PERIODIC BENEFIT RISK EVALUATION REPORT FOR:
GCFLU Quadrivalent Pre-filled Syringe inj.
GCFLU Quadrivalent inj.
GCFLU Quadrivalent Multi inj.

(Influenza Vaccine (Split Virion, Inactivated, Quadrivalent))

Marketing Authorization Holder	GC Biopharma Corp. (Green Cross Corporation) 107, Ihyeon-ro 30beon-gil, Giheung-gu, Yongin-si, Gyeong gi-do, 16924, Republic of Korea
International Birth Date	26-Nov-2015 (GCFLU Quadrivalent Pre-filled Syringe inj.) 01-Apr-2016 (GCFLU Quadrivalent inj.) 20-May-2016 (GCFLU Quadrivalent Multi inj.)
Period Covered by Report	26-Nov-2021 to 25-Nov-2022
Data Lock Point (DLP)	25-Nov-2022
PBRER Version No.	7.0
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Signature Page

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Executive Summary

This document is the seventh Periodic Benefit-Risk Evaluation Report (PBRER) for GCFLU Quadrivalent Pre-filled Syringe inj., GCFLU Quadrivalent inj. and GCFLU Quadrivalent Multi inj. in the format proposed by the ICH note for guidance on Periodic Benefit-Risk Evaluation Reports (ICH Topic E2C (R2)).

It summarizes the safety data covering the period from 26 November 2021 to 25 November 2022. GCFLU Quadrivalent Pre-filled Syringe inj., GCFLU Quadrivalent inj. and GCFLU Quadrivalent Multi inj. will be referred as ***GCFLU QIV*** for the remainder of the report. ***GCFLU QIV*** is quadrivalent inactivated influenza vaccine with four influenza virus strains (two A subtypes and two B subtypes).

This vaccine complies with the WHO recommendations for the 2021-2022 Northern hemisphere influenza season, 2022 Southern hemisphere influenza season, and 2022-2023 Northern hemisphere influenza season.

GCFLU QIV is manufactured using fertilized egg and is indicated for prophylaxis of influenza.

GCFLU QIV provides active immunization against four influenza virus strains (two A subtypes and two B subtypes) contained in the vaccine. Although multiple mechanisms, including cellular immunity, may contribute to vaccine-induced protection against influenza, influenza vaccines induce antibodies against virus Hemagglutinin and Neuraminidase antigens, thereby blocking viral attachment to human respiratory epithelial cells. Specific levels of Hemagglutinin Inhibition antibody titer post-vaccination with inactive influenza virus vaccines have not been correlated with protection from influenza illness but the antibody titers have been used as a measure of vaccine activity. In some human challenge studies of other influenza viruses, antibody titers of >1:40 have been associated with protection from influenza illness in up to 50% of subjects.

GC Biopharma Corp. (Green Cross Corporation) has developed ***GCFLU QIV*** in house and obtained a marketing authorization (MA) for GCFLU Quadrivalent Pre-filled Syringe inj. on 26 November 2015, GCFLU Quadrivalent inj. on 01 April 2016, and GCFLU Quadrivalent Multi inj. on 20 May 2016 in Republic of Korea. In addition, prequalification approval by the WHO was received for GCFLU Quadrivalent inj. and GCFLU Quadrivalent Multi inj. on 21 December 2016 and 03 April 2017, respectively.

During this reporting period, GC Biopharma Corp. has obtained MA for GCFLU Quadrivalent Pre-filled Syringe inj. in Argentina on 01 December 2021, in Myanmar on 23 February 2022, in Indonesia on 09 April 2022, and in Syria on 22 May 2022. Additionally, in Moldova, conditional MA for GCFLU Quadrivalent Pre-filled Syringe inj. obtained on 10 September 2020 was converted to standard MA during this period.

Thus, as of the DLP, MA for GCFLU Quadrivalent Pre-filled Syringe inj. is held in Fourteen (14) countries; Republic of Korea, Iran, Georgia, Guatemala, Ukraine, Moldova, Mongolia, Thailand, Tunisia, Vietnam, Argentina, Myanmar, Indonesia, and Syria. GCFLU Quadrivalent inj. and GCFLU Quadrivalent Multi inj. have been currently approved in only one country, Republic of Korea.

No new license application rejections, failures to obtain a license renewal, drug suspensions or

restrictions on distribution for safety reasons were taken during the period covered by this report.

GC Biopharma Corp.'s current reference safety information (RSI) for ***GCFLU QIV*** is the Summary of Product Characteristics. During the reporting period, there were (2) two times of changes on Quantitative compositions of vaccine virus accordance with WHO recommendations on 24 January 2022 and 10 March 2022 respectively.

There were no MAH-sponsored clinical trials or non-interventional studies completed or ongoing during the reporting period.

Cumulatively, a total of 2,147 individuals were exposed to ***GCFLU QIV*** in eight (8) MAH-sponsored clinical trials.

It is estimated that a total of 15,624,700 doses of ***GCFLU QIV*** were distributed during the reporting period. The cumulative number of distributions since the International Birth Date (IBD) was 50,799,230 doses of ***GCFLU QIV*** in total.

From the Development International Birth Date (DIBD) to the DLP, a total of 53 serious adverse events were reported in subjects who received ***GCFLU QIV*** during the clinical development program.

During the reporting period, 5 serious adverse drug reactions and 17 non-serious adverse drug reactions were reported from spontaneous individual case safety reports. Cumulatively, 46 serious and 272 non-serious adverse reactions have been reported from post-marketing sources since the international birth date.

During this current review period, no new events were identified for evaluation as a potential safety concern. Therefore, no new relevant safety findings which would necessitate a change in the current reference safety information for ***GCFLU QIV*** were identified.

No additional risks have been identified compared to trivalent inactivated influenza vaccines.

The safety data remain in accordance with the safety information presented in the RSI. The overall data continue to support the favorable benefit-risk profile for ***GCFLU QIV***.

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Abbreviations

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
ADEM	Acute disseminated encephalomyelitis
ADR	Adverse Drug Reaction
AE	Adverse Event
ANCA	Anti-neutrophil cytoplasmic antibody
APGAR	Appearance , Pulse, Grimace, Activity, Respiration
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
DIBD	Development International Birth Date
DLP	Data Lock Point
DTaP	Diphtheria, tetanus, acellular pertussis vaccine
FDA	Food and Drug Administration
GBS	Guillain-Barre Syndrome
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HA	Hemagglutinin
HI	Hemagglutinin Inhibition
HLA	Human Leukocyte Antigen
IBD	International Birth Date
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
IgE	Immunoglobulin E
IIT	Investigator Initiated Trial
IIV3	Trivalent inactivated influenza vaccines
IIV4	Quadrivalent inactivated influenza vaccine
IND	Investigational New Drug application
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Republic of Korea Ministry of Food and Drug Safety
MMR	Measles, mumps, rubella
MTX	Methotrexate
NH	Northern Hemisphere
ORS	Oculo-respiratory syndrome
PBRER	Periodic Benefit-Risk Evaluation Report
PCV13	Pneumococcal 13-valent conjugate vaccine
PFS	Pre-filled syringe
PP	per protocol
PQ	Pre-Qualification
PT	Preferred Term
QIV	Quadrivalent influenza vaccines
RA	Rheumatoid Arthritis
ROR	Reporting odds ratio
RSI	Reference Safety Information
SADR	Serious Adverse Drug Reactions
SAE	Serious Adverse Event
SH	Southern Hemisphere

SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
TIV	Trivalent influenza vaccines
US	United States of America
WHO	World Health Organization

1. Introduction

This document is the seventh Periodic Benefit-Risk Evaluation Report (PBRER) for GCFLU Quadrivalent Pre-filled Syringe inj., GCFLU Quadrivalent inj. and GCFLU Quadrivalent Multi inj. in the format proposed by the ICH note for guidance on Periodic Benefit-Risk Evaluation Reports (ICH Topic E2C (R2)). It summarizes the safety data covering the period from 26 November 2021 to 25 November 2022.

The International Birth Dates (IBDs) are 26 November 2015, 01 April 2016, and 20 May 2016 respectively for GCFLU Quadrivalent Pre-filled Syringe inj., GCFLU Quadrivalent inj. and GCFLU Quadrivalent Multi inj. To comply with the Certificate of Pharmaceutical Product issued by the Republic of Korea Ministry of Food and Drug Safety (MFDS) for ***GCFLU QIV***, product information is as below:

- product information for use in the 2021-2022 Northern hemisphere influenza season is as below:
    - GCFLU Quadrivalent Pre-filled Syringe inj. (0.5 mL/PFS); GCFLU Quadrivalent inj. (0.5 mL/vial); GCFLU Quadrivalent Multi inj. (5 mL/vial)
    - In 0.5 mL of the product, purified inactivated influenza virus antigen type A [A/Victoria/2570/2019 IVR-215 (H1N1)] 15μg, purified inactivated influenza virus antigen type A [A/Cambodia/e0826360/2020 IVR-224 (H3N2)] 15 μg, purified inactivated influenza virus antigen type B [B/Washington/02/2019] 15 μg, purified inactivated influenza virus antigen type B [B/Phuket/3073/2013] 15 μg
- product information for use in the 2022 Southern hemisphere influenza season is as below:
    - GCFLU Quadrivalent Pre-filled Syringe inj. (0.5 mL/PFS); GCFLU Quadrivalent inj. (0.5 mL/vial); GCFLU Quadrivalent Multi inj. (5 mL/vial)
    - In 0.5 mL of the product, purified inactivated influenza virus antigen type A [A/Victoria/2570/2019 IVR-215 (H1N1)] 15 μg, purified inactivated influenza virus antigen type A [A/Darwin/9/2021 SAN-010 (H3N2)] 15 μg, purified inactivated influenza virus antigen type B [B/Austria/1359417/2021 BVR-26] 15 μg, purified inactivated influenza virus antigen type B [B/Phuket/3073/2013] 15 μg
- product information for use in the 2022-2023 Northern hemisphere influenza season is as below:
    - GCFLU Quadrivalent Pre-filled Syringe inj. (0.5 mL/PFS); GCFLU Quadrivalent inj. (0.5 mL/vial); GCFLU Quadrivalent Multi inj. (5 mL/vial)
    - In 0.5 mL of the product, purified inactivated influenza virus antigen type A [A/Victoria/2570/2019 IVR-215 (H1N1)] 15μg, purified inactivated influenza virus antigen type A [A/Darwin/9/2021 SAN-010 (H3N2)] 15 μg, purified inactivated influenza virus antigen type B [B/Austria/1359417/2021 BVR-26] 15 μg, purified inactivated influenza virus antigen type B [B/Phuket/3073/2013] 15 μg

GCFLU Quadrivalent Pre-filled Syringe inj., GCFLU Quadrivalent inj. and GCFLU Quadrivalent Multi inj. will be referred as ***GCFLU QIV*** for the remainder of the report.

In addition to the active ingredient, each 0.5 mL sized vial (or PFS) contains the following ingredients: sodium chloride (as a buffer) 4mg; potassium chloride (as a buffer) 0.1 mg; disodium hydrogen phosphate dihydrate (as a buffer) 0.6 mg; potassium dihydrogen phosphate (as a buffer) 0.1 mg; water for injection q.s.; needle (sterilized disposable needle) 25G x 5/8 (0.5 x 16 mm) 1 ea (only for GCFLU Pre-filled syringe inj.). Unlike GCFLU Quadrivalent Pre-filled Syringe inj. and GCFLU Quadrivalent inj., GCFLU Quadrivalent Multi inj. also contains thimerosal (0.01 w/v %) as preservatives. The pharmaceutical form of ***GCFLU QIV*** is a colorless or slightly whitish liquid for injection in a colorless and transparent vial or pre-filled syringe with a needle attached.

GCFLU QIV is manufactured using fertilized egg.

The posology of the products is intramuscular injection of the following doses:

- Aged 6 months and older: a single dose of 0.5 mL
- Children younger than 9 years of age who have not been vaccinated: two doses at an interval of at least 4 weeks.

The mode of action provides active immunization against the four (4) influenza virus strains (two A subtypes and two B subtypes) contained in the product. Although multiple mechanisms, including cellular immunity, may contribute to vaccine-induced protection against influenza, influenza vaccines induce antibodies against virus Hemagglutinin (HA) and Neuraminidase (NA) antigens, thereby blocking viral attachment to human respiratory epithelial cells. Specific levels of Hemagglutinin Inhibition (HI) antibody titer post-vaccination with inactive influenza virus vaccines have not been correlated with protection from influenza illness but the antibody titers have been used as a measure of vaccine activity. In some human challenge studies of other influenza viruses, antibody titers of >1:40 have been associated with protection from influenza illness in up to 50% of subjects.

2. Worldwide Marketing Approval Status

GCFLU Quadrivalent Pre-filled Syringe inj., GCFLU Quadrivalent inj. and GCFLU Quadrivalent Multi inj. were first approved on 26 November 2015, 01 April 2016, and 20 May 2016 respectively in the Republic of Korea for prophylaxis of influenza.

During the reporting period, GC Biopharma Corp. (Green Cross Corporation) has obtained Marketing Authorization (MA) in Argentina on 01 December 2021, in Myanmar on 23 February 2022, in Indonesia on 09 April 2022, and in Syria on 22 May 2022 for GCFLU Quadrivalent Pre-filled Syringe inj. 0.5mL. In addition, conditional MA obtained in Moldova on 10 September 2020 was converted to standard MA during the reporting period.

As of the Data Lock Point (DLP), the MA for GCFLU Quadrivalent Pre-filled Syringe inj. is held in Fourteen (14) countries; Republic of Korea, Iran, Georgia, Guatemala, Ukraine, Moldova, Mongolia, Thailand, Tunisia, Vietnam, Argentina, Myanmar, Indonesia, and Syria. GCFLU Quadrivalent inj.

and GCFLU Quadrivalent Multi inj. is currently approved in only one country, Republic of Korea.

For the reference purpose, GC Biopharma Corp. received World Health Organization (WHO) prequalification (PQ) for GCFLU Quadrivalent inj. on 21 December 2016 and GCFLU Quadrivalent Multi inj. on 03 April 2017.

A detailed list of worldwide marketing authorization status is provided in Table 1.

Table 1 World-wide Market Authorization Status

Country	Status	Date of First Approval	Trade Name(s)
Republic of Korea	Approved	26 November 2015	GCFLU Quadrivalent Pre-filled Syringe inj.
	Approved	01 April 2016	GCFLU Quadrivalent inj.
	Approved	20 May 2016	GCFLU Quadrivalent Multi inj.
Iran	Approved	24 July 2018	GCFLU Quadrivalent Pre-filled Syringe inj. 0.5mL
Georgia	Approved	22 July 2019	GCFLU Quadrivalent Pre-filled Syringe inj. 0.5mL
Guatemala	Approved	28 July 2020	GCFLU Quadrivalent Pre-filled Syringe inj. 0.5mL
Ukraine	Approved	11 August 2020	GCFLU Quadrivalent Pre-filled Syringe inj. 0.5mL
Moldova	Approved	10 September 2020	GCFLU Quadrivalent Pre-fillled Syringe inj. 0.5mL
Mongolia	Approved	23 September 2020	GCFLU Quadrivalent Pre-filled Syringe inj. 0.5mL
Thailand	Approved	26 January 2021	GCFLU Quadrivalent Pre-filled Syringe inj. 0.5mL
Tunisia	Approved	08 April 2021	GCFLU Quadrivalent Pre-filled Syringe inj. 0.5mL
Vietnam	Approved	18 June 2021	GCFLU Quadrivalent Pre-filled Syringe inj. 0.5mL
Argentina	Approved	01 December 2021	GCFLU Quadrivalent Pre-filled Syringe inj. 0.5mL
Myanmar	Approved	23 February 2022	GCFLU Quadrivalent Pre-filled Syringe inj. 0.5mL
Indonesia	Approved	09 April 2022	GCFLU Quadrivalent Pre-filled Syringe inj. 0.5mL
Syria	Approved	22 May 2022	GCFLU Quadrivalent Pre-filled Syringe inj. 0.5mL

3. Actions Taken in the Reporting Interval for Safety Reasons

During this reporting period there was none of the following actions related to ***GCFLU QIV***:

<u>Actions related to investigational drugs:</u>

- Refusal to authorize a clinical trial for ethical or safety reasons
- Partial or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy

- Recall of investigational drug or comparator
- Failure to obtain marketing approval for a tested indication, including voluntary withdrawal of a marketing application
- Risk management activities, including:
  - Protocol modifications due to safety or efficacy concerns (e.g., dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration)
  - Restrictions in study population or indications
  - Changes to the informed consent document relating to safety concerns
  - Formulation changes
  - Addition by regulators of a special safety-related reporting requirement
  - Issuance of a communication to investigators or healthcare professionals
  - Plans for new studies to address safety concerns.

Actions related to marketed drugs:

- Failure to obtain or apply for a marketing approval renewal
- Withdrawal or suspension of a marketing approval
- Suspension of supply by the Marketing Authorization Holder (MAH)
- Risk management activities including:
  - Significant restrictions on distribution or introduction of other risk minimization measures
  - Significant safety-related changes in labelling documents that could affect the development program, including restrictions on use or population treated
  - Communications to health care professionals
  - New post-marketing study requirement(s) imposed by regulator(s).

4. Changes to Reference Safety Information

The following documents are the current Reference Safety Information (RSI) at the DLP of this report and presented in Appendix 1.

- GCFLU Quadrivalent Pre-filled syringe inj.: Summary of Product Characteristics (SmPC) dated 10 Mar 2022
- GCFLU Quadrivalent inj.: SmPC dated 10 Mar 2022
- GCFLU Quadrivalent Multi inj.: SmPC dated 10 Mar 2022

During the reporting period, changes on Quantitative compositions of vaccine virus were made in the contents of RSI, in accordance with WHO recommendations of influenza virus vaccines.

Detailed description of the updates is listed below in Table 2.

Table 2 Changes to Reference Safety Information during the Reporting Period

Date	Before	After
24-Jan-2022	**2. Quantitative composition** Purified Inactivated Influenza Virus Antigen Type A *[A/Cambodia/e0826360/2020 IVR-224 (H3N2)]* Purified Inactivated Influenza Virus Antigen Type B *[B/Washington/02/2019]* This vaccine complies with the WHO recommendations (*Northern Hemisphere*) for 2021-2022 season.	**2. Quantitative composition** Purified Inactivated Influenza Virus Antigen Type A *[A/Darwin/9/2021 SAN-010 (H3N2)]* Purified Inactivated Influenza Virus Antigen Type B *[B/Austria/1359417/2021 BVR-26]* This vaccine complies with the WHO recommendations (*Southern Hemisphere*) for *2022* season.
10-Mar-2022	**2. Quantitative composition** This vaccine complies with the WHO recommendations *(Southern Hemisphere)* for 2022 season.	**2. Quantitative composition** This vaccine complies with the WHO recommendations *(Northern Hemisphere)* for *2022-2023* season.

5. Estimated Exposure and Use Patterns

5.1 Cumulative Subject Exposure in Clinical Trials

No clinical trials, where a subject was exposed to ***GCFLU QIV***, were completed or ongoing during the reporting period.

Cumulatively, since Development International Birth Date (DIBD), there have been total eight (8) MAH-sponsored clinical trials of ***GCFLU QIV*** completed: GC3110A_P1/2a, GC3110A_AD_P3, GC3110A_C_P3, GC3110A_ED_P3, GC3110B_P3, GC3110A_IF_P3, GC3114_P1, and GC3114_P2.

For this report, the exposure to ***GCFLU QIV*** was calculated regardless of usage as test drug or comparator. ***GCFLU QIV*** refers all the quadrivalent influenza vaccine which is marketed or developed in the GC Biopharma Corp., including the high dose injection of the same ingredient, GC3114.

The cumulative number of subjects exposed to ***GCFLU QIV*** from the eight (8) completed clinical trials is presented in Table 3, Table 4, and Table 5.

In summary, regardless of comparator or test drug, total 2,147 subjects were exposed to ***GCFLU QIV*** in the completed clinical trials.

1) GC3110A_P1/2a

GC3110A_P1/2a is a randomized, open label (Part A), double-blind (Part B), active-controlled (Part B) Phase I/II a study to investigate the safety, tolerability, and immunogenicity of GC3110A (quadrivalent influenza vaccine) after intramuscular administered in healthy subjects. In the Part

B of the trial, GCFLU Pre-filled syringe inj. (trivalent influenza vaccine, TIV) was used as comparator (control drug).

The number of subjects enrolled for safety analysis: A total of 84 subjects [$GC3110A_{PartA}$ 9 subjects; $GC3110A_{PartB}$ 51 subjects; $Comparator_{PartB}$ 24 subjects]

2) GC3110A_AD_P3

GC3110A_AD_P3 is a multicenter, randomized, double-blind, active-controlled, parallel Phase III study to investigate the efficacy (immunogenicity) and safety of the GC3110A (quadrivalent influenza vaccine) after intramuscular administration in health subjects. GCFLU Pre-filled syringe inj. (TIV, control 1) and GC3110A (TIV with another B-strain lineage, control 2) were used as comparator.

The number of subjects enrolled for safety analysis: A total of 1,298 subjects [GC3110A 647 subjects; Control 1 group 325 subjects: Control 2 group 326 subjects]

3) GC3110A_C_P3

GC3110A_C_P3 is an open-label (Part 1), single arm (Part 1), randomized (Part 2), double-blind (Part 2), active-controlled (Part 2) Phase III study to evaluate the efficacy (immunogenicity) and safety of GC3110A (quadrivalent seasonal influenza vaccine) in healthy children. In the Part 2 of trial, GC FLU Pre-filled syringe inj. (TIV) was used as comparator. Among those children enrolled, subjects aged between 6 months and 3 years old received 0.25 mL (30 μg HA for 4 strains) instead of 0.5 mL.

The number of subjects enrolled for safety analysis: A total of 542 subjects [$GC3110A_{Part1}$ 15 subjects; $GC3110A_{Part2}$ 423 subjects; $Comparator_{Part2}$ 104 subjects]

4) GC3110A_ED_P3

GC3110A_ED_P3 is a phase III study to investigate the efficacy (immunogenicity) and safety of GC3110A (quadrivalent influenza vaccine) in healthy subjects aged 65 years and older.

The number of subjects enrolled for safety analysis: A total of 274 subjects.

All enrolled subjects received 0.5 mL of GC3110A (GCFLU Quadrivalent Pre-filled Syringe inj.) intramuscularly.

5) GC3110B_P3

GC3110B_P3 is a phase III, randomized, double-blind, multicenter study in healthy adults aged between 18 to 60 years, to compare the immunological efficacy and safety of GC3110B (GCFLU QIV, presented as multi-dose vial of 5 mL) with GCFLU Quadrivalent inj. (single dose, control drug).

The number of subjects enrolled for safety analysis: A total of 413 subjects [GC3110B 206 subjects; Comparator (***GCFLU QIV***) 207 subjects]

A total of four (4) pregnancies were reported during the study. All four subjects gave birth to a healthy baby. One of the subjects went through caesarean section and delivered a twin. There were

no problems during delivery and neither complications nor anomalies noted at birth for the babies of all four subjects.

6) GC3110A_IF_P3

GC3110A_IF_P3 is a phase III, open (Part 1), single arm (Part 1), randomized (Part 2), double-blind (Part 2), active-controlled (Part 2) clinical study, to investigate efficacy (immunogenicity) and safety of GC3110A (QIV). In Part 2 of the study, 0.25 mL of GCFLU Pre-filled Syringe inj. (TIV) was used as comparator. Subjects who have not been vaccinated or have not been infected by influenza were vaccinated two doses at an interval of at least 4 weeks.

The number of subjects enrolled for safety analysis: A total of 209 subjects [$GC3110A_{Part1}$ 10 subjects; $GC3110A_{Part2}$ 160 subjects; $Comparator_{Part2}$ 39 subjects]

7) GC3114_P1

GC3114_P1 is a phase I, randomized, single-blind, active-controlled clinical study to investigate safety and efficacy of GC3114 (High-dose QIV) in healthy adults. All enrolled subjects received 0.5 mL of either GC3114 as test drug or GCFLU Quadrivalent Pre-filled Syringe inj. as comparator.

The number of subjects enrolled for safety analysis: A total of 40 subjects [GC3114 30 subjects; Comparator (***GCFLU QIV***) 10 subjects]

8) GC3114_P2

GC3114_P2 is open-labeled (Part 1), single-group (Part 1), randomized (Part 2), double-blind (Part 2), active-controlled (Part 2) Phase II clinical trial to evaluate safety and efficacy (immunogenicity) of GC3114 in elderly healthy subjects aged 65 years and older. In Part 2 of the study, GCFLU Quadrivalent Pre-filled Syringe inj. was used as comparator.

The number of subjects enrolled for safety analysis: A total of 105 subjects [GC3114 75 subjects; Comparator (***GCFLU QIV***) 30 subjects]

Except for children, elderly, and pregnant women exposed to ***GCFLU QIV*** in GC3110A_C_P3, GC3110A_ED_P3, GC3110B_P3, GC3110A_IF_P3, and GC3114_P2 trial, no special populations (e.g., patients with renal or cardiac impairment; or patients with relevant genetic polymorphisms) have been exposed to ***GCFLU QIV*** since the DIBD.

