COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Efluelda, suspension for injection in pre-filled syringe

(quadrivalent influenza vaccine [split virion, inactivated], 60 micrograms HA/strain)

NL/H/4757/001/DC

Date: 8 October 2020

This module reflects the scientific discussion for the approval of Efluelda, suspension for injection in pre-filled syringe The procedure was finalised on 1 April 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ADEM	Acute Disseminated Encephalomyelitis
AE	Adverse Event
AMI	Acute Myocardial Infarction
ARR	Adjusted Relative Risk
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMI	Cell-mediated Immunity
ELLA	Enzyme-Linked Lectin Assay
ERA	Environmental Risk Assessment
FAS	Full Analysis Set
FFS	Fee-for-Service
GMT	Geometric Mean Titre
GMTr	Geometric Mean Titre ratio
HA	Haemagglutinin
HAI	Haemagglutination Inhibition
ICH	International Conference of Harmonisation
ILI	Influenza-like Illness
IM	Intramuscular
MAH	Marketing Authorisation Holder
NA	Neuraminidase
PCR	Polymerase Chain Reaction
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PPAS	Per-Protocol Analysis Set
QIV-HD	High-dose Quadrivalent Influenza Vaccine
QIV-SD	Standard-dose Quadrivalent Influenza Vaccine
RNA	Ribonucleic Acid
RR	Rate Ratio / Relative isk
rVE	Relative Vaccine Effectiveness
RMP	Risk Management Plan
SAE	Serious Adverse Event
SC	Subcutaneous
SCR	Seroconversion Rates
SD	Standard-dose
SmPC	Summary of Product Characteristics
SN	Seroneutralisation
SOC	System-Organ Class
TIV-HD	High-dose trivalent influenza vaccine
TIV-SD	Standard-dose Trivalent Influenza Vaccine
WHO	World Health Organization

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Efluelda, suspension for injection in pre-filled syringe from Sanofi Pasteur.

The product is indicated for active immunisation in adults 65 years of age and older for the prevention of influenza disease.
The use of Efluelda should be based in accordance with official recommendations on vaccination against influenza.

A comprehensive description of the indications and posology is given in the SmPC.

Influenza is caused by influenza type A and type B viruses, which belong to the genus Orthomyxoviridae and are characterized as enveloped, negative strand, segmented ribonucleic acid (RNA) viruses. The viral envelope contains two major virus-coded glycoproteins, haemagglutinin (HA) and neuraminidase (NA), which form spikes on the virus surface and are key antigens in the host response to influenza in both natural infection and vaccination.

This decentralised procedure concerns an application for a marketing authorization for high-dose quadrivalent inactivated influenza vaccine. The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

High dose
The effectiveness of the influenza vaccine in preventing or attenuating illness depends in part on the age and immune competence of the vaccine recipient. Currently, a standard-dose trivalent influenza vaccine (TIV-SD) contains 15 µg HA antigen of each of 3 virus strains as recommended for a given season, for a total of 45 µg antigen per dose. A standard-dose quadrivalent influenza vaccine (QIV-SD) also contains 15 µg HA antigen of each of 4 virus strains as recommended for a given season, for a total of 60 µg antigen per dose. The immune response to this standard-dose of influenza vaccine is sub-optimal in adults aged 65 years and older compared to younger adults.
Consequently, despite high vaccination rates, people aged 65 years and older may not have sufficient protection against influenza. Therefore, even if vaccination rates are high in older adults, this age group is at increased risk of developing influenza illness and its complications and a significant burden of influenza disease remains.

One approach to combat the observed decreased immune response to influenza vaccination in adults aged 65 years and older is to increase the antigen dose in the vaccine.

Thus, the MAH developed Fluzone High-Dose (TIV-HD) a trivalent influenza vaccine containing 60 µg HA of each of the virus strains for a total of 180 µg HA antigen per dose to improve immune responses to influenza vaccine in adults aged 65 years and older. TIV-HD was licensed in the US in 2009 on the basis of vaccine safety and immunogenicity with a commitment to conduct a confirmatory efficacy trial.

Quadrivalent vaccine
Since the 1980's, two distinct lineages of influenza B viruses have been circulating. Antigenic divergence between the two influenza B strains is significant, which is why there is limited cross reactivity between the two strains as assessed by haemagglutination-inhibiting and neutralizing antibody tests in animal models and in clinical trials. Until recently, influenza vaccines contained a single influenza B component. However co-circulation of the two lineages is common and the recommended B strain included in seasonal influenza vaccines was not the dominant circulating B lineage in approximately 25% of the seasons between 2000 and 2013.

To improve protection against the circulating B-strain that may not be included in the trivalent vaccines, as they contain one B strain from each of the Victoria and Yamagata lineages, the QIV vaccines eliminate the issue of having to choose a strain from only one B lineage and thus mitigate the resulting risk posed by the potential widespread circulation of a strain from the alternate B lineage not contained in the trivalent influenza vaccines.

<u>Development programme/compliance with CHMP guidance</u>
Development of the high-dose influenza vaccine started with a trivalent formulation (Fluzone High-Dose vaccine, hereafter referred to as TIV-HD), which has been licensed in the US since 2009, and was subsequently licensed in Canada, Australia, Brazil, and the United Kingdom (UK).

The clinical data package includes the following:

Clinical data generated with TIV-HD in persons 65 years of age and older in order to demonstrate:
- high dose of HA (60 µg per strain) improved immunogenicity of influenza vaccine, with an acceptable safety profile (Study FIM01)
- superior immune responses compared with TIV-Standard Dose (TIV-SD) (15 µg of HA per strain) (Study FIM05)
- improved protection against influenza compared with TIV-SD (Study FIM12) as well as clinical study effectiveness and real world effectiveness data
- tolerance of TIV-HD based on Study FIM05. Serious adverse events (SAEs) were also analysed in Studies FIM01, FIM05, FIM12, and FIM07

Clinical data to demonstrate non-inferior immunogenicity and similar safety profile of Efluelda compared with TIV-HD in adults 65 years of age and older (Study QHD00013; bridging of the TIV-HD clinical dossier to Efluelda).

Scientific advice

Scientific advice was requested from CHMP in 2017 to address Quality, Non-Clinical, Clinical, and Labelling questions. The advice was adopted by the Committee for Medicinal Products for Human Use (CHMP) on 18 May 2017 (EMEA/H/SA/3560/1/2017/III).

Paediatric development

A second scientific advice was requested to EMA on December 2017 to discuss the MAH's proposed Efluelda clinical paediatric development plan. The advice was adopted by the CHMP on 22 February 2018 (EMEA/H/SA/3560/2/2018/PED/III). The Paediatric Investigational Plan was adopted by the EMA on 04 January 2019 (EMA Decision P/0023/2019):

- A waiver was granted for the paediatric population from birth to less than 6 months of age and the immunocompetent paediatric population from 9 to less than 18 years of age on the grounds that the specific medicinal product does not represent a significant therapeutic benefit.
- For children from 6 months to less than 9 years of age and only the immunocompromised paediatric population from 9 years to less than 18 years of age, a deferral was agreed and the paediatric investigation plan should be completed by June 2027.

II. QUALITY ASPECTS

II.1 Introduction

Efluelda is a colourless opalescent liquid, containing quadrivalent influenza vaccine (split virion, inactivated), 60 micrograms HA/strain.

The vaccine contains influenza virus (inactivated, split) of the following strains*:

- A/Michigan/45/2015 (H1N1) pdm09-like strain (A/Michigan/45/2015, NYMC X-275) - 60 micrograms HA**
- A/Singapore/INFIMH-16-0019/2016 (H3N2)-like strain (A/Singapore/INFIMH-16-0019/2016, IVR-186) - 60 micrograms HA**
- B/Colorado/6/2017-like strain (B/Maryland/15/2016, NYMC BX-69A) - 60 micrograms HA**
- B/Phuket/3073/2013-like strain (B/Phuket/3073/2013, wild type) - 60 micrograms HA**

* propagated in embryonated chicken eggs
** haemagglutinin

0.7 ml of suspension for injection is packed in a Type I glass pre-filled syringe equipped with a bromobutyl rubber plunger stopper and a tip-cap.

The excipients are:

- sodium phosphate-buffered isotonic sodium chloride solution

  - sodium chloride
  - monobasic sodium phosphate
  - dibasic sodium phosphate
  - water for injections
- octoxinol-9

II.2 Drug Substance

The influenza drug substance is comprised of inactivated split viral particles prepared from influenza viruses propagated in embryonated chicken eggs. The final quadrivalent bulk is formulated with four influenza strains (one H1N1, one H3N2, and two B strains: one each from the Yamagata and Victoria lineages).

Manufacturing process

The manufacturing operation uses embryonated chicken eggs to produce monovalent concentrate (drug substance). The harvest fluid (egg allantoic fluid) that contains influenza virus is inactivated, purified, disrupted, concentrated and sterile filtered to produce drug substance. Concentrates, or concentrates of the same strains combined (pooled) to form a monovalent pool, are used to formulate the final bulk drug product.
The description of product-related and process related impurities of the drug substance manufacturing process is sufficient.
Batch results of several development stages are shown and specifications are easily met across all different stages of development and across the different influenza A and B strains.

Quality control of drug substance

The drug substance specifications are sufficiently justified. Batch results have been provided and specifications are easily met across the different stages of development and across the different influenza A and B strains.

Stability of drug substance

All long-term stability study results meet the acceptance criteria for the 9 lots of influenza drug substance when stored at 1°C to 5°C (long-term conditions). No acceptance criteria were applied to the samples stored at the accelerated condition (23°C to 27°C). Overall, the presented stability data support the claimed maximum holding time of 12 months for the drug substance when stored under the stated conditions at 1°C to 5°C.

II.3 Medicinal Product

Pharmaceutical development

Efluelda vaccine is formulated to contain 240 µg HA per 0.7 mL dose, in the ratio of 60 µg HA of each strain, representative of the four prototype strains. It also contains phosphate buffered saline and Triton X-100 which is claimed to stabilise/preserve the vaccine antigens. Efluelda vaccine does not contain a preservative. The strain composition of influenza vaccines is modified periodically to take into account the changes in the prevalent viruses causing influenza.

The vaccine was developed based on Fluzone High-Dose Trivalent Influenza Vaccine Drug Product (TIV-HD). In general, sufficient detailed information is provided about the pharmaceutical and manufacturing process development in support of the commercial product manufacturing. The choice of excipients is justified and their functions explained. As per request, the 'potency stabilizing' claim for the Triton X-100 has been further substantiated and a target concentration is set.

Manufacturing process

The drug product manufacturing process is a straightforward process comprising mixing of drug substance and buffer (with Triton X-100 if required), filtration, and filling into containers. The description is considered concise. Process parameters (and their ranges) are indicated. Overall, the process description is deemed sufficiently supported by the process development/validation.

Sufficient controls (process parameters, in-process controls) are set and the criticality of the process parameters (critical, controlled, key) has been established in the process development/validation. Process validation has been performed for both the formulation and filling process steps.

Control of excipients

The excipients sodium chloride, sodium phosphate dibasic and sodium phosphate monobasic are tested according to pharmacopoeia monograph (Ph.Eur., BP or USP). For the remaining excipients in-house specifications have been laid down. These specifications are acceptable.

Quality control of drug product

Release specifications are provided for the final bulk product, filled product and labelled product. Whilst the specifications are considered overall acceptable, the acceptance criteria for physical examination/appearance has been amended in line with Ph.Eur. requirements. In general, the analytical procedures for batch release and their validation are satisfactorily described. Batch analysis has been performed on three batches of final bulk product and filled product. The batch analysis results show that the finished products consistently meet the proposed specifications.

Stability of drug product

Overall, the presented stability data support the claimed maximum holding time of 6 months for the final bulk product and the 12 months shelf life for filled product when stored under the recommended storage conditions. It has been confirmed that the containers used for the final bulk product and filled product studied for stability are representative for the containers used for the commercial process/product.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

For production of the Influenza Virus Vaccine, from the Master Seed Lots (MSL) up to the Filled Product, no materials of animal origin covered by the EMA/410/01, 'Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products' are used.

