-adapted, cGAG Concentrated gelatin-arginine-glutamate,
FFU Fluorescent focus units, IP Investigational product, SP Sucrose phosphate, *ts* Temperature-sensitive

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

• Study D2560C00006 – A Phase 3 randomised, double-blind study to evaluate the efficacy and safety of MEDI3250 compared to placebo in healthy Japanese children age 7 years through 18 years.

2.3.2. Clinical study

Study D2560C00006 – A Phase 3 randomised, double-blind study to evaluate the efficacy and safety of MEDI3250 compared to placebo in healthy Japanese children age 7 years through 18 years.

Description

This was a phase III, double-blind, randomised, multicentre study in Japan with two groups (N=868 in the vaccine group; N=433 in the control group per group). Subjects received one dose, but children aged 7–8 years not previously vaccinated against seasonal influenza received a second dose after an interval of at least 4 weeks.

No blood samples were collected.

The first subject was enrolled in the study on 24 Oct 2014 and the last study visit was on 02 May 2015.

Methods

Objectives

Primary objective

Efficacy

- To assess the efficacy (the incidence of laboratory-confirmed influenza infection caused by any community-acquired wild-type strains matched to the vaccine) of MEDI3250 compared to placebo.

Safety

- To assess the safety and tolerability of MEDI3250 compared to placebo.

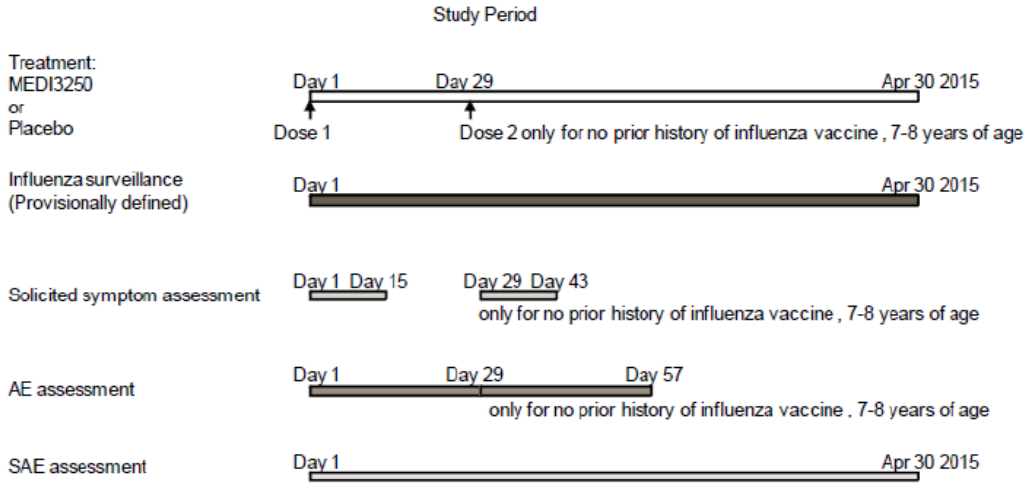
Secondary objective

Efficacy

- To assess the efficacy (the incidence of laboratory-confirmed influenza infection caused by any community-acquired wild-type strains regardless of match to the vaccine) of MEDI3250 compared to placebo

Study design

Phase III, double-blind, randomised, multicentre study in Japan.



Study population

Inclusion criteria

- Aged 7 through 18 years at the time of randomisation.
- Written informed consent was obtained from the subject's legally acceptable representative, and a written informed assent was obtained from the subject if possible.
- Available for illness visits at clinic during the influenza surveillance period.
- Ability of the legal representative to understand and comply with the requirements of the CSP.
- Parent/guardian available by telephone, email, etc.
- Females of childbearing potential, unless surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), had sterile male partner, were premenarchal, or practiced abstinence, had to have used an effective method of avoiding pregnancy (including oral, transdermal, or implanted contraceptives, intrauterine device, female condom with spermicide, diaphragm with spermicide, cervical cap with spermicide, or use of a condom with spermicide by the sexual partner) for 30 days prior to the first dose of the IP, and had to agree to continue using such precautions for 60 days after the final dose of the IP.
- A subject who was considered by the investigator to be at risk of pregnancy had to also have a negative urine pregnancy test at screening and, if screening and Day 0 did not occur on the same day, on the day of vaccination prior to randomisation. Investigator judgment was required to assess each subject's need for pregnancy testing.
- Healthy by medical history and physical examination OR presence of stable underlying chronic medical condition for which hospitalisation had not been required in the previous year.