Table 3 Estimated Cumulative Subject Exposure from Clinical Trials*

Treatment	Number of subjects
GCFLU QIV[1)]	**2,147**
Comparator[2)]	818
Placebo	0

*Data from completed trial as of 25 November 2022

[1)] Regardless of usage as test drug or comparator, the number of all the subjects exposed to marketed or developed ***GCFLU QIV*** including the high dose QIV GC3114

[2)] The number of subjects exposed to comparator other than ***GCFLU QIV***

Table 4 Cumulative Subject Exposure to *GCFLU QIV*[1)] from Completed Clinical Trials by Age and Sex*

Age range	Number of subjects		
	Male	Female	Total
≤2	102	95	197
>2 to 16	213	189	402
>16 to 65	460	699	1,159
>65	153	236	389
Total	**928**	**1,219**	**2,147**

*Data from completed trial as of 25 November 2022
1) Regardless of usage as test drug or comparator, the number of all the subjects exposed to marketed or developed GCFLU QIV including the high dose QIV GC3114

Table 5 Cumulative Subject Exposure to *GCFLU QIV*[1)] from Completed Clinical Trials by Racial Group*

Racial group	Number of subjects
Asian	2,147
Black	0
Caucasian	0
Other	0
Unknown	0
Total	**2,147**

*Data from completed trial as of 25 November 2022
1) Regardless of usage as test drug or comparator, the number of all the subjects exposed to marketed or developed GCFLU QIV including the high dose QIV GC3114

5.2 Cumulative and Interval Patient Exposure from Marketing Experience

5.2.1 Post-Approval Exposure

GCFLU QIV has been distributed through marketing authorization in fourteen (14) countries as presented in Table 1. Also, ***GCFLU QIV*** has been distributed to 32 more countries through import permit or based on WHO PQ approval, via UN procurement agencies such as Pan American Health Organization (PAHO) and United Nations Children's Fund (UNICEF) until the DLP.

GCFLU QIV patient exposure is based on the simplifying assumption that the number of units distributed approximates the number of doses used. The market experience is estimated based on units of ***GCFLU QIV*** commercially and non-commercially distributed during the reporting period.

A total of 15,624,700 doses of ***GCFLU QIV*** were distributed during the reporting period. The

cumulative number of distributions since the IBD was 50,799,230 doses of ***GCFLU QIV*** in total.

The summary on cumulative and interval marketing experience is presented in Table 6 and Table 7.

Table 6 Cumulative Exposure from Marketing Experience (Unit: dose)

Product	Sex			Age (years)				Dose		Formulation		Region				
	Male	Female	UK	2 to 16	>16 to 65	>65	UK	0.5mL	UK	IM	UK	EU	Japan	Mexico	US/Canada	Other
Overall	UK	UK	50,799,230	UK	UK	UK	50,799,230	UK	50,799,230	-	50,799,230	UK	UK	UK	UK	50,799,230
GCFLU Quadrivalent PFS inj. (0.5ml)	UK	UK	38,903,410	UK	UK	UK	38,903,410	UK	38,903,410	-	38,903,410	UK	UK	UK	UK	38,903,410
GCFLU Quadrivalent inj. (0.5ml)	UK	UK	6,498,120	UK	UK	UK	6,498,120	UK	6,498,120	-	6,498,120	UK	UK	UK	UK	6,498,120
GCFLU Quadrivalent Multi inj.* (5ml)	UK	UK	5,397,700	UK	UK	UK	5,397,700	UK	5,397,700	-	5,397,700	UK	UK	UK	UK	5,397,700

Table 6 includes cumulative data obtained from 26-Nov-2015 through 25-Nov-2022.
Table 6 does not include exposure data by indication since all products have a single indication; prophylaxis of influenza.
* For GCLU Quadrivalent Multi inj., the dose was calculated based on the assumption that one vial of the product contained 5mL, a volume for 10 doses.
[Abbreviations] PFS: Pre-filled Syringe; UK: Unknown; IM: intramuscular

Table 7 Interval Exposure from Marketing Experience (Unit: dose)

Product	Sex			Age (years)				Dose		Formulation		Region				
	Male	Female	UK	2 to 16	>16 to 65	>65	UK	0.5mL	UK	IM	UK	EU	Japan	Mexico	US/Canada	UK
Overall	UK	UK	15,624,700	UK	UK	UK	15,624,700	UK	15,624,700	-	15,624,700	UK	UK	UK	UK	15,624,700
GCFLU Quadrivalent PFS inj. (0.5ml)	UK	UK	10,157,900	UK	UK	UK	10,157,900	UK	10,157,900	-	10,157,900	UK	UK	UK	UK	10,157,900
GCFLU	UK	UK	1,791,000	UK	UK	UK	1,791,000	UK	1,791,000	-	1,791,000	UK	UK	UK	UK	1,791,000

Product	Sex			Age (years)				Dose		Formulation		Region				
	Male	Female	UK	2 to 16	>16 to 65	>65	UK	0.5mL	UK	IM	UK	EU	Japan	Mexico	US/Canada	UK
Quadrivalent inj. (0.5ml)																
GCFLU Quadrivalent Multi inj.* (5ml)	UK	UK	3,65,800	UK	UK	UK	3,65,800	UK	3,65,800	-	3,65,800	UK	UK	UK	UK	3,65,800

Table 7 includes interval data obtained from 26-Nov-2021 through 25-Nov-2022.

Table 7 does not include exposure data by indication since all products have a single indication; prophylaxis of influenza.

* For GCFLU Quadrivalent Multi inj., the dose was calculated based on the assumption that one vial of the product contained 5mL, a volume for10 doses.

[Abbreviations] PFS: Pre-filled Syringe; UK: Unknown; IM: intramuscular

5.2.2 Post-Approval Use in Special Populations

- Elderly and pediatric

Annual influenza vaccination is recommended for anyone 6 months and older with very rare exceptions. Pediatric population (of 6 months and older) and elderly population were included in the clinical development program of ***GCFLU QIV.***

Also, two non-interventional studies (Post-marketing surveillance, PMS) were performed for the products manufactured with the final bulk of ***GCFLU QIV***. GC3110E_PMS included 81 elderly subjects, and GC3110J_PMS included 330 infants and toddlers (6 to 23 months old), 1337 children (2 to 11 years old), and 366 adolescents (12 to18 years old). No specific safety concerns were identified in pediatric and elderly patients in both studies.

Information of elderly or pediatric patients was also collected from other foreign clinical trials (non MAH-sponsored) and spontaneous safety reports, but they are not fully listed in this section since the safety and efficacy are established in these populations.

- Pregnancy

Based on the safety reports collected during the reporting period, no cases related to maternal or paternal exposure were reported. Cumulatively, a total of nine (9) cases of exposure during pregnancy and one (1) case of paternal exposure before pregnancy were reported from spontaneous sources and GC3110J_PMS as of DLP [Refer to Section 16.3.5].

According to the RSI, inactivated influenza vaccine (egg-derived) is known that it can be used in all pregnancy cycles regardless of the pregnancy stage. There are more safety data for second trimester and third trimester compared with the first trimester. In addition, according to data on the usage of inactivated influenza vaccine collected globally, no adverse effects of the vaccine on the fetus and maternity were reported.

- Liver impairment

Fourteen (14) patients with liver impairment were included in the non-interventional study in adults (GC3110E_PMS), and no specific concern in these patients was identified.

- Others

From three (3) previously completed investigator-initiated trials (IITs), information on patients who were immunocompromised or receiving immunosuppressant was collected. GC3110L included a total 143 patients with cancers that received ***GCFLU QIV***; 48 patients were receiving immune checkpoint inhibitor and 95 patients were receiving cytotoxic chemotherapy. In another study GC3110H, a total of 320 patients with rheumatoid arthritis (RA) and under the treatment of methotrexate (MTX) received ***GCFLU QIV***. In a subsequent study of GC3110H reported through published literature (Park et al., 2022), a total of 182 RA patients receiving stable MTX treatment were vaccinated with ***GCFLU QIV***. No specific safety concerns were addressed in these patients.

5.2.3 Other Post-Approval Use

Pattern of use of the medicinal product

Before approval for use in children aged 6-35 months for ***GCFLU QIV***, which was approved on 27 September 2018 for GCFLU Quadrivalent Pre-filled syringe inj., cases regarding administration to children aged less than 3 years old (Preferred Term (PT): Product administered to patient of inappropriate age) accounted for most of the medication errors. It is thought that the fact that many marketed flu vaccines are approved for aged 6 months and older, would have caused confusion to the vaccine administrators. However, after the approval for use in patients aged 6-35 months, they were not collected as medication errors anymore, and therefore the number of medication error cases highly decreased.

Other than that, there was no available information on patterns of use of ***GCFLU QIV*** which may be considered relevant for the interpretation of safety data.

Report of use other than approved indication

No report of use other than approved indication (prophylaxis of influenza) was received during the reporting period.

6. Data in Summary Tabulations

6.1 Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA), version 25.1, has been used for coding Adverse Events (AEs) collected during the reporting period. The summary tabulations are arranged in the internationally agreed order by primary MedDRA System Organ Class (SOC) and refer to the Preferred Term (PT) level.

The SmPCs attached in Appendix 1 for this PBRER, have served as the RSI for ***GCFLU QIV*** for determining the listedness for tabulations, where required by national or regional laws or regulations.

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

A cumulative summary tabulation of Serious Adverse Events (SAEs) from the completed MAH-sponsored interventional clinical trials that have been reported from the DIBD to the DLP, organized by SOC and PT, is presented in Appendix 2.

With the exception of the cases reported in clinical trials (interventional clinical studies), cases from other sources including non-interventional post-marketing studies and reports (post-

marketing surveillance or named-patient use etc.) are summarized and discussed in the separate section (section 6.3).

Cumulatively, a total of 75 SAEs were reported through the eight (8) completed MAH-sponsored clinical trials from the DIBD to the DLP; among those, 53 SAEs were reported in ***GCFLU QIV-***administered subjects and 22 SAEs were reported in the comparator (not ***GCFLU QIV***)-treated subjects. There was no Serious Adverse Drug Reaction (SADR).

6.3 Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources

The following types of cases are included in the summary tabulations;

- Serious and non-serious adverse drug reactions from spontaneous Individual Case Safety Reports (ICSRs), including reports from healthcare professionals, consumers, scientific literature, and regulatory authorities;
- Serious adverse reactions from non-interventional studies;
- Solicited reports of serious adverse reactions.

Cumulative and interval summary tabulations of adverse reactions that have been reported from marketed experience with ***GCFLU QIV***, organized by MedDRA SOC and PT, are presented in Appendix 3.

During the reporting period, a total number of 22 adverse drug reactions (considering an initial report which also has several subsequent or follow-up reports as a single event) were received from spontaneous ICSRs; among those, there were 5 serious adverse drug reactions. No serious adverse reactions were reported from non-interventional studies during the reporting period.

Cumulatively from IBD to DLP, a total of 318 ADRs were collected by the MAH from the post-marketing spontaneous ICSRs such as reports from healthcare professionals, consumers, regulatory authority and literature; 46 serious and 272 non-serious reactions. There were no serious adverse drug reactions from non-interventional studies and solicited reports of serious adverse reactions as of DLP.

Among the spontaneous reports received by the MAH until the DLP, there were nine (9) invalid case reports, which were excluded from Appendix 3 because the cases concerned unidentified multiple patients or there was no specific event information reported. The following events were reported from these invalid cases: Alopecia, Arthralgia, Diarrhoea, Dizziness, Erythema, Headache, Incorrect dose administered, Influenza, Influenza like illness, Injection site pain, Myalgia, Pain, Pyrexia, Vaccination site erythema, Vaccination site pain, Vaccination site swelling and unspecified Adverse event.

The tabulation also includes the incidence of non-adverse event reports (special situations); 9 events during the reporting period and 74 events cumulatively.

7. Summaries of Significant safety Findings from Clinical Trials during the Reporting Interval

7.1 Completed Clinical Trials

During the reporting period, no clinical trials were completed, thus, no new safety signals were identified from the completed clinical trials.

7.2 Ongoing Clinical Trials

During the reporting period, no clinical trials were ongoing, thus, no new safety signals were identified from the ongoing studies.

7.3 Long-Term Follow-up

No new information on the effects of long-term treatment was identified during the reporting period.

7.4 Other Therapeutic Use of Medicinal Product

No programs that follow a specific protocol, with solicited reporting as per ICH Guideline E2D (e.g., expanded access programs, compassionate use programs, particular patient use, single-patient Investigational New Drug applications [INDs], treatment INDs, and other organized data collection) have been conducted for ***GCFLU QIV*** by the MAH during the reporting period.

7.5 New Safety Data Related to Fixed Combination Therapies

Not applicable

8. Findings from Non-Interventional Studies

During the reporting period, no non-interventional studies were completed, thus, no new safety information or information with potential impact on benefit-risk assessment were identified from non-interventional studies.

9. Information from Other Clinical Trials and Sources

9.1 Other Clinical Trials

During the reporting period, GC Biopharma Corp. acknowledged a published interim report (Park et al., 2022) regarding a clinical trial on ***GCFLU QIV*** vaccination in RA patients undergoing MTX treatment. The summary of the study is provided in section 11.

9.2 Medication Errors

The safety database of the company was searched using the 'narrow scope' of MedDRA SMQ 'Medication errors'. During the reporting period, eight (8) spontaneous cases of medication error were reported; cumulatively, a total of 59 spontaneous cases of medication error, including one case of 'Incorrect dose administered' reported from multiple unidentified patients. All medication error PTs from the SMQ Narrow scope are presented in the Table 8 below:

Table 8 Overview of Reported Medication Error Events

MedDRA PT	Interval	Cumulative
Accidental exposure to product	0	1
Accidental overdose	0	2
Expired product administered	0	2
Extra dose administered	5	8
Inappropriate schedule of product administration	0	1
Incorrect dose administered	0	10
Incorrect dose administered by device	1	1
Incorrect route of product administration	0	2
Product administered at inappropriate site	0	3
Product administered to patient of inappropriate age	0	20
Product preparation error	0	1
Product storage error	0	3
Wrong product administered	1	2
Wrong technique in product usage process	1	4
Total	**8**	**60**

There is no pattern of medication errors or potential medication errors that is considered relevant to the interpretation of safety data or the overall benefit-risk evaluation of ***GCFLU QIV***. No signals or risks were identified during the reporting period. No additional risk minimization measures are deemed necessary.

10. Non-Clinical Data

No new major safety findings from non-clinical *in vivo* and *in vitro* studies became available during

the period covered by this report.

11. Literature

A full review of the scientific medical literature has been conducted during the reporting period utilizing the following search strategies: 26 November 2021 to 25 November 2022.

- ((quadrivalent AND influenza vaccine) AND (adverse event OR adverse drug reaction OR toxicity OR pregnancy OR drug overdose OR off label use OR medication error OR death OR safety OR adverse experience))
- "GC Flu" and "Quadrivalent"
- Database: PubMed, Google Scholar

The search hits 58 journal articles. Five (5) articles were selected for presentation because they were considered to contain significant safety information relevant to the product. Short summaries of the articles are presented below:

Association of post-vaccination adverse reactions after influenza vaccine with mortality and cardiopulmonary outcomes in patients with high-risk cardiovascular disease: the INVESTED trial *Peikert, A., Claggett, B. L., Kim, K., Udell, J. A., Joseph, J., Desai, A. S., ... & Vardeny, O.* *Eur J Heart Fail. 2022 Nov 6. doi: 10.1002/ejhf.2716*	
Study drugs:	Influenza vaccines (high-dose inactivated TIV; containing 60 µg of hemagglutinin per strain or standard-dose inactivated QIV; containing 15 µg of hemagglutinin per strain)
Aims:	To examine the association between vaccine-related adverse reactions (ARs) and clinical outcomes (morbidity and mortality in patients with high-risk cardiovascular disease).
Study subject:	A total of 5260 patients with recent hospitalization for heart failure or acute myocardial infarction (MI), and with 7154 total vaccinations administered over three seasons.
Methods:	
INVESTED (Influenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure) trial was a randomized, multi-center, double-blind, active-controlled trial in patients hospitalized for heart failure in the previous 24 months or acute myocardial infarction in the previous 12 months and at least one additional risk factor. Eligible patients were randomized to either high-dose inactivated TIV or standard-dose inactivated QIV in a 1:1 ratio and received annual vaccination for up to three influenza seasons between 21 September 2016 and 31 January 2019. The primary outcome was time to first occurrence of all-cause death or cardiopulmonary hospitalization within each enrolling season. Vaccine-related ARs were assessed within 7 days post vaccination and included occurrence and severity. The association of vaccine-related ARs with the primary outcome and specific types of hospitalizations during each season was estimated by Cox proportional hazards models. And to account for differences between participants with and without vaccine-related ARs, propensity-adjusted models were used.	
Results/Safety:	
Among 5210 participants with available information on post-vaccination symptoms, 1968	

participants (37.8%) experienced vaccine-related ARs. Based on the total of vaccines administered, mild vaccine-related ARs were most common and occurred with 28.5% of vaccinations (76.4% of ARs), moderate ARs were experienced with 7.7% of vaccinations (20.6% of ARs), whereas severe ARs were reported only after 1.1% of vaccinations (2.9% of ARs). The most common types of post-vaccination ARs were injection site pain (60.3% of ARs, 22.6% of vaccinations), general myalgia (34.5% of ARs, 12.9% of vaccinations), and overall discomfort (22.0% of ARs, 8.2% of vaccinations).
While participants with mild to moderate vaccine-related ARs experienced lower rates of the primary outcome of all-cause death or cardiopulmonary hospitalization compared to participants without vaccine-related ARs (HR 0.81 [95% CI 0.74–0.90], p<0.001), participants with severe vaccine-related ARs appeared to share a higher risk (HR 1.68 [95% CI 1.17–2.42], p=0.005). At the same time, reduced risk for the primary outcome was found to be concurrently related primarily with local reactions and particularly injection-site pains (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.75–0.92, p<0.001), which may be related to predominantly milder reactogenicity.

Conclusions:

Mild to moderate vaccine-related ARs after influenza vaccination were associated with a reduced incidence of all-cause mortality, hospitalizations for cardiopulmonary, cardiovascular, non-cardiopulmonary, or any causes in patients with a history of hospitalization for heart failure or myocardial infarction, while severe reactions may indicate increased risk. Regarding severe ARs, considering the small number of cases and possible reporting bias, additional validation of a potential association with outcomes is required in future studies. As mild site-associated adverse events are more common, generally well tolerated and may portend a better vaccine response, the findings of the study may help alleviate vaccine hesitancy.

MAH comments:

This article supports the safety of TIV/QIV usage in patients with high-risk cardiovascular diseases. Though the physiological mechanism supporting the research outcome was not clearly elucidated in the article, the MAH agrees to authors' conclusion that mild to moderate ARs may be a marker of immune response and should not deter future vaccination. The MAH believes this article may be a useful evidence to promote influenza vaccination rates by reducing concerns about vaccine-related ARs in patients with high-risk cardiovascular diseases.

A Prospective Cohort Study on Pregnancy Outcomes of Persons Immunized with a Seasonal Quadrivalent Inactivated Influenza Vaccine during Pregnancy

Robinson, C., Oberye, J., van Boxmeer, J., Albano, J. D., Tilson, H., Scialli, A., ... & Edelman. Vaccines (Basel). 2022 Sep 21;10(10):1577. doi: 10.3390/vaccines10101577.

Study drugs:	Afluria Quadrivalent (purified, split, inactivated, egg-derived, non-adjuvanted, quadrivalent influenza virus vaccine (IIV4))
Aims:	To evaluate the safety of IIV4 in terms of adverse pregnancy outcomes and infant-related events
Study subject:	Pregnant persons residing within the US who received IIV4 at any time as part of routine pregnancy care

Methods:

This prospective observational cohort study, a post marketing commitment to FDA, was conducted over four consecutive influenza seasons from 2017–2021. The Syneos Health Registry Coordinating Center served as the single site for the study, but data were collected from obstetrics/gynecology clinics.
Pregnancy outcomes of interest included live birth, still birth, spontaneous abortion, or elective termination. Infant-related events of interest included preterm birth, low birth weight (LBW)

and major congenital malformations (MCMs). Those outcomes and events were summarized overall, by trimester of exposure, and by maternal age at conception categories. Prevalence of every single case was calculated according to each criteria.

Results/Safety:

A total of 483 pregnant persons were given IIV4 and evaluated; 477 (98.8%) reported a live birth, and there were 2 stillbirths, 4 spontaneous abortions, and no elective terminations or maternal deaths. About infant events of interest, no infant deaths were reported. The prevalence rates of infant events were as follows: preterm birth, 7.2% (upper 95% CI, 9.6%); LBW, 5.4% (upper 95% CI, 7.4%); and MCMs, 0.8% (upper 95% CI, 1.9%). Point estimates and upper 95% CIs of the observed prevalence rates were lower than or similar to background prevalence in the general US population. In details, HCPs reported five infants with an MCM, of which cases were gastroschisis (two cases), lymphangioma, syndactyly, and hypoxic ischemic encephalopathy. Among those, gastroschisis cases needed further discussion because temporal association with IIV4 exposure could not be ruled out, but noted but noted young maternal age and urinary tract infection as a contributing factor in each case.

Conclusions:

The findings of this study suggest that IIV4 exposure during pregnancy is not associated with any safety concerns based on comparison of the study results to background prevalence rates reported by the National Vital Statistics System NVSS and CDC Metropolitan Atlanta Congenital Defects Program MACDP. The results are consistent with published data from various databases and surveillance systems that monitor the safety of influenza vaccines in pregnant persons, further supporting the use of influenza vaccines in this group at high risk from influenza.

MAH comments:

This study supports the safety of IIV4 usage in pregnant women. It demonstrated favorable results on pregnancy outcomes and infant-related events, consistent with previous studies of influenza vaccination. Considering the limitation of getting safety information from post-marketing sources, MAH believes this article would provide useful evidence to encourage and recommend influenza vaccination during pregnancy in order to reduce burden of influenza infection in both pregnant women and infants.

Post-marketing surveillance study on influenza vaccine in South Korea using a nationwide spontaneous reporting database with multiple data mining methods

Lee, H., Hong, B., Kim, S., Kim, J. H., Choi, N. K., Jung, S. Y., & Shin, J. Y.
Sci Rep. 2022; 12: 20256. doi: 10.1038/s41598-022-21986-8

Study drug:	All 19 influenza vaccine products available in Korea including GC Flu Prefilled syringe inj. (egg-based, TIV) and GC Flu quadrivalent prefilled syringe inj. (egg-based, QIV)
Aims:	To address knowledge gaps by different data mining methods, and to identify and compare unexpected AEs which are potentially related to influenza vaccination by the subtypes
Study subject:	AE reports following vaccination collected in the Korea Institute of Drug Safety and Risk Management-Korea Adverse Event Reporting System (KIDS-KAERS) database from 2005 to 2019

Methods:

A post-marketing surveillance study was conducted to multiple data mining methods. From all AEs following vaccination collected in the database from 2005 to 2019, a total of 42,211 reports in the database were eligible to inclusion criteria, and the authors identified 38,221 reports after vaccination. Among these, 17,378 were reported for the influenza vaccine. 7639 were reported for QIV, 9641 for TIV, 2744 for cell-based influenza vaccine, and 14,536 for egg-based influenza vaccine.

Based on literature reviews, the study selected the following 5 possible serious and important

AEs observed after influenza vaccination: GBS, febrile conversion, anaphylaxis, narcolepsy, and Bell's palsy. To detect the signals, three signal detection algorithms were used in this study: (a) proportional reporting ratio (PRR), (b) information component (IC), and (c) tree-based scan statistics (TSS). The performance of disproportionality analysis (PRR, IC) and TSS was evaluated based on performance indicators such as sensitivity, specificity, PPV, NPV, accuracy, and AUC to identify which algorithm was more appropriate for detecting safety signals for influenza vaccines.

Results/Safety:

Compared to all other vaccines, 36 AEs including unlabeled 7 AEs were identified as safety signals of influenza vaccines detected by any data mining method at least once. All 5 serious AEs of special interest for influenza vaccine were detected as signals, except for febrile seizure. Among detected signals of influenza vaccine, narcolepsy requires special attention.
In subtype-stratified analyses, when using TIV as a comparator, 13 AEs were detected as safety signals by any data mining method at least once for QIV; 2 AEs (injection site bruising and cachexia) were unlabeled. When using cell-based vaccines as a comparator, 30 AEs were detected as safety signals by any data mining method at least once for egg-based vaccines, 4 of which were unlabeled (leg pain, tremor, injection site mass, and cachexia).
The performance indicators of each data mining method were measured based on the confusion matrix, and overall, TSS demonstrated well balance. TSS showed the highest sensitivity (77.8%), positive predictive value (PPV, 77.8%), accuracy (72.1%), and area under the curve (AUC, 70.1%) and the lowest specificity (62.5%).

Conclusions:

In this PMS study, 7 new safety signals were identified for influenza vaccine including narcolepsy as a serious AE, and TIVs and egg-based influenza vaccine showed a wide range of new safety signals when compared to QIVs and cell-based influenza vaccine, respectively. Further studies are needed to confirm the potential relationship between influenza vaccine and new safety signals. In addition, although TSS showed balanced performance, complementary use of other techniques would be beneficial when large noise due to false positives is expected.

MAH comments:

This article is meaningful for reflecting real world safety data of influenza vaccines including the MAH products, collected in South Korea. The article detected not only known AEs but also unlabeled new safety signals mainly focusing on 5 serious AEs by its subtypes. It also presents the necessity of labeling a few concerned safety signals which are unlabeled in South Korea. Though there are limitations of post-marketing sources such as inconsistent quality of ICSR, and duplicate/under-reporting, the MAH believes that this article includes important safety information related to influenza vaccines and would be worthy as a reference for further pharmacovigilance activities such as signal evaluation for ***GCFLU QIV***. Additionally, the results of performance evaluation comparing 3 data mining methods are considered useful to select the appropriate method for further activities.

A Multicenter, Prospective, Randomized, Parallel-Group Trial on the Effects of Temporary Methotrexate Discontinuation for One Week Versus Two Weeks on Seasonal Influenza Vaccination in Patients with Rheumatoid Arthritis

Park, J. K., Lee, Y. J., Shin, K., Kang, E. H., Ha, Y. J., Park, J. W., ... & Lee, E. B.
Arthritis Rheumatol. 2022 Aug 5. doi: 10.1002/art.42318.