The materials of animal origin not covered by EMA/410/01 used for the production of the vaccine are fertilized specified pathogens free eggs. The MAH may use other suppliers or hatcheries, provided the eggs meet the quality criteria detailed in the dossier section 'Control of Materials - Control of Source and Starting Materials of Biological Origin'.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Efluelda has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The member states agreed on a number of post-approval commitments to be fulfilled by the MAH.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Pharmacology studies were not performed with Efluelda. Considering the clinical experience with the influenza vaccine and the fact that the strains in the vaccine are recommended by the WHO, additional non-clinical studies to demonstrate the efficacy of the vaccine are not necessary.

Studies on secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug interactions have not been performed. In accordance with the Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014), these studies are considered not necessary.

III.2 Pharmacokinetics

Pharmacokinetics studies have not been performed with Efluelda. According to the Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014), studies to determine serum concentrations of antigens are not needed.

III.3 Toxicology

A repeat-dose toxicity study and a local tolerance study were performed, both in New-Zealand white rabbits.

In the repeat-dose study, rabbits received three intramuscular (IM) injections at 2-week intervals with the human dose of Efluelda. Injection site findings and an increase in the number of germinal centres in the spleen were observed as can be expected after intramuscular injection of a vaccine. After 3 doses, moderate inflammation and/or necrosis to muscle fibres were observed in some animals. This is however considered not clinically relevant because only one dose per year is recommended in the SmPC. After 1 and 2 injections, necrosis at the injection site was minimal and inflammation was minimal to slight.

In the local tolerance study, rabbits received one human subcutaneous (SC) dose of Efluelda. Only minimal to slight dermal inflammatory changes were observed at the injection site.

Genotoxicity and carcinogenicity studies were not performed because these studies are not required for influenza vaccines. Reproductive toxicity studies were not performed because the intended target population is 65 years and older. Also, considering the current knowledge regarding the use of influenza vaccines during pregnancy, it is not necessary to perform a reproductive toxicity study.

The total of worst-case exposure levels to leachables that were identified in the final container syringe presentation, did not exceed the acceptable total daily intake for multiple impurities according to ICH guideline M7.

III.4 Ecotoxicity/environmental risk assessment (ERA)

No studies are necessary. Because Efluelda contains inactivated, split virion, it is unlikely to result in a significant risk to the environment. According to the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev 1), vaccines are unlikely to result in a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tabular overview of clinical studies
An overview of pivotal and supportive clinical studies submitted is provided in Table 1.
In support of the current application for the indication of prevention of influenza in adults aged 65 and older, the MAH submitted a comprehensive data package.

Table 1. Overview of pivotal and supportive clinical studies in the development of Efluelda

Study ID	Countries	Design	Study Posology	Study Objective	Subjs by arm entered/compl.	Duration	Diagnosis Incl. criteria
Pivotal studies							
FIM12	United States and Canada;	Phase IIIb/IV, randomised, modified double-blind, active-controlled, multi-centre trial	Licensed TIV-HD: Dose: 0.5 mL containing 60 µg of HA from each strain (total of 180 µg) Licensed TIV-SD: Dose: 0.5 mL containing 15 µg of HA from each strain (total of 45 µg)	Efficacy of TIV-HD relative to TIV-SD with respect to laboratory-confirmed influenza, caused by any influenza viral types/subtypes, associated with a protocol-defined influenza-like illness (ILI).	Year 1: 14 500 subjects Licensed TIV-HD: 7254 subjects Licensed TIV-SD: 7246 subjects Year 2: 17 489 subjects Licensed TIV-HD: 8737 subjects Licensed TIV-SD: 8752 subjects	06 September 2011 to 31 May 2013	Healthy adults 65 years of age and older without moderate-to-severe acute illness
QHD00013	United States	Phase III, randomised, modified double-blind, active-controlled, multi-centre study	Efluelda: Dose: 0.7 mL containing 60 µg of HA from each strain (total of 240 µg) TIV-HD: Dose: 0.5 mL containing 60 µg of HA from each strain (total of 180 µg)	Non-inferiority of antibody responses to Efluelda compared with TIV-HDs as assessed by GMTs and seroconversion rates for the 4 virus strains at 28 days post-vaccination.	Efluelda: 1777 subjects Licensed TIV-HD1: 443 subjects Investigational TIV-HD2: 450 subjects	08 September 2017 to 19 April 2018	Healthy adults 65 years of age and older
Supportive Studies							
FIM01	United States	Phase II, prospective, randomised, double-blind, parallel, active controlled, multicentre trial	TIV-HD: Dose: 0.5 mL containing 60 µg of HA from each strain (total of 180 µg) Licensed TIV-SD: Dose: 0.5 mL containing 15 µg of HA from each strain (total of 45 µg)	Primary Objective: Immunogenicity of TIV-HD compared to TIV-SD. Secondary Objective: Reactogenicity according to freq. and severity of solicited local and systemic AEs.	TIV-HD: 207 subjects Licensed TIV-SD: 208 subjects	11 April 2005 to 28 November 2005	Ambulatory medically stable adults 65 years of age and older
FIM05	United States	Phase III, randomised,	TIV-HD: Dose: 0.5 mL containing	1) To demonstrate lot consistency of the	TIV-HD Total: 2575 subjects	09 October 2006 to 09 July	Medically stable adults 65 years of age

Study ID	Countries	Design	Study Posology	Study Objective	Subjs by arm entered/compl.	Duration	Diagnosis Incl. criteria
		double-blind, active-controlled, multi-centre trial	60 µg of HA from each strain (total of 180 µg) Licensed TIV-SD: Dose: 0.5 mL containing 15 µg of HA from each strain (total of 45 µg)	TIV-HD manufacturing process through evaluation of the immune responses elicited by 3 different lots at 1 month post-vaccination. 2) To demonstrate the superiority of TIV-HD (based on the pooled responses elicited by the 3 vaccine lots) compared to TIV-SD.	TIV-HD1: 857 TIV-HD2: 848 TIV-HD3: 870 Licensed TIV-SD: 1262 subjects	2007	and older
FIM07*	United States	Phase IIIb, randomised, double-blind, active controlled, multi-centre trial	TIV-HD: Dose: 0.5 mL containing 60 µg of HA from each strain (total of 180 µg) Licensed TIV-SD: Dose: 0.5 mL containing 15 µg of HA from each strain (total of 45 µg)	Relative efficacy of TIV-HD to that of TIV-SD in adults 65 years of age and older, with respect to laboratory confirmed influenza illness caused by viral types/subtypes antigenically similar to those contained in the respective annual vaccine formulations	TIV-HD: 6117 subjects Licensed TIV-SD: 3055 subjects	22 September 2009 to 28 May 2010	Ambulatory adults 65 years of age and older, without moderate or severe acute illnesses

Study ID	Countries	Design	Study Posology	Study Objective	Subjs by arm entered/compl.	Duration	Diagnosis Incl. criteria
QHD00008	Japan	Phase I/II, randomised, modified double-blind, multicentre study	Efluelda: Dose: 0.7 mL containing 60 µg of HA from each strain (total of 240 µg) Route: IM or SC QIV-SD (FLUBIK HA [local QIV-SD in Japan]): Dose: 0.5 mL containing 15 µg of HA from each strain (total of 60 µg) Route: SC	1) To describe the safety profile of subjects in each group. 2) To describe the immune responses induced by each group (as assessed by HAI GMTs and seroconversion rates) for the 4 common virus strains 28 days postvaccination.	Efluelda (IM): 60 subjects Efluelda (SC): 60 subjects QIV-SD (SC), Licensed in Japan: 55 subjects	15 September 2017 to 28 November 2017	Healthy adults 65 years of age and older

*terminated due to the 2009 H1N1 pandemic.

IV.2 Pharmacokinetics

There are no dedicated pharmacokinetic (PK) studies. This can be accepted. The PK is not considered informative towards the determination of an optimal dose. The metabolic pathways of vaccines are generally understood. Therefore PK studies are generally not required for vaccines.

IV.3 Pharmacodynamics

Immunogenicity, as a surrogate measure for efficacy, determined by a validated HAI assay, was assessed in all Efluelda and TIV-HD clinical studies included in the application and is described in detail in the sections on clinical efficacy. Assessment of neutralising antibodies by the seroneutralisation (SN) assay and anti-neuraminidase activity with the Enzyme-linked Lectin Assay (ELLA) was also performed. The use of serological surrogates as an approximation for vaccine efficacy is generally recognized by regulatory authorities including the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) (CHMP/VWP/457259/2014).

IV.4 Clinical efficacy

IV.4.1 Dose-response studies

The MAH submitted two dose ranging studies which were conducted early in the development of TIV-HD:

- A Phase I dose ranging study (Division of Microbiology and Infectious Disease Protocol 01-597, NIH Study 01-597), which evaluated the safety and immunogenicity of 3 strengths (15 µg, 30 µg, and 60 µg HA/virus strain) of the TIV-HD in healthy adult subjects 65 years of age and older in the US. Based on this study, the strength of 60 µg of HA per influenza vaccine strain was selected for further development.
- Study FIM01 (NIH Study 04-100), which compared the reactogenicity and immunogenicity of the TIV-HD to Fluzone (i.e., TIV-SD, manufactured by Sanofi Pasteur in the US). The immunogenicity results suggested an improved HAI response with the TIV-HD vaccine as compared to the TIV-SD vaccine, with more subjects developing higher titres in the TIV-HD group. This is particularly evident when reviewing subjects with a four-fold increase in titre compared to baseline. The safety data showed that there is also an increase in reactogenicity and adverse events in the TIV-HD group as compared to the TIV-SD group.

Based upon these studies, further (clinical) evaluation of the TIV-HD (60 µg HA/virus strain) was warranted.

IV.4.2 Main studies

Two studies are considered pivotal to this application:

- Study FIM12 which evaluated the superiority of TIV-HD (60 µg HA per strain) over TIV-SD (15 µg HA per strain) in preventing laboratory confirmed influenza associated with influenza-like illness in adults aged 65 years and older.
- Study QHD00013 which provides the bridge between the TIV-HD vaccine and the and the Efluelda vaccine applied for, through demonstrating non-inferior immunogenicity and similar safety profile of Efluelda compared with two TIV-HD vaccines each with one of the B strains in adults 65 years of age and older.

➢ **FIM12: Efficacy Study of Fluzone High-Dose Vaccine Compared With Fluzone Vaccine in Elderly Adults**

Methods

This was a Phase IIIb/IV, randomised, modified double-blind, active-controlled, multi-centre trial in elderly adults (≥ 65 years of age). The trial compared the efficacy of TIV-HD (Fluzone High-Dose) to that of TIV-SD (TIV standard-dose, Fluzone) in preventing laboratory-confirmed (culture or polymerase chain reaction [PCR]) influenza illness in elderly adults. The trial spanned 2 influenza seasons.

- Study Participants

The study included adults ≥ 65 years of age. Persons with a recent influenza vaccination (<6 months), history of Guillain-Barré syndrome, dementia or cognitive conditions that could interfere with the study, and hypersensitivity to substances in the vaccine or eggs were excluded.

- Treatments

Each study year, participants were randomised in a 1:1 ratio to receive 1 dose of either TIV-HD or TIV-SD prior to the start of the influenza season. Subjects who had participated in the first year and met the eligibility criteria could have been re-enrolled and re-randomised in the second year, and individuals who had not participated in the first year of the study could have been assessed for eligibility and participated in the second year.

- Objectives

The primary efficacy objective for this study was to compare the clinical efficacy of TIV-HD to that of TIV in elderly adults, with respect to laboratory-confirmed influenza, caused by any influenza viral types/subtypes, associated with the occurrence of a protocol-defined influenza-like illness (ILI).

There were 11 secondary objectives regarding efficacy varying by 1) laboratory or culture-confirmed cases, 2) antigenically similar to vaccine types or any influenza viral types/subtypes and 3) associated with the occurrence of a protocol-defined ILI, modified Centers for Disease Control and Prevention (CDC)-defined ILI or respiratory illness.

Further, exploratory objectives concerning effectiveness outcomes (pneumonia rate, rates of new onset or exacerbation of pre-existing cardio-respiratory conditions and healthcare utilisation) and immunogenicity (HAI Correlate of Protection) were included.

- Outcomes/endpoints

The primary endpoint for the evaluation of efficacy was the occurrences of culture- or PCR confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral types/ subtypes, in association with a protocol-defined ILI.

