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Randomized, single-blind, active-controlled phase I clinical trial to evaluate the immunogenicity and safety of GC3114 (high-dose, quadrivalent influenza vaccine) in healthy adults

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ABSTRACT

Influenza is a major medically attended respiratory illness. The impact of influenza on morbidity and mortality is particularly high in the elderly. Immunosenescence attenuates the immune response of influenza vaccine in the elderly. High-dose influenza vaccine contains 60 μg of hemagglutinin per strain, four times more compared with standard-dose (SD) influenza vaccine. This study is a phase I clinical trial investigating the immunogenicity and safety of the GC3114, high-dose, quadrivalent inactivated influenza vaccine (HD-QIV) in healthy adults aged 19–64 years during the 2017–2018 season. Seroprotection rates of HD-QIV were 100.0% for A/H1N1, 96.67% for A/H3N2, 83.33% for B/Yamagata, and 96.67% for B/Victoria. Seroconversion rate for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains were 86.67%, 90.0%, 53.33%, and 53.33%, respectively, in the HD-QIV group. The post-/pre-vaccination geometric mean titer ratio (GMTR) was 15.28 for A/H1N1, 8.19 for A/H3N2, 3.56 for B/Yamagata, and 3.03 for B/Victoria in the HD-QIV group. Seroconversion rate and post-/pre-vaccination GMTR for A/H3N2 were significantly higher in the HD-QIV group than in the SD-QIV group (control). No serious adverse events were reported. In conclusion, GC3114 was safe, well-tolerated, and immunogenic in healthy adults. Clinical Trials Identifier: NCT03357263.

1. Introduction

Influenza is a major medically attended respiratory illness and represents one of the major public health concerns. Annually, 291,243 to 645,832 seasonal influenza-associated respiratory mortalities were estimated to occur [1]. The impact of influenza on mortality is higher in the elderly than in younger people. The estimated annual excess all-cause mortality rate associated with influenza was 46.98 per 100,000 people in the elderly (aged ≥65 years), while it was 5.97 per 100,000 for people of all ages in Republic of Korea [2].

Influenza vaccination is the primary strategy to reduce the influenza-associated disease burden. Immunosenescence causes increased vulnerability to influenza and influenza-related complications and attenuates the immunogenicity of influenza vaccine in the elderly. Thus, a strategy to improve immunogenicity of influenza vaccine in the elderly is required.

High-dose, inactivated influenza vaccine contains 60 μg of hemagglutinin (HA) per strain, which is four times the HA content of standard-dose influenza vaccine [3]. The increased immune response of the high-dose, trivalent inactivated influenza vaccine (HD-TIV) has been expected to provide increased protection against influenza [4]. HD-TIV was approved for use in the elderly (aged ≥65 years) in the US in 2009, and HD-TIV demonstrated improved protection against influenza-like illness (ILI), hospitalization due to all-causes, influenza, pneumonia, and cardiorespiratory events in the elderly [5].

Influenza B viruses account for approximately 25% of influenza cases [6,7]. The number of fatal cases associated with influenza B was greater than that of A/H1N1, though less than that of A/H3N2 [7]. Victoria and Yamagata lineages of influenza B viruses have been co-circulating worldwide, including in Republic of Korea [8,9]. Continuous co-circulation of these two lineages of influenza B viruses and their limited cross-protection emphasize the necessity for the quadrivalent influenza vaccine, especially in persons

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at high-risk of influenza-related morbidity and mortality. However, to date, there have been no high-dose, quadrivalent inactivated influenza vaccine (HD-QIV) approved for use. In this study, the immuogenicity and safety of GC3114, HD-QIV were investigated in healthy adults.

2. Material and methods

2.1. Study design

A randomized, single-blind, active-controlled phase I clinical trial was conducted to investigate the immunogenicity and safety of GC3114 in healthy adults aged 19–64 years at Korea University Guro Hospital in Seoul, Republic of Korea, during the 2017–2018 season (ClinicalTrials Identifier: NCT03357263). The study was conducted from November 20, 2017 through December 27, 2017.