Study drug:	A quadrivalent influenza vaccine (GC Flu, prefilled syringe)
Aims:	To investigate whether discontinuing methotrexate (MTX) for 1 week after seasonal influenza vaccination is noninferior to discontinuing for 2 weeks after vaccination in patients with rheumatoid arthritis (RA)
Study subject:	RA patients who were ages ≥19 years and had received the same dose of MTX for ≥6 weeks

Methods:

RA patients receiving a stable dose of MTX were randomly assigned at a ratio of 1:1 to discontinue MTX for 1 week or for 2 weeks after they received the quadrivalent 2021–2022 seasonal influenza vaccine containing H1N1, H3N2, B/Yamagata, and B/Victoria strains. The primary outcome measure was the proportion of patients with a satisfactory vaccine response, which was defined as ≥4-fold increase in antibody titers, as determined with the hemagglutination inhibition assay, against ≥2 of the 4 vaccine strains at 4 weeks after vaccination. The secondary outcome measures included seroconversion; a positive response to ≥1 antigens, ≥3 antigens, or 4 antigens; the frequency of seroprotection; and the fold change after vaccination in HIA antibody titers against each vaccine antigen relative to the baseline. Adverse events that were associated with vaccination were captured from the patients at each visit or telephone interview. DAS28-CRP level was determined at week 0 and at week 4 after vaccination to monitor an RA flare.

Results/Safety:

The modified intent-to-treat population included 90 patients in the 1-week MTX hold group and 88 patients in the 2-week MTX hold group. The mean ± SD MTX doses were 12.6 ± 3.4 mg/week in the 1-week MTX hold group and 12.9 ± 3.3 mg/week in the 2-week MTX hold group. The proportion of satisfactory vaccine responses did not differ between the groups (68.9% versus 75.0%; P = 0.364). The rate of seroprotection and the fold increase in antibody titers for each of the 4 influenza antigens were similar between the groups. Regarding RA disease activity, 4.5% of patients in the 1-week hold group and 12.9% of patients in the 2-week hold group experienced an RA flare over the 4 weeks after vaccination (P = 0.05). The vaccine was well tolerated. 12 AEs on 1-week hold group and 7 AEs on 2-week hold group were reported. No SAEs related to the vaccine were reported.

Conclusions:

A temporary discontinuation of MTX for 1 week after vaccination was noninferior to a discontinuation of MTX for 2 weeks after vaccination, regarding induction of a satisfactory vaccine response to a seasonal influenza vaccine in patients with RA receiving a stable dose of MTX. The vaccine response in RA patients was comparable to that in the healthy controls and patients who had 1 week of MTX discontinuation had no increase in the risk of an RA flare above the background flare rate seen in patients who continued MTX treatment.

MAH comments:

This study used ***GCFLU QIV*** for 2021–2022 seasonal influenza vaccination. Regarding safety results, only well-known side effects of vaccines were reported, and no new or significant safety issues were found. It is believed that the results describing well-tolerance of influenza vaccine and satisfactory vaccine response can be used as evidence when clinical judgement is made on RA patients, who are recommend for vaccination because of increased risk of infection.

Stevens-Johnson syndrome in a pregnant woman who received the influenza vaccine

Calley, B. J., Saleh, J., Young, K., & Wanat, K. A.
JAAD Case Rep. 2022 May; 23: 35–37. doi: 10.1016/j.jdcr.2022.02.002

Study drugs:	A preservative-free quadrivalent influenza vaccine (Sanofi)
Aims:	To describe a unique presentation of Stevens-Johnson syndrome (SJS) in a 34-year-old pregnant woman after receiving an influenza vaccine

Case description:

A 34-year–old woman who was 29 weeks pregnant was admitted to the hospital for medical management of preeclampsia. Prior to admission, her medications included labetalol, ferrous sulfate, prenatal multivitamins with folic acid, and hydroxyprogesterone IM. On day 1 of her hospital stay, she received intravenous magnesium, and labetalol dosage was increased (200mg BID to 400mg BID). She also received betamethasone on days 1 and 2 of admission. On day 14 of her hospital stay, she received a preservative-free QIV. She had no prior history of influenza

vaccination.
On day 17 of her hospital stay, she developed a sore throat and lesions on her face and chest. These symptoms worsened over the next 24 hours. Tests for pathogens and viruses were negative. On dermatology examination, a dusky bulla was observed at the administration site of the influenza vaccine. Additionally, she had confluent oral-labial erosions, vulvar erosions, erythematous and dusky atypical macular target lesions on her palms, and evolving dusky pink-red macules with subsequent erosions on her trunk. Histopathology demonstrated pauci-inflammatory interface dermatitis and full-thickness epidermal necrosis.
Given the temporal relationship between the administration of the influenza vaccine, observation of the large lesion at the vaccine site, involvement of 2 mucosal sites, full-thickness epidermal necrosis on histopathology, and systemic symptoms, a diagnosis of SJS secondary to influenza vaccination was favored.
On day 22, as a precautionary measure, labetalol was switched to nifedipine. In addition to supportive measures, the patient was started on several steroid treatments. Given the continued evolution of the oral erosions, etanercept 50 mg was administered subcutaneously. One day after the administration of etanercept, her cutaneous erosions improved, and her oral erosions began to re-epithelialize. She was discharged on day 26 of hospitalization. At the 1-week follow-up, her mucosal and cutaneous erosions were healed with residual post-inflammatory hyperpigmentation.

Discussions:

Vaccines, particularly the preservative-free influenza vaccine, have rarely been implicated in SJS, which reported twice up to this point. For this patient, the presence of the large dusky bulla at the site of injection favored the influenza vaccine as the most likely culprit for SJS. Also, the increased labetalol dosage was considered as a possible etiology. However, this seems less likely given the time between medication administration and the localized presentation of epidermal plaques. Erythema multiform major and systemic lupus erythematosus were additionally considered in diagnosis but deemed less likely because of test results and symptoms presented. The hypothesized pathophysiology of SJS involves cytotoxic T cell killing of keratinocytes. And vaccines induce proliferation of various cytokines as immune response to antigen, which results in the activation of cytotoxic T cells. So, individuals with a predisposition for SJS may mount abnormally high cytokine responses to a vaccine or may have heightened sensitivity to a normal cytokine response.

MAH comments:

This case report describes a 34-year-old woman who was admitted to the hospital for medical management of preeclampsia at 29 weeks pregnant and diagnosed with SJS, 3 days after administration with influenza vaccine (Sanofi®). As authors' opinion, the MAH considers that causal relationship between the influenza vaccine and SJS cannot be ruled out considering temporal association and the site of symptoms. However, the MAH rates the level of evidence as low to have an impact on safety profile of ***GCLFU QIV*** because the study was designed based on case analysis and influenza vaccine has rarely been implicated in SJS up to this point. Despite the rarity, there is a need to be cautious of SJS in clinical practices because of its severity. The MAH will continue to monitor not only case reports of SJS but also use of ***GCFLU QIV*** in pregnant women through routine pharmacovigilance activities.

12. Other Periodic Reports

GC Biopharma Corp. is not aware of any periodic report of ***GCFLU QIV*** by any other organizations.

13. Lack of Efficacy in Controlled Clinical Trials

No data from clinical trials indicating lack of efficacy were found in the reporting period.

14. Late Breaking Information

No important and new information on the safety of ***GCFLU QIV*** was received after the DLP that identify any new safety signals or impact the conclusions of this report.

15. Overview of Signals: New, Ongoing, or Closed

The MAH collected safety information regarding ***GCFLU QIV***, whenever available, from various sources as follows:

- Non-clinical studies
- Clinical trials; including research in unapproved indications or populations
- Spontaneous reports on MAH's safety database
- MAH-sponsored websites
- Observational studies such as post-marketing surveillance or registries
- Product usage data and drug utilization information
- Published scientific literature or reports from abstracts including information presented at scientific meetings
- Unpublished manuscripts
- Active surveillance systems
- Systematic reviews and meta-analyses
- Information arising from licensing partners, other sponsors or academic institutions/research networks
- Patient support programs
- Investigations of product quality
- Information from regulatory authorities

New clinically important safety information did not become available from the various sources during the period covering this report; thus, no new safety signals were identified from the safety information. In addition, no ongoing or closed safety signals were identified during the previous reporting period.

16. Signal and Risk Evaluation

16.1 Summary of Safety Concerns

The safety concerns identified at the start of the reporting interval of the current PBRER includes

the following risks and missing information:

1) Important potential risks

- Severe allergic reactions including anaphylaxis
- Vaccination failure
- Guillain-Barre syndrome (GBS)
- Optic neuritis
- Myelitis
- Acute disseminated encephalomyelitis (ADEM)
- Vasculitis
- Convulsion/seizure
- Oculo-respiratory syndrome (ORS)

2) Important identified risks

None

3) Important missing information

- Use in pregnant or lactating women
- Drug interaction with immune-modifying drugs
- Immunocompromised patients

16.2 Signal Evaluation

There were no signals identified and closed during the previous reporting period and current reporting period, thus, there were no signals subject to signal evaluation.

16.3 Evaluation of Risks and New Information

16.3.1 New Information on Important Potential Risks

- Severe allergic reactions including anaphylaxis

Severe allergic reactions including anaphylaxis were identified as important potential risk.

Anaphylactic reaction is a serious allergic reaction of rapid onset that causes, for example, difficulty in breathing and dizziness; it may develop to a life-threatening response involving the whole body.

One (1) case was reported during the reporting period from spontaneous sources.

No new trends suggesting an increased frequency or severity of severe allergic reactions were identified during the reporting period.

- Vaccination failure

Vaccination failure was identified as important potential risk.

No cases were reported during the reporting period.

No new trends suggesting an increased frequency or severity of vaccination failure were identified during the reporting period.

- Guillain-Barre syndrome (GBS)

Guillain-Barre syndrome (GBS) was identified as important potential risk.

Two (2) cases were reported during the reporting period from spontaneous sources.

No new trends suggesting an increased frequency or severity of GBS were identified during the reporting period.

- Optic neuritis

Optic neuritis was identified as important potential risk.

No cases were reported during the reporting period.

No new trends suggesting an increased frequency or severity of optic neuritis were identified during the reporting period.

- Myelitis

Myelitis was identified as important potential risk.

No cases were reported during the reporting period.

No new trends suggesting an increased frequency or severity of myelitis were identified during the reporting period.

- Acute disseminated encephalomyelitis (ADEM)

Acute disseminated encephalomyelitis (ADEM) was identified as important potential risk.

No cases were reported during the reporting period.

No new trends suggesting an increased frequency or severity of ADEM were identified during the reporting period.

- Vasculitis

Vasculitis was identified as important potential risk.

No cases were reported during the reporting period.

No new trends suggesting an increased frequency or severity of vasculitis were identified during the reporting period.

- Convulsion/seizure

Convulsion/seizure was identified as important potential risk.

No cases were reported during the reporting period.

No new trends suggesting an increased frequency or severity of convulsion/seizure were identified during the reporting period.

- Oculo-respiratory syndrome (ORS)

Oculo-respiratory syndrome (ORS) was identified as important potential risk.

No cases were reported during the reporting period.

No new trends suggesting an increased frequency or severity of ORS were identified during the reporting period.

16.3.2 New Information on Important Identified Risks

Important identified risk was not present; thus this section is not applicable.

16.3.3 New Information on Other Potential Risks Not Categorized as Important

Potential risks not categorized as important were not identified; thus this section is not applicable.

16.3.4 New Information on Other Identified Risks Not Categorized as Important

Identified risks not categorized as important were not identified; thus this section is not applicable.

16.3.5 Update on Important Missing Information

- Use in pregnant or lactating women

No spontaneous cases of exposure to ***GCFLU QIV*** during pregnancy were reported during the reporting period.

According to the published literature (Robinson et al., 2022) described in the section 11, the results from a prospective cohort study on pregnancy outcomes with 483 subjects immunized

with seasonal IIV4 during pregnancy suggested that exposure to IIV4 during pregnancy was not associated with any safety concerns, including teratogenic effect, and supported the use of IIV4 in high risk group to protect pregnant women and their newborns against influenza.

In the other published literature (Calley et al., 2022) described in the section 11, one (1) case of Stevens-Johnson syndrome (SJS) that occurred after inoculation of a preservative-free quadrivalent influenza vaccine (Sanofi®) during pregnancy was reported. Although this was a rare case, the case report suggested the possibility of SJS after influenza vaccination in pregnant woman.

No new relevant safety information or information with potential impact on the benefit or risk evaluations in pregnant or lactating women was identified during the reporting period.

- Drug interaction with immune-modifying drugs

No spontaneous safety reports of administration of ***GCFLU QIV*** with immunosuppressants were reported during the reporting period.

According to the published literature (Park et al., 2022) described in the section 11, a multicenter, prospective, randomized, parallel-group trial suggested that 1 week MTX withdrawal after influenza vaccination was non-inferior to the 2 weeks withdrawal to induce a satisfactory vaccine response in RA patients undergoing a stable treatment of MTX.

No relevant safety information or information with potential impact on the benefit or risk evaluations in patients using immunosuppressants was identified during the reporting period.

- Immunocompromised patients

No spontaneous cases of administration of ***GCFLU QIV*** in immunocompromised patients were reported during the reporting period.

No relevant safety information or information with potential impact on the benefit or risk evaluations in immunocompromised patients was identified during the reporting period.

16.4 Characterization of Risks

Important potential risks are characterized based on the cumulative data and other sources respectively for each risk as follows:

Important potential risk 1: Severe allergic reactions including anaphylaxis	
Frequency	No anaphylaxis case was reported in subjects who received ***GCFLU QIV*** from the eight (8) MAH-sponsored trials.
Numbers of cases	One (1) case of anaphylactic shock was reported during the reporting period. Cumulatively, two (2) cases of anaphylaxis were reported from the post-marketing sources until the data lock point.
Extent of use	Approximately 15,624,700 doses during the reporting period; approximately 50,799,230 doses cumulatively
Approximation of the	Anaphylaxis is by definition considered drug-specific; therefore, this

relative and absolute risk	field is not applicable.
Impact on the individual patient	Signs and symptoms of an allergic reaction are chest tightness, breathlessness, and a low blood pressure. The severity spectrum of allergic reactions covers from the severity of mild level to life threatening or fetal.
Public health impact	Prolongation of hospitalization and additional interventions may be needed in case of anaphylaxis. Although clinical outcome of anaphylaxis may be potentially critical, severe allergic reactions including anaphylaxis are not expected to have a major impact with respect to overall public health, considering the low incidence and the fact that it is a well-known risk to vaccine providers.
Patient characteristics relevant to risk	A history of anaphylactic or severe systemic reaction to active ingredients or excipients of influenza vaccines.
The period of risk as it pertains to the duration of treatment	Anaphylaxis usually occurs immediately or after short interval from dosing.
The preventability and reversibility of the event	Patients who have developed a serious allergic reaction previously must not be given ***GCFLU QIV*** again. Patients should contact their doctor if they have serious allergic-type reactions, including redness and flushing, skin rash, and raised areas of the skin that itch; and serious allergic reactions, including anaphylaxis (weakness, drop in blood pressure, difficulty breathing, swelling of the face).
Potential mechanism accountable for the risk/event	Different mechanisms have been proposed as inducers of anaphylaxis as follows: • IgE-mediated hypersensitivity • Mechanism of non–IgE-mediated hypersensitivity with intervention of IgG, FcγRIII • Activation of the complement system with production of anaphylatoxins and release of mediators from mast cells.
The validity of the collated evidence	Any preferred terms (PTs) of the adverse events in narrow SMQ "Anaphylactic reaction" or "Anaphylactic/Anaphylactoid shock conditions" were used to collate the data. No case was reported from the MAH-sponsored clinical trials and two (2) cases were reported from the post-marketing safety database. Having considered the rarity of the event, sample size of the MAH sponsored controlled trials may not be sufficient to draw the any conclusion whether the product induce severe hypersensitivity. Post-marketing safety database has many important limitations, including underreporting, incomplete information, varying quality of reports, and lack of an unvaccinated comparison group. Also, medical records of serious reports obtained through follow-up may not contain important key clinical and/or laboratory information. However, as well described, there is sufficient scientific evidence that any vaccines can induce severe allergic reactions including anaphylaxis; thus the strength of evidence is high.

Important potential risk 2: Vaccination failure	
Frequency	No case of vaccination failure was reported as an adverse event in the subjects who received ***GCFLU QIV*** from eight (8) MAH-sponsored trials.
Numbers of cases	No case of vaccination failure was reported from the post-marketing database until the data lock point.
Extent of use	Approximately 15,624,700 doses during the reporting period; approximately 50,799,230 doses cumulatively
Approximation of the relative and absolute risk	Vaccination failure occurs, by definition, only after vaccination and does not occur among unimmunized individuals; therefore, this field is not applicable.
Impact on the individual patient	May require revaccination. The persons with vaccination failure may have serious influenza complications. For example, the elderly are at higher risk for serious complications from infections like influenza and pneumonia.
Public health impact	Vaccination failure is expected to have a significant impact with respect to overall public health. The suboptimal effectiveness of the influenza vaccine has elicited considerable negative media attention, which has contributed to poor uptake of the vaccine by people.
Patient characteristics relevant to risk	Based on the data from trivalent influenza vaccine, • Old age or pregnancy • Use of immunomodulators, or other immunocompromised state: Patients being treated with immunomodulators: autoimmune diseases, transplantation; other immunocompromised patients • Genetic polymorphism: Various HLA class I (A*2, A*11, B*27 and B*35) and class II (DRB1*07, DRB1*13 and DQB1*06) alleles have been reported to correlate with the serologic response to influenza vaccination. The differences in HLA class I and class II pathway presentations of immunodominant epitopes are likely the source for some proportion of the inter-individual variation in influenza vaccine-induced immune responses. • Importantly, a recent study suggested that decreased influenza vaccine response in humans is associated with polymorphisms in the HO-1 gene.
The period of risk as it pertains to the duration of treatment	During the remaining period of each influenza season after vaccination.
The preventability and reversibility of the event	Elderly may be administered with high dose rather than standard dose of inactivated influenza vaccines.
Potential mechanism accountable for the risk/event	Although T cell alterations play a significant role in age-related humoral immune changes, alterations in B cells also occur. In physiologic aging, impaired antibody responses to seasonal influenza vaccination have been largely attributed to intrinsic B and T cell defects. One mechanism of vaccination failure in pregnant woman may involve shifting immunity away from cell-medicated immunity towards humeral immunity, which could impair vaccine response.

	The reduced quality of the immune response in immune-mediated inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease or psoriasis patients, especially in those under immunotherapy, may thus have a negative effect on the efficacy of vaccination.
The validity of the collated evidence	Any preferred terms (PTs) of the adverse events in narrow SMQ "Lack of efficacy/effect" were used to collate the data (a report should be classified as medically confirmed based on narrative documenting the laboratory confirmation). No cases concerning the events narrow SMQ "Lack of efficacy/effect" have been reported from both MAH sponsored controlled trials or ICSRs, until the DLP. Efficacy of ***GCFLU QIV*** was established in pre-approval clinical trials and information indicating lack of efficacy was not identified. 10 events reporting influenza or influenza like illness were reported from spontaneous sources as of DLP. However, with limited information about patient information, vaccination date, or event onset date, it was difficult to conclude that these events concern vaccination failure. Several factors are known to attribute to vaccination failure. These includes, but not restricted to, vaccine (host)-related factors (immunodeficiency, age-related maturation, or interference due to other infectious agents, etc.) and vaccine-related factors (antigenic interference, or incomplete coverage of strains). Also as flu viruses are constantly changing, the vaccine composition is reviewed each year and updated by WHO, with relevant authorities. Therefore, there is a possibility that the recommended strains cannot provided complete coverage of strains or serotypes. Although the cases of vaccination failure have not been reported until the DLP, it is well known how well the flu vaccine works (or its ability to prevent flu illness) can range widely from season to season. The strength of evidence may be high.

Important potential risk 3: Guillain-Barre syndrome	
Frequency	No case of Guillain-Barre syndrome (GBS) was reported as an adverse event in the subjects who received ***GCFLU QIV*** from the eight (8) MAH-sponsored trials.
Numbers of cases	During the reporting period, two (2) SADRs of GBS were reported; Cumulatively seven (7) cases of GBS were reported from the post-marketing sources until the data lock point, including one (1) case that whether the suspect drug is GC FLU PFS inj. or GCFLU QIV PFS inj. was not confirmed.
Extent of use	Approximately 15,624,700 doses during the reporting period; approximately 50,799,230 doses cumulatively
Approximation of the relative and absolute risk	To the best of our knowledge, few data for approximation of the relative and absolute risks are available: however, according to a retrospective study with 550 identified GBS cases over 33 million person-years, there were no cases of recurrent GBS after influenza vaccination and none within 6 weeks after any trivalent inactivated influenza vaccine; while a meta-analysis reported that influenza

	vaccines increased the risk of GBS (relative risk 1.22, [95% confidence interval 1.01–1.48]).
Impact on the individual patient	The outcome of Guillain-Barre syndrome is generally favorable and resolves with symptomatic treatment as necessary, however, the syndrome might cause neurologic sequelae or even death. A patient who experiences an event of GBS will likely require medical intervention, perhaps hospitalization. Such individuals will incur financial burden, and suffer a significant social impact.
Public health impact	The overall number of individuals affected is expected to be small. Therefore vaccine-induced GBS is not expected to have a major impact with respect to overall public health.
Patient characteristics relevant to risk	The Advisory Committee on Immunization Practices recommends not administering influenza vaccine to individuals who have had a history of GBS within 6 weeks of a prior influenza vaccination if they are not at high risk of severe complications from influenza illness.
The period of risk as it pertains to the duration of treatment	42 days at the most following vaccination, with the highest risk observed in the first 8–21 days.
The preventability and reversibility of the event	Influenza vaccine may not be administered to individuals who have had a history of GBS within 6 weeks of a prior influenza vaccination if they are not at high risk of severe complications from influenza illness. Doctors should carefully monitor patients for GBS by appropriate clinical observations.
Potential mechanism accountable for the risk/event	Guillain-Barré syndrome (GBS) is an autoimmune disorder affecting the peripheral nervous system presenting with acute onset flaccid polyneuropathy. The complete pathogenesis for the development of GBS is widely unknown. However, in the majority of the cases, immune-mediated damage of peripheral nerve cells leads to demyelination resulting in nerve damage. • Influenza vaccine may have antigenic cross-reactivity that stimulates antibody production against human neuronal cells. Antibodies formed with molecular mimicry attack human nerve cells because of structural similarity. • Anti-ganglioside antibodies damaging nerve cells are the known mechanism for the development of GBS. Molecular mimicry with cross-reactivity to neuronal cells supports the causal relationship between the influenza vaccine and GBS. It is suggested that GBS following seasonal influenza vaccine may arise by the following factors. • Humoral or cell-mediated immune reaction to chicken P2 protein present in influenza vaccines (influenza vaccines prepared from the allantoic fluid of chicken embryos) • The presence of endotoxin in influenza vaccine, because of its ability to increase the permeability of the blood–brain barrier, may allow proteins that may have deleterious neurogenic properties to enter into the nervous system and, because of its activity in elevating antibody production, may contribute to the autoimmune conditions observed in GBS. Therefore, the synergistic effects of endotoxin and vaccine induced autoimmunity may

	contribute to the GBS observed in this study following influenza vaccination.
The validity of the collated evidence	Any preferred terms (PTs) of the adverse events in narrow SMQ "Guillain-Barre syndrome" were used to collate the data. No case was reported from the MAH-sponsored clinical trials and having considered the rarity of the event, sample size of the MAH sponsored controlled trials may not be sufficient to draw the any conclusion whether the product induces GBS. A total of seven (7) cases were reported from the post-marketing safety database, however it is not clear whether the incidence of GBS was greater than the background incidence. Considering many important limitations of post-marketing safety database, it is inadequate to accept or reject a causal relationship between the product and GBS. Therefore, the strength of evidence is not sufficient to reject or accept a causal relationship.

Important potential risk 4: Optic neuritis	
Frequency	No cases of optic neuritis were reported as an adverse event in the subjects who received ***GCFLU QIV*** from the eight (8) MAH-sponsored trials.
Numbers of cases	No cases of optic neuritis were reported during the reporting period. Cumulatively, one (1) case of optic neuritis was reported from post marketing sources until the data lock point.
Extent of use	Approximately 15,624,700 doses during the reporting period; approximately 50,799,230 doses cumulatively
Approximation of the relative and absolute risk	While the estimated incidences of optic neuritis in the United States are 7.5 per 100,000 and 2.6 per 100,000, respectively in female and male population, the incidence in Singapore is 0.83 per 100,000. It is not known whether relative or absolute risk by ***GCFLU QIV*** or other quadrivalent inactivated influenza vaccines is changed.
Impact on the individual patient	The patient may have typical features of acute optic neuritis with acute visual loss, periocular pain, visual defects, and recovery of vision after several months. A patient who experiences an event of optic neuritis will likely require medical intervention, perhaps hospitalization. Such individuals will incur financial burden, and suffer a significant social impact.
Public health impact	Generally complete recovery is reported in post-influenza vaccination optic neuritis, though incomplete visual recovery may result due to permanent damage to some of the macular fibres. Given such and the rarity of the event, it is not expected to have a major impact with respect to overall public health.
Patient characteristics relevant to risk	Not known, any influenza vaccine recipients
The period of risk as it pertains to the duration of treatment	Usually within 1 to 3 weeks.
The preventability and reversibility of the	Not preventable.

event	
Potential mechanism accountable for the risk/event	The exact pathophysiologic mechanism of post-vaccination optic neuritis is not clearly defined, but the cause could be understood as autoimmune activation as follows. • The mechanism of autoimmunity remains obscure; however, several mechanisms have been suggested, such as epitope spreading, polyclonal activation of T or B cells, and loss of downregulation of dendritic cells. • One probable cause of autoimmune activation after vaccination is molecular mimicry that is structural similarity between viral and host antigens. Overproduction of cytokines such as interferon or interleukin is also a trigger for the response. The resultant B-cell activation and autoantibody production cause inflammation and demyelinization of the optic nerve with immune complex–mediated vascular injury and blood brain barrier impairment. • The autoimmune/inflammatory clinical syndromes induced by adjuvants used in vaccines.
The validity of the collated evidence	Any preferred terms (PTs) of the adverse events under name of "optic neuritis" or "Neuromyelitis optica" were used to collate the data. No case was reported from the MAH-sponsored clinical trials. However, having considered the rarity of the event, sample size of the MAH sponsored controlled trials may not be sufficient to draw the any conclusion whether the product induces optic neuritis. One (1) case was reported from the post-marketing safety database, however, having considered the rarity, many important limitations of post-marketing safety database, and current scientific evidence (clinical and nonclinical) suggesting the possibility of a causal relationship with the product but insufficient to conclude that this association is causal, it is inadequate to accept or reject a causal relationship between the product and optic neuritis. Therefore, the strength of evidence is not sufficient to reject or accept a causal relationship.