Case definitions

- Protocol-defined ILI: the occurrence of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrently with at least one of the following systemic symptoms: fever (defined as temperature > 37.2°C, chills (shivering), tiredness (fatigue), headache, or myalgia (muscle aches).
- Laboratory-confirmed Influenza: a positive influenza result on either PCR and/or viral culture of a nasopharyngeal swab sample.
- Culture-confirmed Influenza: a positive influenza result on viral culture.
- Modified CDC-defined ILI: the occurrence of fever (defined as temperature > 37.2°C) with cough or sore throat.

Secondary endpoints varied by the laboratory confirmation method (either culture confirmed or culture confirmed and PCR), the definition of ILI and the similarity between the infecting viral strain and the vaccine strains (i.e. any viral (sub)types or (sub)types antigenically similar to those contained in the vaccine).

- Randomisation and blinding (masking)

Subjects were randomised 1:1 to receive either TIV-HD or TIV-SD. A list containing the randomised vaccine assignments was generated by an independent statistician, using a block randomisation. Subjects would also be randomised into the immunogenicity subset during the same interactive voice response system call. No stratification was applied.
The vaccine was administered by an unblinded qualified study staff member. Investigators in charge of safety assessment and respiratory illness data collection did not know which product was administered. The subject did not know which product was administered. The study is therefore considered observer blind.

- Statistical methods

Analyses were performed on the PPAS and the FAS. The FAS comprised all subjects who received study vaccine. The PPAS was considered by the MAH as the principle analysis. As the number of subjects with confirmed influenza between the populations are very close (see numbers analysed in the results), and results are in line with each other, this has no further consequences.

The hypothesis to be tested was H0: Rel.VE ≤ 9.1%, where Rel.VE denotes relative vaccine efficacy, TIV-HD vs. TIV-SD.

By agreement with the FDA, a 9.1% margin for superior vaccine efficacy was used to provide confidence that the risk of the primary end point was at least 10% higher with the administration of TIV-SD than with the administration of TIV-HD.

Subjects who had participated in the first year and met the eligibility criteria could have been re-enrolled and re-randomised in the second year, and individuals who had not participated in the first year of the study could have been assessed for eligibility and participated in the second year. Both the chance to experience an influenza attack, the response to a vaccine may be correlated within a person. The MAH has presented stratified analysis for patients included in both year 1 and year 2, year 2 only and for the whole population to explore whether there is any impact of this re-randomisation on the relative Vaccine Effectiveness (rVE), see section on results below.

Results

- Participant flow

Out of the 31,989 randomised subjects, 31,983 subjects received a study vaccine (1 subject in the TIV-HD Group and 2 subjects in the TIV-SD did not receive a study vaccine during Year 1; 3 subjects in the Fluzone TIV-SD Group did not receive a study vaccine during Year 2).
A total of 5 subjects in the TIV-HD Group and 7 subjects in the TIV-SD during Year 1, and 4 subjects in the TIV-HD Group and 8 subjects in the TIV-SD during Year 2 did not receive the vaccine they were randomised to. A total of 17,489 subjects were enrolled in Year 2, which included 7645 subjects previously enrolled in Year 1 who were re-enrolled and re-randomised in Year 2.
The MAH provided an analysis of rVE for the subgroup enrolled in year 2 previously enrolled in year 1, by vaccine received in year 1 and an analysis of the results of year 1 for the group who did and did not enrol in year 2. These analyses did not suggest a large difference in the estimated rVE the between the two groups for year 1 or for year 2. Similar relative vaccine efficacy was observed, indicating that selection is unlikely to have impacted the results.
In total 1522 (4.76%) of the randomised subjects discontinued the study before the end of the study year.

- Baseline data

The study included more women than men (56.6% vs. 43.4%), subjects had a mean age of 73.3 years with a minimum age of 57.3 years and maximum of 100.0 years. The majority of subjects were white (94.6%). Within the FAS as treated, 10,750 (67.22%) and 10,752 (67.24%) subjects in the TIV-HD and in TIV-SD groups, respectively, had at least one pre-specified chronic comorbidity. Demographic baseline characteristics were balanced between vaccine groups. The study population reflects a population of older adults with a relatively large proportion of subjects with underlying comorbidities.

- Outcomes and estimation

Overall, there were less cases in the TIV-HD group (1.43%) than in the TIV-SD group (1.89%). For the primary outcome, relative vaccine efficacy (rVE) was 24.24% (95% CI 9.69; 36.52), meeting the predefined superiority criteria (LL of 95%CI >9.1%). Similar results were observed in the full analysis set 24.24 (9.71; 36.50). See table Table 2.

In both arms participants received one dose of vaccine before the start of the influenza season. In total 1522 (4.76%) of the randomised subjects discontinued the study before the end of the study year. If study discontinuation is related to vaccine status, this might have

impacted the relative vaccine efficacy. Although expected, and impossible to prevent, the MAH considered 5% a small number compared to the attack rate. Given the influenza attack rate is lower than 2% in both groups (High dose 1.43% [227/15,892] Fluzone 1.89% [300/15,911]), and the lower bound of the confidence interval of rVE just exceeded the pre-set superiority margin of 9.1%; PPAS 24.24% (95% CI 9.69;36.52) FAS 24.24% [95% CI 9.71; 36.50], the 5% discontinuations could have substantial impact.
The fact that the percentage discontinuations is similar in both groups and the discontinuation rate over time is similar between both groups may be indicative of a similar discontinuation pattern.

For some groups the number of cases was very limited and estimates came with considerable uncertainty. The point estimate of laboratory-confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) was higher in year 1 (rVE: 45% (7-69%)) compared to year 2 (rVE: 21% (4-34%), but confidence intervals overlap. Note that the 2011/2012 season (year 1) was dominated by a H3N2 strain with a good match to the vaccine whilst the 2012/2013 season (year 2) was dominated by a H3N2 strain with a poor match to the vaccine, which explains the differences in attack rates between the two years.

Table 2. Efficacy of TIV-HD relative to TIV-SD against <u>laboratory-confirmed influenza</u> caused by <u>any viral types/subtypes</u> (regardless of similarity to those contained in the vaccine) – Per Protocol Analysis Set (FIM12)

	Year 1			Year 2			Combined		
	TIV-HD N=7209 n (%)	TIV-SD N=7207 n (%)	Relative Efficacy % (95% CI)	TIV-HD N=8683 n (%)	TIV-SD N=8704 n (%)	Relative Efficacy % (95% CI)	TIV-HD N=15892 n (%)	TIV-SD N=15911 n (%)	Relative Efficacy % (95% CI)
Associated with protocol-defined influenza-like illness *	23 (0.32)	42 (0.58)	45.25 (6.86; 68.57)	204 (2.35)	258 (2.96)	20.74 (4.39; 34.36)	227 (1.43)	300 (1.89)	24.24 (9.69; 36.52)
Influenza A	16 (0.22)	34 (0.47)	52.95 (12.41; 75.75)	174 (2.00)	215 (2.47)	18.87 (0.46; 33.96)	190 (1.20)	249 (1.56)	23.60 (7.36; 37.08)
A/H1N1	4 (0.06)	6 (0.08)	33.35 (-181.1; 86.17)	4 (0.05)	3 (0.03)	-33.66 (-812.4; 77.39)	8 (0.05)	9 (0.06)	11.00 (-159.9; 70.12)
A/H3N2	11 (0.15)	25 (0.35)	56.01 (7.32; 80.46)	160 (1.84)	197 (2.26)	18.59 (-0.81; 34.33)	171 (1.08)	222 (1.40)	22.88 (5.43; 37.20)
Influenza B	7 (0.10)	8 (0.11)	12.52 (-176.1; 73.00)	30 (0.35)	43 (0.49)	30.06 (-14.09; 57.64)	37 (0.23)	51 (0.32)	27.36 (-13.11; 53.75)
Victoria lineage	2 (0.03)	4 (0.06)	50.01 (-248.8; 95.48)	6 (0.07)	7 (0.08)	14.08 (-198.6; 76.14)	8 (0.05)	11 (0.07)	27.19 (-98.75; 74.57)
Yamagata lineage	3 (0.04)	2 (0.03)	-49.96 (-1695; 82.82)	21 (0.24)	34 (0.39)	38.09 (-9.79; 65.85)	24 (0.15)	36 (0.23)	33.25 (-15.00; 61.91)
Associated with modified CDC-defined influenza-like illness	10 (0.14)	11 (0.15)	9.12 (-135.7; 65.40)	86 (0.99)	110 (1.26)	21.63 (-4.87; 41.59)	96 (0.60)	121 (0.76)	20.57 (-4.70; 39.88)
Influenza A	8 (0.11)	10 (0.14)	20.02 (-125.1; 72.57)	78 (0.90)	94 (1.08)	16.82 (-13.51; 39.19)	86 (0.54)	104 (0.65)	17.21 (-11.24; 38.52)
A/H1N1	1 (0.01)	1 (0.01)	0.03 (-7748; 98.73)	2 (0.02)	1 (0.01)	-100.5 (-11728; 89.56)	3 (0.02)	2 (0.01)	-50.18 (-1698; 82.80)
A/H3N2	6 (0.08)	8 (0.11)	25.02 (-146.4; 78.56)	71 (0.82)	87 (1.00)	18.19 (-13.23; 41.06)	77 (0.48)	95 (0.60)	18.85 (-10.77; 40.71)
Influenza B	2 (0.03)	1 (0.01)	-99.94 (-11696; 89.59)	8 (0.09)	16 (0.18)	49.88 (-24.12; 81.43)	10 (0.06)	17 (0.11)	41.11 (-36.19; 75.90)
Victoria lineage	1 (0.01)	1 (0.01)	0.03 (-7748; 98.73)	2 (0.02)	0 (0.00)	NA	3 (0.02)	1 (0.01)	-200.4 (-15668; 75.88)
Yamagata lineage	1 (0.01)	0 (0.00)	NA	5 (0.06)	14 (0.16)	64.20 (-5.18; 89.91)	6 (0.04)	14 (0.09)	57.09 (-18.86; 86.49)
Associated with respiratory illness	47 (0.65)	57 (0.79)	17.57 (-23.46; 45.19)	268 (3.09)	329 (3.78)	18.34 (3.76; 30.77)	315 (1.98)	386 (2.43)	18.30 (4.94; 29.82)
Influenza A	38 (0.53)	48 (0.67)	20.86 (-23.70; 49.68)	224 (2.58)	264 (3.03)	14.95 (-2.02; 29.14)	262 (1.65)	312 (1.96)	15.93 (0.60; 28.93)
A/H1N1	9 (0.12)	7 (0.10)	-28.54 (-306.1; 57.40)	5 (0.06)	3 (0.03)	-67.07 (-975.8; 67.50)	14 (0.09)	10 (0.06)	-40.17 (-252.7; 42.09)
A/H3N2	27 (0.37)	38 (0.53)	28.97 (-19.44; 58.29)	204 (2.35)	242 (2.78)	15.50 (-2.23; 30.21)	231 (1.45)	280 (1.76)	17.40 (1.33; 30.91)
Influenza B	9 (0.12)	9 (0.12)	0.03 (-184.3; 64.84)	44 (0.51)	65 (0.75)	32.14 (-1.02; 54.80)	53 (0.33)	74 (0.47)	28.29 (-3.42; 50.58)
Victoria lineage	2 (0.03)	4 (0.06)	50.01 (-248.8; 95.48)	11 (0.13)	12 (0.14)	8.11 (-127.5; 63.26)	13 (0.08)	16 (0.10)	18.65 (-80.38; 64.00)
Yamagata lineage	4 (0.06)	3 (0.04)	-33.30 (-810.0; 77.45)	30 (0.35)	50 (0.57)	39.85 (3.55; 63.08)	34 (0.21)	53 (0.33)	35.77 (-0.66; 59.52)

* Primary objective.

Results were consistent for the FAS as randomised. The secondary efficacy outcomes were consistent with the primary outcome, with the rVE consistently positive and ranging from 20 to 50% for the different applied case definitions and laboratory confirmation methods.
Overall, rVEs are higher against antigenically similar strains, which is a more specific outcome, than against any strain. There was no significant difference between laboratory

confirmation methods, i.e. the estimated rVE against culture-confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) associated with the occurrence of a protocol-defined ILI in the PPAS was **23**.13% (95% CI: 7.44; 36.24). For some strata (i.e. against specific strains) the number of cases is very limited and estimates come with considerable uncertainty.
There was no evidence to suggest an impact of either vaccination history, age or sex on the estimated rVE.