A total of 40 healthy adults aged 19–64 years were enrolled to the study. Exclusion criteria for the study were as follows: any previous severe allergy to a prior dose of influenza vaccine; any severe allergy to egg or any other component of the influenza vaccine; vaccination against influenza within the prior 6 months; any disorders in immune function; any history of Guillain-Barré syndrome; any serious chronic diseases or malignancy; presence of hemophilia or any anticoagulation treatment which may be associated with serious hemorrhage after intramuscular injection; presence of erythema or tattoo in the deltoid muscle which might interfere the interpretation of local adverse events; presence of fever (>38.0 °C) in the prior 24 h; any vaccination in the previous 28 days; treatment with any immunosuppressant, immune modifying drug, immunoglobulins, or blood-derived products within the prior 3 months; treatment with antipyretics, analgesics, or non-steroidal anti-inflammatory drugs within the prior 4 h; any other investigational products within the prior 3 months; pregnant or breast-feeding women and those trying to conceive during the participation period of the clinical trial.

The enrolled subjects were randomly assigned to the GC3114 group (30 subjects) or GC FLU® Quadrivalent group (10 subjects) by the Interactive Web Response System. Baseline blood samples were collected before vaccination. The subjects received a 0.5 ml single dose of their assigned vaccine intramuscularly into the deltoid muscle and they were observed for 30 min after vaccination. The primary and secondary outcomes of the study were safety and immunogenicity of GC3114, respectively. Safety was assessed for 21 days post-vaccination: solicited adverse events (AEs) for 7 days, and unsolicited AEs for 21 days. Immunogenicity was measured 21 days after vaccination.

2.2. Vaccines

The study vaccine (GC3114, GC Pharma, Yongin, Gyeonggi-do, Republic of Korea, batch number Q60317001) was an egg-based, high-dose, quadrivalent inactivated split influenza vaccine containing 60 μg of HA per strain. According to the recommended composition of influenza vaccines for use in the 2017–2018 northern hemisphere influenza season by WHO, GC3114 was composed of A/Singapore/GP1908/2015 IVR-180 (A/H1N1), A/Hong Kong/4801/2014 NYMC X-263B (A/H3N2), B/Phuket/3073/2013 (B/Yamagata) and B/Brisbane/60/2008 (B/Victoria). The study vaccine was prepared as a 0.5 ml prefilled syringe. The control vaccine was a GC FLU® Quadrivalent Prefilled syringe (GC Pharma, Republic of Korea, batch number Q60217020), an egg-based, quadrivalent inactivated split influenza vaccine, which was approved in November 2015 in Republic of Korea. The GC FLU® Quadrivalent Prefilled syringe, control vaccine, contained 15 μg of HA per strain, which is standard-dose QIV (SD-QIV). It was also composed of same strains with HD-QIV, which is recommended for use in the 2017–2018 northern hemisphere influenza season by WHO.

2.3. Immunogenicity measurement

Immunogenicity was assessed by hemagglutination inhibition (HI) assay. Sera were pretreated with a receptor-destroying enzyme and diluted to a range of 1:10 to 1:5120. Serum HI antibody levels were determined using test antigens at a concentration of four HA units per 25 μl of virus per assay in a 0.5% of turkey erythrocytes. The serum dilution at which complete inhibition of hemagglutination was achieved was considered as the serum antibody titer. Titers of <1:10 were considered negative and arbitrarily assigned a titer value of 1:5.

The seroprotection rate, seroconversion rate, geometric mean titer (GMT), and post-/pre-vaccination GMT ratio (GMTR) were calculated. The seroprotection rate was defined as the proportion of participants with a HI titer level of $\geq$1:40. The seroconversion rate was defined as the percentage of subjects with either a pre-vaccination HI titer $\geq$1:10 and a $\geq$4-fold increase in post-vaccination HI antibody titer from baseline, or a pre-vaccination HI titer <1:10 and a post-vaccination HI titer of $\geq$1:40.