Important potential risk 5: Myelitis	
Frequency	No case of myelitis was reported as an adverse event in the subjects who received ***GCFLU QIV*** from the eight (8) MAH-sponsored trials.
Numbers of cases	No cases of myelitis were reported during the reporting period. Cumulatively, one (1) case was reported from the post-marketing sources until the DLP.
Extent of use	Approximately 15,624,700 doses during the reporting period; approximately 50,799,230 doses cumulatively
Approximation of the relative and absolute risk	To the best of our knowledge, no data for approximation of the relative and absolute risks are available.
Impact on the	A patient who experiences an event of myelitis will likely require

individual patient	medical intervention, perhaps hospitalization. Such individuals will incur financial burden, and suffer a significant social impact. Although some patients recover from transverse myelitis with minor or no residual problems, others suffer permanent impairments that affect their ability to perform ordinary tasks of daily living.
Public health impact	Given the rarity of myelitis, it is not expected to have a major impact with respect to overall public health.
Patient characteristics relevant to risk	Any influenza vaccine recipients
The period of risk as it pertains to the duration of treatment	Usually central nervous system demyelinating syndrome appears shortly (during the 3–4 weeks following the vaccination).
The preventability and reversibility of the event	Not preventable.
Potential mechanism accountable for the risk/event	Based on the data of trivalent inactivated influenza vaccine, it is hypothesized that neuropathy following influenza vaccine may arise by the following factors. • Molecular mimicry: the infectious/vaccine antigen incorporates an epitope that is structurally similar to a self-antigen and therefore induces self-reactivity. • Bystander activation: enhanced cytokine production promotes the expansion of autoreactive T cells, whose prior number had been insufficient to produce an overt disease. • Polyclonal activation of B cells: increased B cell proliferation, antibody production, and the generation of circulating immune complexes may eventually damage self-tissues. The increased risk of autoimmunity among recipients of a certain vaccine may also stem from other constituents of the vaccine, such as yeast, adjuvant and preservative.
The validity of the collated evidence	Any preferred terms (PTs) of the adverse events under the name of “Myelitis”, “Myelitis transverse” and “Noninfectious myelitis” were used to collate the data. No case was reported from the MAH-sponsored clinical trials, however, having considered the rarity of the event, sample size of the MAH sponsored controlled trials may not be sufficient to draw the any conclusion whether the product induces myelitis. One (1) case was reported from the post-marketing safety database. However, post-marketing safety database has many important limitations including underreporting, incomplete information, varying quality of reports, and a lack of an unvaccinated comparison group. Also, medical records of serious reports obtained through follow-up may not contain important key clinical and/or laboratory information, thus it is inadequate to conclude that the association is causal based on current scientific evidence (clinical and non-clinical). Therefore, the strength of evidence is not sufficient to reject or accept a causal relationship.

Important potential risk 6: Acute disseminated encephalomyelitis (ADEM)	
Frequency	No case of ADEM was reported as an adverse event in the subjects who received ***GCFLU QIV*** from the eight (8) MAH-sponsored trials.
Numbers of cases	No case of ADEM was reported during the reporting period. Cumulatively, one (1) case of ADEM was reported from the post-marketing sources until the DLP.
Extent of use	Approximately 15,624,700 doses during the reporting period; approximately 50,799,230 doses cumulatively
Approximation of the relative and absolute risk	To the best of our knowledge, no data for approximation of the relative and absolute risks are available. More frequently occurs after primary vaccination, than after revaccination
Impact on the individual patient	Patients have fever, altered consciousness, and multifocal neurological findings, which typically appear within 1 day to 3 weeks of immunization and show rapid progression. Focal findings depend on the location and degree of demyelination. A patient who experiences an event of ADEM will likely require medical intervention, perhaps hospitalization. Such individuals will incur financial burden, and suffer a significant social impact.
Public health impact	Given the rarity of ADEM, it is not expected to have a major impact with respect to overall public health.
Patient characteristics relevant to risk	More frequently occurs after primary vaccination, than after revaccination.
The period of risk as it pertains to the duration of treatment	Usually within 3 weeks
The preventability and reversibility of the event	Not preventable.
Potential mechanism accountable for the risk/event	Based on the data of trivalent inactivated influenza vaccine, it is hypothesized that neuropathy following influenza vaccine may arise by the following factors. • Molecular mimicry: the infectious/vaccine antigen incorporates an epitope that is structurally similar to a self-antigen and therefore induces self-reactivity. • Bystander activation: enhanced cytokine production promotes the expansion of autoreactive T cells, whose prior number had been insufficient to produce an overt disease. • Polyclonal activation of B cells: increased B cell proliferation, antibody production, and the generation of circulating immune complexes may eventually damage self-tissues. The increased risk of autoimmunity among recipients of a certain vaccine may also stem from other constituents of the vaccine, such as yeast, adjuvant and preservative
The validity of the collated evidence	Any preferred terms (PTs) of the adverse events under the name of "Acute disseminated encephalomyelitis" were used to collate the data. No case was reported from the MAH-sponsored clinical trials, however, having considered the rarity of the event, sample size of

	the MAH sponsored controlled trials may not be sufficient to draw the any conclusion whether the product induces ADEM. One (1) case was reported from the post-marketing safety database. However, having considered many important limitations of post-marketing safety database, it is inadequate to reject a causal relationship between the product and ADEM. Therefore, the strength of evidence is not sufficient to reject or accept a causal relationship.

Important potential risk 7: Vasculitis	
Frequency	One (1) case of Kawasaki's disease [0.05%; 95% CI: 0.00%~0.26%] was reported as a serious adverse event in the subjects who received ***GCFLU QIV*** in GC3110A_C_P3. No case of vasculitis was reported from other MAH-sponsored trials.
Numbers of cases	No case of Vasculitis was reported from the post-marketing database until the DLP.
Extent of use	Approximately 15,624,700 doses during the reporting period; approximately 50,799,230 doses cumulatively
Approximation of the relative and absolute risk	To the best of our knowledge, no data for approximation of the relative and absolute risks are available.
Impact on the individual patient	A patient who experiences an event of vasculitis will likely require medical intervention, perhaps hospitalization. Such individuals will incur financial burden, and suffer a significant social impact.
Public health impact	Given the rarity of vasculitis, it is not expected to have a major impact with respect to overall public health.
Patient characteristics relevant to risk	Recipients of vaccines containing adjuvants. According to Watanabe T (2017), the majority of the patients who developed vasculitis after influenza vaccination were elderly, and the patients were predominantly female.
The period of risk as it pertains to the duration of treatment	Most of leukocytoclastic vasculitis cases were elderly with onset of the eruption 7 to 14 days after administration of the influenza vaccine.
The preventability and reversibility of the event	Not preventable.
Potential mechanism accountable for the risk/event	Based on the data of trivalent inactivated influenza vaccine, the association between vaccines and induction of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis may be mediated through several mechanisms. The induction of ANCA-associated vasculitis involves a complex interplay of environmental factors in a genetically predisposed individual with loss of immune tolerance. • Antigen-specific mechanism: Molecular mimicry is an antigen-specific phenomenon where there is activation of autoreactive B and T cells due to antigen similarity between the host antigen and microbial antigen. In addition, infection-related signals can also trigger innate immunity. Innate immunity enhances the immunogenicity of host antigens and may play a role in overcoming the regulatory pathways that limit the autoimmune response.

	• Antigen-nonspecific mechanism: Vaccine provides a transient inflammatory setting for bystander activation resulting in release of previously sequestered self-antigens or stimulating an innate immune response. • Autoimmune response provoked by adjuvants: Autoimmune syndrome can be induced by adjuvants. According to literature reporting leukocytoclastic vasculitis (LCV) cases following influenza vaccination, an associated eosinophilic infiltration or mast cell infiltration has been demonstrated in some cases, or direct vessel damage mediated by the vaccine or indirect damage mediated by memory T lymphocytes was assumed. Also, reticulated eruption appeared, possibly caused by cytotoxic lymphokines.
The validity of the collated evidence	Any preferred terms (PTs) of the adverse events in narrow SMQ "Vasculitis" excluding those with known vaccination unrelated etiology (i.e. Diabetic arteritis, Radiation vasculitis, Rheumatoid vasculitis, Type 2 lepra reaction, Viral vasculitis) were used to collate the data. Cumulatively one (1) case was reported from the MAH-sponsored clinical trials and there was no case from post-marketing safety database. Having considered the data of other influenza vaccines, the evidence is inadequate to accept or reject a causal relationship between influenza vaccine and vasculitis although it seems possible that in rare cases vaccination might induce vasculitic disease. Therefore, the strength of evidence is not enough to reject or accept a causal relationship.

Important potential risk 8: Convulsion/seizure	
Frequency	One (1) case of Febrile convulsion [0.05%; 95% CI: 0.00%~0.26%] was reported as serious adverse event in the subject who received ***GCFLU QIV*** in GC3110A_IF_P3. No case of convulsion/seizure was reported as an adverse event in the subjects who received ***GCFLU QIV*** from other MAH-sponsored trial.
Numbers of cases	No case of convulsion/seizure was reported from the post-marketing database during the reporting period. Cumulatively, four (4) cases of convulsion/seizure were reported until the DLP.
Extent of use	Approximately 15,624,700 doses during the reporting period; approximately 50,799,230 doses cumulatively
Approximation of the relative and absolute risk	The risk of febrile seizure with any combination of the vaccines [inactivated influenza vaccine, pneumococcal 13-valent conjugate (PCV13) vaccine, or the diphtheria, tetanus, acellular pertussis (DTaP) vaccine] is small (at most 30 febrile seizures in 100,000 children vaccinated).
Impact on the individual patient	A patient who experiences an event of convulsion/seizure will likely require medical intervention, perhaps hospitalization. Such individuals will incur financial burden, and suffer a significant social impact.
Public health impact	Given the rarity of convulsion, it is not expected to have a major

	impact with respect to overall public health.
Patient characteristics relevant to risk	Children who received the measles, mumps, rubella (MMR) vaccine on the same day simultaneously with trivalent influenza vaccine. Children 12 through 23 months of age, particularly when the flu shot was given at the same time as pneumococcal conjugate vaccine (PCV13) and diphtheria, tetanus, and pertussis (DTaP)-containing vaccine.
The period of risk as it pertains to the duration of treatment	A CDC study of children aged 6 months to 2 years has shown a small increased risk for febrile seizures during the 24 hours after a child receives the inactivated influenza vaccine at the same time as the PCV13 vaccine or the DTaP vaccine.
The preventability and reversibility of the event	Do not vaccinate with trivalent influenza vaccine on the same day as MMR vaccine.
Potential mechanism accountable for the risk/event	Based on the data of trivalent inactivated influenza vaccine, although the mechanistic evidence regarding an association between influenza vaccine and seizures is considered lacking, the following mechanisms have been suggested. • In some instances, fever may contribute to the development of seizures; however, the publications did not provide evidence linking this mechanism to influenza vaccine. • There was a report of seizure development to the corticosteroid therapy used to treat respiratory problems in the vaccinated patient. Takahashi et al. (2006) reported the isolation of lymphocytes reactive to both the neuronal molecule GluRε2 and influenza vaccine from a patient diagnosed with Rasmussen syndrome who had developed a febrile seizure upon infection with influenza A.
The validity of the collated evidence	Any preferred terms (PTs) of the adverse events in narrow SMQ "Convulsions" excluding those with known vaccination unrelated etiology (i.e. Alcoholic seizure, Drug withdrawal convulsion, Post stroke epilepsy, Post stroke seizure) were used to collate the data. Five (5) cases were reported from DIBD to DLP, one (1) case from the MAH-sponsored clinical trials and four (4) cases from post-marketing safety database, respectively. Having considered the data of other influenza vaccines, it is observed that the risk of febrile seizure with any combination of the vaccines [inactivated influenza vaccine, PCV13 vaccine, or the DTaP vaccine] increases minimally (at most 30 febrile seizures in 100,000 children vaccinated). However, considering the extent to which the risk increases, CDC's Advisory Committee on Immunization Practices (ACIP) continues to encourage the vaccination of children according to the vaccination schedule, which allows for the flu, pneumococcal and DTaP vaccinations to be given during the same doctor's visit. However, the causal relationship between seizure/convulsion and influenza vaccine itself has not been clearly identified. Therefore, considering the rarity and sample size of MAH-sponsored clinical trial and incidence observed in post-marketing sources, it is inadequate to accept or reject a causal relationship, and adverse events under this risk will be continuously monitored and assessed.

Important potential risk 9: Oculo-respiratory syndrome	
Frequency	No case of oculo-respiratory syndrome was reported as an adverse event in the subjects who received ***GCFLU QIV*** from the eight (8) MAH-sponsored trials.
Numbers of cases	No event was reported from the post-marketing database under the name of "oculo-respiratory syndrome (ORS)".
Extent of use	Approximately 15,624,700 doses during the reporting period; approximately 50,799,230 doses cumulatively
Approximation of the relative and absolute risk	Oculo-respiratory syndrome is by definition considered influenza vaccination-specific; therefore, this field is not applicable.
Impact on the individual patient	Symptoms are typically mild and resolve quickly without specific treatment usually within 48 hours. However, of those, a patient who experiences an event of oculo-respiratory syndrome could require medical intervention, perhaps hospitalization. Such individuals will incur financial burden, and suffer a significant social impact.
Public health impact	Vaccine providers should reassure patients with ORS that this experience is not a contraindication to revaccination. Although recurrence is possible, such episodes are likely to be mild, and treatment of the symptoms is usually sufficient. It should be balanced against one's own personal risk of influenza infection and the complications that follow in failing to be immunized.
Patient characteristics relevant to risk	Healthy adults < 60 years and female: Review of ORS cases following influenza vaccination in Canada during 2000-2003 showed that approximately 80% of the reactions have occurred in healthy adults < 60 years of age and approximately 75% in females. Individuals previously affected by ORS: Recurrence rate of ORS was estimated higher in individuals previously affected by ORS.
The period of risk as it pertains to the duration of treatment	2–24 hours after influenza vaccination
The preventability and reversibility of the event	Not preventable.
Potential mechanism accountable for the risk/event	Based on the data of trivalent inactivated influenza vaccine, presence of antinuclear antibody, lymphopenia, absence of eosinophils, and low C3, C4, and CH50 levels are observed in the patients with oculo-respiratory syndrome. Low C3, C4, and CH50 levels indicate an activation of the complement system. Complement activation may lead to an inflammatory response and changes in capillary permeability, which could explain the ocular findings of conjunctival injection and hemorrhages. Considering the similar clinical features of dysfunction or deficiencies of the C1 inhibitor (thereby cause activation of the complement) with oculo-respiratory syndrome that result in angioneurotic edema with bouts of nonpruritic edema of the face and the extremities, as well as edema of the larynx and bowel wall, that generally last 48–72 hours, the involvement of complement

	system is suggested as a possible mechanism of oculo-respiratory syndrome.
The validity of the collated evidence	Any preferred terms (PTs) of the adverse events under the name of "Oculo-respiratory syndrome" were used to collate the data. No case was reported from the MAH-sponsored clinical trials, however, having considered the rarity of the event, sample size of the MAH sponsored controlled trials may not be sufficient to draw the any conclusion whether the product induces oculo-respiratory syndrome. No case was reported from the post-marketing safety database, however, having considered many important limitations of post-marketing safety database, it is inadequate to reject a causal relationship between the product and oculo-respiratory syndrome. Therefore, the strength of evidence is not sufficient to reject or accept a causal relationship.

Inactivated influenza vaccine was used for a long period, and to date it has not been reported to be associated with increased risks of embryo-fetal toxicity, oncogenic or mutagenic potential.

Any important risks relating to the active substance have not been identified.

Since ***GCFLU QIV*** is approved to be administered only via the intramuscular route, any important risks related to the other administration routes were not identified.

GCFLU QIV is intended to be administered under medical supervision only, mostly in a hospital setting. Thus, risks associated with non-prescription use are very low.

16.5 Effectiveness of Risk Minimization (if applicable)

The measures in the reference safety information are those known as routine risk minimization measures.

The safety information suggests that the current measures for risk minimization are effective and no additional risk minimization measures are needed for ***GCFLU QIV***.

17. Benefit Evaluation

13 17.1 Important Baseline Efficacy/Effectiveness Information

Influenza vaccination is the principal method to prevent influenza and associated complications. Influenza vaccines need to be given every year for protection against the influenza because flu viruses can change every year. Therefore, each year, a new influenza vaccine is made. Seasonal influenza vaccine such as ***GCFLU QIV*** contains four (4) flu virus strains that are designed to protect a person against four (4) types of flu viruses at the same time.

In general, effects of influenza vaccine are well established from the studies to measure the benefits of seasonal flu vaccination each flu season, although the study results of vaccine effectiveness can vary based on study design, outcome(s) measured, population studied and the season in which the flu vaccine was studied.

The HI (Hemagglutination Inhibition) assay is the primary method used to titer antibodies generated after influenza vaccination. This assay relies on the ability of antibodies in serum to bind to viral hemagglutinin protein, which inhibits erythrocyte agglutination. Generally, an HI antibody titer of 40 is defined as 50% protective against influenza infection compared to HA titer < 10.

During the clinical development of ***GCFLU QIV***, information of efficacy (immunogenicity) for the approved indications was identified based on the eight (8) clinical trials.

The eight (8) clinical trials are as follows: (1) GC3110A_P1/2a, (2) GC3110A_AD_P3, (3) GC3110A_C_P3, (4) GC3110A_ED_P3, (5) GC3110B_P3, (6) GC3110A_IF_P3, (7) GC3114_P1, and (8) GC3114_P2.

Information on efficacy (immunogenicity) of ***GCFLU QIV*** identified is summarized per trial in the following tables.

Table 9 Summary of GC3110A_P1/2a

Study Identifier		GC3110A_P1/2a
Report date		15 May 2015
Sites/countries		1 site/ Korea
Study period		13 May 2014 ~ 20 June 2014
Hypothesis/objectives		The purpose of this study was to evaluate the safety, tolerability, and immunogenicity of GC3110A (GCFLU Quadrivalent Influenza Vaccine) administered intramuscularly in healthy subject.
Design		Part A: Randomized, open-label, single center Part B: Randomized, double-blind, active-controlled, single center
Treatment		• Test drug: GC3110A Four strains recommended by the World Health Organization (WHO) for the 2013-2014 (NH & SH) season: A/California/7/2009 NYMC X-181(H1N1); A/Texas/50/2012 NYMC X-223A(H3N2); B/Massachusetts/02/2012 NYMC BX-51B(Yamagata lineage); B/Brisbane/60/2008(Victoria lineage): 15 μg for each strain • Control drug: GC FLU Pre-filled Syringe inj. • A single intramuscular dose (0.5 mL)
Endpoints	Primary endpoint	① Seroconversion rate ② Seroprotection rate
	Key secondary endpoints	Geometric Mean Titer (GMT) of the HI antibody titers determined before vaccination (Day 0) and 21 days after the vaccination.
Results and Analysis		
Primary analysis population		ITT (intention to treat) population that consisted of 84 subjects / Healthy adults
Effect estimate per	Treatment group	GC3110A (GCFLU Quadrivalent Influenza

comparison			Vaccine) or GC FLU prefilled syringe inj.	
	Number of subjects		GC3110A [Part A (N=9) & Part B (N=51)) N=60	GC FLU PFS inj. N=24
Seroconversion rate for each strain*	A (H1N1)		27 (45.00) [32.41 - 57.59]	11 (45.83) [25.90 - 65.77]
	A (H3N2)		24 (40.00) [27.60 - 52.40]	10 (41.67) [21.94 - 61.39]
	B (Yamagata)		17 (28.33) [16.93 - 39.74]	5 (20.83) [4.59 – 37.08]
	B (Victoria)		21 (35.00) [22.93 – 47.07]	1 (4.17) [0.11- 21.12]
Seroprotection rate for each strain*	A (H1N1)		60 (100.00) [94.04 - 100.00]	24 (100.00) [85.75 - 100.00]
	A (H3N2)		60 (100.00) [94.04 - 100.00]	23 (95.83) [78.88 - 100.00]
	B (Yamagata)		55 (91.67) [84.67 – 98.66]	23 (95.83) [78.88 - 100.00]
	B (Victoria)		52 (86.67) [78.07 – 95.27]	12 (50.00) [30.00 - 70.00]
GMT for each strain	A (H1N1)	Pre	57.23 [40.09 – 81.68]	82.34 [48.72 – 139.18]
		Post	318.16 [241.52-419.10]	403.17 [259.82 - 625.63]
	A (H3N2)	Pre	58.90 [43.10 - 80.50]	67.27 [38.91 - 116.32]
		Post	211.12 [167.93-265.42]	213.57 [149.75 - 304.59]
	B (Yamagata)	Pre	56.24 [40.11 - 78.86]	59.07 [40.52 - 86.12]
		Post	135.32 [103.98-176.12]	130.71 [91.59 - 186.54]
	B (Victoria)	Pre	23.51 [17.40 - 31.77]	21.19 [14.28 - 31.44]
		Post	74.64 [57.73 - 96.50]	30.84 [21.21 - 44.85]

* Subject number (%) Exact [95% CI]

Table 10 Summary of GC3110A_AD_P3

Study Identifier	GC3110A_AD_P3
Report date	22 July 2015
Sites/countries	9 sites/ Korea
Study period	29 October 2014 ~ 09 June 2015
Hypothesis /objectives	The purpose of this study was to investigate the efficacy (immunogenicity) and safety of the GC3110A (GCFLU quadrivalent influenza vaccine) after intramuscular administration in health subjects.
Design	Multi-center, randomized, double-blind, active-controlled, parallel Phase III study

Treatment	• Test drug: GC3110 A (GCFLU quadrivalent influenza vaccine) Four strains recommended by the World Health Organization (WHO) for the 2013-2014 (NH & SH) season: A/California/7/2009 NYMC X-181(H1N1); A/Texas/50/2012 NYMC X-223A(H3N2); B/Massachusetts/02/2012 NYMC BX-51B(Yamagata lineage); B/Brisbane/60/2008(Victoria lineage): 15 μg for each strain • Control drug 1: GCFLU Prefilled syringe inj. A/California/7/2009 NYMC X-181(H1N1); A/Texas/50/2012 NYMC X-223A(H3N2); B/Massachusetts/02/2012 NYMC BX-51B(Yamagata lineage); 15 μg for each strain • Control drug 2: GC3110A (Control drug, trivalent influenza vaccine) A/California/7/2009 NYMC X-181(H1N1); A/Texas/50/2012 NYMC X-223A(H3N2); B/Brisbane/60/2008(Victoria lineage); 15 μg for each strain • A single intramuscular dose (0.5 mL)	
Endpoints	Primary endpoint	① Geometric Mean Titer (GMT) of the HI antibody titers determined before vaccination (Day 0) and 21 days after the vaccination ② Seroconversion rate
	Key secondary endpoints	Seroprotection rate

Results and Analysis

Primary analysis population	PP (per protocol) population that consisted of 1282 subjects and FA (Full Analysis) population that consisted of 1295 subjects and / Healthy adults over 19 years of age			
Effect estimate per comparison	Treatment group		GC3110 A (GCFLU quadrivalent influenza vaccine) or GC FLU prefilled syringe inj.	
	Number of subjects		GC3110A (GCFLU QIV)	GC FLU PFS inj.+ GC3110A (control drug 2)
	PP		N=639	N=643 (323 for strains B)
	FA		N=646	N=649 (325 for strains B)
Seroconversion rate for each strain*	A (H1N1)	PP	359 (56.18) [52.24 - 60.07]	383 (59.56) [55.66 - 63.38]
		FA	366 (56.66) [52.73 - 60.52]	387 (59.63) [55.74 - 63.43]
	A (H3N2)	PP	379 (59.31) [55.39 - 63.15]	359 (55.83) [51.90 - 59.71]
		FA	385 (59.60) [55.70 - 63.41]	363 (55.93) [52.02 - 59.79]
	B Ψ (Yamagata)	PP	339 (53.05) [49.10 - 56.98]	118 (36.88) [31.58 - 42.42]
		FA	344 (53.25) [49.32 - 57.15]	120 (37.04) [31.76 - 42.55]
	B Φ (Victoria)	PP	327 (51.17) [47.22 - 55.11]	167 (51.70) [46.10 - 57.27]

		FA		333 (51.55) [47.62 - 55.46]	168 (51.69) [46.11 - 57.24]
Seroprotection rate for each strain*Ψ	A (H1N1)	PP		608 (95.15) [93.18 - 96.68]	299 (93.44) [90.14 - 95.89]
		FA		615 (95.20) [93.26 - 96.72]	303 (93.52) [90.26 - 95.94]
	A (H3N2)	PP		600 (93.90) [91.75 - 95.62]	307 (95.94) [93.15 - 97.82]
		FA		606 (93.81) [91.66 - 95.54]	310 (95.68) [92.86 - 97.62]
	B (Yamagata)	PP		585 (91.55) [89.12 - 93.59]	286 (89.38) [85.47 - 92.53]
		FA		592 (91.64) [89.23 - 93.66]	289 (89.20) [85.30 - 92.36]
	B (Victoria)	PP		443 (69.33) [65.59 - 72.88]	135 (42.19) [36.71 - 47.81]
		FA		450 (69.66) [65.95 - 73.19]	136 (41.98) [36.54 - 47.56]
GMT for each strain	A (H1N1)	PP	GMT	170.65 [156.06 - 186.60]	174.71 [159.82 -190.99]
			GMT Ratio	1.02 [0.90-1.16]	
		FA	GMT	172.18 [157.53 - 188.20]	174.94 [160.09 - 191.18]
			GMT Ratio	1.02 [0.90 - 1.15]	
	A (H3N2)	PP	GMT	124.78 [116.70 - 133.41]	120.21 [112.46 - 128.49]
			GMT Ratio	0.96 [0.88 - 1.06]	
		FA	GMT	124.76 [116.68 - 133.39]	120.10 [112.34 - 128.38]
			GMT Ratio	0.96 [0.88 - 1.06]	
	B Ψ (Yamagata)	PP	GMT	106.60 [100.29 - 113.32]	85.53 [78.45 - 93.24]
			GMT Ratio	0.80 [0.72 - 0.89]	
		FA	GMT	107.56 [101.13 - 114.39]	85.97 [78.81 - 93.78]
			GMT Ratio	0.80 [0.72 - 0.89]	
	B Φ (Victoria)	PP	GMT	46.50 [43.36 - 49.86]	44.03 [39.91 - 48.57]
			GMT Ratio	0.95 [0.84 - 1.07]	
		FA	GMT	46.84 [43.70 - 50.21]	44.11 [39.99 - 48.64]
			GMT Ratio	0.94 [0.83 - 1.06]	

* Subject number (%) Exact [95% CI]

GMT Ratio: (GCFLU prefilled syringe Injection + GC3110A (control drug 2))/ GC3110A
Ψ Control group: GCFLU prefilled syringe inj. only and not includes GC3110A (control drug)
Φ Control group: GC3110A (control drug) only and not include GCFLU prefilled syringe inj.