Impact of missing data on estimate of relative efficacy
A tipping point analysis with varying assumptions of the influenza attack rates occurring in subjects who discontinued the study and after their discontinuation was performed to show when the assumptions lead to a conclusion of superior efficacy of TIV-HD relative to TIV-SD for the prevention of laboratory-confirmed influenza and when the relative vaccine efficacy (rVE) can no longer be concluded.
The tipping point analysis showed that under conservative but realistic assumptions on attack rates among discontinued subjects from each group, the study conclusion of superior efficacy using the pre-defined 9.1% threshold was maintained. If the attack rate among discontinued subjects was slightly higher in TIV-HD group than in TIV-SD group, under the conservative assumption that among these subjects the estimated rVE is < 0%, the superiority conclusion did not hold using the 9.1% but still a difference between vaccines can be observed with a lower bound of 95% CI remains above 0%. This held up to a 3% difference in attack rates between TIV-HD and TIV-SD groups, corresponding to observed rVEs among discontinued subjects below -250%.

Exploratory outcomes
For Year 1 and Year 2 combined, rates were lower in the TIV-HD group than in the TIV-SD group for pneumonia, new onset or exacerbation of pre-existing cardio-respiratory conditions, hospitalizations, overall medication use, antipyretic/analgesic/NSAID use, and antiviral use (point estimates of the relative risks below 1). The estimated rate for ER visits was higher in the TIV-HD group than in the TIV-SD group point as the estimate of the relative risk is above 1). Due to the limited cases it cannot be concluded that the relative risk for any of the measured effectiveness outcomes is reduced with the TIV-HD compared to the TIV-SD. Considering the CIs mostly cross 1, the multiple comparisons and lack of a confirmative testing strategy, no conclusions can be drawn from these observations.
The results of the exploration for a HAI correlate of protection suggested that there may be different thresholds for different strains however as the correlates of protection analyses confidence intervals were wide and overlap, it was not possible to draw any firm conclusions.

- **QHD00013: Safety and Immunogenicity of High-Dose Quadrivalent Influenza Vaccine Administered by Intramuscular Route in Subjects Aged 65 Years and Older**

Methods
This was a randomised, modified double-blind, active-controlled, multi-centre study conducted in 2670 healthy subjects aged 65 years and older to assess the safety and immunogenicity of the high-dose quadrivalent influenza vaccine (Efluelda) compared to

one of the high-dose trivalent influenza vaccines (TIV-HDs) containing either the B strain from the primary lineage (TIV-HD1, which was the licensed vaccine [Fluzone High-Dose] for the 2017-2018 Northern Hemisphere influenza season) or the B strain from the alternate lineage (TIV-HD2, which was an investigational TIV-HD containing an alternate B strain).

- Study participants

The study included subjects ≥ 65 years of age. Although persons with chronic diseases were not excluded, persons with conditions that might interfere with the immune response were. Considering the objective of the study this is acceptable.

- Treatments

Subjects were randomised to receive either the Efluelda vaccine which contains 2 antigens of type A (H1N1 and H3N2) and 2 antigens of type B (one each from Yamagata and Victoria lineages) or TIV-HD1 or TIV-HD2 which contain 2 antigens of type A (H1N1 and H3N2) and antigen of type B. TIV-HD1 contained the B/Brisbane/60/2008 strain, of the Victoria lineage, TIV-HD2 contained the B/Phuket/3073/2013 strain, of the Yamagata lineage.

- Objectives

Primary

To demonstrate that Efluelda induces an immune response (as assessed by HAI geometric mean titres [GMTs] and seroconversion rates [SCR]) that is non-inferior to responses induced by the TIV-HD1 and TIV-HD2 for the 4 virus strains at 28 days post-vaccination in all subjects.

Secondary

1) To demonstrate that each B strain in Efluelda induces an immune response (as assessed by HAI GMTs and seroconversion rates) that is superior to the response induced by the TIV-HD that does not contain the corresponding B strain in all subjects.
2) To describe the immune response induced by Efluelda, TIV-HD1, and TIV-HD2 by HAI measurement method in all subjects.
3) To describe the immune response 28 days after vaccination by virus SN measurement method in a randomised subset of subjects from each study group.

Safety

To describe the safety profile of all subjects in each trial group.

- Outcomes/endpoints

The primary outcome was the HAI antibody (Ab) titres (GMTs) obtained on D28 and seroconversion rate (titre < 10 [1/dil] at D0 and post-injection titre ≥ 40 [1/dil] at D28, or titre ≥ 10 [1/dil] at D0 and a ≥ 4-fold rise in titre [1/dil] at D28).

Secondary outcomes included immunogenicity assessment by HAI, including titres at D0, ratios between D28/D0, and seroprotection rates (titre ≥ 40 [1/dil]) as well as immunogenicity assessment by SN and ELLA.

Case definitions

- Randomisation and blinding (masking)

The study was randomised, block randomisation was applied for all subjects within strata by sites. The study is presented as a modified double-blind study. However as staff member administering the vaccine were not blind, the study is not considered double blind, but observer-blind.

- Statistical methods

The immunogenicity of Efluelda was compared to that of TIV-HD1 and/or TIV-HD2. For each A strain, the comparison was made with the pooled TIV-HD groups. For each B strain, the comparison was made with the TIV-HD group containing the corresponding B strain. The statistical methodology was based on the use of the 2-sided 95% CI of the ratio of postvaccination GMTs and difference in seroconversion rates between Efluelda and TIV-HD groups.

The non-inferiority of Efluelda to each TIV-HD group in terms of GMTs was demonstrated, if for each of the 3 common strains:

- the lower limit of the 2-sided 95% CI for the difference of log10 (GMTs) > log10 (1/1.5)

Similarly, the non-inferiority of Efluelda to each TIV-HD group in terms of seroconversion rates was demonstrated, if for each of the 3 common strains:

- the lower limit of the 2-sided 95% CI for the difference of seroconversion rates was > -0.1

Analyses were performed for both the Full Analysis Set (FAS) and the Per-protocol Analysis Set (PPAS), but the conclusion was made from PPAS results.

The superiority analyses were demonstrated in all subjects. For each B strain, the immunogenicity of Efluelda was compared to that of TIV-HD group which does not contain the corresponding B strain. The statistical methodology was based on the use of the 2-sided 95% CI of the ratio of postvaccination GMTs and difference in seroconversion rates between the Efluelda group and TIV-HD group. The 95% CIs was calculated using normal approximation of log-transformed titres for GMTs and using the Wilson score method without continuity correction for seroconversion rates. For each strain, the 2-sided 95% CI should lie above 1.5 for GMTs and above 10% for seroconversion rates.
The superiority objective would be achieved if the superiority is demonstrated for both B strains and for both GMTs and seroconversion rates. Analyses were performed for both FAS and PPAS but the conclusion was made from FAS results.
It should be noted that this superiority analyses was tested as a secondary outcome on a different population than the primary outcome. No strategy to protect the type I error seems to be specified for the test for superiority of the B strain versus either the TIV-HD1 or TIV-HD2 group. A hierarchical testing procedure could have been used, but was not specified. Therefore, the type I error is not sufficiently protected.

- Missing data

No replacement was done for missing values. Based on the previous TIV-HD and QIV-SD trials in this population, the amount of missing immunogenicity data was expected to be ≤ 5% in this trial. Usually in vaccine trials, it seems generally reasonable to assume missing immunogenicity data are missing completely at random. Indeed, it is highly unexpected that the dropout (or any other reason for missing data) could be linked to the immune response of the subject. Therefore, confirming the results of the PPAS for the primary analysis with the FAS would be satisfactory in terms of sensitivity analysis. Missing data are assumed to be missing completely at random. It is mentioned that it is unlikely that this assumption is violated, however, it may for example be that patients with lower immune responses got ill and missed a visit. Therefore, if substantial numbers are missing, analysis to test the sensitivity of the assumptions should be performed.

Results

- Participant flow

A total of 2670 subjects were enrolled in the study and randomised to one of the 3 groups: Efluelda group (1777 subjects), TIV-HD1 group (443 subjects), or TIV-HD2 group (450 subjects).
Out of the 2670 randomised subjects, 16 (0.6%) subjects did not complete the study: 10 (0.6%), 3 (0.7%), and 3 (0.7%) subjects in the Efluelda, TIV-HD1, and TIV-HD2 groups, respectively. Two subjects each in the Efluelda group and TIV-HD1 group withdrew due to an AE. Other reasons for discontinuation were lost to follow-up (3 subjects), protocol deviation (7 subjects), and voluntary withdrawal by subject not due to an AE (2 subjects).

The first subject was enrolled on 8 September 2017, the last contact was on 19 April 2018. A total of 2616 adults aged 65 years and older were planned to be enrolled, and a total of 2670 patients were enrolled.

- Baseline data

There were fewer male subjects in the PPAS (42.1% vs 57.9% females), the mean age was 73.0 years, and the majority of subjects were white (90.7%). The percentage of obese subjects was 41.0%, followed by overweight subjects (34.4%), and subjects with normal weight (20.8%). In the PPAS, a total of 1881 (74.3%) subjects received influenza vaccination in the previous year. Previous influenza vaccination data were similar across all study groups. In the Safety Analysis Set 1470 subjects (55.1%) had at least one prespecified medical history reported, for 1245 subjects (46.6%) this was ongoing. The majority concerned diabetes mellitus (28.1%) and hypothyroidism (28.1%).

- Outcomes and estimation

The main results for QHD00013 are presented in Table 3 (GMTs) and Table 4 (Seroconversion rates). The primary objective of non-inferiority of Efluelda to TIV-HD as assessed by GMTs and seroconversion rates was met as the lower limit of the 95% CI was above 0.667 for the ratio of GMTs and above -10% for the differences of seroconversion rates for all influenza strains.

Table 3. Immunogenicity primary objective: Non-inferiority of Efluelda compared to TIV-HD1 and/or TIV-HD2 using GMTs at V02 after vaccination - Per-Protocol Analysis Set (QHD00013)

					QIV-HD/TIV-HDs*		
	Antigen/strain	M	GMT	(95% CI)	GMT ratio	(95% CI)	Non-inferiority§
QIV-HD	A/Michigan/45/2015 (H1N1)	1680	312	(292; 332)	--	--	--
	A/Hong Kong/4801/2014 (H3N2)	1679	563	(525; 603)	--	--	--
	B/Brisbane/60/2008 (B1)	1680	516	(488; 545)	--	--	--
	B/Phuket/3073/2013 (B2)	1680	578	(547; 612)	--	--	--
TIV-HD1	A/Michigan/45/2015 (H1N1)	423	387	(339; 442)	0.81	(0.697; 0.931)	--
	A/Hong Kong/4801/2014 (H3N2)	423	588	(513; 673)	0.96	(0.821; 1.115)	--
	B/Brisbane/60/2008 (B1)	423	476	(426; 532)	1.08	(0.958; 1.224)	Yes
TIV-HD2	A/Michigan/45/2015 (H1N1)	430	362	(317; 413)	0.86	(0.745; 0.993)	--
	A/Hong Kong/4801/2014 (H3N2)	430	600	(524; 687)	0.94	(0.805; 1.092)	--
	B/Phuket/3073/2013 (B2)	430	580	(519; 649)	1.00	(0.881; 1.129)	Yes
TIV-HD Pooled	A/Michigan/45/2015 (H1N1)	853	374	(341; 411)	0.83	(0.744; 0.932)	Yes
	A/Hong Kong/4801/2014 (H3N2)	853	594	(540; 653)	0.95	(0.842; 1.066)	Yes

Abbreviations: CI, confidence interval; GMT, geometric mean titer; QIV-HD, high-dose quadrivalent influenza vaccine, TIV-HD, high-dose trivalent influenza vaccine
M: number of subjects with available data for the considered endpoint
2-sided 95% CI is based on the Student t-distribution of logarithmic transformation of the individual titers. Antilog transformations were applied to the results.
TIV-HD 1 does not contain B2 strain; TIV-HD2 does not contain B1 strain;
* Here TIV-HDs mean any one of the TIV-HD1, TIV-HD2, or TIV-HD pooled groups.
§ Non-inferiority of GMTs is concluded if the lower limit of the 2-sided 95% CI of the ratio of GMTs between groups is > 0.667 for each of the comparisons applicable in this column.
Notation '--' is displayed in all non-applicable cells.
Source: Section 9, Table 9.64