Exclusion criteria

- Subjects who were previously administered influenza vaccine in the 2014–2015 influenza season.
- Previous randomisation in the present study.
- Participation in another clinical study with an IP during the last 3 months.
- Acute illness or evidence of significant active infection at randomisation.

- Fever ≥99.5°F (37.5°C) at randomisation.
- Any drug therapy from 15 days prior to randomisation or expected drug therapy through 28 days after the last dose with the exception of the following classes/types of medications, which are allowed:
    - Contraceptives (change in contraceptive type or method was acceptable as long as guidelines were followed for prevention of pregnancy during change)
    - Topical corticosteroids, topical calcineurin inhibitors, or antifungals for uncomplicated dermatitis
    - Chronic medications (including those taken on an as-needed basis) that had been well tolerated and were not initiated and/or did not have a dosage change within 90 days prior to randomisation
- Current or expected receipt of immunosuppressive medications within a 28-day window around any dose, including an immunosuppressive dose of corticosteroids, which was defined as ☐20 mg/day of prednisone or its equivalent, given daily or on alternate days for ☐15 days (intranasal, intra-articular, and topical corticosteroids were permitted). Note: topical corticosteroids for uncomplicated dermatitis could be used throughout the study according to the judgment of the investigator; topical calcineurin inhibitors could be used in accordance with their package insert at entry and during study participation.
- Any known immunosuppressive condition or immune deficiency disease including known or suspected infection with human immunodeficiency virus (HIV).
- History of allergic disease or reactions likely to be exacerbated by any component of the IP including allergy to eggs, egg proteins, gentamicin, or gelatin or serious, life threatening, or severe reactions to previous influenza vaccinations.
- Use of aspirin or salicylate-containing medications within 28 days prior to randomisation or expected receipt through the entire study.
- History of Guillain-Barré syndrome.
- Use of antiviral agents with activity against influenza virus (including amantadine, rimantadine, oseltamivir, and zanamivir) within 28 days prior to first dose of the IP or anticipated use of such agents in the study period.
- Administration of any live virus vaccine within 30 days prior to enrolment, or if receipt of another live virus vaccine was expected within 30 days of any study vaccination.
- Administration of any inactivated vaccine within 14 days prior to enrolment or if receipt of another inactivated vaccine was expected within 14 days of any study vaccination.
- eceipt of any blood product within 90 days prior to vaccination or expected receipt during this study.
- Pregnant or lactating female.
- Involvement in the planning and conduct of the study (applicable to all AstraZeneca staff and staff at the study site as a legal representative).
- Any condition that, in the opinion of the investigator, could interfere with the interpretation or evaluation of the vaccines.

Sample size

A total sample size of 1008 subjects (MEDI3250: placebo = 672:336) resulting in the PP population of at least 957 subjects provided at least 90% power (i.e., lower bound of two-sided 95% CI for vaccine efficacy lies above zero) to detect vaccine efficacy of 70% for MEDI3250 relative to placebo assuming underlying event rates of 1.8% for MEDI3250 and 6% for placebo.

Table 2. Subject disposition (all enrolled subjects)

	MEDI3250 n (%)	Placebo n (%)	Total n (%)
Number of subjects who provided informed consent	-	-	1,369
Number of subjects not randomized	-	-	68
Not eligible from entry criteria	-	-	0
Loss of follow-up	-	-	0
Withdrawal of consent	-	-	0
Others	-	-	68
Number of subjects randomized	868	433	1,301
Number of subjects vaccinated	868 (100.0)	433 (100.0)	1,301 (100.0)
Number of subjects not vaccinated	0 (0.0)	0 (0.0)	0 (0.0)
Number of subjects excluded from PP population	19 (2.2)	3 (0.7)	22 (1.7)
Number of subjects with important protocol deviation	11 (1.3)	2 (0.5)	13 (1.0)
Subjects excluded from PP population due to issue for efficacy assessment [a)]	8 (0.9)	2 (0.5)	10 (0.8)
Data analysis set			
Intention-to-treat population	868 (100.0)	433 (100.0)	1,301 (100.0)
Per protocol population	849 (97.8)	430 (99.3)	1,279 (98.3)
Safety population	868 (100.0)	433 (100.0)	1,301 (100.0)
Number of subjects withdrawn from the study	3 (0.3)	1 (0.2)	4 (0.3)
Number of subjects who completed the study	865 (99.7)	432 (99.8)	1,297 (99.7)

Source: Appendix 12.2.1, Appendix 12.2.2 and Appendix 12.2.3
n (%): The number of subjects and the percentage
a) Subjects who received anti-viral agents effective against influenza within 14 days after IP administration were excluded from the PP population.