Table 11 Summary of GC3110A_C_P3

Study Identifier		GC3110A_C_P3		
Report date		19 August 2016		
Sites/countries		12 site/ Korea		
Study period		12 September 2015 ~ 27 June 2016		
Hypothesis/objectives		The purpose of this study was to evaluate the safety and efficacy of GC3110A (GCFLU Quadrivalent Influenza Vaccine) administered intramuscularly in healthy children and adolescents.		
Design		Part A: Open-label, single arm, single center Part B: Randomized, double-blind, active-controlled, multi-center		
Treatment		• Four strains recommended by the World Health Organization (WHO) for the 2015-2016 (NH) season: A/California/7/2009 Reassortant virus NYMC X-181 (H1N1); A/Hong Kong/4801/2014 NYMC X-263B (H3N2); B/Brisbane/60/2008; B/Phuket/3073/2013: 15 μg for each strain • A single intramuscular dose for adolescents, children over 9 years old and children under 9 years old who previously vaccinated (0.25 mL for children under 3 years old; 0.5 mL for children over 3 years old and adolescents); two intramuscular injections for influenza vaccine-naive children under 9 years old		
Endpoints	Primary endpoint	① Seroconversion rate ② Seroprotection rate		
	Key secondary endpoints	Geometric Mean Titer (GMT) of the HI antibody titers determined before vaccination and after the final vaccination (28 days after the final dose).		
Results and Analysis				
Primary analysis population		PP (per protocol) population that consisted of 520 subjects / Healthy children and adolescents		
Effect estimate per comparison		Treatment group	GC3110A (GCFLU Quadrivalent Influenza Vaccine) or GC FLU prefilled syringe inj.	
		Number of subjects	GC3110A N=418	GC FLU PFS inj. N=102
Seroconversion rate for each strain*		A (H1N1)	237(56.7) [51.8- 61.5]	46(45.1) [35.2- 55.3]
		A (H3N2)	286(68.4) [63.7- 72.9]	71(69.6) [59.7- 78.3]
		B (Yamagata)	235(56.2) [51.3- 61.0]	44(43.1) [33.4- 53.3]
		B (Victoria)	219(52.4) [47.5- 57.3]	32(31.4) [22.5- 41.3]
Seroprotection rate for each strain*		A (H1N1)	378(90.4) [87.2- 93.1]	91(89.2) [81.5- 94.5]
		A (H3N2)	357(85.4) [81.7- 88.6]	86(84.3) [75.8- 90.8]
		B (Yamagata)	347(83.0) [79.1- 86.5]	77(75.5) [66.0-

				83.5]
	B (Victoria)		322(77.0) [72.7- 81.0]	60(58.8) [48.6- 68.5]
GMT for each strain	A (H1N1)	Pre	22.0 [20.1- 24.1]	25.0 [20.6- 30.4]
		Post	73.5 [68.1- 79.3]	72.7 [61.8- 85.6]
	A (H3N2)	Pre	14.5 [13.1- 15.9]	13.8 [11.4- 16.6]
		Post	88.4 [79.7- 98.0]	100.1 [79.6- 125.9]
	B (Yamagata)	Pre	15.4 [14.3- 16.7]	14.2 [12.0- 16.9]
		Post	52.4 [48.8- 56.3]	43.7 [38.0- 50.3]
	B (Victoria)	Pre	14.1 [13.0- 15.2]	13.4 [11.6- 15.5]
		Post	46.4 [42.9- 50.1]	29.9 [25.8- 34.6]

* Subject number (%) Exact [95% CI]

Table 12 Summary of GC3110A_ED_P3

Study Identifier		GC3110A_ED_P3	
Report date		22 June 2017	
Sites/countries		10 sites/ Korea	
Study period		10 October 2016 ~ 08 May 2017	
Hypothesis/objectives		The purpose of this study was to evaluate the safety and efficacy (Immunogenicity) of GC3110A (Quadrivalent Influenza Vaccine) administered intramuscularly in healthy elderly subjects ≥65 years.	
Design		Phase III, multi-center, open-label, single arm study	
Treatment		• Four strains recommended by the World Health Organization (WHO) for the 2016-2017 (NH) season: A/California/7/2009 NYMC X-181 (H1N1); A/Hong Kong/ 4801/2014 NYMC X-263B (H3N2); B/Brisbane/60/2008 (Victoria lineage) ;B/Phuket/3073/2013 (Yamagata lineage): 15 μg for each strain • A single intramuscular dose (0.5 mL)	
Endpoints	Primary endpoint	① Seroconversion rate ② Seroprotection rate	
	Key secondary endpoints	Geometric Mean Titer (GMT) and Geometric Mean Ratio (GMR) of the HI antibody titers determined (21 days after the vaccination)	
Results and Analysis			
Primary analysis population		FAS (Full Analysis Set) population that consisted of 271 subjects / Healthy elderly subjects ≥ 65 years	
Effect estimate per comparison		Treatment group	GC3110A (GCFLU QIV prefilled syringe inj.)
		Number of subjects	N=271
Seroconversion rate for each strain*		A (H1N1)	99 (36.5) [30.8 - 42.3]
		A (H3N2)	129 (47.6) [41.7 - 53.5]
		B (Yamagata)	110 (40.6) [34.7 - 46.4]
		B (Victoria)	133 (49.1) [43.1 - 55.0]
Seroprotection rate for each strain*		A (H1N1)	220 (81.2) [76.5 - 85.8]
		A (H3N2)	267 (98.5) [97.1 - 100.0]
		B (Yamagata)	258 (95.2) [92.7 - 97.7]
		B (Victoria)	254 (93.7) [90.8 - 96.6]

GMT and GMR for each strain	A (H1N1)	Pre	24.0 [21.6 - 26.7]
		Post	64.2 [57.2 - 72.0]
		Ratio	2.7 [2.4 - 3.0]
	A (H3N2)	Pre	64.4 [57.2 - 72.4]
		Post	201.4 [180.9 - 224.2]
		Ratio	3.1 [2.8 - 3.5]
	B (Yamagata)	Pre	37.4 [34.4 - 40.7]
		Post	88.4 [80.5 - 97.1]
		Ratio	2.4 [2.2 - 2.6]
	B (Victoria)	Pre	30.0 [27.5 - 32.8]
		Post	87.0 [78.3 - 96.8]
		Ratio	2.9 [2.6 - 3.2]

*Subject number (%) [95% CI]

Table 13 Summary of GC3110B_P3

Study Identifier		GC3110B_P3	
Report date		31 August 2017	
Sites/countries		3 sites/ Philippine	
Study period		18 October 2016 ~ 01 December 2016	
Hypothesis/objectives		The purpose of this study was to compare the safety and efficacy of GC3110B with GCFLU Quadrivalent Inj. administered intramuscularly in healthy adults.	
Design		Phase III, randomized, double-blind, multi-center, single country, non-inferiority study	
Treatment		• Four strains recommended by the World Health Organization (WHO) for the 2016-2017 (NH) season: A/California/7/2009 NYMC X-181 (H1N1); A/Hong Kong/ 4801/2014 NYMC X-263B (H3N2); B/Brisbane/60/2008 (Victoria lineage) ;B/Phuket/3073/2013 (Yamagata lineage): 15 μg for each strain • A single injection of 0.5 mL GC3110B (GCFLU Quadrivalent Multi inj.) or GCFLU Quadrivalent inj. was administered intramuscularly in healthy adults aged 18 to 60 years old	
Endpoints	Primary endpoint	Ratio of GMT, using the HI antibody titer at Day 21+3 ($GMT_{control\ drug}/GMT_{test\ drug}$)	
	Key secondary endpoints	① Seroconversion rate ② Seroprotection rate	
Results and Analysis			
Primary analysis population		PP (per protocol) population that consisted of 410 subjects / Healthy adults aged 18 to 60 years	
Effect estimate per comparison	Treatment group	GC3110B (GCFLU Quadrivalent Multi inj.) or GCFLU Quadrivalent inj.	
	Number of subjects	GC3110B N=204	GCFLU Quadrivalent inj. N=206
Ratio of GMT ($GMT_{control\ drug}/GMT_{test\ drug}$) for	A (H1N1)	0.97 [0.807, 1.172], p=0.7698	
	A (H3N2)	0.98 [0.811, 1.193], p=0. 8681	
	B (Yamagata)	1.22 [1.022, 1.468], p=0.0281	

each strain	B (Victoria)	1.21 [1.015, 1.437], *p*=0. 0337	
Seroconversion rate for each strain*	A (H1N1)	176 (86.3) [80.78 - 90.68]	184 (89.3) [84.28 - 93.19]
	A (H3N2)	113 (55.4) [48.29 - 62.34]	121 (58.7) [51.69 - 65.53]
	B (Yamagata)	134 (65.7) [58.73 - 72.17]	154 (74.8) [68.25 - 80.54]
	B (Victoria)	136 (66.7) [59.75 - 73.10]	162 (78.6) [72.41 - 84.03]
Seroprotection rate for each strain*	A (H1N1)	198 (97.1) [93.71 - 98.91]	201 (97.6) [94.43 - 99.21]
	A (H3N2)	183 (89.7) [84.70 - 93.51]	187 (90.8) [85.97 - 94.36]
	B (Yamagata)	183 (89.7) [84.70 - 93.51]	188 (91.3) [86.54 - 94.74]
	B (Victoria)	161 (78.9) [72.68 - 84.31]	183 (88.8) [83.72 - 92.79]

* Subject number (%) Exact [95% CI]

Table 14 Summary of GC3110A_IF_P3

Study Identifier		GC3110A_IF_P3		
Report date		16 August 2018		
Sites/countries		Part 1: 2 sites/ Korea Part 2: 13 sites/ Korea		
Study period		19 September 2017 ~ 09 July 2018		
Hypothesis/objectives		The purpose of this study was to evaluate the efficacy (Immunogenicity) and safety of GC3110A (GCFLU Quadrivalent Influenza Vaccine) in healthy infants over 6 months and less than 3 years of age.		
Design		Part 1: Multi-center, open label, single arm Part 2: Multi-center, randomized, double-blind, active- controlled		
Treatment		• Test drug: GC3110A (0.5 mL) Four strains recommended by the World Health Organization (WHO) for the 2017-2018 (NH) season: A/Singapore/GP1908/2015 IVR-180 (H1N1); A/Hong Kong/4801/2014 NYMC X-263B (H3N2); B/Phuket/3073/2013); B/Brisbane/60/2008: 15 μg for each strain • Control drug: GC FLU Pre-filled Syringe inj. (0.25 mL) A/Singapore/GP1908/2015 IVR-180(H1N1); A/Hong Kong/4801/2014 NYMC X-263B(H3N2); B/Brisbane/60/2008: 7.5 μg for each strain		
Endpoints	Primary endpoint	① Seroconversion rate ② Seroprotection rate		
	Key secondary endpoints	Geometric Mean Titer (GMT) and Geometric Mean Ratio (GMR) of the HI antibody titers determined (28 days after the final dose).		
Results and Analysis				
Primary analysis population		PP (per protocol) population that consisted of 201 subjects and FA (Full Analysis) population that consisted of 208 subjects / PP populations were those included in the FA populations that completed the trial without violation of protocol. /Healthy infants over 6 months and less than 3 years of age		
Effect estimate per comparison	Treatment group		GC3110A (GCFLU QIV prefilled syringe inj.) or GCFLU Prefilled syringe inj.	
	Part		Part 1	Part 2
	Number of subjects	PP	GC3110A N=10	GC3110A N=152 / GCFLU PFS N=39
		FA	GC3110A N=10	GC3110A N=159 / GCFLU PFS N=39

Seroconversion rate for each strain*	A (H1N1)	PP		8 (80.0) [55.2 - 100.0]	116 (76.3) [69.6 – 83.1]	30 (76.9) [63.7 – 90.1]
		FA		8 (80.0) [55.2 - 100.0]	122 (76.7) [70.2 – 83.3]	30 (76.9) [63.7 – 90.1]
	A (H3N2)	PP		8 (80.0) [55.2 -100.0]	120 (78.9) [72.5 – 85.4]	26 (66.7) [51.9 – 81.5]
		FA		8 (80.0) [55.2 -100.0]	124 (78.0) [71.5 – 84.4]	26 (66.7) [51.9 – 81.5]
	B (Yamagata)	PP		7 (70.0) [41.6 – 98.4]	111 (73.0) [66.0 – 80.1]	6 (15.4) [4.1 – 26.7]
		FA		7 (70.0) [41.6 – 98.4]	117 (73.6) [66.7 – 80.4]	6 (15.4) [4.1 – 26.7]
	B (Victoria)	PP		8 (80.0) [55.2 - 100.0]	125 (82.2) [76.2 – 88.3]	27 (69.2) [54.7 – 83.7]
		FA		8 (80.0) [55.2 - 100.0]	131 (82.4) [76.5 – 88.3]	27 (69.2) [54.7 – 83.7]
Seroprotection rate for each strain*	A (H1N1)	PP		9 (90.0) [71.4, 100.0]	122 (80.3) [73.9 – 86.6]	32 (82.1) [70.0 – 94.1]
		FA		9 (90.0) [71.4, 100.0]	128 (80.5) [74.3 – 86.7]	32 (82.1) [70.0 – 94.1]
	A (H3N2)	PP		8 (80.0) [55.2 - 100.0]	129 (84.9) [79.2 – 90.6]	30 (76.9) [63.7 – 90.1]
		FA		8 (80.0) [55.2 - 100.0]	133 (83.6) [77.9 – 89.4]	30 (76.9) [63.7 – 90.1]
	B (Yamagata)	PP		7 (70.0) [41.6 – 98.4]	121 (79.6) [73.2 – 86.0]	11 (28.2) [14.1 – 42.3]
		FA		7 (70.0) [41.6 – 98.4]	127 (79.9) [73.6 – 86.1]	11 (28.2) [14.1 – 42.3]
	B (Victoria)	PP		8 (80.0) [55.2 - 100.0]	130 (85.5) [79.9 – 91.1]	33 (84.6) [73.3 – 95.9]
		FA		8 (80.0) [55.2 - 100.0]	136 (85.5) [80.1 – 91.0]	33 (84.6) [73.3 – 95.9]
GMT and GMR for each strain	A (H1N1)	PP	Pre	8.71 [4.62 - 16.41]	8.37 [7.21 – 9.71]	7.80 [5.97 – 10.18]
			Post	74.64 [32.72 - 170.28]	82.97 [67.09 – 102.62]	66.97 [43.51 – 103.10]
			Ratio	8.57 [3.89 - 18.91]	9.91 [8.01 – 12.27]	8.59 [5.57 – 13.25]
		FA	Pre	8.71 [4.62 - 16.41]	8.33 [7.22 – 9.60]	7.80 [5.97 – 10.18]
			Post	74.64 [32.72 - 170.28]	80.70 [65.70 – 99.13]	66.97 [43.51 – 103.10]
			Ratio	8.57 [3.89 - 18.91]	9.69 [7.88 – 11.91]	8.59 [5.57 – 13.25]
	A (H3N2)	PP	Pre	10.72 [5.75 - 19.97]	10.37 [9.05 – 11.88]	9.65 [7.15 – 13.02]
			Post	69.64 [34.81 - 139.32]	72.36 [60.15 – 87.05]	52.22 [37.75 – 72.23]

			Ratio	6.50 [4.56 - 9.26]	6.98 [5.96 – 8.16]	5.41 [4.10 – 7.14]
		FA	Pre	10.72 [5.75 - 19.97]	10.22 [8.96 – 11.65]	9.65 [7.15 – 13.02]
			Post	69.64 [34.81 - 139.32]	71.43 [59.60 – 85.60]	52.22 [37.75 – 72.23]
			Ratio	6.50 [4.56 - 9.26]	6.99 [6.00 – 8.14]	5.41 [4.10 – 7.14]
	B (Yamagata)	PP	Pre	8.12 [6.60 - 10.00]	8.92 [8.06 – 9.88]	9.31 [7.46 – 11.63]
			Post	56.57 [26.77 - 119.56]	52.11 [43.90 -61.86]	16.74 [12.04 -23.29]
			Ratio	6.96 [3.63 - 13.38]	5.84 [5.00 – 6.82]	1.80 [1.48 – 2.19]
		FA	Pre	8.12 [6.60 - 10.00]	8.85 [8.02 – 9.76]	9.31 [7.46 – 11.63]
			Post	56.57 [26.77 - 119.56]	51.73 [43.78 -61.13]	16.74 [12.04 -23.29]
			Ratio	6.96 [3.63 - 13.38]	5.84 [5.03 – 6.79]	1.80 [1.48 – 2.19]
	B (Victoria)	PP	Pre	7.07 [4.66 - 10.74]	9.73 [8.11 – 11.67]	13.53 [8.61 – 21.24]
			Post	56.57 [26.77 - 119.56]	97.78 [79.52 – 120.22]	92.22 [64.76 – 131.33]
			Ratio	8.00 [4.13 - 15.50]	10.05 [8.64 – 11.69]	6.82 [4.87 – 9.54]
		FA	Pre	7.07 [4.66 - 10.74]	9.66 [8.10 – 11.52]	13.53 [8.61 – 21.24]
			Post	56.57 [26.77 - 119.56]	96.92 [79.30 – 118.45]	92.22 [64.76 – 131.33]
			Ratio	8.00 [4.13 - 15.50]	10.04 [8.67 – 11.61]	6.82 [4.87 – 9.54]

* Subject number (%) [95% CI]

Table 15 Summary of GC3114_P1

Study Identifier	GC3114_P1
Report date	23 April 2018
Sites/countries	1 site/ Korea
Study period	20 November 2017 ~27 December 2017
Hypothesis/objectives	The purpose of this study was to evaluate the safety and efficacy (Immunogenicity) of GC3114 (High dose Quadrivalent influenza vaccine) in healthy adults.
Design	Phase I, single center, randomized, single-blinded, active-controlled study
Treatment	• Four strains recommended by the World Health Organization

		(WHO) for the 2017-2018 (NH) season: A/Singapore/GP1908/2015 IVR-180 (H1N1); A/Hong Kong/4801/2014 NYMC X-263B (H3N2); B/Phuket/3073/2013; B/Brisbane/60/2008 • Test drug: GC3114 (60 μg for each strain) • Control drug: GCFLU Quadrivalent Syringe Inj. (15 μg for each strain) • A single intramuscular dose (0.5 mL)
Endpoints	Primary endpoint	① Seroconversion rate ② Seroprotection rate ③ Geometric Mean Titer (GMT) and Geometric Mean Ratio (GMR) of the HI antibody titers determined before vaccination (Day 0) and 21 days after vaccination.

Results and Analysis

Primary analysis population	FA (Full Analysis) and PP (per protocol) population that consisted of 40 subjects respectively. PP populations were those included in the FA populations that completed the trial without violation of protocol. /Healthy adults aged ≥19 and <65 years				
Effect estimate per comparison	Treatment group			GC3114 (High dose Quadrivalent influenza vaccine) or GCFLU Quadrivalent Pre-filled Syringe inj.	
	Number of subjects	PP and FA		GC3114 N=30	GCFLU QIV PFS N=10
Seroconversion rate for each strain*	A (H1N1)	PP and FA		26 (86.67) [69.28 – 96.24]	5 (50.00) [19.01 – 80.99]
	A (H3N2)	PP and FA		27 (90.00) [73.47 – 97.89]	3 (30.00) [6.67 – 65.25]
	B (Yamagata)	PP and FA		16 (53.33) [35.48 – 71.19]	2 (20.00) [2.52 – 55.61]
	B (Victoria)	PP and FA		16 (53.33) [35.48 – 71.19]	3 (30.00) [6.67 – 65.25]
Seroprotection rate for each strain*	A (H1N1)	PP and FA		30 (100.00) [- – 100.00]	10 (100.00) [- – 100.00]
	A (H3N2)	PP and FA		29 (96.67) [82.78 – 99.92]	10 (100.00) [- – 100.00]
	B (Yamagata)	PP and FA		25 (83.33) [70.00 – 96.67]	7 (70.00) [34.75 – 93.33]
	B (Victoria)	PP and FA		29 (96.67) [82.78 – 99.92]	10 (100.00) [- – 100.00]
GMT and GMR for each strain	A (H1N1)	PP and FA	Pre	17.82 [11.46 – 27.69]	34.82 [15.09 – 80.36]
			Post	272.21 [202.92 - 365.18]	160 [86.21 – 296.96]
			Ratio	15.28 [8.91 - 26.2]	4.59 [1.51 - 14.03]
	A (H3N2)	PP and FA	Pre	15.16 [11.49 - 19.99)	52.78 [24.14 - 115.4]
			Post	124.09 [89.27 - 172.5]	121.26 [75.1 - 195.77]
			Ratio	8.19 [5.77 - 11.62]	2.3 [1.03 - 5.13]

	B (Yamagata)	PP and FA	Pre	16.25 [11.8 - 22.37]	15.16 [7.76 - 29.6]
			Post	57.89 [45.42 - 73.78)	34.82 [19.83 - 61.14]
			Ratio	3.56 [2.71 - 4.68]	2.3 [1.2 - 4.41]
	B (Victoria)	PP and FA	Pre	32.49 [24.52 - 43.05]	34.82 [18.93 - 64.06]
			Post	98.49 [78.49 - 123.59]	74.64 [51.77 - 107.62]
			Ratio	3.03 [2.28 - 4.03]	2.14 [1.13 - 4.06]

* Subject number (%) [95% CI]

Table 16 Summary of GC3114_P2

Study Identifier		GC3114_P2
Report date		30 April 2019
Sites/countries		Part 1: 1 site/ Korea Part 2: 4 sites/ Korea
Study period		01 October 2018 ~13 December 2018
Hypothesis/objectives		The purpose of this study was to evaluate the safety and efficacy (Immunogenicity) of GC3114 (High dose Quadrivalent influenza vaccine) in elderly healthy subjects.
Design		Part 1: Open-labeled, single group Part 2: Randomized, double-blind, active-controlled
Treatment		• Four strains recommended by the World Health Organization (WHO) for the 2018-2019 (NH) season: A/Singapore/GP1908/2015 IVR-180 (H1N1); A/Singapore/INFIMH-16-0019/2016 IVR-186(H3N2); B/Phuket/3073/2013; B/Maryland/15/2016 NYMC BX-69A: • Test drug: GC3114 (60 μg for each strain) • Control drug: GCFLU Quadrivalent PFS inj. (15 μg for each strain) • A single intramuscular dose (0.5 mL)
Endpoints	Primary endpoint	① Seroconversion rate ② Seroprotection rate ③ Geometric Mean Titer (GMT) and Geometric Mean Ratio (GMR) of the HI antibody titers determined before vaccination (Day 0) and 28 days after vaccination
Results and Analysis		
Primary analysis population		FA (Full Analysis) and PP (per protocol) population that consisted of 105 subjects respectively. PP populations were those included in the FA populations that completed the trial without violation of protocol. /Elderly Healthy adults ≥ 65 years
Effect estimate per comparison	Treatment group	GC3114 or GCFLU Quadrivalent PFS inj.
		Part 1 / Part 2
	Number of subjects	GC3114 N=15 / GC3114 N=60 / GCFLU Quadrivalent PFS inj. N=30

Seroconversion rate for each strain*	A (H1N1)	PP and FA		11 (73.33) [44.90 - 92.21]	48 (80.00) [69.88 - 90.12]	18 (60.00) [42.47 - 77.53]
	A (H3N2)	PP and FA		7 (46.67) [21.42 - 71.91]	26 (43.33) [30.79 - 55.87]	10 (33.33) [16.46 - 50.20]
	B (Yamagata)	PP and FA		8 (53.33) [28.09 - 78.58]	34 (56.67) [44.13 - 69.21]	10 (33.33) [16.46 - 50.20]
	B (Victoria)	PP and FA		10 (66.67) [42.81 - 90.52]	45 (75.00) [64.04 - 85.96]	16 (53.33) [35.48 - 71.19]
Seroprotection rate for each strain*	A (H1N1)	PP and FA		14 (93.33) [68.05– 99.83]	57 (95.00) [86.08 - 98.96]	29 (96.67) [82.78 - 99.92]
	A (H3N2)	PP and FA		14 (93.33) [68.05– 99.83]	54 (90.00) [82.41 - 97.59]	27 (90.00) [73.47 - 97.89]
	B (Yamagata)	PP and FA		15 (100.0) [78.20 - 100.0]	52 (86.67) [78.07 - 95.27]	24 (80.00) [65.69 - 94.31]
	B (Victoria)	PP and FA		15 (100.0) [78.20 - 100.0]	56 (93.33) [83.80 - 98.15]	25 (83.33) [70.00 - 96.67]
GMT and GMR** for each strain	A (H1N1)	PP/ FA	Pre	20.95 [11.84- 37.06]	20.00 [14.68 - 27.25]	27.64 [17.37 - 43.99]
			Post	105.56 [74.43 - 149.71]	137.69 [107.33 - 176.64]	115.78 [77.57 - 172.83]
			Ratio	5.04 [3.14 - 8.09]	6.88 [5.27 -9.00]	4.19 [2.76 - 6.37]
	A (H3N2)	PP/ FA	Pre	28.95 [19.79 - 42.33]	26.09 [20.96 - 32.47]	26.39 [18.35 - 37.96]
			Post	80.00 [54.50 - 117.43]	79.08 [62.57 - 99.96]	71.27 [50.37 - 100.85]
			Ratio	2.76 [1.79 -4.26]	3.03 [2.43 - 3.78]	2.70 [1.93 -3.79]
	B (Yamagata)	PP/ FA	Pre	26.39 [18.08 - 38.53]	20.47 [15.99 - 26.19]	23.51 [16.66 - 33.18]
			Post	72.94 [52.96 - 100.45]	72.94 [57.06 - 93.24]	56.57 [38.80 - 82.46]
			Ratio	2.76 [2.16 -3.53]	3.56 [2.96 - 4.30]	2.41 [1.88 -3.07]
	B (Victoria)	PP/ FA	Pre	22.97 [13.84 - 38.13]	26.09 [21.34 - 31.89]	24.06 [17.50 - 33.08]
			Post	91.90 [62.26 - 135.63]	133.00 [106.91 - 165.45]	80.00 [55.83 - 114.63]
			Ratio	4.00 [2.32 - 6.88]	5.10 [4.12 - 6.31]	3.32 [2.44 - 4.54]

* Subject number (%) [95% CI]

** Ratio = (GMT_{post}/GMT_{pre}) [95% CI]

17.2 Newly Identified Information on Efficacy/Effectiveness

During the current review period of this PBRER, no clinical study data was available for the approved indication.