2.4. Safety measurement

The subjects were provided with a diary sheet, thermometer, and ruler and were asked to record the severity of AEs, body temperature, and concomitant medications. Both solicited AEs and unsolicited AEs were collected using a diary sheet. The solicited AEs were collected for 7 days after vaccination. Solicited local AEs included pain, tenderness, redness/erythema, and induration/swelling, and solicited systemic AEs included fever, sweating, chill, nausea/vomiting, diarrhea, fatigue, malaise, headache, myalgia, and arthralgia. The unsolicited AEs were checked until 21 days post-vaccination. The grade of AEs was assessed according to the guideline by the US Food and Drug Administration [10]. An AE was further classified to an AE related to vaccine if a causal relationship was suspected between the vaccination and the event, which was measured by investigators.

2.5. Statistical analysis

Statistical analysis was conducted using SAS software (version 9.4, SAS Institute). Two-sided 95% confidence interval (CI) was calculated for GMT and GMTR. Percentages were calculated with approximate or exact 95% CI. Fisher's exact test was used for analysis of categorical variables and an independent two sample t-test or Wilcoxon rank sum test were used to analyze continuous variables. Results were considered statistically significant when the p-value was less than 0.05.

2.6. Ethics approval

This study protocol was approved by the Institutional Review Board of Korea University Guro Hospital (approval number: 2017GR0133). Written informed consent was obtained from all participants.

3. Results

3.1. Study population

Among the HD-QIV and SD-QIV group, male was 26.7% and 40.0%, respectively (p = 0.45). The median age of the study population was not significantly different between the groups: 39.5 years

in the HD-QIV group and 31.5 years in the SD-QIV group (p = 0.47). There was no significant difference of median body weight between HD-QIV and SD-QIV group: 62.35 kg vs. 58.05 kg (p = 0.15). Two subjects had diabetes mellitus (one in each of the HD-QIV and SD-QIV groups). Among the study population, history of influenza vaccination in the previous season was available for a total 39 subjects; 17 (56.8%) in the HD-QIV group and 5 (50.0%) in the SD-QIV group were vaccinated against influenza viruses during the 2016–2017 influenza season.

3.2. Immunogenicity

Immunogenicity was analyzed on the per protocol set which was the same as the full analysis set, since all enrolled subjects fulfilled the study protocol without major deviation. Seroprotection rates of HD-QIV were 100.0% (95% CI, – to 100.0) for A/H1N1, 96.67% (95% CI, 82.78–99.92) for A/H3N2, 83.33% (95% CI, 70.0–96.67) for B/Yamagata, and 96.67% (95% CI, 82.78–99.92) for B/Victoria (Table 1). For A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, seroconversion rates of HD-QIV were 86.67% (95% CI, 69.28–96.24), 90.0% (95% CI, 73.47–97.89), 53.33% (95% CI, 35.48–71.19), and 53.33% (95% CI, 35.48–71.19), respectively. The seroconversion rate for A/H3N2 was significantly higher in the HD-QIV group than in the SD-QIV group.

The post-/pre-vaccination GMTR for each strain was as follows: A/H1N1, 15.28 (95% CI, 8.91–26.2) in the HD-QIV group and 4.59 (95% CI, 1.51–14.03) in the SD-QIV group; A/H3N2, 8.19 (95% CI, 5.77–11.62) in the HD-QIV group and 2.3 (95% CI, 1.03–5.13) in the SD-QIV group; B/Yamagata, 3.56 (95% CI, 2.71–4.68) in the HD-QIV group and 2.3 (95% CI, 1.2–4.41) in the SD-QIV group; B/Victoria, 3.03 (95% CI, 2.28 to 4.03) in the HD-QIV group and 2.14 (95% CI, 1.13–4.06) in the SD-QIV group. The post-/pre-vaccination GMTR for A/H3N2 was significantly higher in the HD-QIV group than in the SD-QIV group.