Treatments

For children aged 7 through 18 years, the recommended dosage schedule for intranasal administration was 0.2 mL (0.1 mL per nostril). For children aged 7 to 8 years not previously vaccinated against seasonal influenza, the second dose was given after an interval of at least 4 weeks.

Table 3. Doses and treatment regimens

Age	IP	Dose and dosing frequency	Route of administration	Criterion to decide the dose number	First dose	Second dose
7-8	MEDI3250 or placebo	0.1 mL twice	Nasal	No previous vaccination against seasonal influenza	Dosing	Dosing
				Previously vaccinated against seasonal influenza	Dosing	Not given
9-18	MEDI3250 or placebo	0.1 mL twice	Nasal	None	Dosing	Not given

IP Investigational product

Endpoints

Primary endpoint

Efficacy

- The vaccine efficacy of MEDI3250 compared to placebo against the incidence of laboratory-confirmed symptomatic influenza infection caused by any community-acquired wild-type strains matched to the vaccine, occurring during the influenza surveillance period at least 14 days after the last required vaccination. For the primary endpoint, laboratory-confirmed symptomatic influenza infection is defined as the presence of modified CDC-ILI associated with laboratory-confirmed influenza. Modified CDC-ILI is defined as increased temperature ≥100°F (37.8°C) oral or equivalent plus the presence of cough, sore throat, or runny nose/nasal congestion occurring on the same or consecutive days.

Safety

- The reporting period for solicited symptoms for subjects receiving a single dose was IP administration to 14 days after dosing. The reporting period for solicited symptoms for subjects receiving 2 doses was IP administration to 14 days after each dose. Solicited symptoms are events that are considered likely to occur post-dose. For this study, solicited symptoms included: fever ≥100.4°F (38.0°C) by any route; runny/stuffy nose; sore throat; cough; headache; generalised muscle aches; decreased activity level (lethargy) OR tiredness/weakness; decreased appetite

Case definitions

Definition of results of laboratory- confirmed influenza test

Nasal swabs were evaluated for influenza using a PCR-based test. Genotyping, subtyping and sequencing were performed. The results of each test were classified as follows:

Genotyping test: wild type (WT), cold adapted (CA), wild type and cold adapted (MIX) and negative

Subtyping test: strain A/H1N1 (H1), strain A/H3N2 (H3), strain B/Yamagata (BY), strain B/Victoria (BV), and not determined (ND)

Sequencing test: vaccine like (VL), non-vaccine like (NVL) and ND

Isolates that were classified as WT, MIX by the genotyping test were included under the category of influenza due to all strains regardless of match. Isolates that were classified as CA or ND by the genotyping test, and isolates from specimens collected within 14 days post vaccination that were positive for WT influenza virus were not included in the analyses of the study's primary or secondary endpoints.

In the subtype analysis, influenza infection was classified as H1, H3, BY or BV by subtyping. A positive result for influenza due to any vaccine- matched strain was defined as only cases classified as VL by sequencing. Influenza due to mismatched strains was defined as those cases classified as NVL by sequencing.

Statistical Methods

The primary analysis of the primary endpoint was assessed in the PP population. A sensitivity analysis of the primary endpoint was performed in the ITT population.

Vaccine efficacy was designated as laboratory-confirmed symptomatic influenza infection caused by any community-acquired wild-type strains matched to the vaccine, occurring during the influenza surveillance period. The primary endpoint was defined as the rate of laboratory-confirmed symptomatic influenza infection with the presence of modified influenza-like illness per CDC-ILI associated with laboratory-confirmed influenza, and the infection rate in MEDI3250 recipients was compared to that in placebo recipients. Modified CDC-ILI was defined as increased temperature ≥100° F (37.8° C) oral or equivalent plus the presence of cough, sore throat, or runny nose/nasal congestion occurring on the same or consecutive days. Laboratory-confirmed symptomatic influenza infection reported from the time of vaccination through 14 days after the last required vaccination was to be excluded from the analysis of primary variable.