Table 4. Immunogenicity primary objective: Non-inferiority of Efluelda compared to TIV-HD1 and/or TIV-HD2 using seroconversion rates at V02 after vaccination - Per-Protocol Analysis Set (QD00013)

					QIV-HD minus TIV-HDs*		
	Antigen/strain	n/M	%	(95% CI)	Difference of %	(95% CI)	Non-inferiority§
QIV-HD	A/Michigan/45/2015 (H1N1)	841/1669	50.4	(48.0; 52.8)	--	--	--
	A/Hong Kong/4801/2014 (H3N2)	830/1668	49.8	(47.3; 52.2)	--	--	--
	B/Brisbane/60/2008 (B1)	610/1669	36.5	(34.2; 38.9)	--	--	--
	B/Phuket/3073/2013 (B2)	778/1669	46.6	(44.2; 49.0)	--	--	--
TIV-HD1	A/Michigan/45/2015 (H1N1)	236/420	56.2	(51.3; 61.0)	-5.80	(-11.05,-0.45)	--
	A/Hong Kong/4801/2014 (H3N2)	222/420	52.9	(48.0; 57.7)	-3.10	(-8.40,2.25)	--
	B/Brisbane/60/2008 (B1)	164/421	39.0	(34.3; 43.8)	-2.41	(-7.66,2.70)	Yes
TIV-HD2	A/Michigan/45/2015 (H1N1)	219/428	51.2	(46.3; 56.0)	-0.78	(-6.06,4.52)	--
	A/Hong Kong/4801/2014 (H3N2)	206/428	48.1	(43.3; 53.0)	1.63	(-3.67,6.90)	--
	B/Phuket/3073/2013 (B2)	207/428	48.4	(43.5; 53.2)	-1.75	(-7.04,3.53)	Yes
TIV-HD Pooled	A/Michigan/45/2015 (H1N1)	455/848	53.7	(50.2; 57.1)	-3.27	(-7.37,0.86)	Yes
	A/Hong Kong/4801/2014 (H3N2)	428/848	50.5	(47.1; 53.9)	-0.71	(-4.83,3.42)	Yes

Abbreviations: CI, confidence interval; QIV-HD, high-dose quadrivalent influenza vaccine, TIV-HD, high-dose trivalent influenza vaccine
M: number of subjects with available data for the considered endpoint
2-sided 95% CI for the single proportion (%) is based on the Clopper-Pearson method. 2-sided 95% CI for the difference is based on the Wilson score method without continuity correction.
TIV-HD1 does not contain B2 strain; TIV-HD2 does not contain B1 strain;
* Here TIV-HDs mean any one of the TIV-HD1, TIV-HD2, or TIV-HD pooled groups.
§ Non-inferiority in seroconversion is concluded if the lower limit of the 2-sided 95% CI of the differences of seroconversion rates between groups is > -10% for each applicable comparison.
Notation '--' is displayed in all non-applicable cells.
Source: Section 9, Table 9.68

As can be seen in these tables, non-inferiority criteria were met for all strains for both the GMT endpoint as the SCR endpoint. The clinical significance for these criteria is unknown.
The sensitivity analysis which evaluated non-inferiority of Efluelda compared to TIV-HD1 and/or TIV-HD2 using GMTs at V02 after vaccination adjusted to baseline on the Per-Protocol Analysis Set was in line.

The HAI response to the A/H1N1 strain seems to be numerically higher for both TIV-HD vaccines as compared to the Efluelda vaccine with higher GMTs: 387 and 362 with the TIV-HD, combined 374 (TIV-HD1+TIV-HD2) vs 312 with the Efluelda. This is replicated with the seroconversion rates for the TIV-HD1 vaccine (SCR is 56.2% vs 50.4% with the Efluelda) but not with the TIV-HD2 (SCR is 51.2%), and not with the TIV-HD pooled (SCR is 53.7%).

The higher response for the A/H1N1 strain is also reflected by the GMTrs (ratios of the GMT postdose/predose) for the TIV-HD1 vaccine with a GMTr in Efluelda group of 4.38, 95% CI: 4.11-4.66 as compared with 5.57, 95%CI: 4.85-6.39 in the TIV-HD1 vaccine. This was not seen for the TIV-HD2 vaccine (GMTr: 4.76, 95%CI 4.16 – 5.44). Considering the seroprotection rates (% subjects with HAI titre >1:40) the response was similar for all vaccine groups (Efluelda 95.1%; TIV-HD1: 96.7%; TIV-HD2: 95.6%).

The clinical significance for the difference between the response to Efluelda and particularly TIV-HD1 considering the GMTs, GMTrs and SCR, is unknown. As it appears to fall within the variation as also seen between the response to TIV-HD1 and TIV-HD2 it is unlikely to be of much consequence. Also, the SN results point in a different direction.

For the H3N2 strain and the shared B-strains, there is no notable difference between the responses to the Efluelda vaccines and either TIV-HD vaccine considering all endpoints.

Considering the secondary objectives, a higher HAI response (GMT, SCR) to Efluelda over either TIV-HD vaccine for alternating B strains was observed. The pre-set margins for superiority were met, however, no strategy to protect alpha has been pre-specified. Therefore, superiority cannot be claimed.

SN Ab responses expressed as GMT at baseline and post-vaccination and GMTr for each influenza strain for the expanded immunogenicity subset are presented and discussed below (Table 5).

Table 5. SN Ab responses expressed as GMT at baseline and post-vaccination and GMTr for each influenza strain for the expanded immunogenicity subset (QHD00013)

	Efluelda				**TIV-HD1**				**TIV-HD2**				**Pooled TIV-HD**	
	H1N1	H3N2	B1	B2	H1N1	H3N2	B1	B2	H1N1	H3N2	B1	B2	H1N1	H3N2
N	(102)	(102)	(102)	(102)	(102)	(102)	(102)	(102)	(99)	(99)	(99)	(99)	(201)	(201)
Pre-dose (V01)														
M	102	102	102	102	100	100	100	100	99	99	99	99	199	199
GMT	412	497	458	156	427	536	452	155	416	593	430	192	421	564
(95% CI)	(306; 555)	(417; 592)	(359; 583)	(124; 196)	(328; 556)	(436; 660)	(367; 556)	(126; 190)	(311; 555)	(493; 715)	(344; 537)	(152; 242)	(347; 511)	(491; 648)
Post-dose (V02)														
M	102	102	102	102	102	102	102	102	99	99	99	99	201	201
GMT	2229	1404	1288	546	2050	1327	1114	259	1686	1301	590	494	1862	1314
(95% CI)	(1789; 2776)	(1133; 1741)	(1055; 1573)	(438; 682)	(1564; 2687)	(1056; 1667)	(916; 1354)	(207; 325)	(1331; 2135)	(1070; 1583)	(476; 730)	(390; 626)	(1557; 2227)	(1132; 1526)
GMTr	5.40	2.83	2.81	3.51	5.05	2.50	2.47	1.66	4.06	2.19	1.37	2.58	4.53	2.34
(95% CI)	(3.90; 7.48)	(2.31; 3.46)	(2.21; 3.58)	(2.80; 4.39)	(3.86; 6.60)	(2.04; 3.06)	(2.04; 2.99)	(1.41; 1.95)	(3.17; 5.18)	(1.80; 2.67)	(1.16; 1.62)	(2.18; 3.05)	(3.78; 5.42)	(2.04; 2.70)

M: number of subjects with available data

The overall conclusions for the SN analysis is similar as compared to the HA analysis, i.e. similar responses to Efluelda vs TIV-HD1 and TIV-HD2 with regards to the shared strains and

higher responses to the B strain contained in Efluelda but not in TIV-HD1 or TIV-HD2. The GMTs of neutralising antibodies against the A/H1N1 were higher in the Efluelda group compared to the TIV-HD2 group (2229 vs 1686) and similar to that in the TIV-HD1 group (2050), negating any potential concerns from the HAI analyses of possible lower responses to the A strain with the Efluelda vaccine limiting the ability to bridge to the clinical evidence obtained with the TIV-HD vaccine. The GMTr for H3N2 are lower when measured by SN as compared to HA, however these are more or less similar for other strains.
The MAH presented bubble plots to describe the correlation between the SN and HAI assay. These plots (not shown) showed that the correlation between HAI and SN varied by strain but not for the vaccine (QIV or TIV). For the A/H1N1 strain, the HAI assay seemed to underestimate the SN. For H3N2 this was the case with lower titres, but not for the higher titres. Hence the correlation was poorer for the A/H3N2 strain. For the B/Victoria strain, the HAI underpredicts the SN assay; for B/Yamagata the plots are suggestive of a good correlation and similar prediction of the HAI as SN assay.

Table 6 presents a summary of anti-NA Ab response against the N1 antigen in the A/H1N1 strain and the N2 antigen in the A/H3N2 strain from the ELLA at baseline and V02 after vaccination for the expanded immunogenicity subset.

Table 6. Summary of Anti-NA antibody response (ELLA) at baseline and at V02 after vaccination - Expanded Immunogenicity Subset (QHD00013)

	Efluelda		**TIV-HD1**		**TIV-HD2**		**Pooled TIV-HD**	
	A/H1N1	A/H3N2	A/H1N1	A/H3N2	A/H1N1	A/H3N2	A/H1N1	A/H3N2
	(N= 102)	(N= 102)	(N= 102)	(N= 102)	(N= 99)	(N= 99)	(N= 201)	(N= 201)
Pre-dose (V01) M	102	102	100	100	99	99	199	199
GMT	312	41.2	283	42.4	238	45.2	260	43.8
(95% CI)	(255; 382)	(34.5; 49.4)	(226; 356)	(34.9; 51.5)	(185; 308)	(37.0; 55.3)	(220; 308)	(38.1; 50.3)
Post-dose (V02) M	102	100	102	102	98	98	200	200
GMT	505	86.9	478	78.9	398	74.5	437	76.7
(95% CI)	(413; 617)	(70.7; 107)	(386; 591)	(65.1; 95.7)	(320; 496)	(62.5; 88.8)	(375; 509)	(67.4; 87.3)
GMTr	1.61	2.12	1.69	1.90	1.71	1.65	1.70	1.77
(95% CI)	(1.44; 1.81)	(1.84; 2.45)	(1.50; 1.90)	(1.67; 2.15)	(1.54; 1.89)	(1.46; 1.86)	(1.57; 1.83)	(1.62; 1.93)

At baseline, GMTs were similar between the vaccine groups ranging from 238 to 312 for the N1 antigen and 41.2 to 45.2 for the N2 antigen. Post-vaccination, GMTs had increased for the Efluelda, TIV-HD1, TIV-HD2, and TIV-HD pooled. GMTs were similar between each study group ranging from 398 to 505 for the N1 antigen and 74.5 to 86.9 for the N2 antigen. There is some variation in the responses between the vaccine groups, with the GMTr for A/H3N2 higher in the Efluelda group compared to the TIV-HD2 group. The amount of NA in the vaccines used has not been quantified.

- Ancillary analyses

Immunogenicity data (GMTs, seroconversion rates, and seroprotection rates) were assessed by various covariate factors: age (65 - <75 and ≥ 75 years), sex, race (Caucasian and non-Caucasian), previous influenza vaccination status, and baseline seropositivity status. No relevant differences between study groups in any of these subgroups were found.

IV.4.3 Supportive studies

- **QHD00008**: **Phase I/II randomised multi-centre study to determine the safety and immunogenicity (HAI GMT/seroconversion) of Efluelda given either IM or SC as compared to QIV-SD (Flubik HA)**

The study was conducted in Japan. The first subject was included on 15 September 2017 and the last subject visit was completed on 28 November 2017. The study included a sentinel safety cohort (cohort 1), into which 10 Japanese adults aged 65 years and older were randomised 1:1 to receive either Efluelda by IM route or Efluelda by SC route. After review of the local and systemic AEs occurring for 7 days post-vaccination (Day [D] 0 to D7) in Cohort 1, enrolment of the remaining 165 subjects randomised 1:1:1 to receive Efluelda by IM route, Efluelda by SC route, or QIV-SD by SC route (Cohort 2). Randomisation in this cohort was stratified according to age (<75, ≥75), sex (male, female), and site. The comparator vaccine is not licensed in the EU, but in Japan only. For the Efluelda strains the HAI response is evaluated following IM administration as compared to SC administration.