17.3 Characterization of Benefits

In summary, there are no new relevant benefit data and no significant changes to the risk profile of the product. Important baseline efficacy/effectiveness information is provided in Section 17.1.

Brief description of the strength of evidence of benefit

Prophylactic use of seasonal flu vaccination has become the standard procedure for several decades, and there are recommendations to use seasonal vaccination for the prevention of flu by ACIP and other health authorities.

The evidence of efficacy/effectiveness of ***GCFLU QIV*** is mainly based on eight (8) well-designed clinical trials; thus, the strength of evidence based on the data obtained from clinical studies is probably sufficient.

New information that challenges the validity of a surrogate endpoint

No new information on the validity of a surrogate endpoint was identified during the reporting period.

Clinical relevance of the effect size

The principle method to measure immune response to vaccination is the Hemagglutinin Inhibition (HI) titer, which measures the concentration of antibody required to prevent influenza from agglutinating with red blood cells.

Although ***GCFLU QIV*** is a quadrivalent vaccine with the four components updated annually by the WHO, and there can be differences in efficacy from season to season, the observed effect size measured using HI antibody titer in the clinical trials of ***GCFLU QIV*** were considered as sufficient.

No new information that demonstrated lack of treatment effect was available during the period covered by the present report.

Generalizability of treatment response across the indicated patient population

Efficacy of ***GCFLU QIV*** was confirmed in ***GCFLU QIV*** arm of following MAH-sponsored clinical trials: in GC3110A_C_P3 conducted in healthy children aged more than 6 months (119 children aged 6 months to 3 years old, 168 children aged 3 years old to 9 years old, and 150 children over 9 years old and adolescents were recruited to ***GCFLU QIV*** arm; in GC3110A_P1/2a that enrolled 60 healthy adults (mean age of the subjects in ***GCFLU QIV*** arm is between 35.56 and 32.25); in GC3110B_P3 that enrolled 413 healthy adults aged between 18 to 60 years old; in GC3110A_AD_P3 that enrolled 647 healthy adults aged over 19 years; in GC3110A_ED_P3 that enrolled 274 healthy elderlies aged 65 years and older; in GC3110A_IF_P3 that enrolled 210

healthy subjects aged between 6 months and 3 years old; in GC3114_P1 that enrolled 40 healthy adults aged ≥19 and <65 years; and in GC3114_P2 that enrolled 105 healthy elderly subjects aged 65 years and older.

No new information that demonstrated a lack of treatment effect in a subpopulation was available during the period covered by the present report.

Adequacy of characterization of dose-response

The standard dose of ***GCFLU QIV*** is 0.5 mL for children aged over 6 months and adults.

For influenza vaccine naive children younger than 9 years old is recommended to receive 2 doses at an interval of at least 4 weeks.

GC3114_P2 trial demonstrated the efficacy and safety of GC3114 (High dose Quadrivalent influenza vaccine) compared to GCFLU Quadrivalent Pre-filled Syringe inj. in elderly healthy adults aged ≥ 65 years.

Duration of effect

The decline in antibodies is influenced by several factors, including the antigen used in the vaccine, the age of the person being vaccinated, and the person's general health (for example, certain chronic health conditions may have an impact on immunity). When most healthy people with regular immune systems are vaccinated, their bodies produce antibodies to protect themselves throughout the flu season, though the antibody levels decline over time.

No new information on the duration of effect (indicating shortening of the duration of effect) was identified during the reporting period.

Effects of long-term treatment or repeated dose

A single dose or two doses of influenza vaccine has been used for prevention of influenza infection and illness.

Two doses of influenza vaccine could be more effective than a single dose in a certain subpopulation: for example, H1N1 influenza virus after two (2) doses; response after one (1) dose was 50% for children aged 6 through 35 months and 75% for those aged 3 through 9 years.

No new information on the effects of long-term treatment or repeated dose was identified during the period covered by the present report.

Comparative efficacy

Among eight (8) MAH-sponsored trials, seven (7) trials were active-controlled trials: GC3110A_P1/2a, GC3110A_AD_P3, GC3110A_C_P3, GC3110B_P3, GC3110A_IF_P3, GC3114_P1, and GC3114_P2.

Majority of the trials were controlled trials; thus, it was concluded that the comparative efficacy was proved.

Determination of the extent to which efficacy findings from clinical trials are generalizable

to patient populations treated in medical practice

Since the eight (8) MAH-sponsored trials concern subjects aged from 6 months to over 65 years, which cover almost all ages, it suggests that enough evidence for the efficacy was established to use in populations treated in medical practice.

18. Integrated Benefit-Risk Analysis for Approved Indications

18.1 Benefit-Risk Context - Medical Need and Important Alternatives

GCFLU QIV is a quadrivalent inactivated vaccine (IIV4), which is prepared from embryonated chicken eggs and composed of the four (4) currently circulating seasonal influenza virus strains: two (2) influenza A virus types and two (2) B types.

Alternatives are other types of influenza vaccine including live attenuated influenza virus vaccine (LAIV), trivalent inactivated vaccine (IIV3), and cell culture-based vaccine (ccIIV3 or 4) and recombinant vaccine.

GCFLU QIV may help to fill an unmet need, albeit not unmet medical need, by providing expanded options and greater affordability.

18.2 Benefit-Risk Analysis Evaluation

Since ***GCFLU QIV*** has one (1) indication, a single benefit-risk evaluation concerning the indication is provided below. In this PBRER, FDA benefit-risk framework is used as the method of benefit-risk evaluation; it is known as one of the descriptive frameworks to provide a high-level snapshot for the benefit-risk profiles.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition: Prophylaxis of Influenza	**Clinical Manifestations:** Influenza occurs globally with an annual attack rate estimated at 5%–10% in adults and 20%–30% in children. Seasonal influenza is characterized by a sudden onset of fever, cough (usually dry), headache, muscle and joint pain, severe malaise (feeling unwell), sore throat and a runny nose. Most people recover from fever and other symptoms within a week without	Seasonal influenza is an acute viral infection that spreads easily from person to person and may cause serious clinical manifestations. Annual seasonal influenza vaccination is recommended by most of the health authorities for any person aged 6 months and over who wishes to reduce the likelihood of becoming ill with influenza. Therefore, seasonal influenza vaccination is needed.

	requiring medical attention. But influenza can cause severe illness or death especially in people at high risk (pregnant women, children aged 6–59 months, the elderly, individuals with specific chronic medical conditions such as HIV/AIDS, asthma, and chronic heart or lung diseases, and health-care workers). The time from infection to illness, known as the incubation period, is about 2 days.	
	Morbidity of Influenza It is estimated that Influenza infections are associated with substantial medical costs, hospitalizations, lost productivity, and thousands of deaths every year in the United States. The total economic burden of influenza in the US has been estimated as $87.1 billion based on 2003 US population. Direct medical costs averaged $10.4 billion (95% confidence interval [CI], $4.1, $22.2) annually. Projected lost earnings due to illness and loss of life amounted to $16.3 billion (CI, $8.7, $31.0) annually.	Influenza infection and its illness are expected to have a significant impact with respect to overall public health, thus it is suggested that seasonal influenza vaccination is needed.
	Mortality of Influenza: According to the estimations conducted by CDC, the average annual rate of influenza-associated death during 1976-2007 was calculated as 1.4~16.7 deaths per 100,000.	Considering the high attack rate of seasonal influenza infection, mortality is expected to have a significant impact with respect to overall public health, thus it is suggested that seasonal influenza vaccination is needed.
Current Treatment Options: Approved available therapy	**Other influenza vaccines:** The strains of the vaccines are selected each year depend on the annual WHO recommendation; thus other quadrivalent inactivated vaccines (IIV4) having same strains to those of ***GCFLU QIV*** are available. Alternatives are other types of influenza vaccine including live attenuated influenza virus vaccine (LAIV), trivalent inactivated vaccine (IIV3), cell culture-based vaccine (ccIIV3 or 4), and recombinant vaccine.	***GCFLU QIV*** may help to fill an unmet need, albeit not unmet medical need, by providing expanded options and greater affordability.

	Antiviral therapy: Currently, 4 licensed prescription influenza antiviral agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir. **Symptomatic relief:** For relief of fever in children, antipyretic medications other than aspirin or aspirin-containing products (e.g., acetaminophen or non-steroidal anti-inflammatory drugs) are recommended. **Hospitalization:** Patients most often require hospitalization when influenza exacerbates underlying chronic diseases.	
Clinical Benefit	***GCFLU QIV*** has been tested in 8 MAH-sponsored trials: GC3110A_P1/2a, GC3110A_AD_P3, GC3110A_C_P3, GC3110A_ED_P3, GC3110B_P3, GC3110A_IF_P3, GC3114_P1, and GC3114_P2.	As summarized in the tables of the section 17.1 and 17.2, ***GCFLU QIV*** showed clinical benefits.
Risk • Severe allergic reactions including anaphylaxis	***GCFLU QIV arms in clinical trials:*** No cases reported ***Post marketing database:*** Two (2) cases reported	The influenza vaccine is grown in an allantoic fluid in embryonated chicken eggs. The vaccine contains measurable quantities of egg proteins. Both the CDC's ACIP and the American Academy of Pediatrics' Committee on Infectious Diseases have concluded that egg allergy of any severity (including anaphylaxis) is not a contraindication to the administration of further influenza vaccine, but rather a precaution. Considering the current recommendation of ACIP and the academic society, and low incidence of

		the risk, it is believed that they are unlikely to pose a significant risk to result in unfavorable risk/benefit balance.
• Vaccination failure	***GCFLU QIV arms in clinical trials:*** No cases reported ***Post marketing database:*** No cases reported	The persons with vaccination failure may require revaccination and have serious influenza complications. As discussed in section 17 [benefit evaluation], the most of the clinical trials of ***GCFLU QIV*** showed more than 70% of subjects achieving an HI antibody titer of ≥ 1:40 after the final vaccination whose results meet current criteria for effective flu vaccine.
• Guillain-Barre syndrome (GBS)	***GCFLU QIV arms in clinical trials:*** No cases reported ***Post marketing database:*** Seven (7) cases reported	The ACIP recommends not administering influenza vaccine to individuals who have had a history of GBS (Guillain-Barre syndrome) within 6 weeks of a prior influenza vaccination if they are not at high risk of severe complications from influenza illness. The outcome of Guillain-Barre syndrome is generally favorable and it resolves with symptomatic treatment as necessary, however, the syndrome might cause neurologic sequelae or even death. The overall number of individuals affected is expected to be small. Considering the current recommendation of ACIP and low incidence of the risk, it is believed that they are unlikely to pose a significant risk to result in unfavorable risk/benefit balance.
• Optic neuritis	***GCFLU QIV arms in clinical trials:*** No cases reported ***Post marketing database:*** One (1) case reported	Only a single case has been reported from DIBD to DLP. Considering the rarity of the events, it is unlikely to pose a significant risk to result in unfavorable risk/benefit balance.
• Myelitis	***GCFLU QIV arms in clinical trials:*** No cases reported	Only a single case has been reported from DIBD to DLP. Considering the

	Post marketing database: One (1) case reported	rarity of the events, it is unlikely to pose a significant risk to result in unfavorable risk/benefit balance.
• Acute disseminated encephalomyelitis (ADEM)	***GCFLU QIV arms in clinical trials:*** No cases reported ***Post marketing database:*** One (1) case reported	Only a single case has been reported from DIBD to DLP. Considering the rarity of the events, it is unlikely to pose a significant risk to result in unfavorable risk/benefit balance.
• Vasculitis	***GCFLU QIV arms in clinical trials:*** One (1) case reported ***Post marketing database:*** No cases reported	Only a single case has been reported from DIBD to DLP. Considering the rarity of the events, it is unlikely to pose a significant risk to result in unfavorable risk/benefit balance.
• Convulsion/seizure:	***GCFLU QIV arms in clinical trials:*** One (1) case reported ***Post marketing database:*** Four (4) cases reported	Considering the rarity of the events and uncertain background incidence rate, it is unlikely to pose a significant risk to result in unfavorable risk/benefit balance.
• Oculo-respiratory syndrome	***GCFLU QIV arms in clinical trials:*** No cases reported ***Post marketing database:*** No cases reported	No cases have been reported in any clinical trials and post-marketing database; thus it is suggested that ***GCFLU QIV*** poses no additional risks of oculo-respiratory syndrome.
Risk Management	**Risk minimization measures:** The clinical trials showed significant benefit and minimal risks during the use of ***GCFLU QIV***.	Routine pharmacovigilance activities and risk minimization measures will be conducted. The safety information suggests that the current measures for risk minimization are effective and no additional risk minimization measures are needed for ***GCFLU QIV***. The safety information will be updated whenever any important new information is available in routine pharmacovigilance activities and post-authorization studies.

Benefit-Risk Summary Assessment:

Hundreds of scientific publications on the efficacy and/or safety of influenza vaccine are available that document their favorable benefit-to-risk ratio.

Eight (8) well designed trials of ***GCFLU QIV*** showed that clinically significant benefit generated by ***GCFLU QIV*** was similar to other flu vaccines, and the important risks could be managed while without preventing the benefit otherwise generated by the product.

No new trends suggesting an increased frequency or severity of the potential or identified risks have been identified during the period covered by the present report; thus, no new safety signals

were identified from the safety information.
In summary, the safety review of the information collected during the period covered by the present report did not reveal significant safety concerns for ***GCFLU QIV*** as long as it was used as instructed.
No additional risks have been identified compared to trivalent inactivated influenza vaccines (IIV3).
There is no vaccination procedure or medical intervention that bears no risk at all. However, having considered the information of benefit and safety of ***GCFLU QIV***, the benefit of ***GCFLU QIV*** outweighs the risk of its use in the indications and in an appropriate population; and the findings support favorable benefit-to-risk ratio of ***GCFLU QIV***.

19. Conclusions and Actions

During the period covered by the present report, MAH collected the safety information regarding ***GCFLU QIV*** from various sources, such as information from the completed or ongoing clinical trials, long-term follow-up, other therapeutic use of medicinal product, fixed combination therapies that contained ***GCFLU QIV***, non-clinical data, extensive literature searches, and other periodic reports.

From the various sources during the reporting period, new signals or clinically important safety information that affected the risk-benefit balance evaluation were not identified. Analysis results of the integrated safety data were consistent with the current reference safety information for ***GCFLU QIV*** and supported the adequacy of the current reference safety information.

The measures in the reference safety information constitute routine risk minimization measures, and the current routine risk minimization activities are deemed sufficient to manage the risks of ***GCFLU QIV***. Therefore, no additional risk minimization measures are needed.

The safety profile of ***GCFLU QIV*** is closely monitored on a continuous basis. Based on the cumulative data, the benefit-risk profile for ***GCFLU QIV*** remains positive.

20. Appendices

Appendix 1. Reference Safety Information

- GCFLU Quadrivalent Pre-filled Syringe inj.: Summary of Product Characteristics (SmPC) dated 10 Mar 2022
- GCFLU Quadrivalent inj.: SmPC dated 10 Mar 2022
- GCFLU Quadrivalent Multi inj.: SmPC dated 10 Mar 2022

The SmPCs will be provide at the end of this report. Pagination will differ in document appended as it has its own pagination.

Appendix 2. Cumulative Tabulation of Serious Adverse Events from Clinical Trials

System Organ Class (SOC) Preferred Term (PT)	*GCFLU QIV*	Blinded	Comparator	Placebo
Infections and infestations	**37**	**0**	**17**	**0**
Appendicitis	2	0	0	0
Bronchiolitis	5	0	2	0
Bronchitis	2	0	2	0
Croup infectious	3	0	0	0
Cystitis	1	0	0	0
Dengue fever	1	0	0	0
Gastroenteritis	1	0	2	0
Gastroenteritis norovirus	1	0	0	0
Gastroenteritis rotavirus	1	0	0	0
Hand-foot-and-mouth disease	1	0	0	0
Herpes zoster	1	0	0	0
Influenza	3	0	2	0
Nasopharyngitis	0	0	1	0
Peritonsillar abscess	1	0	0	0
Pharyngitis	3	0	0	0
Pneumonia	8	0	5	0
Pneumonia mycoplasmal	0	0	1	0
Pneumonia respiratory syncytial viral	1	0	1	0
Pulmonary tuberculosis	1	0	0	0
Tonsillitis	0	0	1	0
Urinary tract infection	1	0	0	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**2**	**0**	**1**	**0**

System Organ Class (SOC) Preferred Term (PT)	*GCFLU QIV*	Blinded	Comparator	Placebo
Benign breast neoplasm	0	0	1	0
Gastric cancer	2	0	0	0
Blood and lymphatic system disorders	**1**	**0**	**0**	**0**
Lymphadenitis	1	0	0	0
Nervous system disorders	**2**	**0**	**1**	**0**
Febrile convulsion	1	0	1	0
Headache	1	0	0	0
Vascular disorders	**2**	**0**	**0**	**0**
Hypertensive crisis	1	0	0	0
Kawasaki's disease	1	0	0	0
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**1**	**0**
Adenoidal hypertrophy	0	0	1	0
Gastrointestinal disorders	**2**	**0**	**1**	**0**
Gastrointestinal inflammation	1	0	0	0
Haemorrhoids thrombosed	0	0	1	0
Ileus	1	0	0	0
Musculoskeletal and connective tissue disorders	**1**	**0**	**0**	**0**
Arthralgia	1	0	0	0
Reproductive system and breast disorders	**2**	**0**	**0**	**0**
Breast mass	1	0	0	0
Genital prolapse	1	0	0	0
General disorders and administration site conditions	**2**	**0**	**0**	**0**
Impaired healing	1	0	0	0
Pain	1	0	0	0
Injury, poisoning and procedural complications	**2**	**0**	**1**	**0**

System Organ Class (SOC) Preferred Term (PT)	*GCFLU QIV*	Blinded	Comparator	Placebo
Foreign body aspiration	1	0	0	0
Foreign body in gastrointestinal tract	1	0	0	0
Joint dislocation	0	0	1	0
Total	**53**	**0**	**22**	**0**

*Dictionary: MedDRA ver. 25.1

*Data from the completed and ongoing clinical trials as of 25 November 2022

Appendix 3. Numbers of Adverse Drug Reactions by Term from Post-Marketing Sources

System Organ Class (SOC) Preferred Term (PT)	Spontaneous, including regulatory authority and literature					Non-interventional post-marketing study and reports from other solicited sources*	
	Serious		Non-serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
Infections and infestations	**1**	**3**	**0**	**9**	**12**	**0**	**0**
Impetigo	0	0	0	1	1	0	0
Influenza	0	0	0	3	3	0	0
Myelitis	0	1	0	0	1	0	0
Nasopharyngitis	0	1	0	5	6	0	0
Sepsis	1	1	0	0	1	0	0
Blood and lymphatic system disorders	**0**	**0**	**0**	**4**	**4**	**0**	**0**
Lymph node pain	0	0	0	1	1	0	0
Lymphadenitis	0	0	0	2	2	0	0
Lymphadenopathy	0	0	0	1	1	0	0
Immune system disorders	**0**	**1**	**1**	**3**	**4**	**0**	**0**
Anaphylactic reaction	0	1	0	0	1	0	0
Anaphylactic shock	0	0	1	1	1	0	0
Hypersensitivity	0	0	0	2	2	0	0
Metabolism and nutrition disorders	**0**	**0**	**0**	**2**	**2**	**0**	**0**
Abnormal loss of weight	0	0	0	1	1	0	0
Decreased appetite	0	0	0	1	1	0	0
Psychiatric disorders	**0**	**2**	**1**	**3**	**5**	**0**	**0**

System Organ Class (SOC) Preferred Term (PT)	Spontaneous, including regulatory authority and literature					Non-interventional post-marketing study and reports from other solicited sources*	
	Serious		Non-serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
Aggression	0	0	0	1	1	0	0
Confusional state	0	1	0	0	1	0	0
Emotional disorder	0	0	0	1	1	0	0
Insomnia	0	1	0	0	1	0	0
Poor quality sleep	0	0	1	1	1	0	0
Nervous system disorders	**2**	**14**	**4**	**47**	**61**	**0**	**0**
Acute disseminated encephalomyelitis	0	1	0	0	1	0	0
Amnesia	0	0	0	1	1	0	0
Dizziness	0	0	1	11	11	0	0
Dysarthria	0	1	0	0	1	0	0
Encephalopathy	0	1	0	0	1	0	0
Epilepsy	0	1	0	0	1	0	0
Facial paralysis	0	0	0	2	2	0	0
Guillain-Barre syndrome	2	7	0	0	7	0	0
Headache	0	0	1	7	7	0	0
Hypoaesthesia	0	0	0	1	1	0	0
Monoplegia	0	0	0	1	1	0	0
Optic neuritis	0	0	0	1	1	0	0
Paraesthesia	0	0	0	4	4	0	0
Paralysis	0	2	0	1	3	0	0

System Organ Class (SOC) Preferred Term (PT)	Spontaneous, including regulatory authority and literature					Non-interventional post-marketing study and reports from other solicited sources*	
	Serious		Non-serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
Paraplegia	0	1	0	0	1	0	0
Parosmia	0	0	1	1	1	0	0
Peripheral paralysis	0	0	0	1	1	0	0
Radiculitis brachial	0	0	1	1	1	0	0
Restless legs syndrome	0	0	0	1	1	0	0
Seizure	0	0	0	3	3	0	0
Syncope	0	0	0	9	9	0	0
Transient ischaemic attack	0	0	0	1	1	0	0
Trigeminal neuralgia	0	0	0	1	1	0	0
Eye disorders	**0**	**2**	**0**	**7**	**9**	**0**	**0**
Conjunctivitis allergic	0	0	0	1	1	0	0
Diplopia	0	1	0	2	3	0	0
Erythema of eyelid	0	0	0	1	1	0	0
Eye movement disorder	0	0	0	1	1	0	0
Eye paraesthesia	0	0	0	1	1	0	0
Ocular hyperaemia	0	0	0	1	1	0	0
Swelling of eyelid	0	1	0	0	1	0	0
Cardiac disorders	**0**	**2**	**0**	**0**	**2**	**0**	**0**
Arrhythmia	0	1	0	0	1	0	0
Myocarditis	0	1	0	0	1	0	0

System Organ Class (SOC) Preferred Term (PT)	Spontaneous, including regulatory authority and literature					Non-interventional post-marketing study and reports from other solicited sources*	
	Serious		Non-serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
Vascular disorders	**0**	**1**	**0**	**0**	**1**	**0**	**0**
Vascular occlusion	0	1	0	0	1	0	0
Respiratory, thoracic and mediastinal disorders	**0**	**1**	**0**	**4**	**5**	**0**	**0**
Dyspnoea	0	0	0	2	2	0	0
Oropharyngeal pain	0	1	0	0	1	0	0
Respiratory tract oedema	0	0	0	1	1	0	0
Rhinorrhoea	0	0	0	1	1	0	0
Gastrointestinal disorders	**2**	**4**	**2**	**25**	**29**	**0**	**0**
Abdominal discomfort	0	0	1	1	1	0	0
Abdominal pain	0	0	0	1	1	0	0
Diarrhoea	0	0	0	6	6	0	0
Dyspepsia	0	0	0	1	1	0	0
Enteritis	1	1	0	0	1	0	0
Flatulence	0	0	0	1	1	0	0
Lip swelling	0	0	0	1	1	0	0
Nausea	0	0	1	6	6	0	0
Paraesthesia oral	0	1	0	0	1	0	0
Toothache	0	0	0	1	1	0	0
Vomiting	1	2	0	7	9	0	0
Skin and subcutaneous tissue disorders	**0**	**5**	**0**	**29**	**34**	**0**	**0**