Reverse cumulative distribution curves (RCDCs) of HI titers of pre- and post-vaccination for each of the four influenza vaccine strains in the HD-QIV or SD-QIV groups are shown in Fig. 1.

3.3. Safety

Safety analysis was conducted for all subjects who were vaccinated with the study vaccines. There were 160 AEs and among them, a total of 128 AEs were reported in 83.33% (25/30) of the HD-QIV group, while 32 AEs were reported in 90.0% (9/10) of the SD-QIV group. However, no serious AEs were reported and there were no immediate AEs occurring within 30 min of vaccination.

In this study, a total of 152 AEs related to vaccine occurred in 85.0% of subjects: 83.33% (25/30) in the HD-QIV group and 90.0% (9/10) in the SD-QIV group (Table 2). All of the reported AE related to vaccine were solicited reactions. The solicited local AEs related to vaccine included tenderness (83.33%), pain (66.67%), redness/erythema (13.33%), and induration/swelling (13.33%) in the HD-QIV group. Fatigue (46.67%) was the most frequent solicited systemic AE related to vaccine in the HD-QIV group followed by myalgia (43.33%), malaise (33.33%), sweating (23.33%), chill (23.33%), headache (23.33%), arthralgia (6.67%), and nausea/vomiting (3.33%). Frequencies of AEs related to vaccine between the HD-QIV group and the SD-QIV group were not significantly different. Severity of reported AEs related to vaccine were grade 1 or grade 2, except two AEs related to vaccine of grade 3 (tenderness and fatigue) in the HD-QIV group.

4. Discussion

The HD-TIV was designed to improve antigen presentation from antigen presenting cells, inducing greater antigen-specific antibody responses [11]. HD-TIV is one of the promising approaches to enhance protection afforded by influenza vaccines in the elderly [12]. It was first approved for use in older adults aged ≥65 years in the US in 2009.

Higher antibody responses by HD-TIV have been demonstrated in previous studies. Study including 31,989 adults of 65 years of age or older in the US and Canada showed that HD-TIV elicited significantly higher post-vaccination HI antibody GMTs and seroprotection rates for all three vaccine strains than SD-TIV [13].

Table 1
Comparison of the immunogenicity of HD-QIV and SD-QIV in study population.

	HD-QIV (GC3114) (n = 30)	SD-QIV (GC FLU® Quadrivalent) (n = 10)	p*
A/H1N1			
Seroprotection (95% CI), %	100.0 (-, 100.0)	100 (-, 100.0)	–
Seroconversion (95% CI), %	86.67 (69.28, 96.24)	50.0 (19.01, 80.99)	0.03
Pre-vaccination GMT (95% CI)	17.82 (11.46, 27.69)	34.82 (15.09, 80.36)	0.13
Post-vaccination GMT (95% CI)	272.21 (202.92, 365.18)	160.0 (86.21, 296.96)	0.08
GMTR (post-/pre-vaccination) (95% CI)	15.28 (8.91, 26.2)	4.59 (1.51, 14.03)	0.03
A/H3N2			
Seroprotection (95% CI), %	96.67 (82.78, 99.92)	100 (-, 100.0)	1.00
Seroconversion (95% CI), %	90.0 (73.47, 97.89)	30.0 (6.67, 65.25)	<0.01
Pre-vaccination GMT (95% CI)	15.16 (11.49, 19.99)	52.78 (24.14, 115.4)	<0.01
Post-vaccination GMT (95% CI)	124.09 (89.27, 172.5)	121.26 (75.1, 195.77)	0.94
GMTR (post-/pre-vaccination) (95% CI)	8.19 (5.77, 11.62)	2.3 (1.03, 5.13)	<0.01
B/Yamagata			
Seroprotection (95% CI), %	83.33 (70.0, 96.67)	70.0 (34.75, 93.33)	0.39
Seroconversion (95% CI), %	53.33 (35.48, 71.19)	20.0 (2.52, 55.61)	0.08
Pre-vaccination GMT (95% CI)	16.25 (11.8, 22.37)	15.16 (7.76, 29.6)	0.83
Post-vaccination GMT (95% CI)	57.89 (45.42, 73.78)	34.82 (19.83, 61.14)	<0.05
GMTR (post-/pre-vaccination) (95% CI)	3.56 (2.71, 4.68)	2.3 (1.2, 4.41)	0.13
B/Victoria			
Seroprotection (95% CI), %	96.67 (82.78, 99.92)	100 (-, 100.0)	1.00
Seroconversion (95% CI), %	53.33 (35.48, 71.19)	30.0 (6.67, 65.25)	0.28
Pre-vaccination GMT (95% CI)	32.49 (24.52, 43.05)	34.82 (18.93, 64.06)	0.81
Post-vaccination GMT (95% CI)	98.49 (78.49, 123.59)	74.64 (51.77, 107.62)	0.20
GMTR (post-/pre-vaccination) (95% CI)	3.03 (2.28, 4.03)	2.14 (1.13, 4.06)	0.24