At V3 (post-vaccination), the GMTs for both the Efluelda IM and Efluelda SC groups were higher than the QIV-SD SC group for all strains regardless of testing the subjects' sera with either the Efluelda strains or QIV-SD strains, with the ratios of GMTs (Efluelda/QIV-SD) ranging from 1.98 (95% CI: 1.26; 3.10) to 2.89 (95% CI: 1.95; 4.28) for the Efluelda IM group, and from 1.65 (95% CI: 1.06; 2.56) to 2.70 (95% CI: 1.88; 3.86) for the Efluelda SC group. These results are confirmed with the seroconversion rates.

The response is lower against the B strains as compared to the A strains, and GMTs are higher against vaccine strains as compared to non-vaccine strains (i.e. A1like, A2like and B2like). The response to the QIV-SD is consistently lower, both considering GMTs as considering SCR. Although the comparison is not made with an EU licensed vaccine, results are in line with the pivotal study with the trivalent vaccine TIV-HD, study FIM12, and further support the benefit of Efluelda.

- **FIM05: Phase III Lot Consistency, Immunogenicity and Safety Study of Three Lots of Fluzone High Dose Vaccine Compared with One Lot of Standard Fluzone in Adults ≥65 Years of Age**

This phase III study was conducted to demonstrate lot consistency of the Fluzone High Dose (TIV-HD) manufacturing process through evaluation of the immune responses elicited by three different lots at one-month postvaccination. In addition, the study set out to

demonstrate superiority of TIV-HD vaccine (based on the pooled responses elicited by the three vaccine lots) compared to standard-dose Fluzone vaccine (TIV-SD).

Healthy adults ≥ 65 years of age were randomised to one of two trial groups:
- TIV-SD (15 µg of each HA)
- TIV-HD (60 µg of each HA)

Subjects in the high-dose group were further randomised to receive one of the three lots of TIV-HD: Lot 1, Lot 2, or Lot 3.

A total of 3,876 adults aged ≥65 years were randomised, with 2,588 assigned to receive a vaccine from one of three lots of Fluzone HD and 1,288 assigned to receive standard Fluzone. A total of 3,781 subjects completed the trial up to six months. In total, 51.3% of subjects who received TIV-HD and 54.6% of those who received TIV-SD were female. The mean age in all groups was 72.9 years (min: 65, max: 97). The majority of subjects were Caucasian, constituting 91.7% of the subjects in the Fluzone HD group and 92.9% in the control group. Baseline characteristics were well balanced between groups.
The pre-defined criterion for demonstrating lot consistency for all strains and all three lots were met.
Pre-vaccination GMTs were comparable between all groups. The post-vaccination GMTs were higher for the combined TIV-HD group than for the control group for all three strains: 115.79 compared to 67.29 for A/H1N1; 608.87 compared to 332.46 for A/H3N2; and 69.06 compared to 52.34 for B.
The difference in the percentage of TIV-HD subjects who achieved seroconversion compared to the percentage of control subjects was 25.42% for the A/H1N1 strain, 18.38% for the A/H3N2 strain, and 11.81% for the B strain. For the A/H1N1 and A/H3N2 strains, TIV-HD was superior to TIV-SD, as the lower limit of the 95% CI was greater than 10% for both, while for the B strain it was non-inferior, as the lower limit of the 95% CI was greater than -10%. Therefore, for Fluzone HD vaccine overall, the criterion of superiority according to the protocol was met. Also, considering the GMTs, superiority was demonstrated.

IV.4.4 Effectiveness

Considering the relevance for older adults to not only prevent influenza infection but especially prevent complications of influenza, including pneumonia, exacerbations of underlying cardiovascular or respiratory morbidity, prevent hospitalisations and prevent mortality, these data are discussed below.

- **Randomised Controlled Trial: GRC75-EXT (clinical study report): High Dose Influenza Vaccination and Morbidity and Mortality in US Nursing Homes (Gravenstein et al, 2017)**

This concerns a large cluster-randomised controlled trial in nursing homes in the US (*GRC75-EXT)*. The study was preceded by a feasibility study (Gravenstein et al, 2016; 2018). Despite a relatively small sample size, the feasibility study which ran during the 2012-2013 influenza season (A/H3N2 predominating) found that the percentage of all-cause

hospitalizations was significantly lower in residents in nursing homes that received TIV-HD compared with TIV-SD facilities (197 [13.5%] versus 301 [20.1%], respectively; adjusted relative risk [ARR]=0.680; 95% CI: 0.537; 0.862; p=0.001).

GRC75-EXT was conducted during the 2013-2014 influenza season (A/H1N1pdm09 predominating). A total of 823 nursing home facilities were randomised (409 to TIV-HD and 414 to TIV-SD). A total of 53.008 long-stay residents received either TIV-HD or TIV-SD.
The primary objective of study GRC75-EXT was to estimate the differences in hospitalization (related to respiratory infections) during influenza seasons experienced by long-stay nursing home residents between facilities using TIV-HD versus TIV-SD. Secondary objective was to assess the differences in the likelihood of Activities of Daily Living Scale functional decline and mortality rates in the study nursing homes.

All analyses were conducted at the individual resident level using regression-based procedures accounting for clustering by facility. The analysis pre-specifies to account for both main effects and the interaction to appropriately account for the 2 x 2 factorial design. It is mentioned that there was no difference in the staff vaccination rates between facilities assigned to free and usual processes. Therefore, the results presented focus only on the high-dose vaccine versus the standard-dose vaccine.

Based on Medicare Fee-for-Service (FFS) claims, the 6-month incidence of respiratory-related hospitalization in the 2013–2014 influenza season was significantly lower in the TIV-HD vaccine than TIV-SD vaccine facilities (3.4% [0.185 hospital admissions per 1000 resident days] versus 3.9% [0.211 hospital admissions per 1000 resident days]; unadjusted risk ratio=0.888, 95% CI: 0.785–1.005, p=0.061). When adjusting for the pre-specified patient and facility characteristics related to overall hospital admission rates, a 12.7% relative reduction was observed in the incidence of hospital admissions for respiratory illness among FFS Medicare beneficiaries living in TIV-HD vaccine facilities (ARR=0.873, 95% CI: 0.776–0.982, p=0.023).

TIV-HD vaccine was more effective than standard-dose vaccine in reducing all-cause hospitalization in both the FFS group (ARR=0.915, 95% CI: 0.863–0.970, p=0.0028) and the overall long-stay minimum data set group (ARR=0.933, 95% CI: 0.884–0.985, p=0.012) in the 2013–2014 predominantly A/H1N1 influenza season. The number needed to treat to prevent all-cause hospital admissions for the season was 83.7. No statistically significant difference was observed for all-cause mortality or functional decline.
As the study is based upon claims data, laboratory data were not available to confirm influenza. Considering that the design included a randomisation step which, considering the baseline covariates balance between arms, appears to have been successful and considering the size of the study it is a reasonable assumption that unmeasured confounders will also be reasonably well balanced between arms and therefore any differences are likely to be attributed to treatment. Note that this study was conducted during a predominantly A/H1N1 season, which commonly has more limited impact in older adults as compared to influenza A/H3N2. In line, the impact of the TIV-HD vaccine relative to the standard-dose vaccine was larger in the feasibility study when A/H3N2 predominantly circulated.

- **Observational studies**

Several publications have been submitted which report vaccine effectiveness of the TIV-HD vaccine as compared to other influenza vaccines (Table 7), mostly the TIV standard-dose.

Table 7. Overview of retrospective cohort studies to support application for Efluelda

Author / study number	Year	Design	Setting	Season	N	Primary Outcome	Result (primary estimate)
Izurieta et al	2015	retrospective cohort study	Insurance database (≥65 years)	2012 - 2013	TIV-HD: 929 730, TIV-SD: 1 615 545	probable influenza infections (rapid influenza test followed by oseltamivir treatment)	**rVE: 22% (95% CI 15–29)**
Shay et al	2017	retrospective cohort study	Insurance database (≥65 years)	2012–2013 & 2013–2014	2012-2013 TIV-HD: 1 039 645, TIV-SD: 1 683 264; 2013-2014 TIV-HD: 1 508 176 TIV-SD: 1 877 327	post-influenza death, 30 days following inpatient or emergency department encounter listing an influenza (ICD_9)	**2012–2013, rVE: 36.4% (95% CI, 9.0 - 56);** 2013-2014, rVE: 2.5% (95% CI, –46.8 - 35.3)
Richardson et al	2015	retrospective cohort study	Veterans Health Administration Service (≥65 years)	2010–2011	TIV-HD: 25 714, TIV-SD: 139 511	hospitalization for influenza or pneumonia	RR: 0.98 (95% CI: 0.68–1.40)
Young-Xu et al	2018	retrospective matched cohort study	Veterans Health Administration Service (≥65 years)	2015–2016	TIV-HD: 24 682, TIV-SD: 49 091 [matched]	hospitalization associated with pneumonia or influenza	**rVE: 25% (95% CI, 2 – 43)**
Robison et al	2018	retrospective matched cohort study	Portland metropolitan area (=>65 years) linked hospital data with immunization data	2016–2017	TIV-HD: 78 602, TIV-SD: 65 705	PCR-confirmed influenza hospitalization	*Full model* **rVE: 30.7% (95%CI 8 - 48**).
Izurieta et al	2018	retrospective cohort study	Insurance database (≥65 years)	2017–2018	TIV-HD: 8 488 136, TIV-SD: 994 763, Efluelda: 1 822 862	influenza-related hospitalisation (ICD-9)	*rVE: 8% (95% CI 7–10)*

The submitted observational studies all concern retrospective cohort studies, which are prone to confounding. Attempts have been made to account for this through different methods, i.e. selection of the study population, measurement and adjusting for potential confounders, matching, use of propensity scores. The study by Robison et al (2018) underlines the impact that residual confounding may have, showing the impact of matching for additional co-variates on the estimates. The presence of bias in reported estimates can therefore not fully be excluded.

Furthermore, none of the studies apart from Robison et al used a virologically confirmed endpoint and the validity of using ICD9 codes in the different database settings is not entirely clear – i.e. the extent of misclassification of outcomes. This could have an impact on the determination or relative effectiveness estimates.

It is unclear how accurately vaccination status was determined and whether misclassification is an issue – in particular between different types of vaccines.
Another issue may be that persons who receive the HD vaccine could be different to persons who receive the SD vaccine. This is said to have played a potential role in the study by Richardson et al, which took place when supplies of TIV-HD vaccine were limited and these were reserved for the more frail possibly explaining the lack of rVE vs TIV-SD observed in that study.

With these limitations in mind, the studies have certain strengths as well, as they are large in size, use appropriate methods to account for potential confounding (which may or may not be sufficient), but also as studies in both Medicare setting as in the Veterans Health Administration setting replicate the study in different seasons – yet this does result in conflicting estimates (both for the Veterans Health Administration as for the Medicare setting) which may simply be down to the severity of the influenza epidemic in different seasons (in line with the cluster-randomised trial discussed earlier, a larger impact could be expected in A/H3N2 dominated seasons compared to A/H1N1 dominated seasons).

In conclusion, the observational (retrospective cohort) studies may suggest that the increased protection against confirmed influenza could translate in reduced rates of pneumonia, hospitalisation and maybe even death related to influenza, yet the level of evidence is insufficient to be considered conclusive. As this effect was however also observed in the cluster-randomised controlled trial in the nursing home setting discussed earlier, taken together the evidence is considered sufficient to conclude that the increased protection against confirmed influenza associated with the HD influenza vaccine may also translate into increased protection against complications of influenza such as pneumonia and hospitalisation associated with influenza although the impact may vary per season.

IV.5 Clinical safety

Exposure
The safety of Efluelda was assessed in a total of 1897 subjects who received 1 injection of Efluelda in 1 pivotal clinical study (QHD00013; 1777 subjects) and 1 supportive clinical study

(QHD00008; 120 subjects). The safety of Efluelda was followed for 180 days in study QHD00013. Immediate adverse event (AE) information was collected within 30 minutes after vaccination, solicited injection site and systemic reactions were collected up to 7 days after vaccination, unsolicited AEs up to 28 days after vaccination, AEs leading to withdrawal from the study and serious adverse events (SAEs) were collected from D0 through D180.
In addition, a total of 25.564 subjects have been exposed to TIV-HD through its clinical development program and post-marketing clinical trials and approximately 104.5 million doses have been distributed (US, Canada, and Australia) since 2009.