The primary endpoint was evaluated by constructing 2-sided 95% confidence interval (CI) for vaccine efficacy of MEDI3250 compared to placebo. The CI was estimated by an exact conditional method conditioning on the total number of cases which followed a Poisson assumption.

Results

Analysis of demographics / baseline characteristics

Table 4. Summary of demographic characteristics (ITT population)

Characteristics (unit)	Statistic	MEDI3250 (N=868)	Placebo (N=433)	Total (N=1,301)
Age (years)	n	868	433	1,301
	Mean	11.0	10.8	10.9
	SD	3.0	2.8	2.9
	Median	11.0	10.0	10.0
	Minimum	7	7	7
	Maximum	18	18	18
Age category (years)				
7–8	n (%)	215 (24.8)	104 (24.0)	319 (24.5)
9–18	n (%)	653 (75.2)	329 (76.0)	982 (75.5)
Sex				
Male	n (%)	460 (53.0)	207 (47.8)	667 (51.3)
Female	n (%)	408 (47.0)	226 (52.2)	634 (48.7)
Number of Doses of Study Vaccine Received				
1	n (%)	841 (96.9)	421 (97.2)	1,262 (97.0)
2	n (%)	27 (3.1)	12 (2.8)	39 (3.0)
Prior Influenza Vaccination				
Yes	n (%)	788 (90.8)	386 (89.1)	1,174 (90.2)
No	n (%)	80 (9.2)	47 (10.9)	127 (9.8)
Prior Influenza vaccination among subjects age 7–8 years				
Age 7–8 years old		215	104	319
With prior vaccination [a)]	n (%)	188 (87.4)	92 (88.5)	280 (87.8)
Without prior vaccination [a)]	n (%)	27 (12.6)	12 (11.5)	39 (12.2)
Medical history/concurrent illness				
Yes	n (%)	282 (32.5)	123 (28.4)	405 (31.1)
No	n (%)	586 (67.5)	310 (71.6)	896 (68.9)

Source: Appendix 12.2.4
n (%): The number of subjects and the percentage

A total of 1,301 subjects were randomized to either the MEDI3250 or placebo group at a 2:1 ratio and received the IP at 49 study centres in Japan. The number of subjects randomized was 868 subjects in the MEDI3250 group and 433 subjects in the placebo group.

CHMP's comment

There were no notable differences in demographic and other baseline characteristics between the MEDI3250 and placebo groups.

Efficacy results

- *Primary efficacy endpoint (vaccine efficacy: influenza caused by matched strains)*

Table 5. Summary of number and results of swab samples collected for PCR-confirmed influenza test collected from vaccination through the end of the 2014–2015 influenza season (PP population)

	MEDI3250 (N=849)		Placebo (N=430)		Total (N=1,279)	
	n (%)	No. of samples	n (%)	No. of samples	n (%)	No. of samples
Total number of samples collected	532 (62.7)	938	299 (69.5)	550	831 (65.0)	1488
Total number of samples collected within 14 days	86 (10.1)	90	49 (11.4)	52	135 (10.6)	142
Total number of samples collected after at least 14 days	513 (60.4)	848	288 (67.0)	498	801 (62.6)	1346
Total number of positive samples collected [a)]	242 (28.5)	259	150 (34.9)	157	392 (30.6)	416
Total number of positive samples collected within 14 days [a)]	33 (3.9)	33	1 (0.2)	1	34 (2.7)	34
Total number of positive samples collected after at least 14 days [a)]	220 (25.9)	226	149 (34.7)	156	369 (28.9)	382

Source: Appendix 12.2.6
The number of swab samples collected from vaccination through the end of the 2014–2015 influenza season and their results are summarised.
n (%): The number of subjects and the percentage
a): Positive result was defined as a subject with wild type (WT), cold adapted (CA) or WT & CA (MIX) by genotyping.

In the PP population, swab samples for PCR-confirmed virus tests (genotyping, subtyping and sequencing test) were collected from 532 subjects (62.7%) in the MEDI3250 group and from 299 subjects (69.5%) in the placebo group through the end of the 2014–2015 influenza season. Of these subjects, the number of subjects from whom swab samples were collected at least 14 days after vaccination was 513 subjects (60.4%) and 288 subjects (67.0%), respectively. Positive results from swab samples collected at least 14 days after vaccination were reported in 220 subjects (25.9%) in the MEDI3250 group and 149 subjects (34.7%) in the placebo group.