* For seroprotection and seroconversion, Fisher's exact test were used. P-values for pre-vaccination GMT, post-vaccination GMT, and GMTR were extracted using independent two sample t-test.

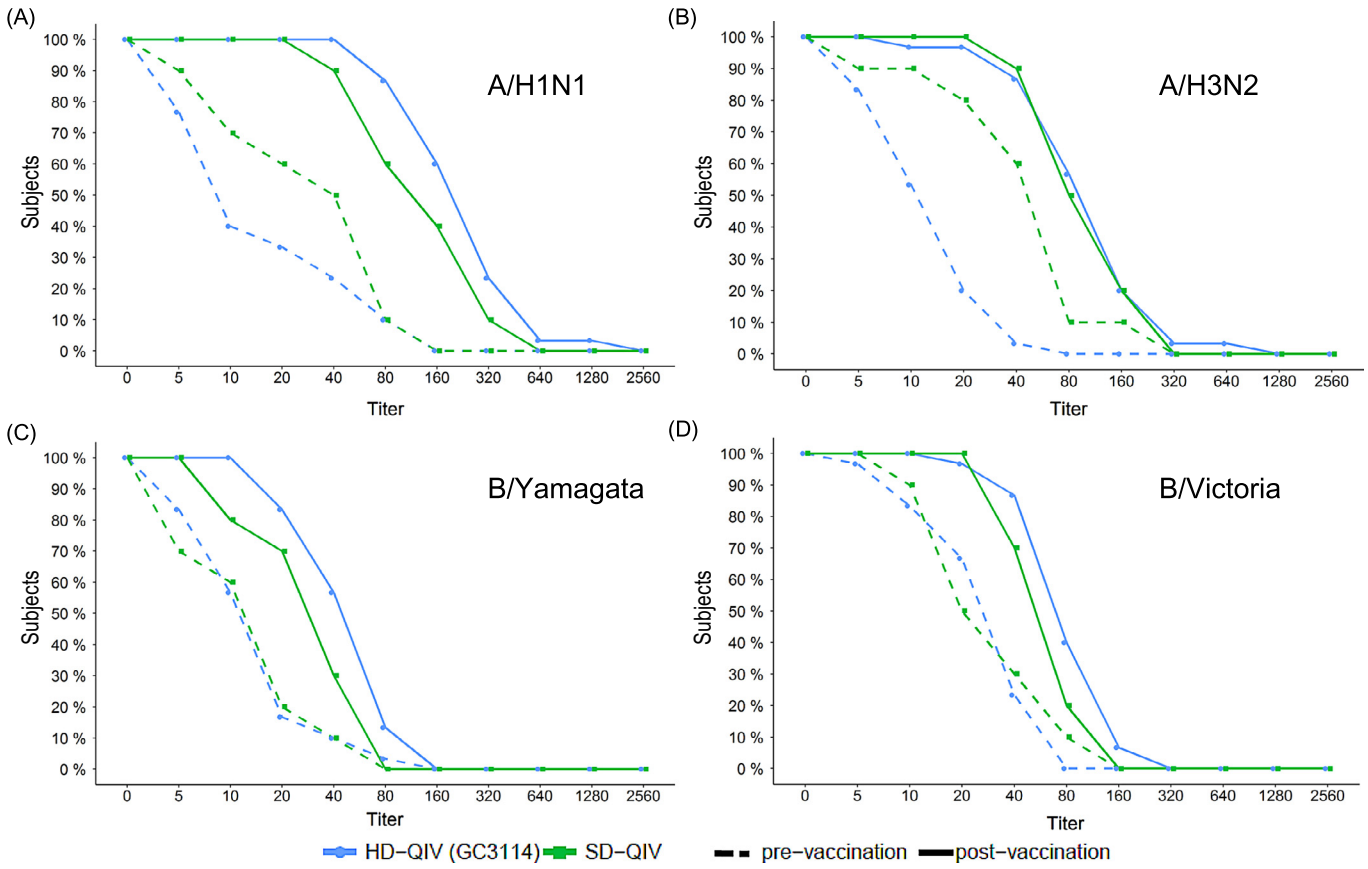

Fig. 1. Reverse cumulative distribution curves of hemagglutination inhibition titers of pre- and post-vaccination with HD-QIV (GC3114) or SD-QIV (GC FLU® Quadrivalent) for each of four influenza vaccine strains. (A) A/H1N1, (B) A/H3N2, (C) B/Yamagata, and (D) B/Victoria. Post-vaccination sera were collected 21 days after vaccination.

Table 2
Comparison of solicited and unsolicited adverse events related to vaccine between HD-QIV (GC3114) and SD-QIV (GC FLU® Quadrivalent) group.

	HD-QIV (GC3114) (n = 30)	SD-QIV (GC FLU® Quadrivalent) (n = 10)	p*
Solicited AEs related to vaccine, n (%)	25 (83.33)	9 (90.0)	1.00
Local	25 (83.33)	8 (80.0)	1.00
Pain	20 (66.67)	7 (70.0)	1.00
Tenderness	25 (83.33)	7 (70.0)	0.39
Redness/erythema	4 (13.33)	1 (10.0)	1.00
Induration/swelling	4 (13.33)	0 (0)	–