Solicited reactions
In study QHD00013, 44.1% of Efluelda recipients reported at least one solicited local reaction. Pain was reported by 41.3%, followed by erythema (6.2%) and swelling (4.9%). Most reactions were mild and resolved within 7 days of onset. Solicited systemic reactions were reported by 31.0% of Efluelda recipients. Myalgia was reported most commonly (22.7%) followed by headache (14.4%) and malaise (13.2%). Fever was reported by 0.4% of recipients. The majority of solicited systemic reactions in the study groups were of Grade 1 intensity, started within the first 3 days after vaccination, and resolved spontaneously within 7 days of onset.

Table 8. Frequency of solicited injection site reactions and systemic adverse events within 7 days after vaccination with Efluelda compared to TIV-HD, in adults 65 years of age and older (QHD00013)

	QIV-HD (N=1777)			TIV-HD (N=893)		
Subjects experiencing at least one:	**n/M**	**%**	**Frequency**	**n/M**	**%**	**Frequency**
General disorders and administration site conditions						
• *Local reactions*						
Injection Site Pain	731/1768	41.3	Very common	324/889	36.4	Very common
Injection Site Erythema	110/1768	6.2	Common	51/889	5.7	Common
Injection Site Swelling	86/1766	4.9	Common	42/887	4.7	Common
Injection Site Induration	66/1766	3.7	Common	31/887	3.5	Common
Injection Site Bruising	23/1765	1.3	Common	10/887	1.1	Common
• *Systemic reactions*						
Malaise	233/1768	13.2	Very common	119/889	13.4	Very common
Shivering	95/1768	5.4	Common	42/889	4.7	Common
Fever	7/1761	0.4	Uncommon	8/885	0.9	Uncommon
Nervous system disorders						
Headache	254/1768	14.4	Very common	121/889	13.6	Very common
Musculoskeletal and connective tissue disorders						
Myalgia	402/1768	22.7	Very common	168/889	18.9	Very common

Source: 5.3.5.1 QHD00013 CSR, Section 9, Table 9.26

n: number of subjects experiencing the endpoint listed in the first column.

M: number of subjects with available data for the relevant endpoint.

Table 9. Solicited systemic reactions after vaccine injection, by maximum intensity during the solicited period - SafAS (QHD00013)

		QIV-HD (N=1777)			TIV-HD Pooled (N=893)		
Subjects experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Any solicited systemic reactions	Any	548/1768	31.0	(28.8 ; 33.2)	264/889	29.7	(26.7 ; 32.8)
Fever	Any	7/1761	0.4	(0.2 ; 0.8)	8/885	0.9	(0.4 ; 1.8)
	Grade 1	3/1761	0.2	(0 ; 0.5)	4/885	0.5	(0.1 ; 1.2)
	Grade 2	1/1761	<0.1	(0 ; 0.3)	2/885	0.2	(0 ; 0.8)
	Grade 3	3/1761	0.2	(0 ; 0.5)	2/885	0.2	(0 ; 0.8)
Headache	Any	254/1768	14.4	(12.8 ; 16.1)	121/889	13.6	(11.4 ; 16.0)
	Grade 1	198/1768	11.2	(9.8 ; 12.8)	96/889	10.8	(8.8 ; 13.0)
	Grade 2	45/1768	2.5	(1.9 ; 3.4)	21/889	2.4	(1.5 ; 3.6)
	Grade 3	11/1768	0.6	(0.3 ; 1.1)	4/889	0.4	(0.1 ; 1.1)
Malaise	Any	233/1768	13.2	(11.6 ; 14.8)	119/889	13.4	(11.2 ; 15.8)
	Grade 1	169/1768	9.6	(8.2 ; 11.0)	93/889	10.5	(8.5 ; 12.7)
	Grade 2	51/1768	2.9	(2.2 ; 3.8)	22/889	2.5	(1.6 ; 3.7)
	Grade 3	13/1768	0.7	(0.4 ; 1.3)	4/889	0.4	(0.1 ; 1.1)
Myalgia	Any	402/1768	22.7	(20.8 ; 24.8)	168/889	18.9	(16.4 ; 21.6)
	Grade 1	325/1768	18.4	(16.6 ; 20.3)	130/889	14.6	(12.4 ; 17.1)
	Grade 2	61/1768	3.5	(2.6 ; 4.4)	32/889	3.6	(2.5 ; 5.0)
	Grade 3	16/1768	0.9	(0.5 ; 1.5)	6/889	0.7	(0.2 ; 1.5)
Shivering	Any	95/1768	5.4	(4.4 ; 6.5)	42/889	4.7	(3.4 ; 6.3)
	Grade 1	70/1768	4.0	(3.1 ; 5.0)	33/889	3.7	(2.6 ; 5.2)
	Grade 2	20/1768	1.1	(0.7 ; 1.7)	6/889	0.7	(0.2 ; 1.5)
	Grade 3	5/1768	0.3	(0.1 ; 0.7)	3/889	0.3	(0.1 ; 1.0)

n: number of subjects experiencing the endpoint listed in the first 2 columns; M: number of subjects with available data for the relevant endpoint

Reactions were reported at a numerically higher rate in recipients of Efluelda as compared to TIV-HD, yet differences were small and frequency categories of reactions were similar.

There was no comparison between Efluelda and QIV-SD administered intramuscularly.

Reactogenicity data from study FIM05 suggest that compared to a SD vaccine, there is a 15% higher rate of pain reported following TIV-HD, approximately 5% higher rates of other local reactions, 5.5% higher rate of myalgia, 6% higher rate of malaise, 4% higher rate of headache and a 1% higher rate of fever. There are also slightly higher rates of moderate to severe reactions following TIV-HD.

In conclusion, reactogenicity is increased with the HD vaccine compared to the SD vaccine.

In study QHD0008 a similar pattern of reactogenicity emerged as in study QHD00013, with overall 41.7% of recipients of Efluelda (IM route) who reported a solicited local reaction, most frequently pain (30%) and 18.3% reporting a solicited systemic reaction, mostly myalgia (15.0%).

Unsolicited AEs

Unsolicited AEs in study QHD00013 were mostly in the system-organ class (SOC) of *infections and infestations*, including upper respiratory tract infection (n=19, 1.1%), and *Respiratory, thoracic and mediastinal disorders* which included cough, reported by 30 (1.7%) subjects in the Efluelda group. 52 subjects reported AEs which were considered possibly related to vaccine, 35 (2.0%) in the Efluelda group and 17 (1.9%) in the TIV-HD group. This included injection site reactions in 13 subjects (0.7%) and 7 subjects (0.8%) in the Efluelda and TIV-HD group, respectively.

Unsolicited non-serious possibly related adverse reactions (systemic) were reported by a total of 22 (1.2%), and 10 subjects (1.1%) in the Efluelda and TIV-HD groups, respectively. Adverse reactions reported following Efluelda were mostly in the SOC *Respiratory, thoracic and mediastinal disorders* (n=5, 0.3%) and *Gastrointestinal disorders* (n=4, 0.2%). None of the adverse reactions were of Grade 3 intensity.

The following unsolicited AEs were additionally considered possibly related to vaccine. These occurred in <1% of subjects: asthenia, dyspepsia, lethargy, night sweats, rash, muscular weakness, vomiting, fatigue, arthralgia, dizziness, pain in extremity, pruritus, urticaria and flushing.

In study QHD0008 6.7% of subjects who received Efluelda (n=4) reported an unsolicited adverse event. One event was considered possibly related to Efluelda (oropharyngeal discomfort).

Deaths
A total of 5 deaths were reported throughout QHD00013 study: 3 (0.2%) subjects in the Efluelda group and 2 (0.2%) subjects in the TIV-HD pooled group. Cause of death was sudden natural causes (n=1, Efluelda), myocardial infarction (n=1, TIV-HD1), prostate cancer (n=1, Efluelda), pneumonia (n=1, TIV-HD1) and acute respiratory infection (n=1, Efluelda). There were no deaths considered by the investigator possibly related to vaccination with Efluelda.

There were no deaths in study QHD0008.

In study FIM05 there were no deaths within the 28 days after vaccination. During the rest of the study deaths were balanced between the two vaccine groups: 16 (0.6%) among TIV-HD subjects and 7 (0.6%) among TIV-SD subjects.

In study FIM12 there were a total of 83 (0.52%) and 84 (0.53%) deaths in the TIV-HD and TIV-SD groups, respectively. Of these deaths, 6 occurred within 30 days after vaccination, all in the TIV-HD group. The causes of these deaths were congestive heart failure, head injury, cerebral haemorrhage, pneumonia, respiratory fume inhalation disorder and myocardial infarction. None of these 6 deaths were considered by the Investigator or Sponsor to be related to vaccination.

Hypothetically, influenza vaccine may trigger acute myocardial infarction (AMI) as influenza infection is associated with AMI. A recent meta-analysis of case control studies has however suggested that influenza vaccines protect against AMI (pooled odds ratio of 0.71 (95% CI 0.56 to 0.91)) (Barnes et al, 2015). Two subjects had underlying risk factors for AMI. A potential role of the Efluelda based upon available information cannot be ruled out, yet there is no strong evidence to implicate causality.
For the two deaths following acute respiratory failure and pneumonia in study QHD00013, there is no indication in the narratives that influenza was suspected or implicated, hence it is unlikely but not impossible that these are vaccine failures. The death following pneumonia in

study FIM12 was too close to vaccination for the vaccine to have been able to have an impact if it were influenza (8 days).

Other serious adverse events
In study QHD00013 there were a total of 162 SAEs which were by majority related to underlying comorbidities. There was one SAE which was considered possibly related to vaccine, a small fibre inflammatory neuropathy 40 days after vaccination. Considering the timing and potential confounding factors the MAH considered the event unlikely related, however based upon available data causality cannot be excluded.

There were no SAEs in study QHD0008.

In study FIM05, 249 (6.5%) subjects reported SAEs (156 [6.1%] TIV-HD subjects and 93 [7.4%] TIV-SD subjects). Two of the SAEs were considered to be related to vaccination by the Investigator including a case of myasthenia gravis following TIV-SD and exacerbation of Crohn's disease following receipt of TIV-HD. Although the MAH considers alternative causes more likely for these SAEs based on available data, causality cannot be excluded.

In study FIM12, a total of 1323 (8.27%) subjects experienced at least 1 SAE in the TIV-HD group and 1442 (9.02%) subjects experienced at least 1 SAE in the TV-SD group. SAEs were most frequently reported in the SOC *Cardiac disorders* (257 [1.61%] subjects in the TIV-HD group and 287 [1.79%] subjects in the TIV-SD group), with the most frequently reported events within this SOC being atrial fibrillation (51 [0.32%] subjects in the TIV-HD group and 67 [0.42%] subjects in the TIV-SD group), cardiac failure congestive (34 [0.21%] subjects in the TIV-HD group and 51 [0.32%] subjects in the TIV-SD group), and myocardial infarction (35 [0.22%] subjects in the TIV-HD group and 31 [0.19%] subjects in the TIV-SD group).

There were three events considered related to vaccine in the TIV-HD group: acute disseminated encephalomyelitis (ADEM), left cranial VIth nerve paralysis 1 day after vaccination and hypovolemic shock 1 day after vaccination. Whilst the investigator considered these events related to vaccination, the MAH did not.

Regarding the case of cranial VIth nerve paralysis with onset 1 day after vaccination, it can be agreed with the MAH that there is an alternative explanation (pre-existing condition of hypertension, the event was potentially triggered by an ischemic reaction). Although it cannot be excluded that the trigger was inflammation of the nerve, as suggested by the MAH the timing of 1 day is too short for this to develop and the findings are more supportive of hypertension as a trigger for microvascular cranial nerve palsy.

The pathophysiology of ADEM is not completely understood, however infections have been considered to be a trigger. Although ADEM has been reported following vaccination, a clear causal relationship has never been demonstrated aside from rabies vaccine. In the present case there is confounding by a probable infection (mycoplasma/mycobacterial) and a period of 117 days between onset and vaccination. If the onset is over 28-42 days after exposure, relatedness becomes unlikely (most cases of ADEM start within the 7 to 14 day period

following an infection).

The hypovolemic shock was most likely due to diarrhoea in which an infectious aetiology was not ruled out.