Table 6. Summary of laboratory confirmed PCR-based influenza virus test (PP population)

	MEDI3250 (N=849)		Placebo (N=430)	
	n (%)	Number of samples	n (%)	Number of samples
The number of subjects and swab samples	220 (25.9)	226	149 (34.7)	156
Genotyping				
Wild type	219 (25.8)	225	149 (34.7)	156
Cold adapted	1 (0.1)	1	0 (0.0)	0
Wild type and cold adapted	0 (0.0)	0	0 (0.0)	0
Negative	0 (0.0)	0	0 (0.0)	0
Subtyping/Sequencing [a)]				
Strain A/H1N1				
Vaccine-like	0 (0.0)	0	0 (0.0)	0
Non-vaccine like	0 (0.0)	0	0 (0.0)	0
Not determined	0 (0.0)	0	0 (0.0)	0
Strain A/H3N2				
Vaccine-like	0 (0.0)	0	0 (0.0)	0
Non-vaccine like	211 (24.9)	217	141 (32.8)	145
Not determined	3 (0.4)	3	0 (0.0)	0
Strain B/Yamagata				
Vaccine-like	0 (0.0)	0	1 (0.2)	1
Non-vaccine like	4 (0.5)	4	5 (1.2)	5
Not determined	1 (0.1)	1	2 (0.5)	2
Strain B/Victoria				
Vaccine-like	0 (0.0)	0	0 (0.0)	0
Non-vaccine like	0 (0.0)	0	0 (0.0)	0
Not determined	0 (0.0)	0	0 (0.0)	0
Not determined/Not determined	0 (0.0)	0	3 (0.7)	3

Source: Appendix 12.2.6
Laboratory confirmed PCR-based influenza virus test was summarised based upon the results of samples collected through the end of the 2014–2015 influenza season and collected at least 14 days after the last required vaccination.
n (%): The number of subjects and the percentage
a): The results were summarised by strain only for samples which were classified as wild type (WT) by genotyping.

Of the swab samples which were classified as influenza positive and which were subtyped and sequenced, only one vaccine-like isolate (matched strain) from the B/Yamagata lineage was detected. No other vaccine-matched strains were isolated.

The majority of isolates detected were non-vaccine like (mismatched) A/H3N2 strains and this subtype was detected in 211 subjects (24.9%) in the MEDI3250 group and 141 subjects (32.8%) in the placebo group. Additionally, B/Yamagata lineage non-vaccine like (mismatched) isolates were detected in 4 subjects (0.5%) in the MEDI3250 group and in 5 subjects (1.2%) in the placebo group. For 3 A/H3N2 strains (3 in the MEDI3250 group) and 3 B/Yamagata strains (one in the MEDI3250 group and 2 in the placebo group), match to vaccine strains could not be determined through sequencing.

Table 7. Vaccine efficacy against matched strains (PP population)

	MEDI3250 (N=849)	Placebo (N=430)	Vaccine Efficacy
	n (%)	n (%)	% (95% CI)
Influenza Attacked (Matched Strains)			
Yes	0 (0.0)	1 (0.2)	100.0 (-1875.3, 100.0)
No	849 (100.0)	429 (99.8)	
Type of matched influenza strains			
Strain A/H1N1			
Yes	0 (0.0)	0 (0.0)	- (- , -)
No	849 (100.0)	430 (100.0)	
Strain A/H3N2			
Yes	0 (0.0)	0 (0.0)	- (- , -)
No	849 (100.0)	430 (100.0)	
Strain B/Yamagata			
Yes	0 (0.0)	1 (0.2)	100.0 (-1875.3, 100.0)
No	849 (100.0)	429 (99.8)	
Strain B/Victoria			
Yes	0 (0.0)	0 (0.0)	- (- , -)
No	849 (100.0)	430 (100.0)	

Source: Appendix 12.2.6
n (%): The number of subjects and the percentage
CI: Confidence interval (2-sided)
Vaccine-matched strains were defined as only cases classified as vaccine like (VL) by sequencing for samples collected at least 14 days after the last required vaccination through the end of the 2014–2015 influenza season.