Systemic	15 (50.0)	6 (60.0)	0.72
Fever	0 (0)	0 (0)	–
Sweating	7 (23.33)	0 (0)	–
Chill	7 (23.33)	2 (20.0)	1.00
Nausea/vomiting	1 (3.33)	1 (10.0)	0.44
Diarrhea	0 (0)	0 (0)	–
Fatigue	14 (46.67)	4 (40.0)	1.00
Malaise	10 (33.33)	3 (30.0)	1.00
Headache	7 (23.33)	2 (20.0)	1.00
Myalgia	13 (43.33)	2 (20.0)	0.27
Arthralgia	2 (6.67)	1 (10.0)	1.00
Unsolicited AEs related to vaccine	0 (0)	0 (0)	–

AE: adverse event.
* Fisher's exact test.

In addition, HD-TIV showed better immunogenicity in adults with 50–64 years of age and also in solid-organ transplant recipients (≥18 years) [14,15]. In this study, seroconversion rate and post-/pre-vaccination GMTR for A/H3N2 was significantly higher in the HD-QIV group than in the SD-QIV group. Previously, HD-TIV was reported to elicit acute, short-lived plasmablast responses rather than long-lived memory B cell responses [16]. Strong activation of T follicular helper cells (Tfh) was suggested to be a predictor of seroconversion and HD-TIV induced greater Tfh activation than SD-TIV [17].