In study FIM07, 408 (6.7%) and 197 (6.5%) subjects in the TIV-HD and TIV-SD groups, respectively, experienced at least 1 SAE. There were three SAEs considered related to vaccination: cardiac chest pain in a subject who received TIV-HD, a case of Bell's palsy in the TIV-SD group and a case of immune thrombocytopenia in the TIV-SD group.

Considering the effect of intrinsic and extrinsic factors on the safety, there was a higher rate of reactogenicity in the younger age cohort of females (65- <75 yrs) which is in line with other vaccine safety evaluations, where a higher rate of reactions is generally observed in women. A higher rate of SAEs in older subjects and those with underlying chronic illnesses is not wholly unexpected, as for example the risk of hospitalisation increases with increasing age or with the presence of underlying chronic illness. There seems to be no relation with related SAEs and age or other intrinsic factors.

Table 10. AEs by age category

	QIV-HD			TIV-HD Pooled		
	65-74 years	75-84 years	85 years and older	65-74 years	75-84 years	85 years and older
CNS (Central Nervous System [confusion/extrapyramidal])‡: n (%) of subjects	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)
(95% CI)	(0.0;0.3)	(0.0;0.6)	(0.0;5.7)	(0.0;0.6)	(0.0;1.9)	(0.0;11.6)
AE related to falling§: n subjects (%)	15 (1.3%)	8 (1.4%)	0 (0%)	14 (2.4%)	2 (0.7%)	0 (0%)
(95% CI)	(0.7;2.2)	(0.6;2.7)	(0.0;5.7)	(1.3;4.1)	(0.1;2.5)	(0.0;11.6)
Cardiovascular events**: n (%) of subjects	8 (0.7%)	17 (3.0%)	0 (0%)	10 (1.7%)	5 (1.7%)	1 (3.3%)
(95% CI)	(0.3;1.4)	(1.7;4.7)	(0.0;5.7)	(0.8;3.2)	(0.6;4.0)	(0.1;17.2)
Infections and infestations††: n (%) of subjects	53 (4.6%)	30 (5.3%)	6 (9.5%)	32 (5.6%)	11 (3.8%)	2 (6.7%)
(95% CI)	(3.5;6.0)	(3.6;7.4)	(3.6;19.6)	(3.8;7.8)	(1.9;6.7)	(0.8;22.1)
Cerebrovascular events‡‡: n (%) of subjects	4 (0.3%)	2 (0.4%)	0 (0%)	1 (0.2%)	1 (0.3%)	0 (0%)
(95% CI)	(0.1;0.9)	(0.0;1.3)	(0.0;5.7)	(0.0;1.0)	(0.0;1.9)	(0.0;11.6)

* AEs = Means unsolicited non-serious AEs recorded in active phase (ie, D0-D28) and SAEs (from D0 to 6-month of follow-up). AEs from Listing 7.4 of Appendix 16 are excluded.
† ie, at Visit 2 (D28)
‡ After review of AE coded via MedDRA in the study (unsolicited non-serious within 28 days + SAEs), selection of 'Confusional state' Preferred Term (PT) inside the Primary SOC 'Psychiatric disorders"
§ After review of AE coded via MedDRA in the study (unsolicited non-serious within 28 days + SAEs), selection of several Preferred Term (PT) inside the Primary SOC 'Injury, poisoning and procedural complications'
** After review of AE coded via MedDRA in the study (unsolicited non-serious within 28 days + SAEs), selection of the two Primary SOC 'Cardiac disorders' and ' Vascular disorders'
†† After review of AE coded via MedDRA in the study (unsolicited non-serious within 28 days + SAEs), selection of the Primary SOC 'Infections and infestations'
‡‡ After review of AE coded via MedDRA in the study (unsolicited non-serious within 28 days + SAEs), selection of several Preferred Term (PT) inside the Primary SOC 'Nervous system disorders'

Post-marketing Data for TIV-HD

Approximately 104.5 million doses of TIV-HD were distributed (US, Canada, and Australia) since 2009. Assuming that persons received one dose and that all the doses distributed were administered, approximately 104.5 million individuals, at the most, may have received TIV-HD since its approval.

The following events have been spontaneously reported during the post-marketing use of TIV-HD. These AEs may occur in people receiving Efluelda:

- Blood and Lymphatic System Disorders: thrombocytopenia, lymphadenopathy
- Immune System Disorders: anaphylaxis, other allergic/hypersensitivity reactions

(including angioedema)
- Eye Disorders: ocular hyperaemia
- Nervous System Disorders: Guillain-Barré syndrome, convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), paraesthesia
- Vascular Disorders: vasculitis, vasodilatation
- Respiratory, Thoracic and Mediastinal Disorders: dyspnoea, wheezing, throat tightness oropharyngeal pain, and rhinorrhoea
- General Disorders and Administration Site Conditions: asthenia, chest pain
- Gastrointestinal Disorders: vomiting

The considerable post-licensure experience with the TIV-HD is considered relevant for the Efluelda as adverse reactions observed during the post-licensure monitoring of safety can be expected with Efluelda as well. This experience is therefore be reflected in the SmPC.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Efluelda.

Table 10. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

Benefits

In support of the application for the Efluelda vaccine for the indication of prevention of influenza in adults aged 65 and older the MAH submitted a comprehensive data package.

Two studies are considered pivotal to this application; firstly study FIM12 which evaluated the superiority of TIV-HD (60 µg HA per strain) over TIV-SD (15 µg HA per strain) in preventing laboratory confirmed influenza associated with influenza-like illness in adults aged 65 years of age and older. Secondly, study QHD00013 which provides the bridge between the TIV-HD vaccine and the Efluelda vaccine, through demonstrating non-inferior immunogenicity and a similar safety profile of Efluelda compared with TIV-HD in adults 65 years of age and older. The methods of both studies were in general acceptable.

For study FIM12 case definitions and defined endpoints for the primary objective were considered appropriate. Study FIM12 demonstrated superiority of TIV-HD as compared to a

standard-dose TIV in providing protection against laboratory-confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) for both study years combined, with an estimated rVE of 24.24% (95% CI 9.69; 36.52). A post-hoc sensitivity analysis showed that with realistic assumptions on the missing data, superiority using the 9.1% margin is maintained, or at least superiority using the (not pre-defined) 0% margin. The design of study QHD00013 had been discussed in the scientific advice and was agreed. However, considering the lack of a correlate of protection the relevance of non-inferiority margins is unknown; therefore all immunological parameters were reviewed before concluding on the immunogenicity of the Efluelda vaccine.
Even though non-inferiority could be concluded according to the pre-defined margins, there was some suggestion of a higher response to A/H1N1 with either TIV-HD as compared to Efluelda when considering the estimated GMTs. This was also reflected by the GMTr (ratios of the GMT post-dose/pre-dose) for the TIV-HD1 vaccine (estimated GMTr in Efluelda group was 4.38, 95% CI: 4.11-4.66 as compared with 5.57, 95% CI: 4.85-6.39 in the TIV-HD1 group) CIs do not overlap but do for the TIV-HD2 vaccine (estimated GMTr: 4.76, 95% CI 4.16 – 5.44). For the seroconversion outcomes the difference was only evident for one of the TIV-HD vaccines. Considering the seroprotection rates the response was similar for all vaccine groups (Efluelda 95.1%; TIV-HD1: 96.7%; TIV-HD2: 95.6%). Considering the neutralising antibodies, the GMTs against the A/H1N1 were considerably higher in the Efluelda group compared to the TIV-HD2 group (2229 vs 1686), and marginally higher compared to the GMT in the TIV-HD1 group (2050). This negates any potential concerns from the HAI analyses of possible lower responses to the A strain with the Efluelda vaccine limiting the ability to bridge to the clinical evidence obtained with the TIV-HD vaccine.
For all other strains (i.e. A/H3N2 and either B strain) the results were similar between the Efluelda and TIV-HD vaccine groups for all endpoints.
In conclusion, study QHD00013 demonstrated that the results from FIM12 were also relevant to the Efluelda vaccine, as the response to the Efluelda vaccine was shown to be non-inferior to TIV-HD vaccines with alternating B strains.
Further, a large cluster-randomised trial in a care home setting backed up with several observational, retrospective cohort studies provide evidence sufficient to conclude that the increased protection against confirmed influenza associated with the HD influenza vaccine may also translate into increased protection against complications of influenza such as pneumonia and hospitalisation associated with influenza, although the impact may vary per season.

Risks
Although relatively few persons >65 years of aged were vaccinated with Efluelda in clinical studies (n=1897; a number that would normally be considered limited for characterising the safety of a new vaccine), there is considerable experience with the TIV-HD vaccine with a total of 25.564 subjects exposed to TIV-HD in clinical trials and approximately 104.5 million doses distributed (US, Canada and Australia) since 2009. Considering the difference between the TIV-HD and Efluelda is the total amount of antigen (60 µg higher in the Efluelda vaccine) it is agreed with the MAH that the safety data collected for TIV-HD is relevant to inform the safety profile of Efluelda.

Reactions to the vaccine are common, with just over 40% of subjects in clinical studies with Efluelda reporting at least one reaction. Considering reactions as reported in QHD00013, this concerned mostly pain in response to injection (41.3%), followed by myalgia reported by 22.7% of subjects, headache (14.4%) and malaise (13.2%). Reactions were mostly mild and of short duration.
Compared to a standard-dose vaccine, reactions were more common with the high-dose vaccine: 15% more subjects reported pain following TIV-HD compared to TIV, other reactions were reported at approximately 5% higher rates at most.
Unsolicited adverse events that were considered possibly related consisted mostly of reactions already listed under solicited adverse events. The following unsolicited adverse events were additionally considered possibly related to vaccine. These occurred in <1% of subjects: asthenia, dyspepsia, lethargy, night sweats, rash, muscular weakness, vomiting, fatigue, arthralgia, dizziness, pain in extremity, pruritus, urticaria, and flushing. These are reflected in the SmPC.
None of the deaths in the clinical studies were considered possibly related to Efluelda or TIV-HD. The frequency of non-serious AEs, deaths, and SAEs after TIV-HD vaccination was comparable to TIV-SD.
Post-marketing experience with TIV-HD is considerable, and spontaneously reported adverse events during the post-marketing use of TIV-HD considered likely to be related to vaccination are reflected in section 4.8 of the SmPC of Efluelda. SAEs following TIV-HD are also known to occur following standard-dose influenza vaccines, including Guillain-Barré syndrome, convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, asthenia, chest pain, anaphylaxis, other allergic/hypersensitivity reactions, thrombocytopenia, lymphadenopathy.
Overall, the safety profile of Efluelda in adults ≥65 years of age is characterised mostly by mild reactogenicity consisting of mainly pain at the injection site.

Benefit/risk balance

The higher dose of HA antigen in Efluelda compared to standard-dose vaccines can be assumed to translate into increased protection against laboratory influenza, as has been demonstrated for the TIV-HD vaccine. The real benefit for the targeted indication is not protection against influenza as much as it is the protection against the complications of influenza. This has been demonstrated in a large cluster-randomised controlled trial with TIV-HD, and is backed up by several observational studies and supplementary analysis from the MAH's pivotal efficacy study with the TIV-HD vaccine. The size of this benefit appears to be dependent on the season, whether it is dominated by A/H1N1 or A/H3N2. The benefit appears greater against A/H3N2. It is known that A/H3N2 has a greater impact on older adults, causing more morbidity and mortality, as compared to A/H1N1, therefore it is considered that Efluelda might have a greater impact when used in vaccination programmes.
The safety profile remains acceptable despite the higher amount of antigen, as whilst reactogenicity is increased as compared to standard-dose vaccines, this remains mild and mostly driven by pain at the injection site. Other adverse events which are considered possibly related to TIV-HD or Efluelda are similar to what is known from other influenza vaccines and there is no specific safety concern with the Efluelda vaccine.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Vaxigrip Tetra (DE/H/1949/001/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Efluelda, suspension for injection in pre-filled syringe has a proven chemical-pharmaceutical quality. The higher dose of HA antigen in Efluelda compared to standard-dose vaccines can be assumed to translate into increased protection against laboratory influenza, as has been demonstrated for the TIV-HD vaccine. The safety profile remains acceptable despite the higher amount of antigen.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. Considering the higher protection against influenza and the complications of influenza in older adults ≥ 65 year as compared to the standard-dose vaccine and the acceptable safety profile of Efluelda, the benefit/risk balance is considered positive. The member states have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 1 April 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

Literature references

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