Influenza caused by any vaccine-matched strain was reported in only one out of 430 subjects (0.2%) in the placebo group. This subject was infected with a B/Yamagata lineage strain. No subjects in the MEDI3250 group had influenza caused by a matched strain during the surveillance period. A point estimate of vaccine efficacy (2-sided 95% CI), calculated by the method described in Section 5.7.2.2, was 100.0% (-1875.3, 100.0).

CHMP's comment

The majority of influenza isolates detected during the study were mismatched A/H3N2 strains. A single matched strain from the B/Yamagata lineage was detected in the placebo group during the study. The point estimate of vaccine efficacy was 100% for any matched strain but did not reach statistical significance (95% CI: -1875.3, 100.0). Thus, the study did not meet its primary endpoint, vaccine efficacy against strains matched to vaccine, as only one matched strain circulated.

- *Secondary endpoint (vaccine efficacy: influenza caused by all strains regardless of match)*

Table 8. Vaccine efficacy for all strains regardless of match (PP population)

	MEDI3250 (N=849)	Placebo (N=430)	Vaccine Efficacy
	n (%)	n (%)	% (95% CI)
Influenza Attacked (Any Strain)[a)]			
Yes	219 (25.8)	149 (34.7)	25.6 (7.7, 39.8)
No	630 (74.2)	281 (65.3)	

Source: Appendix 12.2.6
n (%): The number of subjects and the percentage
CI: Confidence interval (2-sided)
a): Influenza caused by any strain was defined as cases classified as wild type (WT), or wild type & cold adapted (MIX) by genotyping.

In the PP population, the incidence of influenza caused by all strains regardless of match to the vaccine was 25.8% (219/849 subjects) in the MEDI3250 group and 34.7% (149/430 subjects) in the placebo group. The point estimate of vaccine efficacy (2-sided 95% CI) for all strains regardless of match was 25.6% (7.7, 39.8). This is a notable achievement as, according to the recent reports (CDC, 2015; Katz, 2015), the majority of the strains that circulated were highly mismatched A/H3N2 strains with 8-fold to 32-fold antigenic variation to the vaccine strain based on ferret anti-sera during the 2014–2015 influenza season in the United State. Worldwide the 2014–2015 influenza season also was characterized by circulation of A/H3N2 strains from clades 3C.3A and 3C.2A that were highly mismatched to the vaccine A/Texas/50/2012 strain (clade 3C.1).

CHMP's comment

The study did meet its secondary endpoint demonstrating statistically significant vaccine effectiveness against all strains regardless of match with the point estimate of vaccine efficacy of 25.6% (95% CI: 7.7, 39.8).

- *Subgroup analyses*

Table 9. Summary of subgroup analyses on secondary efficacy endpoint (PP population)

Sub-group	Influenza Attacked	MEDI3250 (N=849) n (%)	Placebo (N=430) n (%)	Vaccine efficacy % (95% CI)
Age				
7–8 years		211	103	
	Yes	72 (34.1)	50 (48.5)	29.7 (-2.9 , 51.7)
	No	139 (65.9)	53 (51.5)	
9–18 years		638	327	
	Yes	147 (23.0)	99 (30.3)	23.9 (0.8 , 41.4)
	No	491 (77.0)	228 (69.7)	
Sex				
Male		451	206	
	Yes	125 (27.7)	71 (34.5)	19.6 (-9.2 , 40.4)
	No	326 (72.3)	135 (65.5)	
Female		398	224	
	Yes	94 (23.6)	78 (34.8)	32.2 (7.2 , 50.3)
	No	304 (76.4)	146 (65.2)	
Prior vaccination				
With prior vaccination		770	383	
	Yes	205 (26.6)	137 (35.8)	25.6 (6.9 , 40.3)
	No	565 (73.4)	246 (64.2)	
Without prior vaccination		79	47	
	Yes	14 (17.7)	12 (25.5)	30.6 (-64.3 , 70.2)
	No	65 (82.3)	35 (74.5)	

Source: Appendix 12.2.6
n (%): The number of subjects and the percentage
CI: Confidence interval (2-sided)
Influenza attacked for the secondary efficacy endpoint was defined as cases infected by all strains regardless of match (i.e., cases classified as wild type (WT), or wild type & cold adapted (MIX) by genotyping).