System Organ Class (SOC) Preferred Term (PT)	Spontaneous, including regulatory authority and literature					Non-interventional post-marketing study and reports from other solicited sources*	
	Serious		Non-serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
Angioedema	0	0	0	1	1	0	0
Cold sweat	0	0	0	1	1	0	0
Dermatitis allergic	0	0	0	1	1	0	0
Erythema	0	0	0	2	2	0	0
Fixed eruption	0	0	0	1	1	0	0
Hyperhidrosis	0	0	0	1	1	0	0
Nail discolouration	0	0	0	1	1	0	0
Petechiae	0	0	0	2	2	0	0
Pruritus	0	1	0	4	5	0	0
Rash	0	1	0	6	7	0	0
Rash macular	0	0	0	1	1	0	0
Rash papular	0	0	0	1	1	0	0
Skin disorder	0	1	0	0	1	0	0
Urticaria	0	2	0	7	9	0	0
Musculoskeletal and connective tissue disorders	**0**	**0**	**1**	**14**	**14**	**0**	**0**
Arthralgia	0	0	0	2	2	0	0
Back pain	0	0	0	2	2	0	0
Limb discomfort	0	0	0	1	1	0	0
Muscle tightness	0	0	0	1	1		
Musculoskeletal stiffness	0	0	0	1	1	0	0

System Organ Class (SOC) Preferred Term (PT)	Spontaneous, including regulatory authority and literature					Non-interventional post-marketing study and reports from other solicited sources*	
	Serious		Non-serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
Myalgia	0	0	1	6	6	0	0
Pain in extremity	0	0	0	1	1	0	0
Reproductive system and breast disorders	**0**	**0**	**0**	**1**	**1**	**0**	**0**
Postmenopausal haemorrhage	0	0	0	1	1	0	0
General disorders and administration site conditions	**0**	**10**	**7**	**121**	**131**	**0**	**0**
Asthenia	0	0	0	2	2	0	0
Chills	0	1	0	7	8	0	0
Face oedema	0	0	1	1	1	0	0
Fatigue	0	0	0	5	5	0	0
Feeling hot	0	0	1	2	2	0	0
Hyperthermia	0	0	0	4	4	0	0
Hypothermia	0	0	0	1	1	0	0
Influenza like illness	0	0	0	4	4	0	0
Injection site bruising	0	0	0	1	1	0	0
Injection site erythema	0	1	0	2	3	0	0
Injection site haemorrhage	0	0	0	1	1	0	0
Injection site induration	0	0	0	1	1	0	0
Injection site pain	0	0	0	13	13	0	0
Injection site swelling	0	1	0	8	9	0	0
Injection site urticaria	0	0	0	1	1	0	0

System Organ Class (SOC) Preferred Term (PT)	Spontaneous, including regulatory authority and literature					Non-interventional post-marketing study and reports from other solicited sources*	
	Serious		Non-serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
Malaise	0	0	1	3	3	0	0
Oedema	0	0	0	1	1	0	0
Oedema peripheral	0	1	0	0	1	0	0
Pain	0	1	0	23	24	0	0
Peripheral swelling	0	1	0	2	3	0	0
Pyrexia	0	4	0	17	21	0	0
Tenderness	0	0	0	1	1	0	0
Vaccination site bruising	0	0	1	1	1	0	0
Vaccination site discolouration	0	0	0	1	1	0	0
Vaccination site erythema	0	0	0	1	1	0	0
Vaccination site exfoliation	0	0	0	1	1	0	0
Vaccination site pain	0	0	2	11	11	0	0
Vaccination site pruritus	0	0	1	2	2	0	0
Vaccination site swelling	0	0	0	2	2	0	0
Vaccination site urticaria	0	0	0	1	1	0	0
Vaccination site warmth	0	0	0	1	1	0	0
Investigations	**0**	**1**	**1**	**3**	**4**	**0**	**0**
Blood pressure increased	0	1	1	1	2	0	0
Inflammatory marker increased	0	0	0	1	1	0	0
Liver function test abnormal	0	0	0	1	1	0	0

System Organ Class (SOC) Preferred Term (PT)	Spontaneous, including regulatory authority and literature					Non-interventional post-marketing study and reports from other solicited sources*	
	Serious		Non-serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
Injury, poisoning and procedural complications	**0**	**0**	**8**	**70**	**70**	**0**	**0**
Accidental exposure to product	0	0	0	1	1	0	0
Accidental overdose	0	0	0	2	2	0	0
Expired product administered	0	0	0	2	2	0	0
Exposure during pregnancy	0	0	0	9	9	0	0
Extra dose administered	0	0	5	8	8	0	0
Inappropriate schedule of product administration	0	0	0	1	1	0	0
Incorrect dose administered	0	0	0	9	9	0	0
Incorrect dose administered by device	0	0	1	1	1	0	0
Incorrect route of product administration	0	0	0	2	2	0	0
Paternal exposure before pregnancy	0	0	0	1	1	0	0
Product administered at inappropriate site	0	0	0	3	3	0	0
Product administered to patient of inappropriate age	0	0	0	20	20	0	0
Product preparation error	0	0	0	1	1	0	0
Product storage error	0	0	0	3	3	0	0
Product use complaint	0	0	0	1	1	0	0
Wrong product administered	0	0	1	2	2	0	0
Wrong technique in product usage process	0	0	1	4	4	0	0
Product issues	**0**	**0**	**1**	**4**	**4**	**0**	**0**

System Organ Class (SOC) Preferred Term (PT)	Spontaneous, including regulatory authority and literature					Non-interventional post-marketing study and reports from other solicited sources*	
	Serious		Non-serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
Device infusion issue	0	0	1	1	1	0	0
Needle issue	0	0	0	2	2	0	0
Product container seal issue	0	0	0	1	1	0	0
Total	**5**	**46**	**26**	**346**	**392**	**0**	**0**

* Dictionary: MedDRA ver. 25.1

* This does not include MAH-sponsored interventional clinical trial

SUMMARY OF PRODUCT CHARACTERISTICS

GCFLU Quadrivalent Pre-filled Syringe inj.

Green Cross Corporation

* The Summary of Product Characteristics (SmPC) has been structured in accordance with Article 11 of Directive 2001/83/EC, and the presented information is pertinent to the Korean Licensure of the product.

1. NAME OF THE MEDICINAL PRODUCT

GCFLU Quadrivalent Pre-filled Syringe inj.

2. QUANTITATIVE AND QUANTITATIVE COMPOSITION

1 pre-filled syringe 0.5 mL contains,

Purified Inactivated Influenza Virus Antigen Type A [A/Victoria/2570/2019 IVR-215 (H1N1)]	15 µg
Purified Inactivated Influenza Virus Antigen Type A [A/Darwin/9/2021 SAN-010 (H3N2)]	15 µg
Purified Inactivated Influenza Virus Antigen Type B [B/Austria/1359417/2021 BVR-26]	15 µg
Purified Inactivated Influenza Virus Antigen Type B [B/Phuket/3073/2013]	15 µg
Sodium chloride	4 mg
Potassium chloride	0.1 mg
Disodium hydrogen phosphate dihydrate	0.6 mg
Potassium dihydrogen phosphate	0.1 mg
Water for injection	q.s.

This vaccine complies with the WHO recommendations (Northern Hemisphere) for 2022-2023 season.

3. PHARMACEUTICAL FORM

Pre-filled syringe containing colorless or slightly whitish liquid

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylaxis against influenza caused by influenza A subtype viruses and type B viruses in persons aged 6 months and older.

4.2 Posology and Method of Administration

An intramuscular injection of the following dose and immunization of one dose is necessary in every year at same volume.
Aged 6 months and older: A single dose of 0.5 mL
The children younger than 9 years of age who have not been vaccinated should be vaccinated two doses at an interval of at least 4 weeks.
The preferred sites for intramuscular injection are the anterolateral aspect of the thigh (or the deltoid muscle of the upper arm if muscle mass is adequate) in children 6 through 35 months of age, or the deltoid muscle of the upper arm in children from 36 months of age and adults.

The safety and efficacy of the vaccine was not established in children younger than 6 months.

4.3 Contraindications

Examine subjects by history taking and visual inspection and if necessary, by auscultation and percussion. Vaccination is prohibited when subject is diagnosed as one of the following cases. However, if it is seems to be infected with influenza and determined that there is no concern for disabilities due to vaccination, vaccination may be permitted.

1) Febrile patient or person with malnutrition.
2) Patients with cardiovascular disorders, kidney disorders, or liver disease in which the disease is in acute phase, stadium increment, or in active phase.
3) Patients with acute respiratory disease or other active infectious disease.
4) Patients in latent and convalescence period.
5) Person who showed anaphylaxis by the components of the product.
6) Person with hypersensitivity to egg, chicken, any other chicken component, and the product component.
7) Person who had fever within 2 days or a symptom of allergy such as generalized rash after the injection at previous vaccination.
8) Person who showed the symptom of convulsion within 1 year before vaccination.
9) Person who showed Guillain-Barre syndrome or person with neurological disorders within 6 weeks from the previous influenza vaccination.
10) Person diagnosed with immunodeficiency disease.
11) Person in inappropriate condition to be vaccinated.

4.4 Special Warnings and Precautions for Use

4.4.1 General precautions

1) Advise the subjects or their guardians that the subjects should keep equilibrium, keep the injection site clean, and when the symptoms of high fever, convulsion appear, they should consult a physician quickly.
2) Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.
3) Influenza vaccine should be administered before prevailing. Vaccination can be delayed according to epidemiological situation.
4) Influenza vaccine should be administered with current-year recommended strains.

4.5 Interaction with other medicinal products and other forms of interaction

1) There is no data or study on co-administration of this product with other vaccines.
2) The immunological response may be diminished if the patient is undergoing

immunosuppressant treatment.

3) Following influenza vaccination, false positive results in serologic tests using the ELISA method to detect antibodies against HIV-1, Hepatitis C, and especially HTLV-1 have been observed (The Western Blot technique disproves the false-positive ELISA test results). These transient false-positive results could be due to the IgM response by the vaccine.

4.6 Pregnancy and Nursing Mothers

Pregnancy

- Inactivated Influenza vaccine (egg-derived) is known that it can be used in all pregnancy cycles regardless of the pregnancy stage. There are more safety data for second trimester and third trimester compared with the first trimester. In addition, according to data on the usage of inactivated influenza vaccine collected globally, no adverse effects of the vaccine on the fetus and maternity were reported.

- In addition, no direct or indirect adverse effects related to reproductive toxicity and developmental toxicity were observed in animal studies conducted using this vaccine. However, clinical trials have not evaluated the safety of the pregnant women when administered this vaccine.

Nursing Mothers

- Inactivated Influenza vaccine (egg-derived) is known that it can be used to lactating women. Restricted data indicate that the vaccine is not known whether the product is excreted in human milk. However, there is no adequate study of vaccination in animals during lactation, and clinical trials have not evaluated the safety of nursing mothers when administered this vaccine.

4.7 Effects on ability to drive and use machines

Some of the effects mentioned under section 4.8 “Undesirable Effects” may affect the ability to drive or use machines.

4.8 Undesirable Effects

1) There is possibility of local reactions such as redness, swelling and pain, or systemic reactions such as fever, chills, headache, fatigue and vomiting. But they usually disappear within 2-3 days.
2) In rare cases, acute disseminated encephalomyelitis (ADEM) may occur.
   Fever, headache, convulsions, dyskinesia and consciousness disorder usually occur within 2 weeks following the administration of the vaccine. When these symptoms are suspected, appropriate medical treatment should be available by diagnosis with MRI and so on.
3) Allergic reaction or anaphylactic shock may occur in very rare cases.
4) Transient disorders of systemic and local nervous system may rarely occur. Palsy, neuralgia, cerebral hemorrhage or inflammation of the nervous system (ex: Guillain-Barre syndrome) have been reported.
5) Safety of the vaccine was evaluated for the 4 clinical studies performed with healthy children, adults, and elderly.
   In children aged 6 through 35 months who received the vaccine, 115 subjects (67.6%) out of

170 subjects showed adverse events. Adverse drug reactions were 82 subjects (48.2%) and no serious adverse drug reactions were reported. In children aged 3 through 18 years who received the vaccine, 218 subjects (68.3%) out of 319 subjects showed adverse events. Adverse drug reactions were 204 subjects (63.9%) and no serious adverse drug reactions were reported.
In adults aged 19 through 64 years who received the vaccine, 415 subjects (71.2%) out of 583 subjects showed adverse events. Adverse drug reactions were 399 subjects (68.4%) and no serious adverse drug reactions were reported.
In elderly over 65 years of age who received the vaccine, 148 subjects (43.8%) out of 338 subjects showed adverse events. Adverse drug reactions were 140 subjects (41.4%) and no serious adverse drug reactions were reported.

(1) Solicited adverse drug reactions within 7 days of vaccination are listed in the table below.

		Children aged 6 through 35 months (n=170)	Children aged 3 through 18 years (n=319)	Adults aged 19 through 64 years (n=583)	Elderly over 65 years of age (n=338)
Local	Pain	27.6%	52.7%	48.9%	21.0%
	Tenderness		54.5%	56.8%	27.5%
	Erythema/Redness	11.8%	6.6%	7.9%	3.8%
	Induration/Swelling	5.9%	8.2%	5.8%	3.6%
Systemic	Drowsiness[1)]	15.9%	-	-	-
	Fever	6.5%	3.1%	0.9%	0.3%
	Sweating	2.4%	2.2%	4.3%	2.7%
	Chills	2.4%	5.0%	7.7%	4.4%
	Nausea/Vomiting	2.4%	0.6%	2.2%	0.9%
	Diarrhea	5.9%	0.3%	1.5%	1.2%
	Fatigue	-	15.4%	25.6%	10.7%
	Malaise	-	11.0%	7.5%	8.3%
	Headache	0.6%	6.9%	13.4%	7.1%
	Muscle aches	7.6%	8.2%	26.4%	6.5%
	Arthralgia	-	1.6%	5.8%	3.6%

1) Drowsiness only applies for children and 6 months through 35 months

(2) Unsolicited adverse drug reactions occurring within 28 days or 21 days of vaccination were reported in 4 subjects (2.4%) from children aged 6 through 35 months (Infections and infestations: 3 subjects, Skin and subcutaneous tissue disorders: 1 subject), 3 subjects (0.9%) from children aged 3 through 18 years (General disorders and administration site conditions: 2 subjects, Infections and infestations: 1 subject), 13 subjects (2.2%) from adults (Infections and infestations: 5 subjects, investigations: 2 subjects, Respiratory thoracic and mediastinal disorders: 2 subjects, Musculoskeletal and connective tissue disorders: 1 subject, Nervous system disorders: 1 subject, Skin and subcutaneous tissue disorders: 1 subject, General disorders and administration site conditions: 2 subjects), and 4 subjects (1.2%) from elderly (Infections and infestations: 1 subject, General disorders and administration site conditions: 1 subject, investigations: 1 subject, Nervous system disorders: 1 subject)

(3) Serious adverse events occurring within 6 months of vaccination were reported in 13 subjects (7.6%) from children aged 6 through 35 months (Pneumonia: 4 cases, Influenza: 3

cases , Bronchitis: 2 cases , Pneumonia respiratory syncytial viral: 1 case, Bronchiolitis: 1 case, Croup infectious: 1 case, Gastroenteritis norovirus: 1 case, Gastroenteritis rotavirus: 1 case, Urinary tract infection: 1 case, Gastrointestinal infection: 1 case, Impaired healing: 1 case, Foreign body in gastrointestinal tract: 1 case, Febrile convulsion: 1 case), 5 subjects (1.6%) from children aged 3 through 18 years (Pharyngitis: 1 case, Headache: 1 case, Mesenteric lymphadenitis: 1 case, Acute gastroenteritis: 1 case, Peritonsillar Abscess: 1 case, Acute appendicitis: 1 case), 5 subjects (0.9%) from adults (Cystitis: 1 case, Pulmonary Tuberculosis: 1 case, Breast mass: 1 case, Ileus : 1 case, Gastric cancer: 1 case), and 4 subjects (1.2%) from elderly (Pain: 1 case, Arthralgia: 1 case, Herpes zoster: 1 case, Gastric cancer: 1 case), but they were evaluated as 'not related' to the product.

6) Results of post-marketing surveillance in South Korea

(1) The results of post-marketing surveillance conducted domestically for 4 years on 2,060 adult subjects aged 19 years and older in order to go through a re-examination showed that the incidence of adverse events was 10.49% (216 out of 2,060 subjects, 578 cases in total), regardless of causal relationship.

Among these, no serious adverse events and serious adverse drug reactions have been reported.

In addition, unexpected adverse events and unexpected adverse drug reactions are listed in the following table according to their frequency of onset.

		Unexpected Adverse Events Regardless of Causal Relationship 2.33% (48 out of 2,060 subjects, 72 cases)	Unexpected Adverse Drug Reactions of Which Causal Relationship Cannot Be Ruled Out 0.29% (6 out of 2,060 subjects, 7 cases)
Rarely (≥ 0.01% and < 0.1%)	Respiratory, thoracic, and mediastinal disorders	Asthma	Cough
	Gastrointestinal disorders	Dyspepsia, benign gastrointestinal neoplasm, gastrointestinal disorder NOS, hemorrhoids	-
	General disorders and administration site condition	Injection site inflammation	Injection site inflammation
	Nervous system disorders	Apathy, insomnia, dizziness, cerebral ischemia	Apathy, dizziness
	Eye disorders	Blepharitis, conjunctivitis	-
	General disorders and administration site condition	Back pain	-
	Vascular	Hypertension	-

	disorders		
	Cardiac disorders	Palpitation	Palpitation
	Metabolism and nutrition disorders	Hyperlipidemia	-
	Infections and infestations	Fungal dermatitis, moniliasis	-
Uncommonly (≥ 0.1% and < 1%)	Respiratory, thoracic, and mediastinal disorders	Rhinitis, sinusitis, cough, upper respiratory tract infection	-
	Gastrointestinal disorders	Gastritis, gastroesophageal reflux, abdominal pain, irritable bowel syndrome	-
	Skin and subcutaneous tissue disorders	Dermatitis, pustular rash, contact dermatitis, urticaria	-
	General disorders and administration site condition	Cellulitis, injection site pruritus	Injection site pruritus

(2) The results of post-marketing surveillance conducted domestically for 4 years on 2,033 pediatric subjects aged ≥ postnatal 6 months and < 19 years showed that the incidence of adverse events was 30.74% (625 out of 2,033 subjects, 1,221 cases in total), regardless of causal relationship. Among these, serious adverse events and serious adverse drug reactions are listed in the following table according to their frequency of onset.

		Serious Adverse Events 0.10% (2 out of 2,033 subjects; 2 cases)	Serious Adverse Drug Reactions 0.00% (0 out of 2,033 subjects; 0 cases)
Rarely (≥ 0.01% and < 0.1%)	White cell and reticuloendothelial system disorders	Kawasaki disease*	-
	Respiratory system disorders	Bronchitis	-

* Unexpected serious adverse event

In addition, unexpected adverse events and unexpected adverse drug reactions are listed in the following table according to their frequency of onset.

	Unexpected Adverse Events Regardless of Causal Relationship 7.82% (159 out of 2,033	Unexpected Adverse Drug Reactions of Which Causal Relationship Cannot Be Ruled Out 0.49% (10 out of 2,033

		subjects; 178 cases)	subjects, 10 cases)
Rarely (≥ 0.01% and < 0.1%)	Application site disorders	Cellulitis, Injection site bruising	Injection site bruising
	Body as a whole-general disorders	Leg pain, Influenza-like symptoms, Hypothermia, Temperature changed sensation	Leg pain, Hypothermia, Temperature changed sensation
	Gastrointestinal system disorders	Constipation, Gastroesophageal reflux	-
	Skin and appendages disorders	Acne, Dermatitis contact, Dermatitis fungal, Skin disorder	Rash pustular
	Resistance mechanism disorders	Moniliasis	Otitis media
	White cell and reticuloendothelial system disorders	Kawasaki disease, Lymphadenopathy	-
	Secondary terms - events	Varicella	-
Uncommonly (≥ 0.1% and < 1%)	Respiratory system disorders	Sinusitis, Cough, Asthma	-
	Application site disorders	Injection site pruritus	Injection site pruritus
	Gastrointestinal system disorders	Abdominal pain, Stomatitis	-
	Skin and appendages disorders	Dermatitis, Rash pustular, Urticaria, Pruritus	Urticaria
	Resistance mechanism disorders	Otitis media	-
	Vision disorders	Conjunctivitis	-
Commonly (≥ 1% and < 10%)	Respiratory system disorders	Rhinitis	-

(3) Adverse events from domestic post-marketing surveillance and spontaneously reported data on side effects were comprehensively assessed at the end of post-marketing surveillance along with the adverse events data (1989 to December 31, 2020) reported for all drugs that have been licensed for domestic marketing. Among the adverse events that were reported more frequently with statistical significance for this drug than the adverse events reported

for all other drugs, following adverse events were newly identified. However, these results do not mean that the causal relationship between the relevant ingredient and the following adverse events has been demonstrated.

- Systemic and injection site adverse events: Injection site inflammation, injection site warmth, injection site pruritus, injection site bruising
- Infection: Rhinitis (rhinorrhea)

4.9 Overdose
Cases of administration of more than the recommended dose (overdose) have not been reported with this product.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB02

5.2 Pharmacokinetic properties
Not applicable

5.3 Non-clinical safety data
Repeat dose toxicity study (including local tolerance test) and reproductive/developmental toxicity study were conducted in compliance with GLP requirements. Any drug-related adverse effect was not observed in the studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Sodium chloride
Potassium chloride
Disodium hydrogen phosphate dihydrate
Potassium dihydrogen phosphate
Water for injection

6.2 Incompatibilities
Incompatibilities with other drugs have not been evaluated.

6.3 Shelf-life
12 months from the date of manufacture.

6.4 Special precautions for storage
Store at 2-8°C without freezing in hermetic container and protect from light.

6.5 Nature and contents of container

0.5 mL pre-filled syringe x In-house packing unit
(With attached sterilized disposable needle)

6.6 Special precautions for disposal and other handling

1) Before use check this product visually for particles or discoloration. If either is present, do not use.
2) The injection site is usually lateral upper arm and disinfected with ethanol or tincture of iodine. Repeated injections at the same site should be avoided.
3) Intravenous administration is prohibited.
4) The tip of needle should not penetrate blood vessel.
5) Do not mix with other vaccines in same syringe.
6) The vaccine should be shaken well and mixed homogeneously before use
7) Pre-filled syringes are disposable and should not be reused.

7. MARKETING AUTHORISATION HOLDER

Green Cross Corporation

107, Ihyeon-ro 30beon-gil, Giheung-gu, Yongin-si, Gyeonggi-do, Korea

8. MARKETING AUTHORISATION NUMBER(S)

5035

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 Nov 2015

10. DATE OF REVISION OF THE TEXT

10 Mar 2022

SUMMARY OF PRODUCT CHARACTERISTICS

GCFLU Quadrivalent inj.

Green Cross Corporation

* The Summary of Product Characteristics (SmPC) has been structured in accordance with Article 11 of Directive 2001/83/EC, and the presented information is pertinent to the Korean Licensure of the product.

1. NAME OF THE MEDICINAL PRODUCT

GCFLU Quadrivalent inj.

2. QUANTITATIVE AND QUANTITATIVE COMPOSITION

1 vial 0.5 mL contains,

Purified Inactivated Influenza Virus Antigen Type A [A/Victoria/2570/2019 IVR-215 (H1N1)]	15 µg
Purified Inactivated Influenza Virus Antigen Type A [A/Darwin/9/2021 SAN-010 (H3N2)]	15 µg
Purified Inactivated Influenza Virus Antigen Type B [B/Austria/1359417/2021 BVR-26]	15 µg
Purified Inactivated Influenza Virus Antigen Type B [B/Phuket/3073/2013]	15 µg
Sodium chloride	4 mg
Potassium chloride	0.1 mg
Disodium hydrogen phosphate dihydrate	0.6 mg
Potassium dihydrogen phosphate	0.1 mg
Water for injection	q.s.

This vaccine complies with the WHO recommendations (Northern Hemisphere) for 2022-2023 season.

3. PHARMACEUTICAL FORM

Solution for injection containing colorless or slightly whitish liquid

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylaxis against influenza caused by influenza A subtype viruses and type B viruses in persons aged 6 months and older.

4.2 Posology and Method of Administration

An intramuscular injection of the following dose and immunization of one dose is necessary in every year at same volume.
Aged 6 months and older: A single dose of 0.5 mL
The children younger than 9 years of age who have not been vaccinated should be vaccinated two doses at an interval of at least 4 weeks.
The preferred sites for intramuscular injection are the anterolateral aspect of the thigh (or the deltoid muscle of the upper arm if muscle mass is adequate) in children 6 through 35 months of age, or the deltoid muscle of the upper arm in children from 36 months of age and adults.

The safety and efficacy of the vaccine was not established in children younger than 6 months.

4.3 Contraindications

Examine subjects by history taking and visual inspection and if necessary, by auscultation and percussion. Vaccination is prohibited when subject is diagnosed as one of the following cases. However, if it is seems to be infected with influenza and determined that there is no concern for disabilities due to vaccination, vaccination may be permitted.

1) Febrile patient or person with malnutrition.
2) Patients with cardiovascular disorders, kidney disorders, or liver disease in which the disease is in acute phase, stadium increment, or in active phase.
3) Patients with acute respiratory disease or other active infectious disease.
4) Patients in latent and convalescence period.
5) Person who showed anaphylaxis by the components of the product.
6) Person with hypersensitivity to egg, chicken, any other chicken component, and the product component.
7) Person who had fever within 2 days or a symptom of allergy such as generalized rash after the injection at previous vaccination.
8) Person who showed the symptom of convulsion within 1 year before vaccination.
9) Person who showed Guillain-Barre syndrome or person with neurological disorders within 6 weeks from the previous influenza vaccination.
10) Person diagnosed with immunodeficiency disease.
11) Person in inappropriate condition to be vaccinated.