Enhanced immune response induced by HD-TIV would be expected to contribute to better influenza vaccine effectiveness (VE). In recent meta-analysis, HD-TIV showed higher VE in preventing ILI, hospitalization due to all-causes, influenza, pneumonia, and cardiorespiratory events in older adults (≥65 years) compared with SD-TIV [5]. HD-TIV was more effective against hospitalization

associated with influenza or pneumonia in the elderly during the 2015–2016 season, in which A/H1N1 epidemic was dominant [18]. HD-TIV showed significantly better effectiveness for prevention of post-influenza mortality during the 2012–2013 season in the US, where A/H3N2 influenza strain was dominant [19]. During the 2012–2013 season, low VE against A/H3N2 was evident and this was considered to be associated with mutations in the egg-adapted A/H3N2 vaccine strain [20]. Further study is needed to investigate whether HD vaccine induce a broader immune response to mismatch strains than SD vaccine.

Influenza A is more prevalent virus of seasonal influenza epidemics and the causative strain for all past pandemic influenza. However, the disease burden of influenza B is not negligible. In Republic of Korea, influenza B was responsible for 5.6–54.8% of influenza positive samples from the 2012–2013 season through the 2017–2018 season according to the national surveillance [21]. There is limited cross-protection between the two lineages of influenza B viruses and it is not easy to predict which lineage of influenza B will circulate. QIV may therefore be beneficial, particularly in the elderly and in high-risk groups of influenza. It has been reported that the use of QIV is estimated to be cost-effective over TIV in older adults [22,23]. In this study, the value of post-/pre-vaccination GMTR for influenza B strains seemed to be lower than for influenza A viruses in the HD-QIV group, which is in agreement with similar observations reported previously [13,14].

Increased dose of antigen in vaccines could induce more frequent and severe AEs related to vaccine following vaccination. In a previous study, reactogenicity was more common in the elderly who received HD-TIV compared with SD-TIV; however, these were well tolerated [24]. In this study, the frequency of AEs related to vaccine in subjects vaccinated with HD-QIV was comparable to those of the SD-QIV group. However, two AEs related to vaccine of grade 3 were reported in the HD-QIV group, while all AEs related to vaccine in the SD-QIV group were grade 2 and or lower. No unsolicited AEs related to vaccine were reported in this trial.

This study has several limitations. First, immunogenicity was assessed by HI assay and neutralizing antibody titers were not measured. However, HI assay is one of the standard serological assays for immunologic assessment of influenza vaccine. Serological technique of HI assay is well established and reproducible [25]. We presented data from HI assay using GMT and RCDCs. The RCDCs allow visualization of the immune response across the study population [26]. The number of study subjects in this study was small and longevity of the immune response induced by influenza vaccination was not assessed. In addition, the age range of study subjects was 19–64 years, while approved HD-TIV is primarily for use in individuals aged $\geq$65 years. However, the primary endpoint of this phase I clinical trial was safety assessment of GC3114 in healthy adults. In addition, this was a pilot study, thus superiority of immune response of HD-QIV versus SD-QIV was not demonstrated. Further confirmatory studies on the safety and immunogenicity of GC3114 is required in the adults aged 65 years and older.

Introduction of HD-QIV is important to improve protection against influenza in the elderly. However, to date, there is no HD-QIV licensed for public use. In addition, there is currently no approved HD-TIV in Republic of Korea. In this study, the safety and immunogenicity of HD-QIV were investigated. Increased dose of antigen in HD-QIV has raised concerns that it poses a higher risk of reactogenicity. However, the reactogenicity of HD-QIV was not significantly different from SD-QIV in our study. Further studies on the safety of HD-QIV in larger population will be required in the future. In conclusion, GC3114, a HD-QIV, was safe, well-tolerated, and immunogenic in healthy adults aged 19–64 years in Republic of Korea.

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Declaration of Competing Interest

None

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