In the subgroup analyses using the primary efficacy endpoint, no particular findings were noted because only a single matched strain was isolated during the study. In the subgroup analyses using the secondary efficacy endpoint, statistically significant vaccine efficacy was observed with a point estimate of 23.9% (2 sided 95% CI: 0.8, 41.4) for the subgroup of subjects 9 through 18 years of age, 32.2% (2 sided 95% CI: 7.2, 50.3) for female subjects, and 25.6% (2 sided 95% CI: 6.9, 40.3) for subjects with a history of prior vaccination. For other strata, similar vaccine efficacies of 20 to 30% were noted though they did not reach statistical significance.

The results for the ITT population were similar to those for the PP population.

CHMP's comment

No particular findings regarding vaccine efficacy were observed from the result of subgroup analyses of the primary endpoint by age, sex and prior vaccination, as only a single vaccine matched strain was isolated. In subgroup analyses performed for the secondary endpoint, no obvious interactions between vaccine efficacy and each stratum were noted.

Safety results

The mean (SD) and median (range: min–max) follow-up periods were 189.1 days (8.8) and 190.0 days (30–191) in the MEDI3250 group, and 189.4 days (6.4 days) and 190.0 days (57–191) in the placebo group.

Table 10. Follow-up period (safety population)

	Statistic	MEDI3250 (N=868)	Placebo (N=433)	Total (N=1,301)
Follow up days	Mean	189.1	189.4	189.2
	SD	8.8	6.4	8.1
	Median	190.0	190.0	190.0
	Range	30–191	57–191	30–191

Source: Appendix 12.2.1
SD: Standard deviation
Range: min–max
Follow-up period was defined as total days from first vaccination through the end of the 2014–2015 influenza season (provisionally, up to 30 April 2015, but, the actual date on the last visit of the last subject was 2 May 2015).

- *Solicited local and general adverse events*

The overall incidence of subjects with any solicited symptom was 41.7% (362/868 subjects) in the MEDI3250 group and 40.6% (176/433 subjects) in the placebo group. The rate difference (2-sided 95% CI) between groups was 1.1% (-4.7, 6.7) and there was no notable difference in the incidence of solicited symptoms between the MEDI3250 and placebo groups. Subgroup analysis of solicited symptoms by age, and the number of vaccinations received showed no obvious differences between groups.

The most common solicited symptoms (≥10% in either group) were runny/stuffy nose (33.2%), cough (12.4%) and sore throat (10.1%) in the MEDI3250 group, and runny/stuffy nose (27.7%), cough (15.9%) and sore throat (14.1%) in the placebo group. The incidence rates for individual symptoms were similar between groups, except for a slightly higher incidence of runny/stuffy nose in the MEDI3250 group (rate difference: 5.5%, 2-sided 95% CI: 0.1, 10.6).

Table 11. Summary of solicited symptoms by age and dose number (safety population)

	MEDI3250 (N=868)			Placebo (N=433)		
	Age 7-8 (N=215)		Age 9-18	Age 7-8 (N=104)		Age 9-18
	After 1st Dose (N=215) n (%)	After 2nd Dose (N=27) n (%)	(N=653) n (%)	After 1st Dose (N=104) n (%)	After 2nd Dose (N=12) n (%)	(N=329) n (%)
Number of subjects without Solicited Symptoms	117 (54.4)	21 (77.8)	390 (59.7)	55 (52.9)	9 (75.0)	204 (62.0)
Number of subjects with any Solicited Symptom [a)]	98 (45.6)	6 (22.2)	263 (40.3)	49 (47.1)	3 (25.0)	125 (38.0)
Temperature(Fever ≥100.4°F (38.0°C) by any route)	13 (6.0)	1 (3.7)	12 (1.8)	5 (4.8)	0 (0.0)	7 (2.1)
Runny/Stuffy nose	77 (35.8)	5 (18.5)	210 (32.2)	32 (30.8)	1 (8.3)	88 (26.7)
Sore throat	17 (7.9)	1 (3.7)	70 (10.7)	16 (15.4)	1 (8.3)	44 (13.4)
Cough	32 (14.9)	4 (14.8)	73 (11.2)	20 (19.2)	2 (16.7)	47 (14.3)
Headache	21 (9.8)	1 (3.7)	61 (9.3)	8 (7.7)	1 (8.3)	28 (8.5)
Generalized muscle aches	2 (0.9)	0 (0.0)	7 (1.1)	1 (1.0)	0 (0.0)	1 (0.3)
Decreased activity level (lethargy) OR tiredness/weakness	10 (4.7)	0 (0.0)	27 (4.1)	2 (1.9)	0 (0.0)	9 (2.7)
Decreased appetite	7 (3.3)	0 (0.0)	13 (2.0)	5 (4.8)	1 (8.3)	4 (1.2)