4.4 Special Warnings and Precautions for Use

4.4.1 General precautions

1) Advise the subjects or their guardians that the subjects should keep equilibrium, keep the injection site clean, and when the symptoms of high fever, convulsion appear, they should consult a physician quickly.
2) Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.
3) Influenza vaccine should be administered before prevailing. Vaccination can be delayed according to epidemiological situation.
4) Influenza vaccine should be administered with current-year recommended strains.

4.5 Interaction with other medicinal products and other forms of interaction

1) There is no data or study on co-administration of this product with other vaccines. If co-administration is inevitably required, injection site should be different. It should be noted that the adverse events may be increased.

2) The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.

3) Following influenza vaccination, false positive results in serologic tests using the ELISA method to detect antibodies against HIV-1, Hepatitis C, and especially HTLV-1 have been observed (The Western Blot technique disproves the false-positive ELISA test results). These transient false-positive results could be due to the IgM response by the vaccine.

4.6 Pregnancy and Nursing Mothers

Pregnancy

- Inactivated Influenza vaccine (egg-derived) is known that it can be used in all pregnancy cycles regardless of the pregnancy stage. There are more safety data for second trimester and third trimester compared with the first trimester. In addition, according to data on the usage of inactivated influenza vaccine collected globally, no adverse effects of the vaccine on the fetus and maternity were reported.

- In addition, no direct or indirect adverse effects related to reproductive toxicity and developmental toxicity were observed in animal studies conducted using this vaccine. However, clinical trials have not evaluated the safety of the pregnant women when administered this vaccine.

Nursing Mothers

- Inactivated Influenza vaccine (egg-derived) is known that it can be used to lactating women. Restricted data indicate that the vaccine is not known whether the product is excreted in human milk. However, there is no adequate study of vaccination in animals during lactation, and clinical trials have not evaluated the safety of nursing mothers when administered this vaccine.

4.7 Effects on ability to drive and use machines

Some of the effects mentioned under section 4.8 “Undesirable Effects” may affect the ability to drive or use machines.

4.8 Undesirable Effects

1) There is possibility of local reactions such as redness, swelling and pain, or systemic reactions such as fever, chills, headache, fatigue and vomiting. But they usually disappear within 2-3 days.

2) In rare cases, acute disseminated encephalomyelitis (ADEM) may occur.
Fever, headache, convulsions, dyskinesia and consciousness disorder usually occur within 2 weeks following the administration of the vaccine. When these symptoms are suspected, appropriate medical treatment should be available by diagnosis with MRI and so on.

3) Allergic reaction or anaphylactic shock may occur in very rare cases.

4) Transient disorders of systemic and local nervous system may rarely occur. Palsy, neuralgia, cerebral hemorrhage or inflammation of the nervous system (ex: Guillain-Barre syndrome) have been reported.

5) Safety of the vaccine was evaluated for the 4 clinical studies performed with healthy children, adults, and elderly.
In children aged 6 through 35 months who received the vaccine, 115 subjects (67.6%) out of

170 subjects showed adverse events. Adverse drug reactions were 82 subjects (48.2%) and no serious adverse drug reactions were reported. In children aged 3 through 18 years who received the vaccine, 218 subjects (68.3%) out of 319 subjects showed adverse events. Adverse drug reactions were 204 subjects (63.9%) and no serious adverse drug reactions were reported.

In adults aged 19 through 64 years who received the vaccine, 415 subjects (71.2%) out of 583 subjects showed adverse events. Adverse drug reactions were 399 subjects (68.4%) and no serious adverse drug reactions were reported.

In elderly over 65 years of age who received the vaccine, 148 subjects (43.8%) out of 338 subjects showed adverse events. Adverse drug reactions were 140 subjects (41.4%) and no serious adverse drug reactions were reported.

(1) Solicited adverse drug reactions within 7 days of vaccination are listed in the table below.

		Children aged 6 through 35 months (n=170)	Children aged 3 through 18 years (n=319)	Adults aged 19 through 64 years (n=583)	Elderly over 65 years of age (n=338)
Local	Pain	27.6%	52.7%	48.9%	21.0%
	Tenderness		54.5%	56.8%	27.5%
	Erythema/Redness	11.8%	6.6%	7.9%	3.8%
	Induration/Swelling	5.9%	8.2%	5.8%	3.6%
Systemic	Drowsiness[1)]	15.9%	-	-	-
	Fever	6.5%	3.1%	0.9%	0.3%
	Sweating	2.4%	2.2%	4.3%	2.7%
	Chills	2.4%	5.0%	7.7%	4.4%
	Nausea/Vomiting	2.4%	0.6%	2.2%	0.9%
	Diarrhea	5.9%	0.3%	1.5%	1.2%
	Fatigue	-	15.4%	25.6%	10.7%
	Malaise	-	11.0%	7.5%	8.3%
	Headache	0.6%	6.9%	13.4%	7.1%
	Muscle aches	7.6%	8.2%	26.4%	6.5%
	Arthralgia	-	1.6%	5.8%	3.6%

1) Drowsiness only applies for children and 6 months through 35 months

(2) Unsolicited adverse drug reactions occurring within 28 days or 21 days of vaccination were reported in 4 subjects (2.4%) from children aged 6 through 35 months (Infections and infestations: 3 subjects, Skin and subcutaneous tissue disorders: 1 subject), 3 subjects (0.9%) from children aged 3 through 18 years (General disorders and administration site conditions: 2 subjects, Infections and infestations: 1 subject), 13 subjects (2.2%) from adults (Infections and infestations: 5 subjects, investigations: 2 subjects, Respiratory thoracic and mediastinal disorders: 2 subjects, Musculoskeletal and connective tissue disorders: 1 subject, Nervous system disorders: 1 subject, Skin and subcutaneous tissue disorders: 1 subject, General disorders and administration site conditions: 2 subjects), and 4 subjects (1.2%) from elderly (Infections and infestations: 1 subject, General disorders and administration site conditions: 1 subject, investigations: 1 subject, Nervous system disorders: 1 subject)

(3) Serious adverse events occurring within 6 months of vaccination were reported in 13 subjects (7.6%) from children aged 6 through 35 months (Pneumonia: 4 cases, Influenza: 3 cases , Bronchitis: 2 cases , Pneumonia respiratory syncytial viral: 1 case, Bronchiolitis: 1

case, Croup infectious: 1 case, Gastroenteritis norovirus: 1 case, Gastroenteritis rotavirus: 1 case, Urinary tract infection: 1 case, Gastrointestinal infection: 1 case, Impaired healing: 1 case, Foreign body in gastrointestinal tract: 1 case, Febrile convulsion: 1 case), 5 subjects (1.6%) from children aged 3 through 18 years (Pharyngitis: 1 case, Headache: 1 case, Mesenteric lymphadenitis: 1 case, Acute gastroenteritis: 1 case, Peritonsillar Abscess: 1 case, Acute appendicitis: 1 case), 5 subjects (0.9%) from adults (Cystitis: 1 case, Pulmonary Tuberculosis: 1 case, Breast mass: 1 case, Ileus : 1 case, Gastric cancer: 1 case), and 4 subjects (1.2%) from elderly (Pain: 1 case, Arthralgia: 1 case, Herpes zoster: 1 case, Gastric cancer: 1 case), but they were evaluated as 'not related' to the product.

6) Results of post-marketing surveillance in South Korea

(1) The results of post-marketing surveillance conducted domestically for 4 years on 2,060 adult subjects aged 19 years and older in order to go through a re-examination showed that the incidence of adverse events was 10.49% (216 out of 2,060 subjects, 578 cases in total), regardless of causal relationship.

Among these, no serious adverse events and serious adverse drug reactions have been reported.

In addition, unexpected adverse events and unexpected adverse drug reactions are listed in the following table according to their frequency of onset.

		Unexpected Adverse Events Regardless of Causal Relationship 2.33% (48 out of 2,060 subjects, 72 cases)	Unexpected Adverse Drug Reactions of Which Causal Relationship Cannot Be Ruled Out 0.29% (6 out of 2,060 subjects, 7 cases)
Rarely (≥ 0.01% and < 0.1%)	Respiratory, thoracic, and mediastinal disorders	Asthma	Cough
	Gastrointestinal disorders	Dyspepsia, benign gastrointestinal neoplasm, gastrointestinal disorder NOS, hemorrhoids	-
	General disorders and administration site condition	Injection site inflammation	Injection site inflammation
	Nervous system disorders	Apathy, insomnia, dizziness, cerebral ischemia	Apathy, dizziness
	Eye disorders	Blepharitis, conjunctivitis	-
	General disorders and administration site condition	Back pain	-
	Vascular disorders	Hypertension	-

	Cardiac disorders	Palpitation	Palpitation
	Metabolism and nutrition disorders	Hyperlipidemia	-
	Infections and infestations	Fungal dermatitis, moniliasis	-
Uncommonly (≥ 0.1% and < 1%)	Respiratory, thoracic, and mediastinal disorders	Rhinitis, sinusitis, cough, upper respiratory tract infection	-
	Gastrointestinal disorders	Gastritis, gastroesophageal reflux, abdominal pain, irritable bowel syndrome	-
	Skin and subcutaneous tissue disorders	Dermatitis, pustular rash, contact dermatitis, urticaria	-
	General disorders and administration site condition	Cellulitis, injection site pruritus	Injection site pruritus

(2) The results of post-marketing surveillance conducted domestically for 4 years on 2,033 pediatric subjects aged ≥ postnatal 6 months and < 19 years showed that the incidence of adverse events was 30.74% (625 out of 2,033 subjects, 1,221 cases in total), regardless of causal relationship. Among these, serious adverse events and serious adverse drug reactions are listed in the following table according to their frequency of onset.

		Serious Adverse Events 0.10% (2 out of 2,033 subjects; 2 cases)	Serious Adverse Drug Reactions 0.00% (0 out of 2,033 subjects; 0 cases)
Rarely (≥ 0.01% and < 0.1%)	White cell and reticuloendothelial system disorders	Kawasaki disease*	-
	Respiratory system disorders	Bronchitis	-

* Unexpected serious adverse event

In addition, unexpected adverse events and unexpected adverse drug reactions are listed in the following table according to their frequency of onset.

	Unexpected Adverse Events Regardless of Causal Relationship 7.82% (159 out of 2,033 subjects; 178 cases)	Unexpected Adverse Drug Reactions of Which Causal Relationship Cannot Be Ruled Out 0.49% (10 out of 2,033 subjects, 10 cases)

Rarely (≥ 0.01% and < 0.1%)	Application site disorders	Cellulitis, Injection site bruising	Injection site bruising
	Body as a whole-general disorders	Leg pain, Influenza-like symptoms, Hypothermia, Temperature changed sensation	Leg pain, Hypothermia, Temperature changed sensation
	Gastrointestinal system disorders	Constipation, Gastroesophageal reflux	-
	Skin and appendages disorders	Acne, Dermatitis contact, Dermatitis fungal, Skin disorder	Rash pustular
	Resistance mechanism disorders	Moniliasis	Otitis media
	White cell and reticuloendothelial system disorders	Kawasaki disease, Lymphadenopathy	-
	Secondary terms - events	Varicella	-
Uncommonly (≥ 0.1% and < 1%)	Respiratory system disorders	Sinusitis, Cough, Asthma	-
	Application site disorders	Injection site pruritus	Injection site pruritus
	Gastrointestinal system disorders	Abdominal pain, Stomatitis	-
	Skin and appendages disorders	Dermatitis, Rash pustular, Urticaria, Pruritus	Urticaria
	Resistance mechanism disorders	Otitis media	-
	Vision disorders	Conjunctivitis	-
Commonly (≥ 1% and < 10%)	Respiratory system disorders	Rhinitis	-

(3) Adverse events from domestic post-marketing surveillance and spontaneously reported data on side effects were comprehensively assessed at the end of post-marketing surveillance along with the adverse events data (1989 to December 31, 2020) reported for all drugs that have been licensed for domestic marketing. Among the adverse events that were reported more frequently with statistical significance for this drug than the adverse events reported for all other drugs, following adverse events were newly identified. However, these results do not mean that the causal relationship between the relevant ingredient and the following adverse events has been demonstrated.

- Systemic and injection site adverse events: Injection site inflammation, injection site warmth,

injection site pruritus, injection site bruising
- Infection: Rhinitis (rhinorrhea)

4.9 Overdose
Cases of administration of more than the recommended dose (overdose) have not been reported with this product.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB02

5.2 Pharmacokinetic properties
Not applicable

5.3 Non-clinical safety data
Repeat dose toxicity study (including local tolerance test) and reproductive/developmental toxicity study were conducted in compliance with GLP requirements. Any drug-related adverse effect was not observed in the studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Sodium chloride
Potassium chloride
Disodium hydrogen phosphate dihydrate
Potassium dihydrogen phosphate
Water for injection

6.2 Incompatibilities
Incompatibilities with other drugs have not been evaluated.

6.3 Shelf-life
12 months from the date of manufacture.

6.4 Special precautions for storage
Store at 2-8℃without freezing in hermetic container and protect from light.

6.5 Nature and contents of container
0.5 mL/vial x In-house packing unit

6.6 Special precautions for disposal and other handling

1) Before use check this product visually for particles or discoloration. If either is present, do not use.
2) The injection site is usually lateral upper arm and disinfected with ethanol or tincture of iodine. Repeated injections at the same site should be avoided.
3) Intravenous administration is prohibited.
4) The tip of needle should not penetrate blood vessel.
5) Do not mix with other vaccines in same syringe.
6) The vaccine should be shaken well and mixed homogeneously before use.

7. MARKETING AUTHORISATION HOLDER

Green Cross Corporation

107, Ihyeon-ro 30beon-gil, Giheung-gu, Yongin-si, Gyeonggi-do, Korea

8. MARKETING AUTHORISATION NUMBER(S)

5040

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01 Apr 2016

10. DATE OF REVISION OF THE TEXT

10 Mar 2022

SUMMARY OF PRODUCT CHARACTERISTICS

GCFLU Quadrivalent Multi inj.

Green Cross Corporation

* The Summary of Product Characteristics (SmPC) has been structured in accordance with Article 11 of Directive 2001/83/EC, and the presented information is pertinent to the Korean Licensure of the product.

1. NAME OF THE MEDICINAL PRODUCT

GCFLU Quadrivalent Multi inj. 5mL

2. QUANTITATIVE AND QUANTITATIVE COMPOSITION

1 mL contains,

Purified Inactivated Influenza Virus Antigen Type A [A/Victoria/2570/2019 IVR-215 (H1N1)]	30 µg
Purified Inactivated Influenza Virus Antigen Type A [A/Darwin/9/2021 SAN-010 (H3N2)]	30 µg
Purified Inactivated Influenza Virus Antigen Type B [B/Austria/1359417/2021 BVR-26]	30 µg
Purified Inactivated Influenza Virus Antigen Type B [B/Phuket/3073/2013]	30 µg
Sodium chloride	8 mg
Potassium chloride	0.2 mg
Disodium hydrogen phosphate dihydrate	1.2 mg
Potassium dihydrogen phosphate	0.2 mg
Thimerosal	0.01 w/v%
Water for injection	q.s.

This vaccine complies with the WHO recommendations (Northern Hemisphere) for 2022-2023 season.

3. PHARMACEUTICAL FORM

Solution for injection containing colorless or slightly whitish liquid

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylaxis against influenza caused by influenza A subtype viruses and type B viruses in persons aged 6 months and older.

4.2 Posology and Method of Administration

An intramuscular injection of the following dose and immunization of one dose is necessary in every year at same volume.

Aged 6 months and older: A single dose of 0.5 mL

The children younger than 9 years of age who have not been vaccinated should be vaccinated two doses at an interval of at least 4 weeks.

The preferred sites for intramuscular injection are the anterolateral aspect of the thigh (or the

deltoid muscle of the upper arm if muscle mass is adequate) in children 6 through 35 months of age, or the deltoid muscle of the upper arm in children from 36 months of age and adults.

The safety and efficacy of the vaccine was not established in children younger than 6 months.

4.3 Contraindications

Examine subjects by history taking and visual inspection and if necessary, by auscultation and percussion. Vaccination is prohibited when subject is diagnosed as one of the following cases. However, if it is seems to be infected with influenza and determined that there is no concern for disabilities due to vaccination, vaccination may be permitted.

1) Febrile patient or person with malnutrition.
2) Patients with cardiovascular disorders, kidney disorders, or liver disease in which the disease is in acute phase, stadium increment, or in active phase.
3) Patients with acute respiratory disease or other active infectious disease.
4) Patients in latent and convalescence period.
5) Person who showed anaphylaxis by the components of the product.
6) Person with hypersensitivity to egg, chicken, any other chicken component, and the product component.
7) Person who had fever within 2 days or a symptom of allergy such as generalized rash after the injection at previous vaccination.
8) Person who showed the symptom of convulsion within 1 year before vaccination.
9) Person who showed Guillain-Barre syndrome or person with neurological disorders within 6 weeks from the previous influenza vaccination.
10) Person diagnosed with immunodeficiency disease.
11) Person in inappropriate condition to be vaccinated.

4.4 Special Warnings and Precautions for Use

4.4.1 General precautions

1) Advise the subjects or their guardians that the subjects should keep equilibrium, keep the injection site clean, and when the symptoms of high fever, convulsion appear, they should consult a physician quickly.
2) Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.
3) Influenza vaccine should be administered (September – November) before prevailing. Vaccination can be delayed according to epidemiological situation.
4) Influenza vaccine should be administered with current-year recommended strains.

4.5 Interaction with other medicinal products and other forms of interaction

1) There is no data or study on co-administration of this product with other vaccines. If co-administration is inevitably required, injection site should be different. It should be noted that the adverse events may be increased.
2) The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.
3) Following influenza vaccination, false positive results in serologic tests using the ELISA method to detect antibodies against HIV-1, Hepatitis C, and especially HTLV-1 have been observed (The Western Blot technique disproves the false-positive ELISA test results). These transient false-positive results could be due to the IgM response by the vaccine.

4.6 Pregnancy and Nursing Mother

Pregnancy

- Inactivated Influenza vaccine (egg-derived) is known that it can be used in all pregnancy cycles regardless of the pregnancy stage. There are more safety data for second trimester and third trimester compared with the first trimester. In addition, according to data on the usage of inactivated influenza vaccine collected globally, no adverse effects of the vaccine on the fetus and maternity were reported.

- In addition, no direct or indirect adverse effects related to reproductive toxicity and developmental toxicity were observed in animal studies conducted using this vaccine. However, clinical trials have not evaluated the safety of the pregnant women when administered this vaccine.

Nursing Mothers

- Inactivated Influenza vaccine (egg-derived) is known that it can be used to lactating women. Restricted data indicate that the vaccine is not known whether the product is excreted in human milk. However, there is no adequate study of vaccination in animals during lactation, and clinical trials have not evaluated the safety of nursing mothers when administered this vaccine.

4.7 Effects on ability to drive and use machines

Some of the effects mentioned under section 4.8 “Undesirable Effects” may affect the ability to drive or use machines.

4.8 Undesirable Effects

1) There is possibility of local reactions such as redness, swelling and pain, or systemic reactions such as fever, chills, headache, fatigue and vomiting. But they usually disappear within 2-3 days.
2) In rare cases, acute disseminated encephalomyelitis (ADEM) may occur.
   Fever, headache, convulsions, dyskinesia and consciousness disorder usually occur within 2 weeks following the administration of the vaccine. When these symptoms are suspected, appropriate medical treatment should be available by diagnosis with MRI and so on.
3) Allergic reaction or anaphylactic shock may occur in very rare cases.
4) Transient disorders of systemic and local nervous system may rarely occur. Palsy, neuralgia,

cerebral hemorrhage or inflammation of the nervous system (ex: Guillain-Barre syndrome) have been reported.

5) Safety of the vaccine was evaluated for the 4 clinical studies performed with healthy children, adults, and elderly.

In children aged 6 through 35 months who received the vaccine, 115 subjects (67.6%) out of 170 subjects showed adverse events. Adverse drug reactions were 82 subjects (48.2%) and no serious adverse drug reactions were reported. In children aged 3 through 18 years who received the vaccine, 218 subjects (68.3%) out of 319 subjects showed adverse events. Adverse drug reactions were 204 subjects (63.9%) and no serious adverse drug reactions were reported.

In adults aged 19 through 64 years who received the vaccine, 415 subjects (71.2%) out of 583 subjects showed adverse events. Adverse drug reactions were 399 subjects (68.4%) and no serious adverse drug reactions were reported.

In elderly over 65 years of age who received the vaccine, 148 subjects (43.8%) out of 338 subjects showed adverse events. Adverse drug reactions were 140 subjects (41.4%) and no serious adverse drug reactions were reported.

(1) Solicited adverse drug reactions within 7 days of vaccination are listed in the table below.

		Children aged 6 through 35 months (n=170)	Children aged 3 through 18 years (n=319)	Adults aged 19 through 64 years (n=583)	Elderly over 65 years of age (n=338)
Local	Pain	27.6%	52.7%	48.9%	21.0%
	Tenderness		54.5%	56.8%	27.5%
	Erythema/Redness	11.8%	6.6%	7.9%	3.8%
	Induration/Swelling	5.9%	8.2%	5.8%	3.6%
Systemic	Drowsiness[1)]	15.9%	-	-	-
	Fever	6.5%	3.1%	0.9%	0.3%
	Sweating	2.4%	2.2%	4.3%	2.7%
	Chills	2.4%	5.0%	7.7%	4.4%
	Nausea/Vomiting	2.4%	0.6%	2.2%	0.9%
	Diarrhea	5.9%	0.3%	1.5%	1.2%
	Fatigue	-	15.4%	25.6%	10.7%
	Malaise	-	11.0%	7.5%	8.3%
	Headache	0.6%	6.9%	13.4%	7.1%
	Muscle aches	7.6%	8.2%	26.4%	6.5%
	Arthralgia	-	1.6%	5.8%	3.6%

1) Drowsiness only applies for children and 6 months through 35 months

(2) Unsolicited adverse drug reactions occurring within 28 days or 21 days of vaccination were reported in 4 subjects (2.4%) from children aged 6 through 35 months (Infections and infestations: 3 subjects, Skin and subcutaneous tissue disorders: 1 subject), 3 subjects (0.9%) from children aged 3 through 18 years (General disorders and administration site conditions: 2 subjects, Infections and infestations: 1 subject), 13 subjects (2.2%) from adults (Infections and infestations: 5 subjects, investigations: 2 subjects, Respiratory thoracic and mediastinal disorders: 2 subjects, Musculoskeletal and connective tissue disorders: 1 subject, Nervous system disorders: 1 subject, Skin and subcutaneous tissue disorders: 1 subject, General

disorders and administration site conditions: 2 subjects), and 4 subjects (1.2%) from elderly (Infections and infestations: 1 subject, General disorders and administration site conditions: 1 subject, investigations: 1 subject, Nervous system disorders: 1 subject)

(3) Serious adverse events occurring within 6 months of vaccination were reported in 13 subjects (7.6%) from children aged 6 through 35 months (Pneumonia: 4 cases, Influenza: 3 cases , Bronchitis: 2 cases , Pneumonia respiratory syncytial viral: 1 case, Bronchiolitis: 1 case, Croup infectious: 1 case, Gastroenteritis norovirus: 1 case, Gastroenteritis rotavirus: 1 case, Urinary tract infection: 1 case, Gastrointestinal infection: 1 case, Impaired healing: 1 case, Foreign body in gastrointestinal tract: 1 case, Febrile convulsion: 1 case), 5 subjects (1.6%) from children aged 3 through 18 years (Pharyngitis: 1 case, Headache: 1 case, Mesenteric lymphadenitis: 1 case, Acute gastroenteritis: 1 case, Peritonsillar Abscess: 1 case, Acute appendicitis: 1 case), 5 subjects (0.9%) from adults (Cystitis: 1 case, Pulmonary Tuberculosis: 1 case, Breast mass: 1 case, Ileus : 1 case, Gastric cancer: 1 case), and 4 subjects (1.2%) from elderly (Pain: 1 case, Arthralgia: 1 case, Herpes zoster: 1 case, Gastric cancer: 1 case), but they were evaluated as ‘not related’ to the product.

4.9 Overdose
Cases of administration of more than the recommended dose (overdose) have not been reported with this product.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB02

5.2 Pharmacokinetic properties
Not applicable

5.3 Non-clinical safety data
Repeat dose toxicity study (including local tolerance test) and reproductive/developmental toxicity study were conducted in compliance with GLP requirements. Any drug-related adverse effect was not observed in the studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Sodium chloride
Potassium chloride
Disodium hydrogen phosphate dihydrate
Potassium dihydrogen phosphate
Water for injection
Thimerosal

6.2 Incompatibilities
Incompatibilities with other drugs have not been evaluated.

6.3 Shelf-life
12 months from the date of manufacture.

6.4 Special precautions for storage
Store at 2-8℃ without freezing in hermetic container and protect from light.

6.5 Nature and contents of container
5 mL/vial x In-house packing unit

6.6 Special precautions for disposal and other handling

1) Before use check this product visually for particles or discoloration. If either is present, do not use.
2) The injection site is usually lateral upper arm and disinfected with ethanol or tincture of iodine. Repeated injections at the same site should be avoided.
3) Intravenous administration is prohibited.
4) The tip of needle should not penetrate blood vessel.
5) Do not mix with other vaccines in same syringe.
6) The vaccine should be shaken well and mixed homogeneously before use.

7. MARKETING AUTHORISATION HOLDER
Green Cross Corporation
107, Ihyeon-ro 30beon-gil, Giheung-gu, Yongin-si, Gyeonggi-do, Korea

8. MARKETING AUTHORISATION NUMBER(S)
5043

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20 May 2016

10. DATE OF REVISION OF THE TEXT
10 Mar 2022