Source: Appendix 12.2.10
Note: Solicited symptoms recorded for 14 days after each vaccination were summarised.
Note: The number of subjects without solicited symptoms shows the number of subjects who had no solicited symptoms recorded for 14 days after vaccination.
a): A subject with at least one solicited symptom was counted once.
n (%): The number of subjects and the percentage

- *TEAEs (treatment-emergent adverse event)*

A treatment-emergent adverse event (TEAE) was defined as the development of an undesirable medical condition or the deterioration of a pre-existing medical condition during the 28 days (+7 days) after the last dose of the IP, whether or not considered causally related to the IP.

In subgroup analysis by age and dose number for AEs, no clear difference in the incidence of TEAEs was observed between groups in each stratum. But, the incidence of TEAEs in children 7–8 years of age was slightly higher than that in children 9 through 18 years of age for both the MEDI3250 and placebo groups. The incidence of TEAEs in the MEDI3250 group was 28.8% (62/215 subjects) after the first dose and 33.3% (9/27 subjects) after the second dose in subjects aged 7–8 years, and 21.6% (141/653 subjects) in subjects aged 9 through 18 years. The incidence rates for TEAEs in the corresponding age groups in the placebo group were 36.5% (38/104 subjects), 25.0% (3/12 subjects) and 21.9% (72/329 subjects), respectively.

A total of 5 TEAEs related to the vaccine were noted during the study. They were cough, nasal discomfort, diarrhoea and urticaria each in one subject in the MEDI3250 group, and nasopharyngitis in one subject in the placebo group. All TEAEs related to the IP were mild in intensity and were confirmed to have resolved.

- *SAEs*

No fatal events were reported in this study. SAEs were reported in 6 subjects (3 in the MEDI3250 group and 3 in the placebo group). All SAEs were noted in subjects aged 9 through 18 years and none were considered to be related to IP administration. Only one SAE, in the placebo group, was a TESAE which was defined as an event reported after IP administration through 28 days after the last dose. No TEAEs leading to death or study discontinuation were reported.

CHMP's comment

The generated safety data are consistent with previous data on Fluenz Tetra, generated during the influenza surveillance period of about 6 months (ca. 189 days).

2.3.3. Discussion on clinical aspects

This phase III randomized, double-blind, placebo controlled trial in 1301 subjects aged 7-18 years in Japan confirms the safety profile of Fluenz Tetra, but efficacy against matching strains could not be demonstrated, due to ciculation of mismatched strains. In the 2014-2015 influenza season, the majority of influenza isolates detected during the study were mismatched A/H3N2 strains.

The study did not meet its primary efficacy endpoint, efficacy against matched strains, as only a single vaccine-matched strain was recovered during the study. The study did meet its secondary endpoint, efficacy against all strains regardless of match, though the efficacy estimate was somewhat low, i.e. 25.6% (95% CI: 7.7, 39.8), due to the fact that the majority of circulating strains were highly mismatched to the vaccine strains.

The safety profile of Q/LAIV was comparable to that of placebo, and vaccination was demonstrated to be safe and well tolerated in Japanese children aged 7 to 18 years, and in line with the earlier clinical trial data.

The Safety data regarding use of Fluenz Tetra was originally based on data from Fluenz Tetra clinical studies in 1,382 children and adolescents 2 to 17 years of age. With this study the safety database is enlarged with 849 subjects Fluenz Tetra recipients. The Rapporteur therefore requests an update of section 4.8 of the SmPC, in particular of the safety summary.

3. CHMP overall conclusion and recommendation

Overall conclusion

The article 46 paediatric submission is considered fulfilled but regulatory action is required to update section 4.8 of the SmPC.

The provided data do not cause concern regarding efficacy or safety of Fluenz Tetra.

The benefit/risk balance of Fluenz Tetra therefore remains positive.

Recommendation

☒ Fulfilled:

The following regulatory action is required:

The MAH is requested to update Section 4.8 of the SmPC, in particular the safety summary.